

Elevated C-reactive Protein in Adolescents With Bipolar Disorder: A Potential Biomarker?

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BACKGROUND

- Bipolar disorder (BD) largely begins in adolescence but is often mis- or under-diagnosed for many years, causing significant morbidity and mortality.
- Better identification of children at risk for developing BD could potentially be aided by the discovery of relevant biomarkers.
- Levels of C-reactive protein (CRP), a peripheral inflammatory marker, have been shown to be increased in adults with BD, as compared to controls.
- CRP levels have not been previously comprehensively evaluated in adolescents with BD.

HYPOTHESIS

CRP is elevated in adolescents with BD, as compared to adolescents with anxiety disorders (ADs) and healthy controls.

METHODS

- Retrieved CRP blood level values for patients aged 12-17 years from the TriNetX database, which is a large global federated health research network of data from 34 health care organizations across the US.
- Excluded patients with acute and chronic inflammatory diseases. Grouped cohorts by healthy controls (n = 2760), BD (n = 37), and anxiety disorders (ADs, n = 157), based on ICD-10 codes.

Cohort	ICD-10 codes included	ICD-10 codes excluded
Healthy	(none)	All psychiatric diagnoses
BD	BD and manic episode	All other psychiatric diagnoses
ADs	Anxiety, obsessive-compulsive, stress-related, somatoform	All other psychiatric diagnoses

Conditions excluded from all cohorts	Criteria for conditions
Systemic connective tissue disorders	Patients with ICD-10 codes M08, M30-36
Inflammatory bowel diseases	Patients with ICD-10 codes K50-52
Malignant neoplasms	Patients with ICD-10 codes C00-D49
Seasonal respiratory infections	Samples collected in October-April
Trauma or severe infection	CRP levels ≥ 100 mg/L

	Healthy	Bipolar	Anxiety	p value
N	2760	37	157	
Age (years)	15.3 \pm 1.8	15.2 \pm 1.6	15.6 \pm 1.8	0.078
Sex				
Female	1390 (50.4%)	11 (29.7%)	93 (59.2%)	0.003
Male	1370 (49.6%)	26 (70.3%)	64 (40.8%)	0.003
Race/Ethnicity				
Black	537 (19.5%)	2 (5.4%)	30 (19.1%)	0.043
White	1499 (54.3%)	27 (73%)	95 (60.5%)	0.279
Other	140 (5.1%)	0	4 (2.5%)	0.123
Hispanic or Latino	151 (5.5%)	7 (18.9%)	10 (6.4%)	0.019
BMI (kg/m ²)	21.4 \pm 5.5	20.9 \pm 5.7	23.0 \pm 6.7	0.002

- CRP levels were averaged within each patient and pooled across years and then log+1 transformed to meet statistical assumptions. Differences in CRP were examined using multivariate linear regressions with patient demographics and BMI included as covariates. To account for potential confounding factors, weight propensity score analysis was performed. Differences were then identified with post hoc multiple comparison Tukey tests. p value <0.05 = significant.

Adolescents with bipolar disorder had significantly higher blood levels of C-reactive protein than those with anxiety disorders and healthy controls.

	CRP (mean \pm SE, mg/L)	
	Unweighted	Weighted
Healthy (n = 2760)	2.41 \pm 0.14	2.68 \pm 0.20
Bipolar disorder (n = 37)	9.23 \pm 1.96	9.56 \pm 0.67
Anxiety disorders (n = 157)	1.66 \pm 0.26	1.81 \pm 0.16

Table 1. Mean CRP values for each cohort.

