Controlled Study of Metabolic Syndrome Among Offspring of Parents With Bipolar Disorder

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Abstract

Objectives: Bipolar disorder (BD) is highly heritable and associated with increased rates of metabolic syndrome (MetS). However, little is known about MetS in offspring of parents with BD. We therefore examined this topic in the Pittsburgh Bipolar Offspring Study cohort.

Methods: Participants included 199 parents (n = 116 BD, diagnosed using *DSM-IV*; n = 83 non-BD) and 330 offspring (mean age 19.9 ± 5.3 years), including 198 high-risk offspring of parents with BD (n = 80 affected with a mood disorder) and 132 control offspring. We defined MetS and its components using International Diabetes Federation (IDF) guidelines (primary) and National Cholesterol Education Program (NCEP) guidelines (secondary). Multivariable analyses controlled for age and socioeconomic status in offspring. Sensitivity analyses controlled for psychotropic medications.

Results: There was higher prevalence of MetS in parents with BD as compared to controls. NCEP-defined MetS was significantly more prevalent among affected high-risk offspring (16.3%) and controls (15.2%) vs unaffected high-risk offspring (6.0%; $\chi^2 = 6.54$, $P = .04$). There was greater mean number of MetS components (IDF: 1.7 ± 1.1; NCEP: 1.4 ± 1.0) among affected high-risk offspring vs unaffected high-risk offspring (IDF: 1.2 ± 1.0; NCEP: 1.0 ± 1.0) and controls (IDF: 1.3 ± 1.2; NCEP: 1.1 ± 1.1; IDF: $H[2] = 10.26$, $P = .006$; NCEP: $H[2] = 9.18$, $P = .01$). Most findings became nonsignificant in multivariable analyses. Some between-group results became nonsignificant after controlling for second-generation antipsychotics.

Conclusions: This preliminary study found increased risk of MetS among affected high-risk offspring, which may be attributable to socioeconomic status. Prospective studies may determine timing of MetS onset in relation to mood disorder onset, and the role of socioeconomic status in moderating this association.

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Bipolar disorder (BD), one of the most disabling medical conditions, has a worldwide prevalence of 2.3%.[1] The onset of BD often occurs during adolescence, and in such early-onset cases there is increased illness burden.[2] In addition to the increase in psychiatric symptoms, these individuals have premature mortality,[3,4] the leading cause of which is vascular, including coronary artery disease and stroke.[4,5] There is widely replicated international evidence of increased risk and premature onset of cardiovascular disease (CVD) among individuals with BD.[4] This elevated risk is observed not only in clinical samples but also in general population samples in which BD is largely untreated,[6] providing evidence that the increased risk of CVD in BD is not simply a result of psychotropic medications. Indeed, an American Heart Association scientific statement positioned BD and major depressive disorder (MDD) among youth as risk factors for early-onset CVD.[7] Unfortunately, there has been limited advancement in reducing CVD risk in individuals with BD, made evident by the fact that while CVD mortality has reduced in the general population in the past 20 years, CVD mortality has continued to rise in individuals with psychiatric conditions, including BD.[8–11]

Adults with BD demonstrate an increased prevalence of traditional cardiovascular risk factors (CVRFs) including type II diabetes (T2D), hypertension, obesity, and dyslipidemia.[4,12] Even among youth early in their course of BD, there is evidence of increased CVRFs, which have been associated with mood symptoms, psychiatric comorbidities, psychiatric hospitalizations, physical and sexual abuse, suicidality, neurocognitive dysfunction, and brain structure.[13–19] Metabolic syndrome (MetS) is a clustering of CVRFs, specifically obesity, dyslipidemia (elevated triglycerides and/or reduced high-density lipoprotein cholesterol [HDL-C], hypertension, and hyperglycemia), and has been associated with BD. In adults with BD, MetS prevalence is up to 60%, which is

Clinical Points

- Although bipolar disorder is associated with increased cardiovascular risk, little is known regarding cardiovascular risk among offspring of parents with bipolar disorder.
- Lower socioeconomic status and personal history of mood disorders are associated with greater risk of metabolic syndrome and its components among offspring of parents with bipolar disorder.

significantly greater than the general population rates of 20%–25%.[20–22] Furthermore, a study of youth with BD reported a 19.8% prevalence of MetS, which is substantially higher compared to the general population rate of 2.1% in adolescents and 7.0% in young adults.[23–25] Given the high degree of heritability of BD, with first-degree relatives of individuals with BD having up to 10-fold increased risk of BD, and heritability estimates of 70%–90%,[26,27] the question arises as to whether there is also heritability of CVRFs in families affected by BD.

Relatively few studies have assessed the heritability of CVRFs in association with serious mental illness. First-degree, unaffected adult relatives of individuals with schizophrenia have a higher prevalence of T2D/abnormal glucose levels, and hypertension, as compared to healthy controls.[28–30] Likewise, one study found higher blood pressure and decreased insulin sensitivity among unaffected young adults with a family history with depression vs healthy controls.[31] Similarly, unaffected adults with a family history of BD have higher risk of CVD, stroke, T2D/hyperglycemia, and dyslipidemia.[32–35] For instance, a study looking at unaffected adult (n = 18) and youth (n = 30) relatives of three adults with BD-I demonstrated higher prevalence of abnormal glucose, total cholesterol, and low-density cholesterol levels in both adult and youth relatives, with unaffected adult relatives also demonstrating abnormal leptin and insulin resistance values.[36]

The current study aims to bridge gaps in knowledge regarding the familiality of the vascular-bipolar connection by examining MetS and its components: central obesity, elevated blood pressure, elevated glucose, and dyslipidemia (elevated triglycerides and decreased HDL-C).[18,37,38] Here, we examined MetS and its components across three groups of offspring: offspring of a parent with BD and themselves having a mood disorder (ie, affected high-risk offspring), high-risk offspring without a mood disorder (ie, unaffected high-risk offspring), and unaffected offspring of control parents (ie, control offspring). We hypothesized that the prevalence of MetS and the individual components would be significantly higher among affected high-risk offspring as compared to control offspring, with unaffected high-risk offspring being intermediate between the other two groups.

