Inflammatory Markers and Brain-Derived Neurotrophic Factor as Potential Bridges Linking Bipolar Disorder and Cardiovascular Risk Among Adolescents

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ABSTRACT

Objective: Bipolar disorder (BD) is associated with increased rates of cardiovascular disease (CVD). Brain-derived neurotrophic factor (BDNF) and inflammatory markers are leading biomarkers in BD. We examined whether these biomarkers underlie the link between BD and CVD proxies among adolescents with bipolar spectrum disorders.

Methods: Subjects were 60 adolescents, 13–19 years old (40 with BD and 20 healthy controls [HCs]). Semistructured interviews determined diagnoses based on *DSM-IV*. Serum was assayed for BDNF, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Carotid intima media thickness (cIMT) and flow-mediated dilation were assessed using ultrasound. Procedures were conducted at a subspecialty clinic (January 2011–May 2014).

Results: Adolescents with BD had significantly greater waist circumference (BD: 81.72 cm [11.67 cm], HC: 75.64 cm [8.63 cm]; $U = 547.5$, $P = .021$), body mass index (BMI) (BD: 25.50 kg/m^2 [5.29 kg/m^2], HC: 21.76 kg/m^2 [3.43 kg/m^2]; $U = 608.5$, $P < .0001$), pulse pressure (BD: 42.31 mm Hg [10.57 mm Hg], HC: 33.84 mm Hg [6.69 mm Hg]; $U = 561.5$, $P < .001$), and IL-6 (BD: 8.93 pg/mL [7.71 pg/mL], HC: 4.96 pg/mL [6.38 pg/mL]; $U = 516.0$, $P < .0001$) than HC adolescents. Subjects with BD-I (n = 14) and BD-II (n = 16) had greater IL-6 versus HCs ($F_{3,51} = 5.29$, $P = .003$). Controlling for BMI and age did not alter these findings. IL-6 was higher in symptomatic (n = 19) and asymptomatic BD (n = 21) versus that found in HCs ($F_{2,52} = 7.96$, $P = .001$). In symptomatic BD, lower BDNF was associated with greater mean cIMT ($\rho = -0.507$, $P = .037$).

Conclusions: This study found evidence of increased inflammation among adolescents with BD. While present findings suggest a potential interplay between symptomatic status, biomarkers, and atherosclerosis proxies, there were no significant differences in cIMT or flow-mediated dilation in adolescents with BD compared to HCs. This may indicate that there is potential opportunity for CVD prevention strategies in adolescents with BD.

J Clin Psychiatry 2017;78(3):e286–e293
https://doi.org/10.4088/JCP.16m10762

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A recent statement from the American Heart Association positioned bipolar disorder (BD) and major depressive disorder (MDD) among youth as tier II moderate-risk conditions associated with accelerated atherosclerosis and early cardiovascular disease (CVD).[1] Risk of new onset CVD in BD is about 3 times greater than in psychiatrically healthy adults, and there is a 1.5- to 2.5-fold increase in mortality due to a cardiovascular event compared to the general population.[2,3] Beyond the increased mortality risk, adults with BD develop CVD 17 years earlier than adults without mood disorders.[4] Importantly, mortality due to CVD is predicted by symptomatic burden in adults with BD, independent of BD diagnosis and treatments and traditional CVD risk factors.[5] Reasons for excessive and premature CVD in BD are poorly understood.

Investigating noninvasive structural and functional proxies for atherosclerotic risk in adolescents with BD allows the opportunity to understand the biology underlying the BD-CVD link in a group with limited exposure to the symptoms and treatments of BD compared to adults. Carotid intima media thickness (cIMT), a structural measure of atherosclerotic risk, and flow-mediated dilation (FMD), a nitric oxide (NO)–mediated functional measure of atherosclerotic risk, are important noninvasive proxies for CVD risk. These measures are particularly useful in youth, when "hard" end points such as myocardial infarction are rare.[6] Even in adolescents with BD who present with various medications, comorbidities, and mood states, cIMT and FMD are associated with traditional CVD risk factors such as decreased high-density lipoproteins (HDL) and elevated fasting glucose, triglycerides, and greater waist circumference.[7] Thus, cIMT and FMD are valid CVD risk proxies for adolescents with BD,[6–9] similar to healthy control (HC) adolescents and adolescents with CVD risk diseases (eg, type I diabetes mellitus [T1DM]).

