sciendo

SJCAPP

Scandinavian Journal of Child and Adolescent Psychiatry and Psychology
Vol. 11:44-59 (2023) DOI 10.2478/sjcapp-2023-0005

Research Article **Open Access**

Further Evidence of an Association Between a Positive Child Behavior Checklist-Bipolar Profile and a Diagnosis of Pediatric Bipolar Disorder: A Meta-Analysis

Maura DiSalvo[1], Chloe Hutt Vater[1], Allison Green[1,2], K. Yvonne Woodworth[1], Abigail Farrell[1,3], Joseph Biederman[1,4], Stephen Faraone [5,*]

[1]Pediatric Psychopharmacology Program, Division of Child and Adolescent Psychiatry, Massachusetts General Hospital, United States
[2]Department of Psychological and Brain Sciences, Indiana University, United States
[3]Department of Psychology, University of Houston, United States
[4]Boston Department of Psychiatry, Massachusetts General Hospital, United States
[5]Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, United States

***Corresponding author:** sfaraone@childpsychresearch.org

Abstract

Background: Previous research has found that a unique profile of the Child Behavior Checklist comprising of aggregate elevations of the Attention, Anxiety/Depression and Aggression scales (A-A-A profile, CBCL-Bipolar (BP) profile, CBCL-Dysregulation profile (DP); henceforth CBCL-BP/DP profile) is associated with a clinical diagnosis of pediatric bipolar (BP) disorder.
Objective: The main aim of the study is to evaluate the strength of the association between the CBCL-BP/DP profile and the clinical diagnosis of pediatric BP disorder through a meta-analysis.
Methods: A literature search was performed to identify studies that examined the association between a positive CBCL-BP/DP profile and a clinical diagnosis of pediatric BP disorder. The meta-analyses first examined studies assessing the rates of a positive CBCL-BP/DP profile in youth with BP disorder versus those with 1) ADHD, anxiety/depression, or disruptive behavior disorders (DBDs), and 2) non-bipolar controls. The second analysis evaluated studies examining the rates of pediatric BP disorder in youth with and without a positive CBCL-BP/DP profile.
Results: Eighteen articles met our inclusion and exclusion criteria, and fifteen articles had adequate data for meta-analysis. Results showed that BP youth were at significantly increased odds of having a positive CBCL-BP/DP profile compared to those with other psychiatric disorders (i.e., ADHD, anxiety/depression, or DBDs) (pooled OR=4.34, 95% CI=2.82, 8.27; $p<0.001$) and healthy control groups (pooled OR=34.77, 95% CI=2.87, 420.95; $p=0.005$). Further, meta-analysis results showed that youth with a positive CBCL-BP/DP profile were at significantly increased odds of having a BP disorder diagnosis compared to those without (pooled OR=4.25, 95% CI=2.12, 8.52; $p<0.001$).
Conclusion: Our systematic review and meta-analysis of the extant literature provides strong support for the association between the CBCL-BP/DP profile and pediatric BP disorder.

Keywords: Bipolar disorder, CBCL, Child Behavior Checklist, mood disorders, children, youth

Introduction:

Although the diagnosis of pediatric bipolar disorder has been controversial, a meta-analysis of population studies reported that pediatric bipolar (BP) spectrum disorders afflict 3.9% of youth worldwide (1). It included seven studies from the United States, and 12 from South America, Central America, or Europe. The prevalence of BP I disorder was 0.6%. Rates of bipolar spectrum disorders were not higher in the United States than in other Western countries.

Pediatric BP disorder is associated with increased risks of distress and disability including academic, social, and family problems, as well as high rates of hospitalization, suicidal ideation, psychosis, and substance use disorders (2-6). Even subthreshold manifestations of pediatric BP disorder have been associated with significant morbidity and disability (7). Therefore, efforts at improving tools to help identify youth suspected of being at risk for pediatric

BP disorder in clinical practice could help mitigate its poor outcomes.

Our research group and others have shown that a unique profile of the Child behavior Checklist (CBCL), an empirically derived, easy to use, parent-report instrument with excellent psychometric properties (8, 9), can be useful in aiding in the identification of youth at risk of having bipolar I (BP-I) disorder (10-14). This unique profile consisting of an aggregated elevated scores on the Attention Problems, Aggressive Behavior, and Anxious/Depressed scales (combined score ≥210 or 2 SDs), has been strongly associated with a clinical diagnosis of pediatric BP-I (11-13), and has been variedly referred to as the CBCL-AAA profile, CBCL-Bipolar (BP) profile, and CBCL-Dysregulation profile (DP) (15-17). For the purposes of clarity, we will refer to this profile as the CBCL-BP/DP profile. The items constituting the profile are in the Supplement.

Two decades ago, we conducted a preliminary meta-analysis (18) with the goal of determining the consistency of behavioral problems, as measured by the CBCL scales, associated with pediatric bipolar disorder rather than the diagnosis of the disorder itself. Results showed that the CBCL scales included in the CBCL-BP/DP profile efficiently distinguished pediatric BP disorder from ADHD (18). However, these CBCL scales were examined individually and as continuous measures. Since that time, the CBCL-BP/DP profile was derived and additional papers have been published examining the association between the CBCL-BP/DP profile and a clinical diagnosis of pediatric BP disorder, calling for a re-examination of this important topic.

Further evidence that the CBCL-BP/DP profile can assist clinicians in identifying youth who are at risk of having a BP diagnosis could aid mental health and primary care providers in ensuring these high-risk youth are referred to an appropriate level of care. This issue is particularly relevant considering the critical importance of the differential diagnosis between pediatric unipolar and bipolar disorder, as misdiagnosis of pediatric BP disorder could lead to inappropriate care, including treatment with antidepressant or stimulant medications, which could result in worsening of mood symptoms, suicidality, and hospitalizations (19-22) in those at risk to have BP disorder.

The main aim of the current study was to re-evaluate the strength of the association between the CBCL-BP/DP profile and the clinical diagnosis of pediatric BP disorder. To this end, we performed a meta-analysis of all available studies examining whether the CBCL-BP/DP profile is associated with a pediatric BP diagnosis. We first examined the rate of a positive CBCL-BP profile/DP in youth with and without BP disorder. We then examined the rate of BP disorder in youth with and without a positive CBCL-BP/DP profile. Based on the previous meta-analysis and our own work, we hypothesized that the CBCL-BP/DP profile would be strongly associated with a clinical diagnosis of pediatric BP disorder.

Methods

Literature Search

We conducted a literature search of the peer-reviewed literature published through January 28, 2022, to identify studies that examined the association between a clinical diagnosis of pediatric BP disorder with the CBCL-BP/DP profile. We searched the PubMed and PsychInfo electronic databases using the terms (Child Behavior Checklist [Title/Abstract] OR CBCL[Title/Abstract]) AND (Dysregulation [Title/Abstract] OR Emotional Dysregulation [Title/Abstract] OR Bipolar Disorder [Title/Abstract] OR BPD [Title/Abstract]).

Three authors (MD, CHV, JB) screened the articles for relevance and eligibility. Disagreement between the three reviewers was minimal. All three authors (MD, CHV, JB) involved in each step of reviewing the abstracts, full text, and data extraction agreed regarding the final data set. The authors first screened, reviewed, and assessed the reference lists of the retrieved papers. As shown in the PRISMA chart (Figure 1), our initial search identified 417 potentially relevant articles for inclusion. After removing 168 duplicate papers, 249 articles were screened based on the title and abstract and 127 articles were removed because they had titles and abstracts irrelevant to the topic of this review. The remaining 122 articles that had relevant titles and/or abstracts were sought for retrieval and the full reports were assessed for eligibility based on the following criteria: 1) the study assessed the magnitude of the association between the CBCL-BP/DP profile as a categorical measure and diagnosed BP disorder; 2) the study sample was comprised of children and adolescents (ages 6-17); and 3) the study reported the data necessary to calculate odds ratios for meta-analysis (see Data Extraction below for details). Excluded were articles not published in the English language, review articles, editorials, and commentaries. Based on these inclusion and exclusion criteria, 107 articles were excluded, leaving us with 15 relevant articles for meta-analysis. Specific reasons why articles were excluded are detailed in the results.