METHODS

Participants

The current study is a subset of the larger Pittsburgh Bipolar Offspring Study (BIOS), which aims to understand the development and course of psychopathology and the related underlying neurobiology among offspring of parents with BD.[39] BIOS recruitment was initiated in 2002 and completed in 2022. As part of a supplemental study (National Institute of Mental Health grant MH060952), MetS assessments were initiated in 2013. A total of 529 participants, including parents and offspring, had at least one MetS assessment and were included in the current study: 116 parent probands with BD together with 198 of their offspring and 83 proband parent controls healthy or with non-BD psychopathology together with 132 of their offspring. Parents with BD were required to fulfill *DSM-IV* criteria for BD-I/BD-II subtypes. As per the overall BIOS study, exclusion criteria included current or lifetime diagnoses of schizophrenia, mental retardation, secondary mood disorders (ie, due to substance use, medical conditions, or medication use), and living more than 200 miles away from Pittsburgh, Pennsylvania. Control parents, who could be healthy or have non-BD psychiatric disorders, were group matched with the BD parents by age, sex, and neighborhood (based on area code and the first 3 digits of the telephone number and zip code). The exclusion criteria for the control parents were the same as those for the parents with BD, with the additional requirements that neither of the biological parents, nor their first-degree relatives, could have BD or a family history of BD. Control parents were recruited by the University Center for Social and Urban Research, University of Pittsburgh, in an approximate ratio of one control parent for every two parents with BD, and in the current substudy, the approximate ratio is two control parents for every three parents with BD. The study was approved by the University of Pittsburgh institutional review board and by the Centre for Addiction and Mental Health Research Ethics Board. Written informed consent was obtained from all parents and assent from any child participants.[39]

Interviews and Psychiatric Diagnoses

Detailed information regarding the overall BIOS study can be found in prior publications.[39] Briefly, parent probands were directly assessed for *DSM-IV* disorders using the Structural Clinical Interview for *DSM-IV*[40] and the attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, conduct disorder, and separation anxiety disorder sections of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL).[41] For nonparticipating coparents and nonparticipating siblings, psychiatric history was obtained from the parent

proband using the Family History Research Diagnostic Criteria method[42] plus the ADHD, oppositional defiant disorder, conduct disorder, and separation anxiety items from the K-SADS-PL.

Parents were interviewed about their offspring, and the offspring were directly interviewed for the presence of nonmood psychiatric disorders using the K-SADS-PL. All offspring diagnoses were made using *DSM-IV* criteria, with additional operationalized criteria for BD not-otherwise-specified (NOS).[43] Onset of a mood episode was defined as the first episode of MDD or BD. Onset of BD was defined as the first episode of mania, hypomania, mixed, or operationalized criteria for BD-NOS.

Socioeconomic status was determined using the Hollingshead scale, where an education score (1–7) and occupation score (1–9) are assigned for each parent and then weighted to obtain a single score that reflects one of the 5 social strata (1 through 5, with 1 a reference to unskilled/menial labor and 5 a reference to major professionals).[44] Interviewers were blind to parental diagnoses.

Anthropometrics, Metabolic Assessment, and Medical History

Physical and metabolic assessments occurred between 7 and 10 AM and included in-home blood tests, anthropometric measurements (ie, height, weight, abdominal circumference, and blood pressure), and questionnaires/interviews (ie, personal and family medical history, and lifestyle behaviors). Approximately 90% of assessments were completed in the participants' homes using devices brought by the interviewers (see below). Bachelors- or masters-level interviewers performed all assessments after intensive training with the diagnostic instruments and a minimum of 80% agreement with a certified rater. Interviewers assessing parental psychopathology were different from those assessing offspring psychopathology, to ensure blinding. All data (parent, offspring, and family) were confirmed by a child psychiatrist, who was blinded to the parents' psychiatric status when evaluating offspring psychopathology. All diagnoses were made according to the best-estimate procedure.[45] Personal and family medical history were examined using the Coronary Artery Risk Development in Young Adults (CARDIA) Medical History and the CARDIA Family Medical History form, respectively.[46–49]

Height, weight, waist circumference, and blood measure assessments were conducted according to established guidelines.[50–54] Weight and body fat percentage was measured using the Tanita Body Composition Analyzer BF-350, height with a portable SECA electronic stadiometer, waist circumference with the SECA 201 measuring tape, and blood pressure with the LifeSource Digital Blood Pressure Monitor. Fasting glucose and lipids (high-density lipoprotein, low-density lipoprotein, and triglycerides) were measured using reliable finger-stick kits (Cholestech LDX Analyzer System) that provide results on-site. Participants were instructed to fast for at least 10 hours prior to the metabolic assessment visit.

Definition of MetS

The primary definitions for MetS and its components were based on the International Diabetes Federation (IDF) criteria, requiring the presence of central obesity (adults: waist circumference (WC)>37 inches for men, >31.5 inches for women; adolescents under the age of 16 years: 90th percentile for age and sex), plus any two of high triglycerides (≥150 mg/dL), low HDL-C (<40 mg/dL for men, <50 mg/dL for women), high systolic (>130 mm Hg) and/or diastolic (>85 mm Hg) blood pressure, and high fasting glucose (≥100 mg/dL).[54]

As a secondary approach, MetS was also defined using the National Cholesterol Education Program (NCEP) criteria, which are identical to the IDF criteria with the following exceptions: central obesity is defined as WC >40 inches for men and >35 inches for women, and MetS requires any three of central obesity, high triglycerides, low HDL-C, high systolic and/or diastolic blood pressure, and high fasting glucose.[55] Furthermore, NCEP criteria did not provide specific WC cutoffs for individuals <18 years, and thus, the same measures were applied to all offspring, irrespective of age.