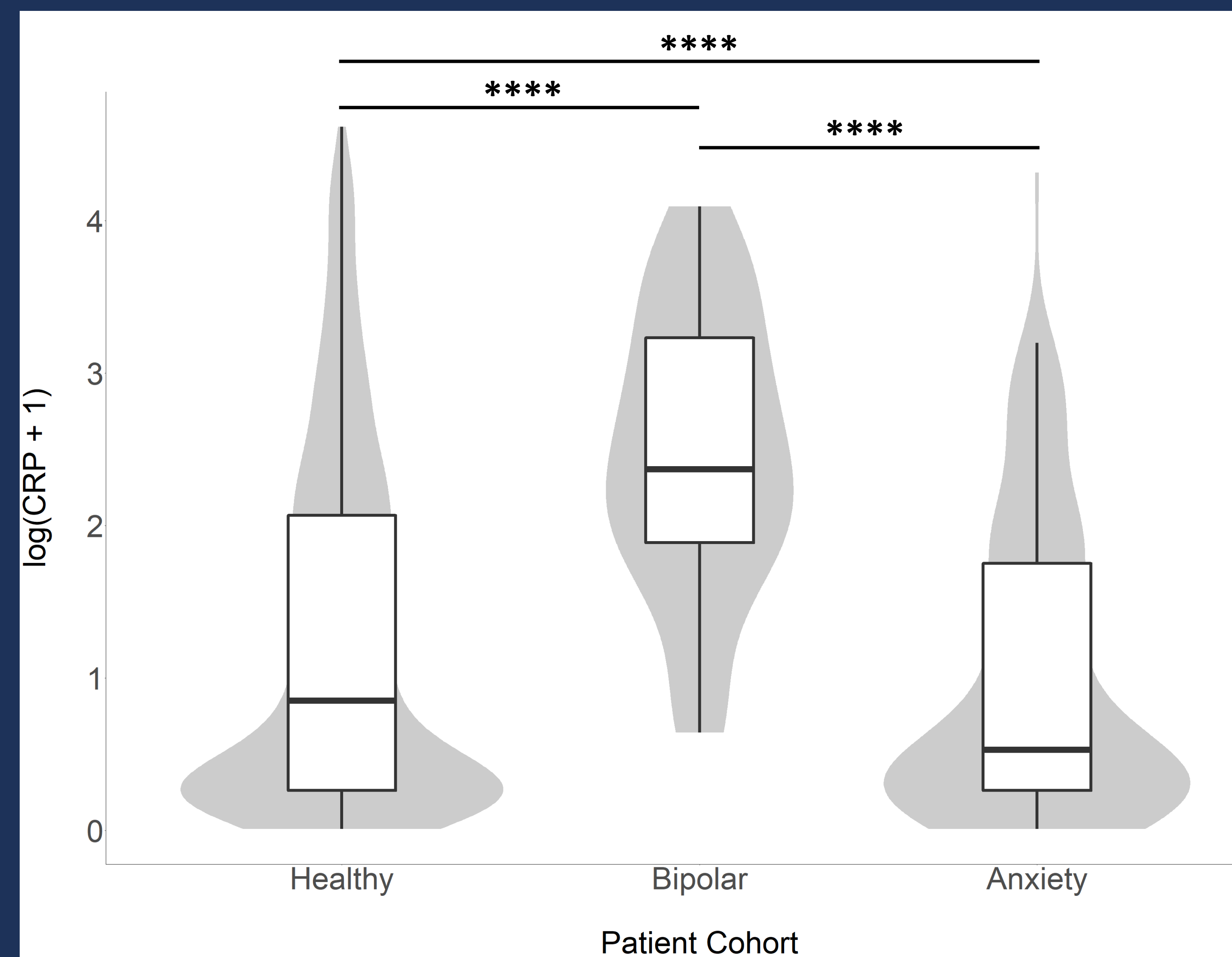


Figure 1. Violin plots comparing CRP levels of patients with anxiety disorders, patients with bipolar disorder, and healthy controls. Box/whisker plots show the median value (horizontal line), and upper and lower quartiles (upper and lower box). **** = p \leq 0.0001

RESULTS

- Mean CRP levels were significantly different among the three cohorts (Table 1). Mean CRP levels were significantly higher in adolescents with BD as compared to adolescents with ADs and healthy controls (Tables 1 and 2, Figure 1).
- Significant effects were found of sex, with increased levels in males (3.85 \pm 0.34 mg/L) vs. females (3.23 \pm 0.35 mg/L), and race (Table 2).
- No significant effects were found of BMI or age.

After reanalysis using a propensity score weighted regression (matched on sex, race, age, and mean BMI):

- Mean CRP levels were still significantly greater in BD patients as compared to adolescents with ADs and healthy controls (Table 1, Table 2).
- Significant effects were again found of sex, with increased levels in males (4.27 \pm 0.28 mg/L) vs. females (3.34 \pm 0.24 mg/L, Table 2, Fig. 2).
- A significant effect of age was found (Table 2), with CRP levels decreasing with increasing ages (Fig. 3).
- Again, no significant effects were found of BMI (Table 2).