Data Extraction

The following variables were extracted from the available studies: sample size, setting (outpatient or inpatient), mean age, and percent males. Detailed information regarding the diagnosis of BP disorder

was also extracted and included: structured interview used, informant for the structured interview, individual who administered the structure interview, and what version of DSM was used. For articles that compared youths with a clinical diagnosis of BP disorder with a comparison group, we extracted the number of youths with and without a positive CBCL-BP/DP profile in each group. For articles that compared youths with and without a positive CBCL-BP profile, we extracted the number of youths with and without pediatric BP diagnoses in each group.

Analytic Approach

We computed two meta-analyses of odds ratios. The first was for studies examining the rates of a positive CBCL-BP/DP profile in youth with BP disorder versus two comparison groups: 1) youth with ADHD, anxiety/depression, or disruptive behavior disorders (DBDs) (termed "youth with other psychiatric disorders" henceforth), and 2) youth who were identified to not have BP disorder and were referred to as "controls." These comparator groups were not defined a priori and were a result of what had been included in the studies identified for inclusion in the meta-analysis. We combined the multiple psychiatric disorders into one group for analysis given that they are highly comorbid. If a study had multiple comparison groups, we included each in our analysis under the appropriate comparator category. Because of the repeated use of the BP disorder group in studies with multiple comparison groups, measures are not statistically independent of one another and standard statistical procedures will produce inaccurate p-values. To address this intra-sample clustering and to compute accurate p-values for estimates of effect sizes, variance estimates were adjusted using Huber's (1967) formula as implemented in Stata (23). This formula is a "theoretical bootstrap" that produces robust statistical tests. The method works by entering the cluster scores (i.e., sum of scores within families) into the formula for the estimate of variance. The resulting p-values are valid even when observations are not statistically independent. The second meta-analysis was for studies examining the rates of BP disorder in youth with and without a positive CBCL-BP/DP profile. Our meta-analyses used the random effects model of DerSimonian and Laird(24), which

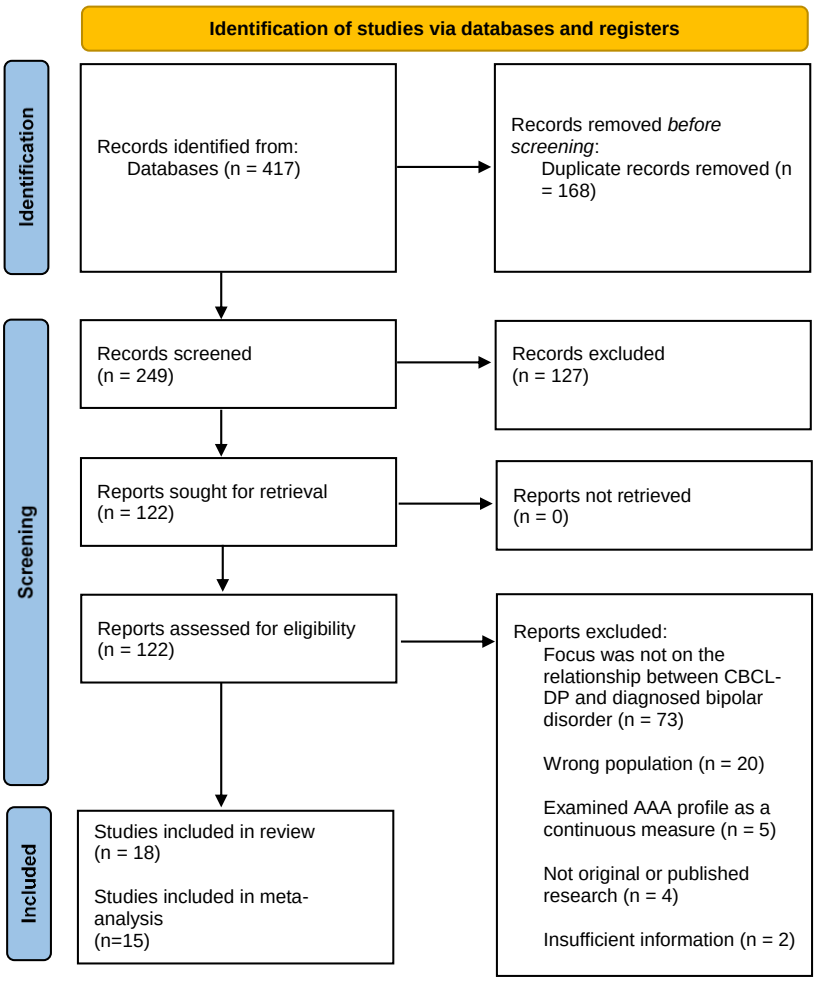

FIGURE 1. PRISMA Flow chart of study inclusion

computes a pooled effect size weighted by sample size. We used the I^2 index to assess heterogeneity of effect sizes (25). Its value lies between 0 and 100 and estimates the percentage of variation among effect sizes that can be attributed to heterogeneity. A significant I^2 suggests that the effect sizes analyzed are not estimating the same population effect size. We used the Egger method to assess for publication biases (26). All analyses were two-tailed and performed at the 0.05 alpha level using Stata (Version 17.0)(23).

Results

As shown in the PRISMA chart (Figure 1), after screening out duplicate articles (n=168) and articles that did not reference the CBCL-BP/DP profile in the title or abstract (n=127), the literature search identified 122 articles that were relevant. Those articles were retrieved and carefully assessed for eligibility. Of the 122, 18 met all our inclusion and exclusion criteria. Excluded were studies that either 1) were not focused on the relationship between CBCL-BP/DP profile and diagnosed BP disorder (n=73); 2) examined the wrong population (i.e., preschoolers; youth of parents with a clinical diagnosis of BP disorder but no clinical diagnosis themselves, termed youth at risk; or adults) (n=20); 3) examined the CBCL-AAA profile as a continuous measure (n=5); 4) were not original or published research (n=4); or 5) did not give number of youth in each group (n=2). Furthermore, two of the 18 articles that met our inclusion and exclusion criteria were excluded because they used duplicate datasets to other included articles. For the analysis of a positive CBCL-BP/DP profile among youth with and without a BP disorder, we excluded the article that had the lowest number of comparator groups. For the analysis of BP disorder among youth with and without a positive CBCL-BP/DP profile, since the number of comparator groups were the same for each study, we excluded the older study. Additionally, another study that met inclusion and exclusion criteria was exclude because there were zero bipolar disorder cases at follow-up in both the positive and negative CBCL-BP/DP profile groups (n=1). It is standard practice to exclude studies with no events in both arms in meta-analyses of odds ratios, as they provide no indication of either the direction or magnitude of the effect size (27). Thus, 15 articles were included in the final meta-analyses. Given that all studies included in the original review were published prior to the derivation of the CBCL-BP/DP profile, none were included in this meta-analysis and were excluded during the first phase of screening.