Both the IDF and NCEP guidelines are validated approaches for categorizing MetS and its components,[54,55] are reliable markers of long-term CVD risk in youth, and also have the potential to monitor ongoing risk in relation to lifestyle modifications or treatment.[56]

Statistical Analyses

Bivariate analyses compared parents with BD vs parents without BD (ie, control parents). Of note, within the current sample, none of the coparents had BD. For offspring, bivariate analyses compared affected high-risk offspring vs unaffected high-risk offspring vs control offspring. Given that the number of control offspring with mood disorders was not sufficient for an additional group [n = 20 control offspring with a mood disorder; n = 3 BD, n = 13 MDD, and n = 4 other depressive disorders (ie dysthymia and depression NOS)], we opted to exclude them from analyses. Between-group differences in demographic and clinical variables were evaluated using *t* tests (two-way comparisons), analysis of variance (three-way comparisons), χ^2 tests, and Kruskal-Wallis nonparametric tests as appropriate. Multivariable analyses, controlling for age and parental socioeconomic status (henceforth written as socioeconomic status) in offspring, were binary logistic regression for dichotomous variables (prevalence of MetS and prevalence of high MetS components), ordinal

Table 1.
Demographic and Clinical Characteristics of Parents

	Parents with BD[a] (n = 116)	Control parents[a] (n = 83)	Statistic[b]	*P*	Effect size[c]
Age, y	49.3 ± 8.0	49.4 ± 7.4	0.09	.93	0.01
Female	98 (84.5)	68 (81.9)	0.23	.63	0.03
Caucasian	101 (87.1)	65 (78.3)	2.68	.10	0.12
Socioeconomic status	3.0 ± 1.2	3.3 ± 1.2	2.60	.11	0.01
Number of offspring	1.7 ± 0.9	1.7 ± 0.9	0.23	.82	0.03
BD-I	82 (70.7)	-	-	-	-
BD-II	34 (29.3)	-	-	-	-
MDD[d]	-	26 (31.3)	-	-	-
Depression NOS	-	5 (6.0)	-	-	-
Dysthymic disorder[d]	-	4 (4.8)	-	-	-
Any anxiety disorder	84 (72.4)	18 (21.7)	49.83	<.001*	0.50
Substance use disorder	59 (50.9)	10 (12.0)	32.18	<.001*	0.40

[a]Values for all continuous variables are written as mean ± standard deviation and for categorical variables are written as n (% within group).
[b]Statistic = *t* for dimensional variables, *H* (1 degree of freedom) for ordinal variables, or χ^2 for categorical variables.
[c]Effect size = Cohen D for *t* test, partial η^2 for *H* test, or Cramer *V* for χ^2 test.
[d]MDD and dysthymia are not mutually exclusive.
* = Significant difference at $\alpha = 0.05$.
Abbreviations: BD = bipolar disorder, MDD = major depressive disorder, NOS = not otherwise specified.

logistic regression for ordinal variables (mean number of MetS components), and analysis of covariance for continuous variables (dimensional cardiometabolic measures). Effect sizes for all variables were calculated as described by Cohen (Cramer V for categorical variables, Cohen's D for continuous variables for two-group comparisons, and partial η^2 for ordinal variables and for continuous variables for three-group comparisons). All *P* values are based on 2-tailed tests with $\alpha = 0.05$. Three sensitivity analyses were conducted, controlling for any psychotropic medication, controlling for second generation antipsychotics (SGAs), and removing participants on SGAs, respectively. Due to power considerations, sensitivity analyses did not covary for age or socioeconomic status. Two exploratory analyses examined the interaction effects of offspring mood disorder by parental mood disorder and the interaction effects of offspring mood disorder by socioeconomic status, respectively, on MetS and its components, covarying for age and socioeconomic status.

In order to enable a comprehensive evaluation of MetS and its criteria, including categorical, ordinal, and dimensional analyses, we opted to not correct for multiple comparisons in this exploratory study.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the parent groups are presented in Table 1. There were no significant differences in the age, sex, race, socioeconomic status, or the number of offspring between parents with BD vs control parents.

Demographic and clinical characteristics of the offspring groups are presented in Table 2. The overall sample included 330 offspring, 198 high-risk offspring of parents with BD and 132 offspring of control parents. Among the high-risk offspring, 80 had a mood disorder (n = 31 BD and n = 49 depressive disorder). None of the control offspring had a mood disorder. High-risk offspring with mood disorders had significantly higher age, lower socioeconomic status, and higher prevalence of other psychiatric disorders and were more likely to be on psychotropic medications [ie, SGAs, lithium, nonselective serotonin reuptake inhibitor (SSRIs) antidepressants, benzodiazepines, anticonvulsants, and α-antagonists] compared to unaffected high-risk offspring and to control offspring.

MetS Analyses

Parents. MetS and its components among parents are presented in Table 3. Parents with BD were significantly more likely to meet criteria for IDF-defined MetS (59.1%) and NCEP-defined MetS (57.8%) as compared to controls (IDF: 41.5%; NCEP: 41.0%) (IDF: $\chi^2 = 5.98$, $P = .01$, $V = 0.17$; NCEP: $\chi^2 = 5.46$, $P = .02$, $V = 0.17$). Pertaining to individual MetS components, the high waist circumference criterion was more common among parents with BD (IDF: 84.3%; NCEP: 73%) as compared to controls (IDF: 68.0%; NCEP: 50%) (IDF: $\chi^2 = 7.11$, $P = .01$, $V = 0.19$; NCEP: $\chi^2 = 11.00$, $P = .001$, $V = 0.24$). Dimensional measures of body mass index ($P = .02$), waist circumference ($P = .01$), hip circumference ($P = .02$), body fat percentage ($P = .001$), and weight ($P = .04$) were all higher in parents with BD vs controls.

Table 2.