The question arises as to what biological processes may underlie the BD-CVD association. Inflammation is a process that has been robustly associated with both BD and CVD. In adults with BD, peripheral levels of proinflammatory markers (PIMs) are elevated during mania[10–15] and depression[12,14,15] and return to a similar level as observed in HCs during euthymia.[15–19] Although there are few data regarding inflammation among adolescents with BD, a prior study[20] found that 40% of adolescents with BD had levels of high-sensitivity c-reactive protein (CRP) that reflect increased CVD risk in adults. Notably, inflammation has been shown

Clinical Points

- Adolescents with bipolar disorder are at an elevated risk for premature atherosclerosis.
- Inflammatory and neurotrophic factors may underlie the bipolar disorder–cardiovascular disease (CVD) link.
- Despite elevated inflammation in adolescents with bipolar disorder, especially when symptomatic, ultrasound proxies of CVD did not differ from findings in healthy controls. This evidence indicates a potential window of opportunity for the prevention of accelerated atherosclerosis.

to predict CVD in the general population, and the evaluation of inflammatory markers has become integrated in the clinical evaluation of CVD.[21–24] CRP, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) have been shown to be associated with CVD risk factors, proatherosclerotic diseases/states (eg, metabolic syndrome [MetS] and type 2 diabetes mellitus [T2DM]), and CVD outcomes and mortality.[22,25,26] Moreover, changes in vascular structure and function, as well as inflammation, are present as early as adolescence and are associated with CVD risk proxies in adults.[27,28] Inflammation may therefore subserve the BD-CVD link.[1,29–31]

Trophic factors comprise another putative link between BD and CVD. Neurotrophins are proteins that centrally and peripherally regulate cellular processes.[32–35] Several studies have noted reduced brain-derived neurotrophic factor (BDNF) levels during mania and depression.[31,36–43] Reduced BDNF levels are implicated in vascular endothelial dysfunction and are associated with CVD.[44–47] Despite the theoretical link, prior studies have not examined whether BDNF is related to CVD risk in BD.

Given findings in prior literature that BD is associated with increased inflammatory and decreased trophic markers, along with prior literature supporting similar association in CVD, we set out to examine the association of these markers with CVD proxies in adolescents with BD who are at increased risk for early CVD. In this study, we compared adolescents with BD and HC adolescents with regard to noninvasive atherosclerosis proxies (cIMT, FMD) and putative biomarkers (PIMs and BDNF), with consideration of the role of BD subtypes and symptomatic status.

METHODS

Study procedures were approved by the Research Ethics Board at Sunnybrook Health Science Centre, Toronto, Ontario, Canada, and were in accordance with the Helsinki Declaration of 1975. Prior to study procedures, written informed consent was obtained from all adolescent participants and their guardians, ensuring that all participants were aware of potential risks involved in participating.

Sample

Adolescents (N = 60, 13–19 years old) were recruited from a subspecialty clinical research program, focusing on adolescent BD, at a tertiary academic health sciences center. Healthy control adolescents were recruited via advertisements posted in community centers, public transit, and local papers. All participants were English-speaking, and adolescents were excluded from the study if they had an infectious illness within the past 14 days, were unable to provide informed consent (ie, due to developmental delay or psychosis), or had/were taking medication for a cardiac or inflammatory condition (any cardiac condition or autoimmune, infectious, or inflammatory illness). Healthy controls were excluded if they or a first- or second-degree family member had MDD, BD, psychosis, and/or schizophrenia or had current drug dependence/abuse. Conditions such as attention-deficit/hyperactivity disorder and anxiety disorders were not excluded.