Table 1 describes the 15 studies that were included in the meta-analysis along with the three additional studies that met inclusion criteria but were excluded due to using duplicate samples or having zero bipolar disorder cases. Twelve of the 18 studies were cross-sectional and six were longitudinal. Twelve of the studies were conducted in the United States and six examined international samples. Five studies examined rates of a positive CBCL-BP/DP profile in youth with and without a clinical diagnosis of BP disorder, and all found a higher rate of a positive CBCL-BP/DP profile in youth with a diagnosis of pediatric BP disorder versus comparison groups. Thirteen studies examined the rates of BP disorder in youth with and without a positive CBCL-BP/DP profile, but the rates of BP diagnoses in many studies were low, such that an association between a positive CBCL-BP/DP profile and a clinical diagnosis of BP disorder was only reported by six studies. However, it is also important to note that all 13 studies found that a positive CBCL-BP/DP profile was associated with significant psychopathology and suicidality.

Two of the eighteen articles were excluded from the meta-analysis because they contained a data set that was duplicated by another paper, and another article was excluded because the rate of BP disorder at follow-up was zero in those with and without a positive CBCL-BP/DP (28). Thus, fifteen of the eighteen studies were included in the meta-analysis; four studies were included in the first analysis and eleven studies were included in the second analysis.

Studies comparing a positive CBCL-BP/DP profile in youth with and without a clinical diagnosis of BP disorder

Five studies (17, 29-32) compared the rates of a positive CBCL-BP/DP profile in youth with and without a clinical diagnosis of BP disorder, but one study was excluded due to use of a duplicate data set(17). Two studies included in the meta-analysis had multiple comparison groups (29, 31).

Four studies contributing five comparison groups compared the rates of a positive CBCL-BP/DP profile in youth with BP disorder and those with other psychiatric disorders (ADHD, anxiety/depression, or DBD) (30, 31). The pooled OR was greater than one and statistically significant, indicating significantly increased odds of having a positive CBCL-BP/DP profile in youth with a clinical diagnosis of BP disorder compared to those with other psychiatric disorders (pooled OR=4.34, 95% CI=2.82, 8.27; $p<0.001$) (Figure 2). Results remained significant after correcting for intra-sample clustering ($p=0.02$). Overall, heterogeneity was high and significant ($I^2=72.1\%$, $p=0.006$), suggesting significant variability between study effects. There was no evidence of publication bias as determined by Egger's test ($p=0.81$).

TABLE 1. Summary of studies that (A) compare rates of a positive CBCL-Bipolar (BP) profile/Dysregulation profile (DP) in subjects with and without BP disorder, and (B) compare rates of BP disorder in subjects with and without CBCL-BP profile/DP

A. Studies that compare rates of a positive CBCL-BP profile in subjects with and without BP disorder

Author and year	*Sample*	*Assessment for BP Diagnosis*	*CBCL BP Profile Definition*	*Included in Meta-Analysis?*	*Main Findings & Comments*
Diler 2009 (29)	BP: N=157 (BP-I N=79; BP-II N=3; BP-NOS N=79) (+CBCL-BP N=92) MDD/ANX: N=101 (+CBCL-BP N=23) DBD: N=127; (+CBCL-BP N=47) Healthy Controls: N=128; (+CBCL-BP N=14) Clinical sample (COBY Study) US Cross-sectional Mean age: 9.4	Structured Interview: K-SADS	+CBCL-BP profile defined as sum of scores on Anxiety/Depression, Attention Problems, and Aggressive Behaviors subscales of the CBCL with a cut off score of 210 or higher (2 SD above normal)	Yes	60% of children with BP disorder diagnosis had a positive CBCL-BP profile Children with BP disorder diagnosis were significantly more likely than children with MDD/anxiety, DBDs or healthy controls to have a positive CBCL-BP profile
Doerfler 2011 (30)	BP: N=27 (N=13 with mania; N=14 with hypomania); (+CBCL-BP N=10) ADHD: N=249 (+CBCL-BP N=44) Clinical sample US Cross-Sectional Mean age: 11	Structured Interview: K-SADS-E	+CBCL-BP profile defined as elevated scores (T score >70) on the Anxiety/Depression, Attention Problems, and Aggressive Behaviors subscales of the CBCL	Yes	Children with a BP disorder diagnosis were significantly more likely to have a positive CBCL-BP profile than children with ADHD
Biederman 2013 (17)	BP-I: N=140 (+CBCL-BP N=80) Controls (without ADHD or mood disorders): N=129 (+CBCL-BP N=0) Clinical sample US Cross-sectional Mean age: 10	Structured Interview: K-SADS-E	+CBCL-BP profile defined as sum of scores on Anxiety/Depression, Attention Problems, and Aggressive Behaviors subscales of the CBCL with a cut off score of 210 or higher (2 SD above normal). "Intermediate" CBCL-BP profile defined as a score of ≥180 and <210	No, duplicate sample (12)	62% of children with a BP disorder diagnosis had a positive CBCL-BP profile and 80% of profile-negative BP subjects had an intermediate (^{3}180 <210) score BP youth with a positive CBCL-BP profile were more likely to have an earlier onset of BP disorder compared to BP disorder youth with a negative BP profile. They also had higher rates of psychiatric comorbidities, were more likely to need special help in school, and had lower IQs and lower GAF scores

TABLE 1. *continued*

Author and year	*Sample*	*Assessment for BP Diagnosis*	*CBCL BP Profile Definition*	*Included in Meta-Analysis?*	*Main Findings & Comments*
Uchida 2014 (31)	BP-I: N=140 (+CBCL-BP N=80) ADHD: N=83 (+CBCL-BP N=7) Control: N=114 (CBCL-BP N=1) Clinical sample US Cross-sectional Mean age: 10.3	Structured Interview: K-SADS-E	+CBCL-BP profile defined as sum of scores on Anxiety/Depression, Attention Problems, and Aggressive Behaviors subscales of the CBCL with a cut off score of 210 or higher (2 SD above normal)	Yes	Youth with BP disorder diagnosis were significantly more likely than both control subjects and those with ADHD to have a positive CBCL-BP profile
Kweon 2016 (32)	BP: N=18 (BP-I N=2; BP-II N=11; BP-NOS N=5) (+CBCL-BP N=3) Depression: N=56 (+CBCL-BP N=3) Clinical sample Korea Cross-sectional Mean age: 14.9	Structured Interview: K-SADS-PL	+CBCL-BP profile defined as sum of scores on Anxiety/Depression, Attention Problems, and Aggressive Behaviors subscales of the CBCL with a cut off score of 210 or higher (2 SD above normal)	Yes	17% of youth with a BP disorder diagnosis had a positive CBCL-BP profile, compared to 5% of subjects with depression (NS) (limited power due to small sample size) A positive CBCL-BP profile was strongly correlated with manic/hypomanic symptoms measured on other scales
B. Studies that compare rates of BP disorder in subjects with and without CBCL-BP profile					
Volk 2007 (33)	+CBCL-BP: N=33 (BP N=0) Comparison subjects: N=1313 (BP-I N=1, BP-II N=1) Community sample from previous research study on twins with ADHD US Cross-sectional Mean age: 13	Missouri Assessment for Genetics Interview for Children	+CBCL-BP profile defined as T-scores ≥ 70 on the Anxious/ Depressed, Aggressive Behavior, and Attention Problems subscales	Yes	A positive CBCL-BP profile correlated with diagnoses of ADHD, ODD and CD as well as high rates of suicidality Caveat: Very low overall rate of BP disorder in the sample
Holtmann 2008 (34)	+CBCL-BP: N=62 (BP N=0); Psychiatric Controls: N=461 (BP =2) Clinical sample Germany Cross-sectional Mean age: 11.3	ICD-10 diagnoses based on the diagnostic guidelines of the German society for child and adolescent psychiatry	+CBCL-BP profile defined as T-scores ≥ 70 on the Anxious/ Depressed, Aggressive Behavior, and Attention Problems subscales	Yes	A positive CBCL-BP profile correlated with disruptive behavior disorders No subjects with a positive CBCL-BP profile received a diagnosis of BP disorder Youth with a positive CBCL-BP profile were more likely to report suicidal ideation, and scored higher in all CBCL subscales compared to those with a negative -CBCL-BP profile Caveat: rate of BP diagnoses was extremely low (0.2%)