Demographic and Clinical Characteristics of Offspring

	Affected high-risk offspring[a] (n = 80)	Unaffected high-risk offspring[a] (n = 118)	Control offspring[a] (n = 132)	Statistic[b]	*P*	Effect size[c]
Age, y	21.3 ± 4.7	19.7 ± 5.6	19.2 ± 5.3	4.09	.02[d*]	0.02
Female	45 (56.3)	61 (51.7)	63 (47.7)	1.47	.48	0.07
Caucasian	60 (75.0)	97 (82.2)	100 (75.8)	2.01	.37	0.08
Parental socioeconomic status	2.7 ± 1.2	3.2 ± 1.1	3.2 ± 1.2	10.65	.005[d,f*]	0.03
Any Axis I disorders	80 (100.0)	51 (43.2)	41 (31.3)	100.0	<.001[d,e,f*]	0.55
Any BD	31 (39.2)	-	-	-	-	-
BD-I	2 (2.5)	-	-	-	-	-
BD-II	4 (5.3)	-	-	-	-	-
BD-NOS	25 (31.3)	-	-	-	-	-
Any depressive disorders	49 (61.3)	-	-	-	-	-
MDD	32 (40.0)	-	-	-	-	-
Depression NOS	15 (18.8)	-	-	-	-	-
Dysthymic disorder	2 (2.5)	-	-	-	-	-
Any anxiety disorder	35 (43.8)	23 (19.5)	17 (12.9)	28.13	<.001[d,f*]	0.29
ADHD	37 (46.3)	32 (27.1)	27 (20.5)	16.41	<.001[d,f*]	0.22
Disruptive behavior disorder	27 (33.8)	8 (6.8)	12 (9.1)	33.17	<.001[d,f*]	0.32
Substance use disorder	15 (18.8)	4 (3.4)	6 (4.5)	18.95	<.001[d,f*]	0.24
Any psychotropic medications	27 (33.8)	17 (14.4)	13 (9.8)	20.97	<.001[d,f*]	0.25
SGAs	11 (13.8)	5 (4.2)	2 (1.5)	14.99	.001[d,f*]	0.21
Lithium	2 (2.5)	0 (0)	0 (0)	6.29	.04*	0.14
SSRIs	6 (7.5)	5 (4.2)	6 (4.5)	1.20	.55	0.06
Other antidepressants	12 (15.0)	3 (2.5)	0 (0)	27.53	<.001[d,f*]	0.29
Stimulants	8 (10.0)	8 (6.8)	7 (5.3)	1.71	.43	0.07
Benzodiazepines	5 (6.3)	0 (0)	1 (0.8)	11.82	.003[d,f*]	0.19
Anticonvulsants	5 (6.3)	4 (3.4)	0 (0)	7.64	.02[d,e*]	0.15
α-Antagonists	2 (2.5)	2 (1.7)	0 (0)	2.96	.23	0.10

[a]Values for all continuous and ordinal variables are written as mean ± standard deviation and for categorical variables are written as n (% within group).
[b]Statistic = *F* for dimensional variables, *H* (2 degrees of freedom) for ordinal variables, or χ^2 for categorical variables. * = Significant difference at $\alpha = 0.05$.
[c]Effect size = partial η^2 for *F* and *H* tests, or Cramer *V* for χ^2 test.
[d,e,f]Post-hoc comparisons: d = control vs affected high-risk offspring; e = control vs unaffected high-risk offspring; f = affected vs unaffected high-risk offspring.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BD = bipolar disorder, MDD = major depressive disorder, NOS = not otherwise specified, SGAs = second-generation antipsychotics, SSRIs = selective serotonin reuptake inhibitors.

Offspring. Offspring MetS and its components are presented in Table 4. There were significant between-group differences in the prevalence of NCEP-defined MetS: 16.3% in affected high-risk offspring, 6.0% in unaffected high-risk offspring, and 15.2% in control offspring ($\chi^2 = 6.54$, $P = .04$, and V = 0.14). Post hoc pairwise analyses revealed that between-group differences were based on affected high-risk offspring ($P = .02$) and control offspring ($P = .02$) having significantly higher prevalence of NCEP-defined MetS as compared to unaffected high-risk offspring. This finding remained significant after controlling for offspring age and socioeconomic status ($\chi^2 = 6.27$, $P = .04$). Pairwise contrasts revealed that control offspring had a significantly higher prevalence of NCEP-defined MetS as compared to unaffected high-risk offspring ($P = .02$).

There were significant between-group differences in mean number of IDF-defined MetS components: 1.7 ± 1.1 in affected high-risk offspring, 1.2 ± 1.0 in unaffected high-risk offspring, and 1.3 ± 1.2 in control offspring ($H[2] = 10.26$, $P = .006$, $\eta_p^2 = 0.03$). Post hoc analyses revealed that between-group differences were driven by significantly higher number of MetS components in affected high-risk offspring as compared to unaffected high-risk offspring ($P = .002$) and control offspring ($P = .008$). Similarly, there were significant between-group differences in mean number of NCEP-defined MetS components ($H[2] = 9.18$, $P = .01$, $\eta_p^2 = 0.02$), with post hoc analyses revealing that this was driven by affected high-risk offspring (1.4 ± 1.0) being significantly higher as compared to unaffected high-risk offspring (1.0 ± 1.0; $P = .003$) and controls (1.1 ± 1.1; $P = .02$). However, these findings did not remain significant after controlling for age and socioeconomic status (IDF: $\chi^2 = 4.90$, $P = .09$; NCEP: $\chi^2 = 3.64$, $P = .16$).

Sensitivity Analyses

Sensitivity analyses controlling for any psychotropic medication, and for SGAs specifically, are listed in Supplementary Tables 1 and 2. When controlling for SGAs, the NCEP-defined MetS prevalence finding remained significant. Pairwise contrasts indicated that control offspring had significantly higher prevalence of NCEP-defined MetS as compared to unaffected

Table 3.