Assessment

Interviews. The Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version (K-SADS-PL),[48] a semistructured diagnostic interview, was used to determine diagnoses. A child-adolescent psychiatrist confirmed diagnoses (B.I.G.). *DSM-IV* criteria were used for bipolar I disorder (BD-I) and bipolar II disorder (BD-II); BD not otherwise specified (BD-NOS) was defined using operationalized criteria from the Course and Outcome of Bipolar Youth (COBY) study, via information gathered in the Mania Rating Scale (MRS) and Depression Rating Scale (DRS) in the K-SADS-PL.[49] Symptomatic status was determined from Psychiatric Status Rating (PSR) scores of 3 or greater for hypomania or depression on the Adolescent Longitudinal Interval Follow-up Evaluation (ALIFE).[50–52] PSR scores during the week of the study procedures were used to define symptomatic groups. *Symptomatic* was defined as a PSR score of 3 or more on either depression or hypomania ratings.[50–52] *Asymptomatic* was defined as a PSR score of less than 3 (ie, 2 or 1) for both depression and hypomania ratings.[50–52] PSR scores of 1 or 2 indicate euthymia/within normal fluctuations of mood (ie, 1 or 2 symptoms may be present, but with substantially lower severity, eg, "feeling better—but not yet back to usual self," and brief duration [less than 1 day]).[50–52] Socioeconomic status (SES) was determined using the 4-factor Hollingshead Scale.[53] Lifetime exposure to psychotropic medications was collected from the treatment history section and medical history questionnaire of the K-SADS-PL. Family history of psychiatric illnesses was also obtained via the Family History Screen in the K-SADS-PL. Participants were interviewed directly, and parents/guardians were separately interviewed about the participant, family history, and social status measures.

Vascular imaging. Two-dimensional Doppler ultrasound (Phillips, iU22), with a high-frequency (10 MHz) linear-array transducer, was used for FMD and cIMT imaging procedures, with duplicate far-wall scans performed for reliability. Ultrasound procedures began with participants lying down and rested for at least 10 minutes. cIMT was measured with the subject lying down with their neck extended and head at a 45-degree angle away from the side being examined. Three regions of the carotid artery were

assessed for left and right sides (common cIMT, bulb IMT, and internal common cIMT; regions as described in Urbina et al[6]).[54] FMD measurements were conducted immediately following cIMT measures, with the subject remaining in a recumbent position. Brachial artery FMD of the right arm of each participant was assessed with concurrent 3-lead electrocardiogram recordings. Lower-arm placement of the blood pressure cuff was used, with cuff inflation to 50 mm Hg above systolic blood pressure for 5 minutes. A stand was used to hold the transducer steady on the participant's brachial artery. Post-cuff deflation FMD was recorded for 5 minutes and analyzed as the average FMD postdeflation and the maximum FMD postdeflation. FMD was calculated as a percentage-change in brachial artery diameter postdeflation compared with baseline measurements.

Phlebotomy and anthropomorphic measurements. Participants fasted (no food or drink, except for water) 10 hours prior to blood draw, which was completed between 9 AM and 11 AM. All participants were instructed not to use illicit drugs, smoke tobacco, or consume alcohol for 24 hours prior to the appointment. Adherence to fasting and abstinence from drugs was assessed via interview and self-report. Fasting glucose, triglycerides, total cholesterol, HDL, and low-density lipoprotein (LDL) were assessed. Blood samples were centrifuged at 3,000 rpm for 15 minutes, and serum was collected and stored at −80°C.

Duplicate subject weight and height measurements were recorded to the nearest 0.5 cm and 0.1 kg, respectively. Weight adjustments were made to account for clothing (1.4 kg for long pants and long shirt/sweatshirt, 1.1 kg for short pants or short-sleeves, and 0.9 kg for short pants and short sleeves were subtracted from weight) and used to calculate adjusted body mass index (BMI). Subjects were instructed to raise their arms up and away from their trunk, and bend sideways, to find the location of their waist. Waist circumference was measured using a flexible tape measure, with subjects standing up straight.

Blood pressure was assessed before and after ultrasound procedures; a 10-minute rest period was given before each blood pressure measurement. Pulse pressure (PP) was calculated as the difference between systolic blood pressure and diastolic blood pressure. Ultrasound procedures were conducted as noted in previous literature and in accordance with recommendations from the American Heart Association.[6,7,55]

Assays

Serum was assessed for cytokine levels, IL-6, and TNF-α, using company kit procedures for the Human Cytokine Magnetic Bead Panel (HCYTOMAG-60 K; Miliplex Map, EMD Millipore, Germany). BDNF was assessed following company kit instructions for Sandwich ELISA procedures (CYT306; ChemiKine, EMD Millipore, Germany).