TABLE 1. *continued*

Author and year	*Sample*	*Assessment for BP Diagnosis*	*CBCL BP Profile Definition*	*Included in Meta-Analysis?*	*Main Findings & Comments*
McGough 2008 (35)	+CBCL-BP: N=45 (BP N=3) CBCL-Attention problems: N=103 (BP N=2) Comparison subjects: N=392 (BP N=5) Research study of sibling pairs with ADHD probands US Cross-sectional Mean age: 10.6	Structured Interview: K-SADS-PL	+CBCL-BP profile defined as T-scores ≥70 on the Anxious/ Depressed, Aggressive Behavior, and Attention Problems subscales CBCL-Attention problems group defined as T-scores >70 on the Attention Problems subscale, but <70 on the Aggressive Behavior and Anxious/Depressed subscales Comparison subjects had a CBCL score of <70 on all 3 subscales	Yes	A positive CBCL-BP profile was associated with increased generalized anxiety disorder, oppositional defiant disorder, conduct disorder, and parental substance abuse Caveat: Bipolar spectrum disorders represented less than 2% of the overall sample
Meyer 2009 (36)	+CBCL-BP: N=16 (BP diagnosis at Time 4 N=2; Time 5 N=5). Comparison subjects: N=81 (BP diagnosis at Time 4 N=6; Time 5 N=4). High risk sample (mothers with BP, depression, or control) US Longitudinal, 23-year follow up Mean age (Time 4): 15.7	Structured Interview	+CBCL-BP profile defined as T-score ≥ 60 on the Attention Problems, Aggressive Behavior, and Anxious/Depressed subscales at least once during childhood and/or adolescence (1 SD)	Yes	31% of youth with a positive CBCL-BP profile developed BP disorder overtime Children with a positive CBCL-BP profile were at significantly higher risk for ongoing, severe, psychiatric symptomatology including behavior and emotional comorbidities in general, and bipolar disorder, anxiety, ADHD, cluster B personality disorders in particular
Biederman 2009 (12)	+CBCL-BP: N=28 (BP N=10) Comparison subjects: N= 176 (BP N=39) Research subjects from longitudinal ADHD study US Longitudinal (10-year follow-up for males; 5-year follow-up for females) Mean age: 10.8	Structured Interview: Age <18: K-SADS-E Age ≥18: Structured Clinical Interview for DSM-III-R	+CBCL-BP profile defined as sum of scores on Anxiety/Depression, Attention Problems, and Aggressive Behaviors subscales of the CBCL with a cut off score of 210 or higher (2 SD above normal)	Yes	Over a mean follow up period of 7.4 years, a positive CBCL-BP profile predicted subsequent diagnoses of bipolar disorder, major depressive disorder and conduct disorder, as well as impaired psychosocial functioning and higher risk for psychiatric hospitalization

TABLE 1. *continued*

Author and year	*Sample*	*Assessment for BP Diagnosis*	*CBCL BP Profile Definition*	*Included in Meta-Analysis?*	*Main Findings & Comments*
Althoff 2010 (15)	+CBCL-BP: N=57 (BP N=0) Comparison subjects: N= 1516 (BP N=6) Children from Dutch birth registries Netherlands Longitudinal (total follow-up period of 14 years) Mean age: 9.9	Structured interview: Composite International Diagnostic Interview (CIDI)	+CBCL-BP profile defined by latent class analysis (LCA) as the class with the highest elevations on the Attention Problems, Aggressive Behavior, and Anxious/Depressed subscales. No specific cutoff was reported in the paper	Yes	The presence of a positive CBCL-BP profile at Wave 1 in childhood was associated with increased rates of adult anxiety disorders, mood disorders, disruptive behavior disorders, and drug abuse 14 years later Only the associations with anxiety disorders and disruptive behavior disorders with a positive CBCL-BP profile remained after controlling for co-occurring disorders
Biederman 2012 (13)	ADHD and +CBCL-BP: N=45 ADHD and CBCL-DESR: N=86 ADHD only: N=111 Healthy Controls: N=244 Research subjects from longitudinal ADHD study US Longitudinal (4 year follow up for males; 5 years follow up for females) Mean age: 11.3	Structured Interview: Age <18: K-SADS-E Age ≥18: Structured Clinical Interview for DSM-III-R and DSM-IV Axis I Disorders	+CBCL-BP profile defined as sum of scores on Anxiety/Depression, Attention Problems, and Aggressive Behaviors subscales of the CBCL with a cut off score of 210 or higher (2 SD above normal). CBCL-DESR defined as a score of ≥180 and <210	No, duplicate sample (12)	Children with ADHD and a positive CBCL-BP profile had more impairing ADHD symptoms, higher rates of psychiatric hospitalizations, and higher rates of CD, ODD, and bipolar disorder compared to ADHD and control subjects
Wilens 2013 (37)	+CBCL-BP: N=43 (BP N=35) CBCL-DESR: N=50 (BP N=26) CBCL < 180: N=210 (BP N=13) Community and clinical sample from a longitudinal study of adolescents with BD US Longitudinal Mean age: 13	Structured Interview: Age <18: K-SADS-E Age ≥18: Structured Clinical Interview for DSM-IV Axis I Disorders	+CBCL-BP profile defined as sum of scores on Anxiety/Depression, Attention Problems, and Aggressive Behaviors subscales of the CBCL with a cut off score of 210 or higher (2 SD above normal). CBCL-DESR defined as a score of ≥180 and <210	Yes	Subjects with a positive CBCL-BP profile had higher risk for psychiatric disorders including BP disorder, CD, multiple anxiety disorders, and ADHD Subjects with a positive CBCL-BP profile were 5-7 times more likely to have a combined drug and alcohol problem than subjects without a positive CBCL-BP profile