Metabolic Syndrome, Its Components, and Related Cardiometabolic Measures Among Parents

	Parents with BD[a] (n = 116)	Control parents[a] (n = 83)	Statistic[b]	*P*	Effect size[c]
Meets criteria for MetS					
IDF	68 (59.1)	34 (41.5)	5.98	.01*	0.17
NCEP	67 (57.8)	34 (41.0)	5.46	.02*	0.17
Mean number of MetS components					
IDF	2.8 ± 1.4	2.5 ± 1.5	1.40	.24	0.002
NCEP	2.7 ± 1.5	2.4 ± 1.5	2.13	.15	0.01
Prevalence of MetS components					
Waist circumference, IDF	97 (84.3)	56 (68.3)	7.11	.01*	0.19
Waist circumference, NCEP	84 (73.0)	41 (50.0)	11.00	.001*	0.24
Blood pressure	58 (50.9)	43 (52.4)	0.05	.83	0.02
Fasting glucose	49 (42.2)	37 (44.6)	0.11	.74	0.02
Triglycerides	51 (44.3)	33 (39.8)	0.42	.52	0.05
HDL-C	66 (57.9)	42 (51.2)	0.86	.35	0.07
Dimensional cardiometabolic measures					
Glucose (mg/dL)	105.6 ± 30.9	110.0 ± 48.1	0.79	.43	0.11
Total cholesterol (mg/dL)	193.3 ± 42.5	191.8 ± 38.9	0.27	.79	0.04
HDL-C (mg/dL)	47.8 ± 16.4	51.8 ± 20.1	1.56	.12	0.23
LDL-C (mg/dL)	115.3 ± 35.6	113.7 ± 34.9	0.30	.77	0.05
Triglycerides (mg/dL)	169.0 ± 121.1	150.5 ± 104.7	1.12	.26	0.16
Systolic blood pressure (mm Hg)	129.5 ± 19.8	128.7 ± 20.8	0.30	.77	0.04
Diastolic blood pressure (mm Hg)	82.1 ± 11.6	81.1 ± 12.2	0.61	.54	0.09
Body mass index (lb/in2)	32.2 ± 7.6	29.7 ± 8.1	2.27	.02*	0.33
Body fat %	39.3 ± 10.7	34.0 ± 11.2	3.25	.001*	0.48
Waist circumference (in)	40.0 ± 6.9	37.3 ± 7.7	2.55	.01*	0.37
Hip circumference (in)	45.3 ± 5.3	43.4 ± 6.1	2.39	.02*	0.34

[a]Values for all continuous and ordinal variables are written as mean ± standard deviation and for categorical variables are written as n (% within group).
[b]Statistic = *t* for dimensional variables, *H* (1 degree of freedom) for ordinal variables, or χ^2 for categorical variables. * = Significant difference at $\alpha = 0.05$.
[c]Effect size = Cohen D for *t* test, partial η^2 for *H* test, or Cramer V for χ^2 test.
Abbreviations: HDL-C = high-density lipoprotein cholesterol, IDF = International Diabetes Federation, LDL-C = low-density lipoprotein cholesterol, MetS = metabolic syndrome, NCEP = National Cholesterol Education Program.

high-risk offspring ($P = .02$). The mean number of IDF-defined and NCEP-defined MetS components also remained significant, with the same pairwise contrasts as the primary analyses.

Since a small number of participants in our sample were taking SGAs (n = 18), sensitivity analyses were repeated with these participants excluded (Supplementary Table 3). The overall between-group patterns remained similar, although some became nonsignificant (ie, NCEP-defined MetS and number of MetS components) and others became significant (ie, IDF-defined high WC).

Exploratory Interaction Analyses

Exploratory analyses examined the interaction effects of offspring mood disorder by parental mood disorder on MetS and its components. Offspring mood disorder was associated with significantly greater IDF-defined WC among offspring of parents with vs without a mood disorder ($\chi^2 = 7.30$, $P = .01$). Similar associations were observed for dimensional measures of body mass index ($F = 5.26$, $P = .02$), WC ($F = 4.11$, $P = .04$) and hip circumference ($F = 5.83$, $P = .02$). In addition, offspring mood disorder was associated with significantly lower HDL-C and glucose levels among offspring of parents with vs without a mood disorder ($\chi^2 = 5.10$, $P = .02$ and $\chi^2 = 4.45$, $P = .04$, respectively).

There were no significant interaction effects of offspring mood disorder by socioeconomic status on MetS or any of its components.

DISCUSSION

This study addresses a gap in knowledge regarding cardiometabolic risk among offspring of parents with BD. As expected, parents with BD had elevated rates of MetS and its components vs control parents. Furthermore, we found that affected high-risk offspring and control offspring had a greater prevalence of NCEP-defined

Table 4.

Metabolic Syndrome, Its Components, and Related Cardiometabolic Measures Among Offspring