Statistical Analyses

Descriptive statistics were calculated for all relevant variables. Shapiro-Wilk test confirmed that our biomarker data are not normally distributed. Nonparametric analyses (Mann-Whitney *U*) and bivariate correlation analyses (Spearman correlation coefficient) and general linear models and linear regressions (model inclusion $P < .20$) were completed as appropriate. Log-transformed IL-6 was used in linear models. Statistical analyses were performed using SPSS 22 for Windows (SPSS Inc, Chicago, Illinois). False discovery rate (FDR) was used to correct for multiple comparisons, with maximum acceptable FDR α set to .05.[56]

RESULTS

Demographic and clinical characteristics are presented in Table 1. Adolescents with BD were significantly older than HC adolescents. Sensitivity analyses compared the impact of removing the youngest and oldest individuals from analyses since these values were near outliers (>2 SD). There was no significant difference when groups were age-matched (extreme aged values removed). Therefore, for sample size considerations, the whole group was used in the analyses. The BD group consisted of 14 subjects with BD-I, 16 subjects with BD-II, and 10 subjects with BD-NOS. Within the BD sample, 19 were symptomatic (5 were hypomanic, of which 4 had a PSR of 5 or 6, and 14 were depressed, of which 7 had a PSR of 5 or 6) and 21 were asymptomatic.

Adolescents with bipolar disorder had significantly greater waist circumference, BMI, pulse pressure, and IL-6 levels compared to HC adolescents. IL-6 remained significantly greater in adolescents with BD after controlling for age and BMI in linear regressions. Traditional CVD risk factors (ie, waist circumference, blood pressure, BMI, cholesterol, HDL, LDL, fasting glucose, and triglycerides) were not significantly associated with PIMs or BDNF in adolescents with BD. There were no significant differences between groups in cIMT or FMD measures.

In a general linear model with IL-6 as the dependent variable, we found significant differences between BD subtypes and HCs ($F_{3,51} = 5.29$, $P = .003$). Post hoc comparisons confirmed that BD-I and BD-II subgroups, but not BD-NOS, each had greater levels of IL-6 compared to HC adolescents ($P < .05$) (Figure 1A). There was a significant linear association of IL-6 increasing across groups (HC to BD-I subtypes; $\rho = 0.476$, $P = .0002$).

Similarly, a general linear model with symptomatic status (symptomatic BD vs asymptomatic BD vs HC), revealed significant differences in the dependent variable, IL-6 ($F_{2,52} = 7.96$, $P = .001$). Post hoc comparisons confirmed that adolescents with symptomatic BD had the highest IL-6 levels, and HC adolescents had the lowest levels ($P < .05$) (Figure 1B). There was a significant linear association, with increasing IL-6 across HC, asymptomatic, and symptomatic groups ($\rho = 0.443$, $P = .0007$). All general linear models and linear associations between BD subtypes and symptomatic status remained significant after controlling for multiple comparisons ($P < .05$).

TNF-α analyses were undertaken after removing 4 outliers (≥2 standard deviations from the mean; 3 BD-II [71.37,