TABLE 1. *continued*

Author and year	*Sample*	*Assessment for BP Diagnosis*	*CBCL BP Profile Definition*	*Included in Meta-Analysis?*	*Main Findings & Comments*
Mbekou 2014 (38)	+CBCL-BP: N=150 (BP N=10) Comparison subjects: N=247 (BP N=6) Clinical sample Canada Cross-sectional Mean age: 14.1	DSM-IV-TR diagnostic information was obtained from patients' clinical files and included for analyses.	+CBCL-BP profile defined as sum of scores on Anxiety/Depression, Attention Problems, and Aggressive Behaviors subscales of the CBCL with a cut off score of 210 or higher (2 SD above normal)	Yes	There were no significant differences in the number of youths diagnosed with BP disorder in children with a positive CBCL-BP profile versus those with a negative profile A positive CBCL-BP profile was a strong indicator of psychopathological severity through its association with more comorbidities and more suicidality
Peyre 2015 (39)	+CBCL-BP: N=42 (BP N=1); Comparison subjects: N=130 (BP N=1) Participants form a nonrandomized longitudinal study of youth with ADHD eligible for methylphenidate treatment France Cross-sectional (baseline analysis) Mean age: 10.9	Structured Interview: K-SADS-PL	+CBCL-BP profile defined as T-scores >70 on the Attention Problems, Aggressive Behavior, and Anxious/Depressed subscales of the CBCL	Yes	A positive CBCL-BP profile was associated with ODD, anxiety disorders, MDD, emotionality, and "self-directness" Caveat: rate of BP diagnoses was extremely low (0.1%)
Caporino 2016 (28)	+CBCL-BP: N=17 (BP N=0) Comparison subjects: N=47 (BP N=0) Participants from two RCTs on CBT for anxiety Longitudinal (7-19 years) US Mean age: not reported	Structured interview: Composite International Diagnostic Interview (CIDI)	Latent profile analysis (LPA) was used to stratify patients into dysregulated (+CBCL-BP) versus non-dysregulated based on CBCL Attention Problems, Aggressive Behavior, and Anxious/Depressed subscale scores. No specific cutoff was reported in the paper, but the mean scores were <70 for each subscale for the non-dysregulated group and ≥70 for the Attention Problems and Anxious/Depressed subscales for the dysregulated group.	No, neither group developed BP disorder by follow-up	At the 7- to 19-year follow-up, the dysregulated group had significantly higher rates of PTSD, agoraphobia, panic attacks, and OCD within the last year, as well as rates of lifetime PTSD
Dolitzsch 2016 (40)	+CBCL-BP: N=32 (BP N=2); Comparison subjects: N=181 (BP N=4) Youth from residential institutions Switzerland Cross-sectional Mean age: 15.3	Structured Interview: K-SADS-PL	+CBCL-BP profile defined as having a T-score ≥67 on the Anxious/Depressed, Attention Problems, and Aggressive Behavior subscales of the CBCL	Yes	A positive CBCL-BP profile carried a high (>2) relative risk for manic episodes, bipolar disorder, cyclothymia, hyperkinetic conduct disorder, mixed disorders of conduct and emotion, and suicidal ideation

TABLE 1. *continued*

Author and year	*Sample*	*Assessment for BP Diagnosis*	*CBCL BP Profile Definition*	*Included in Meta-Analysis?*	*Main Findings & Comments*
Joshi 2018 (41)	ASD with +CBCL-BP: N=44 (BP N=20) ASD without +CBCL-BP: N=59 (BP N=9) Clinical sample of youth with ASD US Cross-sectional Mean age: 12.1	Structured Interview: K-SADS-E	+CBCL-BP profile defined as sum of scores on Anxiety/Depression, Attention Problems, and Aggressive Behaviors subscales of the CBCL with a cut off score of 210 or higher (2 SD above normal)	Yes	ASD youth with a positive CBCL-BP profile had a greater severity of autism, significantly higher rates of disruptive behavior disorders, MDD, and BP disorder, and had more psychosocial dysfunction

Two studies compared the rates of a positive CBCL-BP/DP profile in youth with BP disorder and in control groups (29, 31). These were clinical healthy control groups who were free of any lifetime episode of any major psychiatric disorder in the Diler et al. (29) study and free of ADHD and mood disorders in the Uchida et al.(31) study. The pooled OR was greater than one and statistically significant, indicating significantly increased odds of having a positive CBCL-BP/DP profile in youth with a clinical diagnosis of BP disorder compared to control groups (pooled OR=34.77, 95% CI=2.87, 420.95; p=0.005) (Figure 2). Overall, heterogeneity was high and significant (I^2=82.7%, p=0.02), suggesting significant variability between study effects. There were too few studies to assess publication bias. It should be noted that the pooled OR calculated for youth with BP disorder versus control groups is less precise due to the small number of studies contributing to the analysis. Because the large pooled OR has a wide confidence interval, its magnitude needs to be interpreted with caution.

Studies comparing the rates of BP disorder in youth with and without a positive CBCL-BP profile

Thirteen studies (12, 13, 15, 28, 33-41) compared the rates of BP disorder in youth with and without a positive CBCL-BP/DP profile, however one study was excluded due to use of a duplicate data set (13) and another study was excluded because the rate of BP disorder at follow-up was zero in those with and without a positive CBCL-BP/DP profile (28). Thus, eleven studies had extractable data and were included in the meta-analysis. The pooled OR was greater than one and statistically significant, indicating significantly increased odds of having a clinical diagnosis of BP disorder in youth with a positive CBCL-BP/DP profile compared to those without it (pooled OR=4.25, 95% CI=2.12, 8.52; p<0.001) (Figure 3). Heterogeneity was high and significant (I^2=60.9%, p=0.004), suggesting significant variability between study effects. There was no evidence of publication bias as determined by Egger's test (p=0.21).

Discussion

The results of our literature search and meta-analyses showed that youth with a diagnosis of BP disorder were at significantly increased odds of having a positive CBCL-BP/DP profile when compared to those with ADHD, DBD, anxiety/depression, and

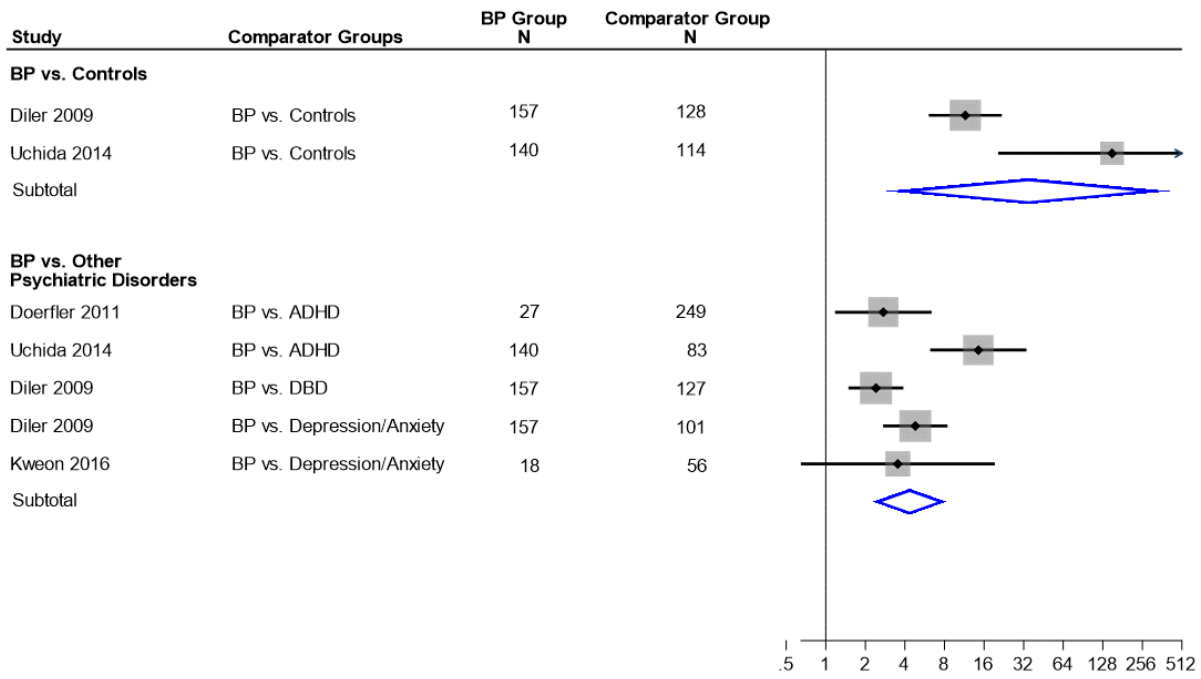

FIGURE 2. Forest plot for the meta-analysis of positive CBCL-BP profiles in youths with bipolar disorder vs. youth with ADHD, controls, youths with disruptive behavior disorders, and youths with depression/anxiety. Odds ratios >1 indicate increased odds for the CBCL-BP profile in youth with bipolar disorder.