	Affected high-risk offspring[a] (n = 80)	Unaffected high-risk offspring[a] (n = 118)	Control offspring[a] (n = 132)	Statistic[b]	*P*	Effect size[c]
Meets criteria for MetS						
IDF	17 (21.3)	11 (9.5)	20 (15.4)	5.30	.07	0.13
NCEP	13 (16.3)	7 (6.0)	20 (15.2)	6.54	.04[e,f*]	0.14
Mean number of MetS components						
IDF	1.7 ± 1.1	1.2 ± 1.0	1.3 ± 1.2	10.26	.006[d,f*]	0.03
NCEP	1.4 ± 1.0	1.0 ± 1.0	1.1 ± 1.1	9.18	.01[d,f*]	0.02
Individual MetS components						
Waist circumference, IDF	38 (47.5)	38 (32.8)	45 (34.6)	4.99	.08	0.12
Waist circumference, NCEP	17 (21.3)	16 (13.8)	23 (17.7)	1.89	.39	0.08
Blood pressure	19 (24.1)	22 (18.8)	27 (20.9)	0.79	.68	0.05
Fasting glucose	12 (15.2)	15 (12.9)	14 (10.8)	0.89	.64	0.05
Triglycerides	18 (22.8)	12 (10.3)	24 (18.5)	5.78	.06	0.13
HDL-C	46 (57.5)	52 (44.8)	57 (43.8)	4.24	.12	0.11
Dimensional cardiometabolic measures						
Glucose (mg/dL)	91.0 ± 9.2	88.9 ± 13.1	89.0 ± 15.5	0.70	.50	0.004
Total cholesterol (mg/dL)	163.1 ± 32.7	158.5 ± 29.8	161.3 ± 32.1	0.55	.58	0.003
HDL-C (mg/dL)	45.6 ± 15.5	47.2 ± 12.7	48.0 ± 13.2	0.77	.47	0.005
LDL-C (mg/dL)	95.8 ± 23.4	92.5 ± 24.9	96.4 ± 27.1	0.68	.51	0.005
Triglycerides (mg/dL)	108.6 ± 52.2	94.8 ± 60.3	97.6 ± 56.3	1.49	.23	0.01
Systolic blood pressure (mm Hg)	118.9 ± 13.0	117.2 ± 14.0	120.0 ± 17.5	1.08	.34	0.01
Diastolic blood pressure (mm Hg)	73.8 ± 10.2	72.6 ± 9.8	73.5 ± 11.4	0.36	.70	0.002
Body mass index (lb/in^2)	26.9 ± 6.6	24.6 ± 6.9	25.7 ± 7.6	2.36	.10	0.01
Body fat %	28.1 ± 11.6	25.4 ± 11.8	25.9 ± 11.3	1.32	.27	0.01
Waist circumference (in)	33.6 ± 5.7	31.7 ± 5.9	32.6 ± 7.3	2.06	.13	0.01
Hip circumference (in)	41.7 ± 5.7	39.9 ± 5.5	40.3 ± 6.0	2.51	.08	0.02

[a]Values for all continuous and ordinal variables are written as mean ± standard deviation and for categorical variables are written as n (% within group).
[b]Statistic = *F* for dimensional variables, *H* (2 degrees of freedom) for ordinal variables, or χ^2 for categorical variables. * = Significant difference at α=0.05.
[c]Effect size = partial η^2 for *F* and *H* test, or Cramer *V* for χ^2 test.
[d,e,f]Post-hoc comparisons: d = control vs affected high-risk offspring; e = control vs unaffected high-risk offspring; f = affected vs unaffected high-risk offspring.
Abbreviations: HDL-C = high-density lipoprotein cholesterol, IDF = International Diabetes Federation, LDL-C = low-density lipoprotein cholesterol, MetS = metabolic syndrome, NCEP = National Cholesterol Education Program.

MetS compared to unaffected high-risk offspring. Additionally, we found an increased number of IDF-defined and NCEP-defined MetS components among affected offspring of parents with BD vs unaffected BD offspring and control offspring. The majority of offspring findings were no longer significant when controlling for covariates, specifically socioeconomic status. With few minor exceptions, the overall pattern of findings was maintained in sensitivity analyses that controlled for any psychotropic medication and for SGAs specifically. These findings provide tentative evidence that affected youth offspring of parents with BD may have elevated cardiovascular risk, which may warrant more assertive monitoring and potential intervention.

The prevalence of IDF-defined MetS in affected high-risk offspring (21.3%) in this study parallels a previous study in 162 youth with BD that demonstrated a prevalence of 19.8%,[23] which is markedly elevated compared to the general population (2.1% in adolescents and 7.0% in young adults).[23–25] Furthermore, as compared to youth in the general population, affected high-risk offspring in the current study had higher prevalence of IDF-defined abdominal obesity (47.5%, vs 17.6% in adolescents and 21.1% in young adults), high blood pressure (24.1%, vs 11.7% in adolescents and 2.6% in young adults), high glucose levels (15.2%, vs 9.2% in adolescents and 4.8% in young adults), high triglyceride levels (22.8%, vs 9.1% in adolescents and 19.4% for young adults), and low HDL-C levels (57.5%, vs 22.7% in adolescents and 35.2% in young adults).[25,57,58] A number of explanations that have previously been invoked regarding the association of mood disorders and MetS may also contribute to current findings. These explanations include sleep disturbance, sedentary lifestyle, suboptimal nutrition, and underlying biological mechanisms such as inflammation.[59]

Similar to a previous study of youth and young adults with BD,[23] this study found that controlling for psychotropic medications had limited impact on the overall findings, suggesting that the enhanced MetS prevalence and its components in affected high-risk offspring go beyond the potential cardiometabolic side effects of psychotropic medications.

The majority of findings among offspring were no longer significant after controlling for socioeconomic status, which was lower among affected high-risk

offspring as compared to the other 2 groups. The difference is socioeconomic status among offspring groups parallels adult literature, which consistently demonstrates lower socioeconomic status (measured using Hollingshead or partial measures such as household income and highest educational level) in adults and youth with BD as compared to the general population.[60–63] Prior familial studies on this topic have not included socioeconomic status as a covariate.[31–36] Nonetheless, we opted to do so because of prior evidence that low socioeconomic status is associated with increased cardiometabolic disease in adults.[64] While studies in youth have yielded mixed findings depending on the geographic location,[65,66] lower socioeconomic status is associated with increased prevalence of MetS in North America.[67,68] There is evidence that the association between MetS and BD may be moderated by socioeconomic status,[69] as adults with BD and other serious mental illness (schizophrenia spectrum disorders and major depression) have greater risk for MetS and its components if they have a lower socioeconomic status (defined as the Swiss socioeconomic position), as compared to patients with a high socioeconomic status, and the general population.[70] There are multiple social, economic, and biological mechanisms through which socioeconomic status could impact MetS.[71–73] For instance, socioeconomic disadvantage may put youth at higher risk for experiencing early life adversities (ie, exposure to violence and household dysfunction), which have been highlighted by the American Heart Association as being associated with cardiometabolic outcomes over the youth's life course into adulthood.[72,73] Hence, socioeconomic status should be an important consideration when developing preventative and treatment approaches for young people with a family history of BD, as these individuals may be particularly susceptible to cardiometabolic burden.