Table 1. Demographic, Biological, and Clinical Characteristics Across Groups

Variable	Adolescents With BD (n = 40)	Healthy Adolescents (n = 20)	Statistic (FDR Corrected *P* Value)[a]
Demographic and clinical characteristic			
Male sex, %	32.5	50	$\chi^2 = 1.727$, $P = .189$
Age, mean (SD), y	17.41 (1.64)	16.06 (1.67)	$U = 580$; $P = .005$ (.016)
Socioeconomic status, mean (SD)[b]	4.03 (1.21)	4.35 (0.81)	$U = 386.5$, $P = .832$
Caucasian race, %	90	75	$\chi^2 = 4.478$, $P = .345$
Age at onset of illness, mean (SD), y	13.59 (3.38)	0 (0)	
Duration of illness, mean (SD), y	3.37 (3.03)	0 (0)	
Mania score, mean (SD)[c]	9.67 (12.00)	0.63 (1.38)	$U = 528.5$, $P = .004$ (.015)
Depression score, mean (SD)[d]	12.63 (12.38)	0.32 (0.95)	$U = 659.5$, $P < .0001$ (.0006)
Functioning score, mean (SD)[e]	62.28 (14.32)	89.85 (6.16)	$U = 46.0$, $P < .0001$ (.0006)
Medication, %			
Anticonvulsants	11.4	0	
Antipsychotic	47.5	0	
Antidepressant (SSRI)	30.0	0	
Stimulant	17.5	5.0	
Lithium	20.0	0	
Biological marker, mean (SD)			
Triglycerides (mmol/L)	1.01 (0.58)	0.783 (0.36)	$U = 480.5$, $P = .100$
LDL (mmol/L)	2.31 (0.65)	1.98 (0.55)	$U = 462$, $P = .081$
HDL (mmol/L)	1.40 (0.36)	1.44 (0.32)	$U = 338.0$, $P = .592$
Fasting glucose (mmol/L)	4.58 (0.44)	4.69 (0.49)	$U = 321.0$, $P = .411$
Waist circumference (cm)	81.72 (11.67)	75.64 (8.63)	$U = 547.5$, $P = .021$
BMI (kg/m^2)	25.50 (5.29)	21.76 (3.43)	$U = 608.5$, $P < .0001$ (.0006)
Systolic blood pressure (mm Hg)	114.23 (11.07)	110.26 (7.16)	$U = 458.5$, $P = .192$
Diastolic blood pressure (mm Hg)	71.72 (10.17)	76.42 (4.93)	$U = 242.5$, $P = .027$
Pulse pressure (mm Hg)	42.31 (10.57)	33.84 (6.69)	$U = 561.5$, $P < .001$ (.0046)
IL-6 (pg/mL)	8.93 (7.71)	4.96 (6.38)	$U = 516.0$, $P < .0001$ (.0006)
TNF-α (pg/mL)	16.55 (22.48)	26.08 (86.89)	$U = 432.0$, $P = .026$
BDNF (pg/mL)	90.10 (98.07)	114.50 (121.44)	$U = 283.0$, $P = .591$
Imaging measure, mean (SD)			
Maximum cIMT (mm)	0.52 (0.07)	0.54 (0.07)	$U = 330.0$, $P = .335$
Mean cIMT (mm)	0.44 (0.04)	0.45 (0.04)	$U = 334.0$, $P = .370$
Maximum FMD (mm)	6.18 (3.83)	6.63 (4.94)	$U = 386.0$, $P = .949$
Mean FMD (mm)	1.91 (2.69)	2.18 (3.10)	$U = 314.0$, $P = .349$

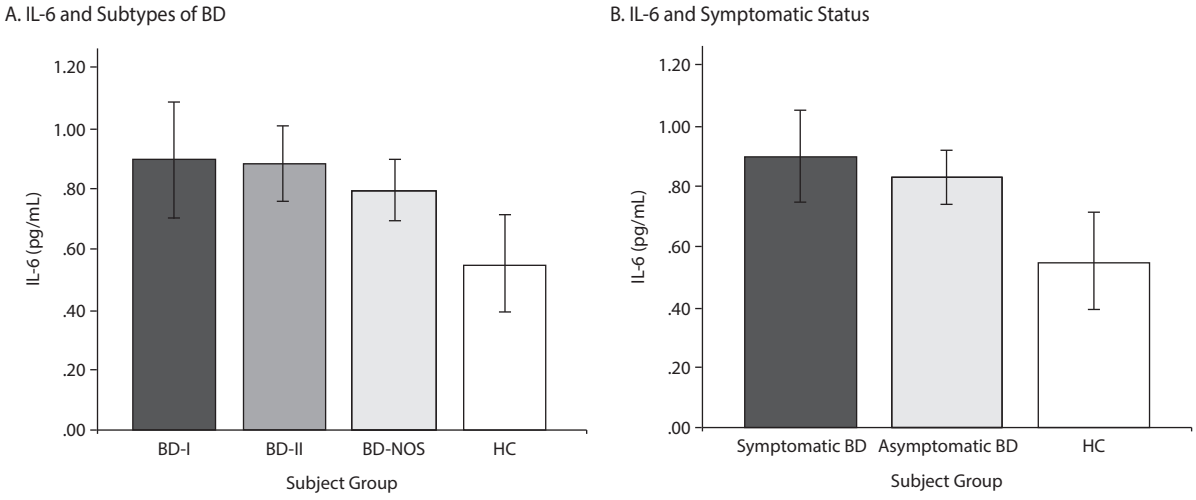
[a]FDR corrected *P* value (q) is presented for values remaining significant after correcting for multiple comparisons.
[b]Socioeconomic status score (1–5) based on Hollingshead scale, with higher scores reflecting higher socioeconomic status.
[c]The mania score is the Mania Rating Scale score for the past month.
[d]The depression score is the Depression Rating Scale score for the past month.
[e]The functioning score is the current Children's Global Assessment Scale score.
Abbreviations: BD = bipolar disorder, BDNF = brain-derived neurotrophic factor, BMI = body mass index, cIMT = carotid intima media thickness, FDR = false discovery rate, FMD = flow-mediated dilation, HDL = high-density lipoprotein, IL-6 = interleukin-6, LDL = low-density lipoprotein, SSRI = selective serotonin reuptake inhibitor, TNF-α = tumor necrosis factor-α.