	Unweighted			Weighted		
	F value	df	p value	F value	df	p value
Cohort	21.15	2	< 0.0001	379.59	2	< 0.0001
Sex	10.70	1	0.001	25.93	1	< 0.0001
Race	9.55	4	< 0.0001	10.36	4	< 0.0001
Age	3.28	1	0.070	42.42	1	< 0.0001
BMI	2.70	1	0.100	1.87	1	0.1717

Table 2. Multivariate linear regression showing differences in CRP between Cohorts, Sex, Race, Age, and BMI.

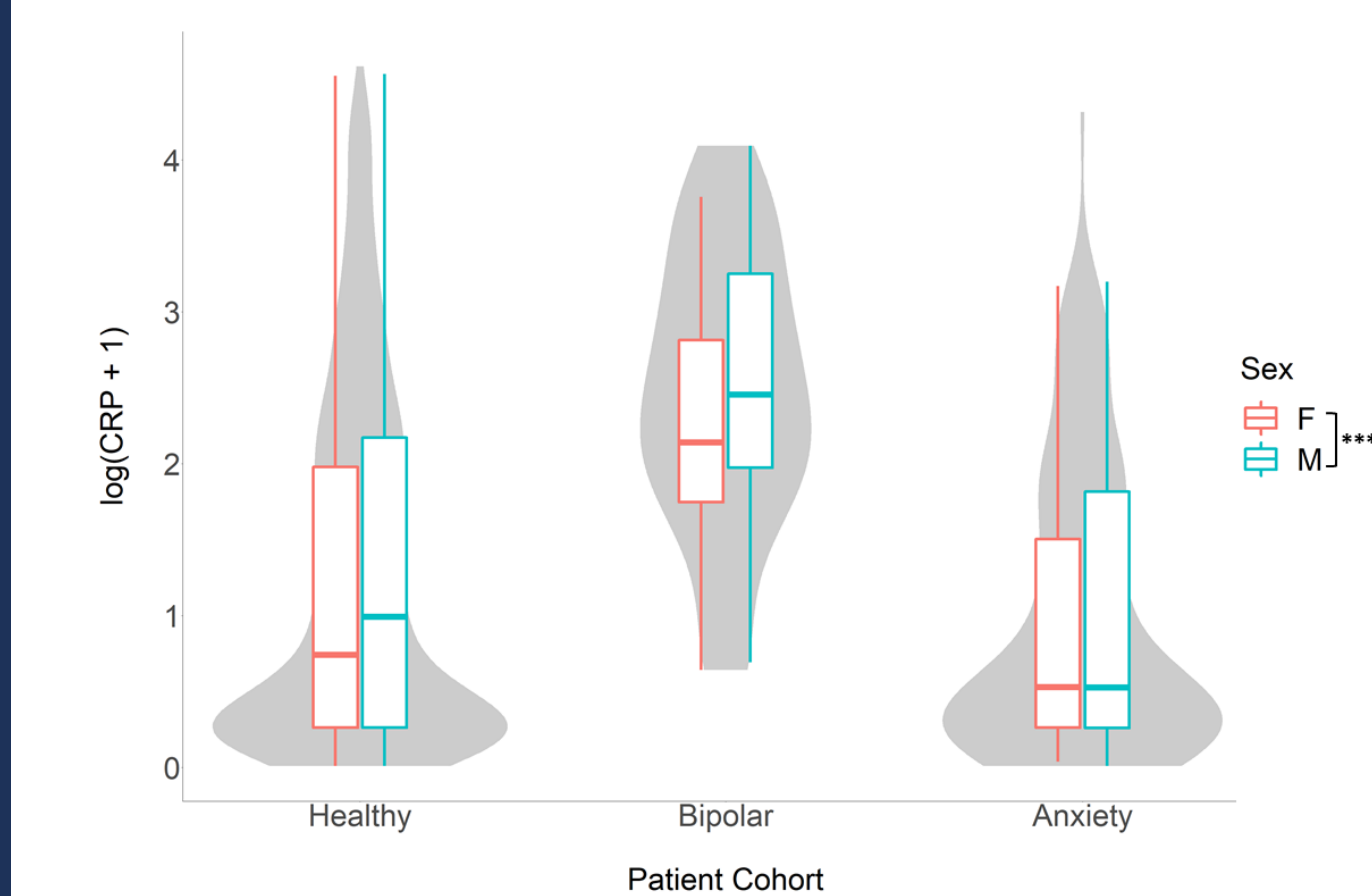


Figure 2. Violin/box plots comparing CRP levels between sex (Female: F, Male: M), among Anxiety, Bipolar and Healthy patients, with the median value (horizontal line), and upper and lower quartiles (upper and lower box). **** = p \leq 0.0001