The current study found that unaffected high-risk offspring had significantly lower prevalence of NCEP-defined MetS and its components as compared to control offspring. We note that the prevalence of IDF-defined MetS in the control parents was approximately double that of the general adult population,[22] and the same was true of control offspring.[24,25] Indeed, the prevalence of MetS among affected high-risk offspring was approximately triple that of the general population.[24,25] Control parents were recruited to the Pittsburgh BIOS based on zip code matching, allowing for neighborhoods to be matched between control and proband parents. While this is a particularly rigorous approach to selecting controls, it likely also accounted for more variance in MetS and MetS components as compared to other approaches to selecting controls that do not yield the same level of matching. Specifically, the presence of depression (ie, MDD: 31.3%; depression NOS: 6.0%; dysthymic disorder: 4.8%), anxiety disorder (21.7%), and substance use disorder (21.7%) in control parents, conditions also associated with increased MetS, likely attenuated between-group differences. Another potential contributor could be the implementation of healthful preventative lifestyle strategies in the household, related to the parent's BD status, which may act to mitigate higher MetS risk in the unaffected offspring. Lastly, we cannot exclude the notion that it is the BD diagnosis in the offspring that drives the cardiometabolic burden, as opposed to the effects of parental BD diagnosis on the offspring. This would have to be assessed in a larger offspring sample that includes a fourth group encompassing offspring of control parents that have BD.

There are certain limitations within this study that should be considered. First, this study is based on a single measurement of MetS components, and as such, precludes conclusions regarding causality or directionality of the observed associations. For future studies, repeated-measures analyses and/or a prospective design would help elucidate the temporal associations between MetS and mood symptoms in high-risk offspring. Second, given the relatively low rates of MetS and its components in this young sample relative to adults, the sample size did not provide adequate power to evaluate small effect sizes. For instance, the effect sizes for the prevalence of MetS (0.13–0.14) and mean number of MetS components (0.02–0.03) were small. However, small effect sizes can still be clinically relevant. For example, though the effect size linking mid-life blood pressure and incident dementia is small, blood pressure optimization is an established dementia prevention strategy.[74–77] Third, there are sources of residual confounding. Control parents had a high prevalence of non-BD psychopathology (eg, 31.3% of control parents had MDD), whereas most prior studies on the topic have included healthy controls without any psychiatric comorbidities and/or relatives without psychiatric comorbidities.[32,33,35] The inclusion of control parents with psychiatric comorbidity could be a potential confounder within this study, given that unaffected relatives of individuals with depression have been shown to have increased cardiometabolic burden.[31] Given the small sample size and limited power, we opted to control for age and socioeconomic status in offspring, which differed between groups. Future studies with larger samples are warranted to evaluate small effect sizes and enable more comprehensive covariate modeling so that additional factors such as psychiatric comorbidity, psychotropic medications, and early life adversity can be included in the primary model in parallel. Fourth, the young age of some of the offspring suggests that a significant proportion of offspring currently categorized as not having BD will go on to develop a mood disorder. Fifth, this study did not evaluate molecular genetic risk for MetS or its components in the participants. As such, while the findings in the at-risk group did not remain significant after adjusting for socioeconomic status, we

cannot discount potential genetic contributions towards MetS in these individuals. Sixth, we cannot exclude the notion that it is the BD diagnosis in the offspring that drives the cardiometabolic burden, as opposed to the effects of parental BD diagnosis on the offspring. It would have been ideal to include a fourth group comprised of control offspring with BD. Given that only 3 youth from the current sample would have qualified for this group, which is insufficient for analyses, future studies are warranted to evaluate MetS risk among youth with BD who do not have parental BD.

In conclusion, despite its limitations, this study addresses a gap in the literature regarding the prevalence of MetS and its components in young offspring of parents with BD. The study provides tentative evidence of increased number of MetS components among affected high-risk offspring as compared to the general population. The finding that unaffected high-risk offspring had a lower prevalence of MetS as compared to study controls was unexpected and may relate to the high rate of non-BD psychiatric disorders, including depression, in the control parents. Importantly, the prevalence of MetS in the unaffected high-risk offspring was nonetheless higher than the general population. This study also serves as a reminder of the importance of socioeconomic status when evaluating the intersection of BD with cardiovascular risk. Future studies with prospective, repeated-measures designs are warranted to evaluate the replicability, directionality, timing, and mechanistic inferences of, and the role of confounders (eg, psychiatric comorbidities) on, the observed findings. Continued research on this topic will help guide early screening and intervention strategies for youth that are personalized to incorporate both family history of BD and personal history of mood disorders.

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Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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Author Contributions: Kulkarni primarily wrote the manuscript and performed statistical analyses. Dimick and Kennedy assisted with dataset quality control. B. Goldstein contributed to study conception and design and assisted with manuscript preparation. All authors contributed to revisions of the manuscript and have approved the final manuscript.

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Supplementary Material: Available at Psychiatrist.com.

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Supplementary Material

Article Title: Controlled Study of Metabolic Syndrome Among Offspring of Parents With Bipolar Disorder

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Material

Supplementary Table 1. Summary of multivariable statistics in analyses additionally controlling for psychotropic medication.

	Statistic[a]	*p*
Meets criteria for MetS:		
IDF	4.98	0.08
NCEP	6.94	0.03[c,d]*
Mean number of MetS components:		
IDF	10.40	0.006[b,d]*
NCEP	8.35	0.02[b,d]*
Individual MetS components:		
Waist circumference, IDF	5.98	0.05[b,d]*
Waist circumference, NCEP	1.74	0.42
Blood pressure	0.49	0.78
Fasting glucose	0.73	0.69
Triglycerides	5.65	0.06
HDL-C	5.10	0.08
Dimensional cardiometabolic measures:		
Glucose (mg/dl)	0.45	0.64
Total Cholesterol (mg/dl)	0.49	0.62
HDL-C (mg/dl)	1.27	0.28
LDL-C (mg/dl)	0.66	0.52
Triglycerides (mg/dl)	1.38	0.25
Systolic blood pressure (mmHg)	1.10	0.33
Diastolic blood pressure (mmHg)	0.31	0.73
Body mass index (lb/in^2)	2.23	0.11
Body fat %	1.28	0.28
Waist circumference (in)	1.79	0.17
Hip circumference (in)	2.33	0.10

[a]Statistic= F for dimensional variables, χ^2 (2 degrees of freedom) for ordinal variables and for categorical variables. *= Significant difference for α=0.05.