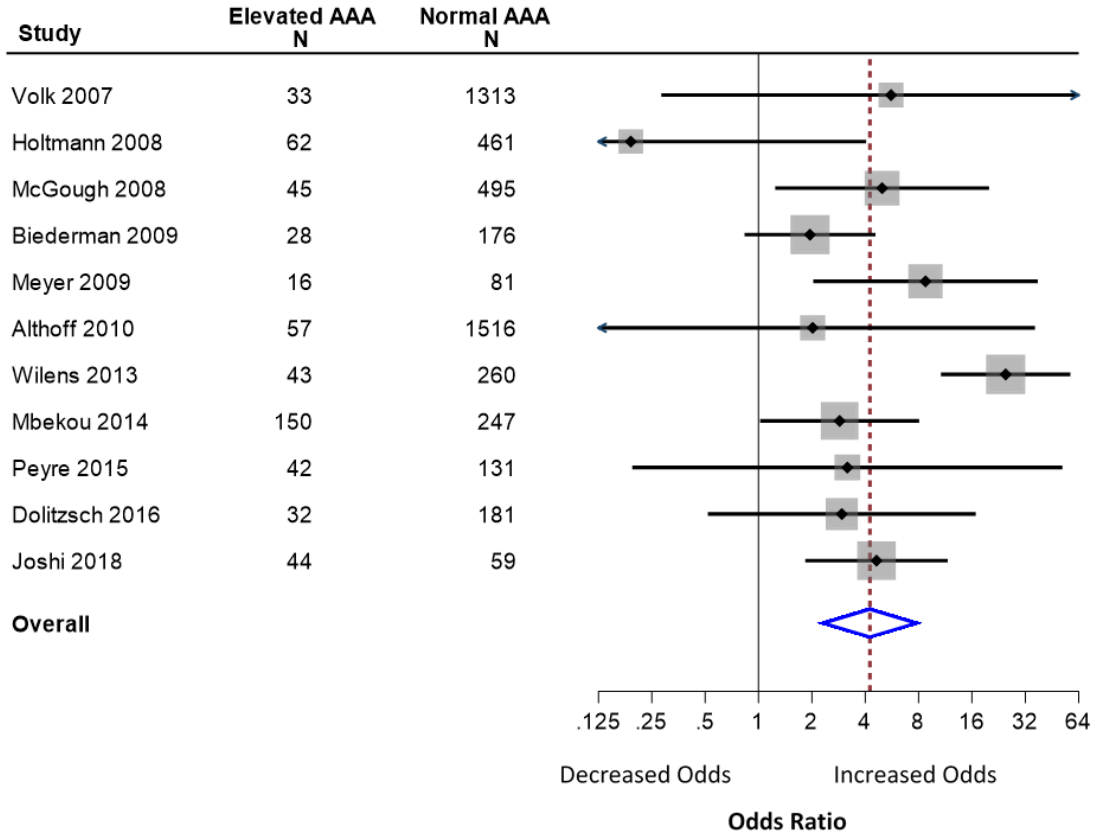

FIGURE 3. Forest plot for the meta-analysis of bipolar disorder diagnoses in youths with and without a positive CBCL-BP profile. Odds ratios >1 indicate increased odds for a bipolar disorder diagnosis in youth with the CBCL-BP profile compared to youth without it.

controls. Furthermore, youth with a positive CBCL-BP/DP profile were at significantly increased odds of having a clinical diagnosis of BP disorder when compared to those without it. These findings are consistent with and expand upon a previous meta-analysis, performed almost 20 years ago, which also found that the CBCL-BP/DP profile could distinguish between youth with BP disorder and those with ADHD(18). These findings are also consistent with previous data showing that a positive CBCL-BP/DP profile is associated with a clinical diagnosis of pediatric BP disorder both cross-sectionally and longitudinally(11-13, 42).

While other groups have found that a positive CBCL-BP/DP profile has limited ability to differentiate BP disorder from other psychiatric diagnoses, they have noted that a positive CBCL-BP/DP profile was associated with high levels of psychopathology, multiple psychiatric diagnoses, suicidality, and poor psychosocial functioning (16, 29, 30, 32-36, 43, 44). For example, Holtmann et al. (43) found that youth with a positive CBCL-BP/DP profile at age 8-11 had increased rates of ADHD, mood and substance use disorders, suicidal ideation and attempts, and poorer functioning at age 19, but noted that none of the patients in the sample were diagnosed with BP disorder. Such differences among studies are understandable given that some controversy remains about how to implement the DSM criteria for BP disorder in youth, especially for young children (45).

Meyer et al. (36) found that 31% of high risk offspring of parents with BP disorder who had a positive CBCL-BP/DP profile developed BP disorder over the course of a 20 year follow up, but also concluded that several other conditions (ADHD, cluster B personality disorder, anxiety) were equally or more likely to be predicted by this profile. Given that pediatric BP disorder has a high overlap with psychiatric disorders such as ADHD, anxiety, and mood and substance use disorders, and has high rates of suicidality, it seems reasonable to hypothesize that a profile that would predict pediatric BP disorder would also predict a similar constellation of psychiatric impairments.

Studies that examined pediatric BP disorder among youth with and without a positive CBCL-BP/DP profile were less likely to find an association between a positive CBCL-BP/DP profile and a BP disorder diagnosis than those studies that examined a positive CBCL-BP/DP profile among youth with and without BP disorder. Because the prevalence of pediatric BP disorder in many of the studies examining pediatric BP as an outcome was very low (<2%; (33-35, 38) they may have had low power to detect the association. In addition, prevalence and the positive predictive value (PPV; i.e., the probability that a person with a positive test has the disorder) of an assessment tool have a direct relationship; as prevalence decreases, so does the PPV. Thus, in these studies with a low prevalence of BP disorder, it is not surprising that the relationship between a positive CBCL-BP/DP profile and a BP disorder diagnosis was not robust.

None of the studies we reviewed provided information about disruptive mood dysregulation disorder (DMDD). Given that that disorder had been created, in part, to reduce diagnoses of pediatric BP disorder (46), it is reasonable to hypothesize that the CBCL-BP/DP profile would be positive for many patients diagnosed with DMDD. We should also consider the possibility that the CBCL-BP/DP profile may be a non-specific indicator of severe emotional dysregulation, which is often seen in ADHD and other disorders (47). For example, in a study of 417 newly referred youth, we compared youth positive for the CBCL-BP/DP profile, those with more modest scores on the sum of the constituent subscales ($\geq$ 180 and <210) and those with scores < 180. Patients with the CBCL-BP/DP profile were significantly more impaired on all measures of social and executive functioning compared to the other two groups, but the group with modest elevations also showed impairments compared with those with no elevation (48). Future work will need to further address these issues.

Our findings have significant clinical and public health implications. While the results support the idea that the CBCL-BP/DP profile may be a useful tool for identifying youth who may be at high risk of having a clinical diagnosis of BP disorder, they also support the notion that it could be a useful marker of the presence of significant psychopathology and dysfunction in youth. As the CBCL is easy to administer, reliable, inexpensive, and available in multiple languages, it could easily be used in both pediatric and child psychiatry clinics to aid in identifying youth at high risk for compromised outcomes. In addition, six out of the 18 studies presented in our paper utilized international samples, providing evidence that the CBCL may be a useful tool for international collaboration in the field of pediatric BP disorder.

Although the CBCL-BP/DP profile is not diagnostic of pediatric BP disorder, a diagnosis that requires careful psychiatric evaluation to diagnose, it may be a useful tool for helping clinicians identify youth at high risk of severe psychopathology and could potentially be used as part of a triage system in primary care or community clinics to assists in determining whether referral to a specialist is needed for a particular patient.