56.96, 107.31 pg/mL] and 1 HC [351.76 pg/mL]). TNF-α was significantly greater in adolescents with BD (11.38 ± 10.28 pg/mL, n = 36) compared to HCs (4.37 ± 2.65 pg/mL, n = 15; $t_{2,49} = 2.59$, $P = .012$), which is the opposite direction when outliers are included. TNF-α remained significantly greater in adolescents with BD after controlling for age and BMI in linear regressions. A general linear model of BD-I versus BD-II versus BD-NOS versus HCs revealed significant differences in TNF-α between groups ($F_{3,47} = 3.01$, $P = .039$), with significant differences only between BD-I and HC groups ($P = .026$; post hoc Bonferroni) (Figure 2A). There was a significant linear association of TNF-α decreasing across groups (BD-I to HC; $\rho = -0.330$, $P = .018$).

A general linear model of symptomatic BD versus asymptomatic BD versus HC also revealed significant differences in TNF-α between groups ($F_{2,48} = 4.64$, $P = .014$), with post hoc analyses showing that symptomatic BD was significantly different from HC ($P = .011$) (Figure 2B). There was a significant linear association of TNF-α decreasing across groups (symptomatic BD to HC; $\rho = -0.409$, $P = .003$). All TNF-α subsample analyses remained significant after correction for multiple corrections ($P < .05$). Approximately half of the subjects with BD were taking antipsychotics. Binary logistic regressions were completed to assess medication effects on inflammatory markers. No significant differences were observed between BD medication groups.

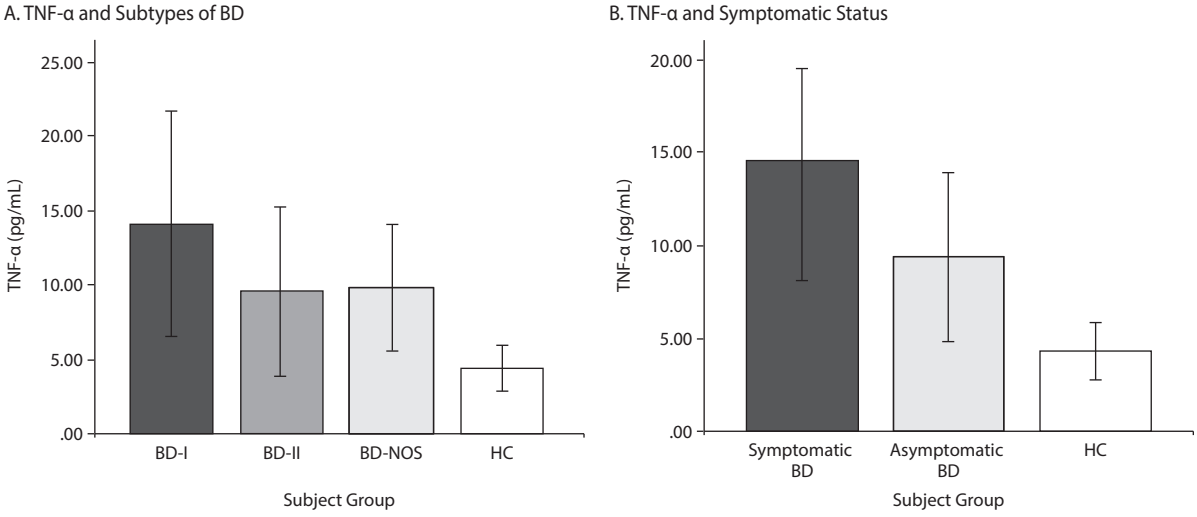
In linear regression models, IL-6 and TNF-α were elevated in BD, and there was no significant between-group (BD vs HC) difference in BDNF. Adding age, BMI, or age and BMI to the linear regression for BDNF did not change nonsignificant findings. Including age and BMI individually and together as covariates for TNF-α and IL-6 models also did not change reported findings. When holding age constant, IL-6 is still significantly elevated in BD compared to HC (T = 3.35, $P = .002$), and when holding age and BMI constant, the IL-6 finding remains significant (T = 3.28,