[b,c,d]Post-hoc comparisons: b= control vs affected high-risk offspring; c= control vs unaffected high-risk offspring; d= affected vs unaffected high-risk offspring.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IDF, international diabetes federation; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NCEP, national cholesterol education programme.

Supplementary Table 2. Summary of multivariable statistics in analyses additionally controlling for second generation antipsychotics.

	Statistic[a]	*p*
Meets criteria for MetS:		
IDF	4.56	0.10
NCEP	6.91	0.03[c]*
Mean number of MetS components:		
IDF	7.92	0.02[b,d]*
NCEP	6.31	0.04[b,d]*
Individual MetS components:		
Waist circumference, IDF	4.96	0.08
Waist circumference, NCEP	1.73	0.42
Blood pressure	0.37	0.83
Fasting glucose	0.47	0.79
Triglycerides	5.62	0.06
HDL-C	2.81	0.25
Dimensional cardiometabolic measures:		
Glucose (mg/dl)	0.42	0.66
Total Cholesterol (mg/dl)	0.73	0.48
HDL-C (mg/dl)	0.41	0.67
LDL-C (mg/dl)	0.67	0.52
Triglycerides (mg/dl)	1.48	0.23
Systolic blood pressure (mmHg)	1.29	0.28
Diastolic blood pressure (mmHg)	0.32	0.73
Body mass index (lb/in^2)	2.04	0.13
Body fat %	1.21	0.30
Waist circumference (in)	1.72	0.18
Hip circumference (in)	2.26	0.11

[a]Statistic= F for dimensional variables, χ^2 (2 degrees of freedom) for ordinal variables and for categorical variables. *= Significant difference for α=0.05.

[b,c,d]Post-hoc comparisons: b= control vs affected high-risk offspring; c= control vs unaffected high-risk offspring; d= affected vs unaffected high-risk offspring.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IDF, international diabetes federation; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NCEP, national cholesterol education programme.

Supplementary Table 3. Sensitivity analyses excluding 18 offspring taking second-generation antipsychotics.

	Affected high-risk offspring[a] (n=69)	Unaffected high-risk offspring[a] (n=112)	Control offspring[a] (n=130)	Statistic[b]	*p*	Effect size[c]
Meets criteria for MetS:						
IDF	14 (20.3)	10 (9.0)	19 (14.8)	4.65	0.10	0.12
NCEP	9 (13.0)	6 (5.4)	19 (14.6)	5.70	0.06	0.14
Mean number of MetS components:						
IDF	1.6±1.1	1.2±1.0	1.3±1.2	6.82	0.03[d,f]*	0.02
NCEP	1.3±1.0	1.0±1.0	1.1±1.1	5.33	0.07	0.01
Individual MetS components:						
Waist circumference, IDF	34 (49.3)	36 (32.4)	44 (34.4)	5.83	0.05[d,f]*	0.14
Waist circumference, NCEP	15 (21.7)	15 (13.5)	22 (17.2)	2.07	0.36	0.08
Blood pressure	13 (19.1)	21 (18.8)	26 (20.5)	0.12	0.94	0.02
Fasting glucose	9 (13.2)	14 (12.5)	14 (10.9)	0.26	0.88	0.03
Triglycerides	15 (21.7)	12 (10.7)	23 (18.0)	4.34	0.11	0.12
HDL-C	38 (55.1)	49 (43.8)	56 (43.8)	2.76	0.25	0.10
Dimensional cardiometabolic measures:						
Glucose (mg/dl)	90.4±9.4	88.7±13.2	89.1±15.6	0.33	0.72	0.002
Total Cholesterol (mg/dl)	164.1±33.8	158.6±30.1	161.7±31.8	0.68	0.51	0.004
HDL-C (mg/dl)	46.4±14.6	47.3±12.8	48.1±13.2	0.34	0.72	0.002
LDL-C (mg/dl)	95.8±24.4	92.3±25.2	96.5±27.2	0.75	0.47	0.01
Triglycerides (mg/dl)	107.5±53.8	95.8±60.9	97.6±56.4	0.96	0.38	0.01
Systolic blood pressure (mmHg)	117.4±12.2	117.2±14.3	119.9±17.5	1.11	0.33	0.01
Diastolic blood pressure (mmHg)	73.6±10.5	72.6±9.8	73.4±11.5	0.25	0.78	0.002
Body mass index (lb/in^2)	26.5±6.5	24.6±7.0	25.7±7.5	1.57	0.21	0.01
Body fat %	28.2±11.7	25.5±11.8	25.8±11.1	1.32	0.27	0.01
Waist circumference (in)	33.3±5.6	31.7±6.0	32.5±7.3	1.39	0.25	0.01
Hip circumference (in)	41.6±5.8	39.9±5.6	40.3±5.9	1.98	0.14	0.01

[a]Values for all continuous and ordinal variables are written as mean ± standard deviation, categorical variables are written as n (% within group).

[b]Statistic= F for dimensional variables, H (2 degrees of freedom) for ordinal variables, or χ^2 for categorical variables. *= Significant difference at α=0.05.

[c]Effect Size = partial η^2 for F and H test, or Cramer's V for χ^2 test.

[d,e,f]Post-hoc comparisons: d= control vs affected high-risk offspring; e= control vs unaffected high-risk offspring; f= affected vs unaffected high-risk offspring.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IDF, international diabetes federation; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NCEP, national cholesterol education programme.