Our meta-analyses found substantial heterogeneity among studies. This likely reflects the unresolved

controversies about how to best diagnose BP disorder in youth. Our group defines pediatric bipolar disorder according to DSM criteria for BP-I; however, criteria for defining pediatric bipolar disorder varied across studies. Six of the fifteen studies included in the meta-analysis used a diagnostic interview and KSADS-E (12, 31, 37) or K-SADS-PL (29, 32, 35) to assess for bipolar spectrum disorders (BP-I, BP-II, and cylothymia)(35). BP-I (12, 29, 31, 32, 37), BP-II (29, 32, 37), or bipolar not otherwise specified (BP-NOS) (29, 32) according to DSM-III-R (12) and DSM-IV criteria (12, 29, 31, 32, 35, 37). Additionally, three studies used a diagnostic interview and K-SADS-E (30, 41) or K-SADS-PL (39) to diagnose for bipolar disorder according to DSM-IV criteria but did not specify how bipolar disorder was defined (30, 39, 41), two studies assessed for ICD-10 diagnoses of bipolar disorders using the diagnostic guidelines of the German society for child and adolescent psychiatry (34) or the K-SADS-PL (40), one study only used diagnostic interviews to assess for BP-I or BP-II according to DSM-IV criteria (36), one study used a diagnostic interview and the Composite International Diagnostic Interview (CIDI) to assess for BP-I or BP-II according to DSM-IV criteria (15), one study used the Missouri Assessment for Genetics Interview for Children (MAGIC) to assess for BP-I and BP-II according to DSM-IV criteria (33), and one study obtained DSM-IV-TR diagnostic information from patients' clinical files and did not specify how bipolar disorder was defined (38).

As reviewed by Goldstein et al. (45), controversies about pediatric BP include what is the best measurement tool for diagnosing BP disorder and whether informants are essential for diagnosis. Marangoni et al. (49) note that when conduct and oppositional disorders are comorbid with ADHD, those disorders will increase aggressive behaviors and make the diagnosis of BP disorder less sure. They also point out that some symptoms characteristic of BD can be difficult to differentiate from the severe end of emotional and cognitive states common in youth. These uncertainties likely added to the heterogeneity of results among studies.

Our findings should be reviewed considering some methodological limitations. Because this was a meta-analysis it is limited by the quality of the data available in the published literature and the data they provided. Because the studies did not provide consistent data about age or studied a wide age range, we could not conduct separate analyses for children and adolescents. The number of available papers examining this subject was relatively small and the number of papers that were able to be used in the meta-analysis was even smaller. As a result, the small number of studies included in the analysis of a positive CBCL-BP/DP profile among youth with BP disorder versus controls produced a pooled OR with an extremely wide confidence interval, indicating a lack of precision. Thus, this result should be interpreted with caution. Additionally, we had to exclude one study that had zero patients with BP disorder at follow-up in both the positive and negative CBCL-BP/DP profile groups (28). Studies with zero events provide no indication of either the direction or magnitude of the effect size, thus we do not know how this paper would have impacted the results. Furthermore, there was substantial heterogeneity in the samples, which may make our results not easily generalizable to all samples. One potential source of heterogeneity could be the different definitions used to define a positive CBCL-BP/DP profile. While most studies used a CBCL-AAA T-score ≥210 or T-scores ≥70 on all three scales that make up the CBCL-AAA to define a positive CBCL-BP/DP profile, four studies used different definitions (Table 1). For these four studies, a positive CBCL-BP/DP profile was defined by T-scores ≥60 on all three CBCL-AAA scales (36), T-scores ≥67 on all three CBCL-AAA scales(40), or by latent class analysis or latent profile analysis with no specific cut-off reported (15, 28). The number of studies was too small to perform an analysis stratified by CBCL-BP/DP profile definitions, thus we do not know how the differences in definitions impacted the results. Given the discordance in how the CBCL-BP/DP profile is defined throughout the literature, more work needs to be done to identify the most appropriate cutoff for this profile.

Another potential source of heterogeneity is from combining ADHD, anxiety/depression, and DBDs into one comparator group called "other psychiatric disorders." The number of studies were too small to perform stratified analyses based on the different comparator disorders, but these disorders are highly comorbid, supporting the decision to combine them into one comparator group. Future research would benefit from more studies examining the rates of a positive CBCL-BP/DP profile in youth with a clinical diagnosis of BP disorder versus youth with other specific psychiatric diagnoses. Additionally, we did not utilize a protocol to perform this meta-analysis and did not perform a systematic review of each paper for biases, which may increase the risk of bias in our findings.

Despite these considerations, our systematic review and meta-analysis showed that the presence of a positive CBCL-BP/DP profile in youth may be a useful tool to help in identifying youth with a likely diagnosis of BP disorder and other significant psychopathology and dysfunction.

Acknowledgments
This research was supported by the MGH Pediatric Psychopharmacology Council Fund. We would like to thank Carrie Vaudreuil, MD, and Amy Yule, MD, for their contributions to the coordination of this study.

Funding
This study was supported in part by the MGH Pediatric Psychopharmacology Council Fund (to JB).

Conflict of interest
Maura DiSalvo, Chloe Hutt Vater, K. Yvonne Woodworth, and Abigail Farrell have no conflicts of interest relevant to this article to disclose. Allison Green received funding from the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under award number T32HD007475. In 2023, Dr. Joseph Biederman received research support from the following sources: AACAP, Feinstein Institute for Medical Research, Genentech, Headspace Inc., NIDA, Pfizer Pharmaceuticals, Roche TCRC Inc., Sunovion Pharmaceuticals Inc., Takeda/Shire Pharmaceuticals Inc., Tris, and NIH. Dr. Biederman and his program received royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Biomarin, Bracket Global, Cogstate, Ingenix, Medavent Prophase, Shire/Takeda, Sunovion, and Theravance; these royalties were paid to the Department of Psychiatry at MGH. Through Partners Healthcare Innovation, Dr. Biederman had a partnership with MEMOTEXT to commercialize a digital health intervention to improve adherence in ADHD. Through MGH corporate licensing, Dr. Biederman held a US Patent (#14/027,676) for a non-stimulant treatment for ADHD, a US Patent (#10,245,271 B2) on a treatment of impaired cognitive flexibility, and a patent pending (#61/233,686) on a method to prevent stimulant abuse. In 2022: Dr. Biederman received honoraria from UC Davis for Grand Rounds and the MGH Psychiatry Academy for tuition-funded CME courses. In 2021: Dr. Biederman received an honorarium for a scientific presentation from Multi-Health Systems, and a one-time consultation for Cowen Healthcare Investments. He received honoraria from AACAP, the American Psychiatric Nurses Association, BIAL - Portela & Cª. S.A. (Portugal), Medscape Education, and MGH Psychiatry Academy for tuition-funded CME courses. In 2020: Dr. Biederman received an honorarium for a scientific presentation from Tris and from the Institute of Integrated Sciences – INI (Brazil), and research support from the Food & Drug Administration. He received honoraria from Medlearning Inc, NYU, and MGH Psychiatry Academy for tuition-funded CME courses. In the past year, Dr. Stephen Faraone received income, potential income, travel expenses continuing education support and/or research support from Aardvark, Akili, Genomind, Ironshore, KemPharm/Corium, Noven, Ondosis, Otsuka, Rhodes, Supernus, Takeda, Tris and Vallon. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received support from: Alcobra, Arbor, Aveksham, CogCubed, Eli Lilly, Enzymotec, Impact, Janssen, Lundbeck/Takeda, McNeil, NeuroLifeSciences, Neurovance, Novartis, Pfizer, Shire, and Sunovion. He also receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health*; Oxford University Press: *Schizophrenia: The Facts;* and Elsevier: *ADHD: Non-Pharmacologic Interventions.* He is also Program Director of www.adhdinadults.com. Dr. Faraone is supported by the European Union's Horizon 2020 research and innovation programme under grant agreement No 965381; NIMH grants U01AR076092-01A1, 1R21MH1264940, R01MH116037; Oregon Health and Science University, Otsuka Pharmaceuticals, Noven Pharmaceuticals Incorporated, and Supernus Pharmaceutical Company.