Figure 1. Peripheral IL-6 Levels Across Groups[a]



[a]Error bars: 95% CI.
Abbreviations: BD = bipolar disorder, HC = healthy control adolescents, IL-6 = interleukin-6, NOS = not otherwise specified.

Figure 2. Peripheral TNF-α Levels Across Groups[a]



[a]Error bars: 95% CI.
Abbreviations: BD = bipolar disorder, HC = healthy control adolescents, NOS = not otherwise specified, TNF-α = tumor necrosis factor-α.

$P = .002$). Similarly, for TNF-α, when holding age constant ($T = 3.09$, $P = .003$), as well as age and BMI constant ($T = 2.7$, $P = .009$), TNF-α remains significantly higher in adolescents with BD compared to HCs.

Lastly, there was evidence for a relationship between biomarkers and vascular imaging measures among symptomatic BD adolescents. Lower BDNF levels were associated with significantly thicker mean cIMT among adolescents with symptomatic BD ($\rho = -0.507$, $P = .037$; $n = 18$), but not among those with asymptomatic BD ($\rho = 0.117$, $P = .614$; $n = 21$) or HC adolescents ($\rho = 0.404$, $P = .121$; $n = 16$). Maximum cIMT was not significantly associated with BDNF in symptomatic BD subjects ($\rho = -0.446$, $P = .073$). Similarly, maximum and mean FMD were not significantly associated with symptomatic BD ($\rho = 0.174$, $P = .504$; $\rho = 0.321$, $P = .198$, respectively). In HC and asymptomatic BD, BDNF was not significantly associated with FMD or cIMT measures.

DISCUSSION

This study brings together 2 core themes in BD, namely biomarkers and cardiovascular risk. We found that adolescents with BD had higher levels of IL-6 compared to HC adolescents and that this difference was observed in BD-I and BD-II but not in BD-NOS. Moreover, between-group comparison based on symptomatic status found that IL-6 was highest in symptomatic BD, followed by asymptomatic

BD, followed by HC. Similarly, TNF-α was elevated in BD compared to HC, specifically BD-I compared to HC, and was significantly higher in symptomatic BD compared to HC. Finally, among symptomatic BD adolescents, but not asymptomatic BD adolescents or HC adolescents, lower BDNF levels were associated with significantly thicker mean cIMT. While preliminary, these findings highlight an area that future work can build upon to potentially aid in early detection and classification of CVD risk.

IL-6 has been shown to be associated with both cIMT and FMD in those with/or at risk for CVD and in healthy populations.[57,58] Moreover, IL-6 has been demonstrated to regulate and modulate CRP, a widely used biomarker for CVD risk and cardiovascular events.[59] Therefore, while we did not assess CRP in this study, IL-6 is associated with both cIMT and FMD, modulates CRP, and has been shown to be elevated in CVD and BD.[15,26] Similarly, TNF-α has been shown to be associated with proatherogenic alterations in chronic inflammatory states and is associated with thicker cIMT.[60,61] Elevated TNF-α has also been shown to be associated with poor FMD and endothelial dysfunction in patients with rheumatoid arthritis, T2DM, and postmyocardial infarction.[62–65] Interestingly, anti–TNF-α treatment in those with rheumatoid arthritis led to improvements in FMD.[64,65]