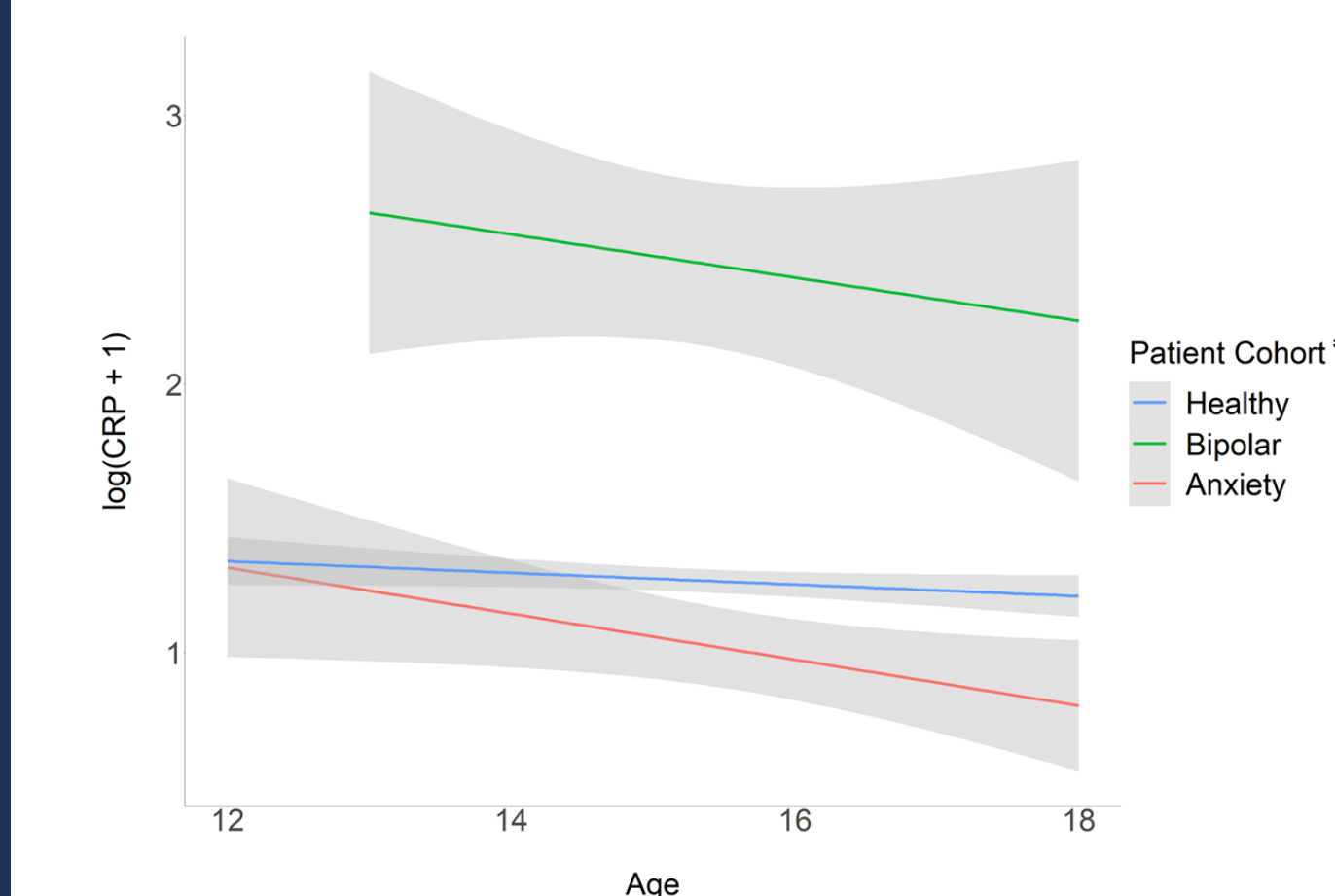


Figure 3. Differences in mean CRP levels across ages (gray ribbon = confidence interval). **** = p \leq 0.0001

CONCLUSIONS

CRP levels were elevated in adolescents with BD, as compared to controls and adolescents with ADs, suggesting a unique process in BD that may be modulated by sex and age. The differences in CRP levels were not significantly affected by BMI. As a result, CRP may represent a biomarker that could be used as part of the assessment of an adolescent's risk for developing BD. Additionally, these data suggest a role for inflammation in the pathophysiology of BD in adolescents.