Why the vascular ultrasound measures were not significantly different between BD and HC groups or why inflammatory markers were not significantly associated with vascular measures is uncertain. It is theoretically possible that the operator-dependent nature of the ultrasound measures underlies the lack of detection of between-group differences. However, we previously confirmed that impaired cIMT and FMD are associated with increased levels of traditional CVD risk factors (eg, elevated BMI and cholesterol), supporting the validity of these measures.[7] One can speculate that while cIMT and FMD are already linked with CVD risk factors, the duration of illness among these adolescents with BD has not been sufficient to impart vascular impairment. The absence of detectable vascular impairment indicates that there is potential for prevention of accelerated atherosclerotic development in BD during adolescence. Moreover, most mood-stabilizing and antidepressant medications are known to have anti-inflammatory effects, as well as proneurotrophic effects, such that one cannot rule out the possibility that medications contributed to the negative finding.[41,66,67] Future studies with larger sample sizes would enable the assessment of atherosclerosis proxies and the role of inflammation, with the inclusion of important covariates such as symptomatic status and determination of potential interactions.

In contrast to the current findings, a recent small study[68] of adolescents (9–20 years of age) with BD-I (n = 16), adolescents at familial risk for developing BD (n = 15), and HC adolescents (n = 13) found no significant differences in inflammatory marker levels between groups. Prior studies[1,20] have found that inflammatory markers are related to symptoms and other clinical characteristics in BD, but they did not include an HC comparison group.

These findings are constrained by several limitations. First, this study was not powered to detect small effect sizes; a larger sample would have provided greater power to detect differences and to include more comprehensive covariate analysis. Second, the cross-sectional design of the study prevents us from examining directional hypotheses. Third, the groups were not well matched for age or BMI. However, results remained unchanged in sensitivity analyses that were restricted to age-matched groups, and between-group differences in TNF-α and IL-6 were independent of BMI and age in linear regressions. Fourth, all participants with BD were taking psychiatric medication; as such, it was not possible to parse medication effects from diagnosis effect. Despite these limitations, this is the first study to assess the BD-CVD link, integrating noninvasive atherosclerosis proxies and peripheral biomarkers in a case-control study, and provides important preliminary results to guide further investigation.

Additional studies are needed to better understand the directionality of the observed findings. Longitudinal studies in particular are needed to understand how inflammation and BDNF fluctuate with symptomatic episodes and, in turn, to understand how such fluctuation may correspond with atherosclerosis and CVD over time. Although prior studies of adults have found that symptom burden in BD is relevant to CVD risk, those studies have not included novel PIMs and/or neurotrophins.[5,69,70] The current study found that BDNF is associated with cIMT only among symptomatic BD adolescents. We speculate that levels of BDNF and inflammatory markers among symptomatic BD adolescents may confer risk for the development and progression of atherosclerosis and CVD in adulthood.

This is the first study to assess putative biomarkers and noninvasive atherosclerosis proxies in a BD control sample of adolescents. The lack of a significant difference in atherosclerosis proxies (despite our prior demonstration of the validity of cIMT and FMD in this population[7]) highlights that there is key opportunity for preventative treatment to potentially alter the course of illness and delay or reduce CVD outcomes. Adolescence comprises a crucial window of opportunity to intervene, prevent, or delay CVD in BD. If our preliminary findings are replicated in future studies, this may suggest that reduced BDNF and elevated inflammation among symptomatic adolescents with BD may serve as surrogate targets for intervention to modify both symptomatic course and CVD outcomes. For example, investigation of lifestyle modifications including those related to exercise, diet, and sleep, in addition to pharmacologic approaches, may increase BDNF and reduce inflammation.[71–73] Finally, present findings provide preliminary support for the concept of BD as a multisystem disease in which vascular pathology may play an important role. This concept can potentially be leveraged to yield much needed progress in terms of novel therapeutics, biomarker discovery, and stigma reduction in BD.

Submitted: February 23, 2016; accepted July 28, 2016.

Online first: February 14, 2017.

Potential conflicts of interest: None of the authors have any conflicts of interest to report.

Funding/support: Heart and Stroke Foundation (Ontario, Canada), grant no. NA7231.

Role of the sponsor: The sponsor had no role in the study design, study execution, data analysis, or manuscript preparation.

Previous presentation: Findings were presented in part as a poster at the 70th Annual Meeting of the Society for Biological Psychiatry; May 14–16, 2015; Toronto, Ontario, Canada.

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