References

1. Van Meter A, Moreira ALR, Youngstrom E. Updated Meta-Analysis of Epidemiologic Studies of Pediatric Bipolar Disorder. J Clin Psychiatry. 2019;80(3).

2. Wozniak J, Petty CR, Schreck M, Moses A, Faraone SV, Biederman J. High level of persistence of pediatric bipolar-I disorder from childhood onto adolescent years: a four year prospective longitudinal follow-up study. J Psychiatr Res. 2011;45(10):1273-82.

3. Wilens TE, Biederman J, Martelon M, Zulauf C, Anderson JP, Carrellas NW, et al. Further Evidence for Smoking and Substance Use Disorders in Youth With Bipolar Disorder and Comorbid Conduct Disorder. J Clin Psychiatry. 2016;77(10):1420-7.

4. Martin A, Volkmar F. Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.

5. Rademacher J, DelBello MP, Adler C, Stanford K, Strakowski SM. Health-related quality of life in adolescents with bipolar I disorder. J Child Adolesc Psychopharmacol. 2007;17(1):97-103.

6. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. Dev Psychopathol. 2006;18(4):1023-35.

7. Vaudreuil CAH, Faraone SV, Di Salvo M, Wozniak JR, Wolenski RA, Carrellas NW, et al. The morbidity of subthreshold pediatric bipolar disorder: A systematic literature review and meta-analysis. Bipolar Disord. 2019;21(1):16-27.

8. Achenbach TM. Manual for the Child Behavior Checklist/4-18 and the 1991 Profile. Burlington, VT: University of Vermont, Department of Psychiatry; 1991.

9. Achenbach TM, Edelbrock C. The Child Behavior Checklist. Burlington: University Associates in Psychiatry; 1983.

10. Hazell P, Lewin T, Carr V. Confirmation that Child Behavior Checklist clinical scales discriminate juvenile mania from attention deficit hyperactivity disorder. J Paediatr Child Health. 1999;35:199-203.

11. Faraone SV, Althoff RR, Hudziak JJ, Monuteaux MC, Biederman J. The CBCL predicts DSM bipolar disorder in children: A receiver operating characteristic curve analysis. Bipolar Disord. 2005;7(6):518-24.

12. Biederman J, Petty CR, Monuteaux MC, Evans M, Parcell T, Faraone SV, et al. The child behavior checklist-pediatric bipolar disorder profile predicts a subsequent diagnosis of bipolar disorder and associated impairments in ADHD youth growing up: a longitudinal analysis. J Clin Psychiatry. 2009;70(5):732-40.

13. Biederman J, Petty CR, Day H, Goldin RL, Spencer T, Faraone SV, et al. Severity of the aggression/anxiety-depression/attention child behavior checklist profile discriminates between different levels of deficits in emotional regulation in youth with attention-deficit hyperactivity disorder. J Dev Behav Pediatr. 2012;33(3):236-43.

14. Cordeiro ML, Farias AC, Whybrow PC, Felden EPG, Cunha A, da Veiga V, Jr., et al. Receiver Operating Characteristic Curve Analysis of Screening Tools for Bipolar Disorder Comorbid With ADHD in Schoolchildren. J Atten Disord. 2020;24(10):1403-12.

15. Althoff RR, Verhulst FC, Rettew DC, Hudziak JJ, van der Ende J. Adult outcomes of childhood dysregulation: a 14-year follow-up study. J Am Acad Child Adolesc Psychiatry. 2010;49(11):1105-16.

16. Masi G, Muratori P, Manfredi A, Pisano S, Milone A. Child behaviour checklist emotional dysregulation profiles in youth with disruptive behaviour disorders: clinical correlates and treatment implications. Psychiatry Res. 2015;225(1-2):191-6.

17. Biederman J, Martelon M, Faraone SV, Woodworth KY, Spencer TJ, Wozniak JR. Personal and familial correlates of bipolar (BP)-I disorder in children with a diagnosis of BP-I disorder with a positive child behavior checklist (CBCL)-severe dysregulation profile: A controlled study. J Affect Disord. 2013;147(1-3):164-70.

18. Mick E, Biederman J, Pandina G, Faraone SV. A preliminary meta-analysis of the child behavior checklist in pediatric bipolar disorder. Biol Psychiatry. 2003;53(11):1021-7.

19. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M. Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005;44(3):213-35.

20. Biederman J, Mick E, Prince J, Bostic JQ, Wilens TE, Spencer T, et al. Systematic chart review of the pharmacologic treatment of comorbid attention deficit hyperactivity disorder in youth with bipolar disorder. J Child Adolesc Psychopharmacol. 1999;9(4):247-56.

21. Wozniak J, Biederman J. A pharmacological approach to the quagmire of comorbidity in juvenile mania. J Am Acad Child Adolesc Psychiatry. 1996;35(6):826-8.

22. Bhowmik D, Aparasu RR, Rajan SS, Sherer JT, Ochoa-Perez M, Chen H. Risk of manic switch associated with antidepressant therapy in pediatric bipolar depression. J Child Adolesc Psychopharmacol. 2014;24(10):551-61.

23. StataCorp. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC; 2021.

24. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88.

25. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.

26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.

27. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions: Cochrane; 2022.

28. Caporino NE, Herres J, Kendall PC, Wolk CB. Dysregulation in Youth with Anxiety Disorders: Relationship to Acute and 7- to 19-Year Follow-Up Outcomes of Cognitive-Behavioral Therapy. Child Psychiatry Hum Dev. 2016;47(4):539-47.

29. Diler RS, Birmaher B, Axelson D, Goldstein B, Gill M, Strober M, et al. The Child Behavior Checklist (CBCL) and the CBCL-bipolar phenotype are not useful in diagnosing pediatric bipolar disorder. J Child Adolesc Psychopharmacol. 2009;19(1):23-30.

30. Doerfler LA, Connor DF, Toscano PF, Jr. Aggression, ADHD symptoms, and dysphoria in children and adolescents diagnosed with bipolar disorder and ADHD. J Affect Disord. 2011;131(1-3):312-9.

31. Uchida M, Faraone SV, Martelon M, Kenworthy T, Woodworth KY, Spencer TJ, et al. Further evidence that severe scores in the aggression/anxiety-depression/attention subscales of child behavior checklist (severe dysregulation profile) can screen for bipolar disorder symptomatology: a conditional probability analysis. J Affect Disord. 2014;165:81-6.

32. Kweon K, Lee HJ, Park KJ, Joo Y, Kim HW. Child behavior checklist profiles in adolescents with bipolar and depressive disorders. Compr Psychiatry. 2016;70:152-8.

33. Volk HE, Todd RD. Does the child behavior checklist juvenile bipolar disorder phenotype identify bipolar disorder? Biol Psychiatry. 2007;62(2):115-20.

34. Holtmann M, Goth K, Wockel L, Poustka F, Bolte S. CBCL-pediatric bipolar disorder phenotype: severe ADHD or bipolar disorder? J Neural Transm. 2008;115(2):155-61.

35. McGough JJ, Loo SK, McCracken JT, Dang J, Clark S, Nelson SF, et al. CBCL pediatric bipolar disorder profile and ADHD: comorbidity and quantitative trait loci analysis. J Am Acad Child Adolesc Psychiatry. 2008;47(10):1151-7.

36. Meyer SE, Carlson GA, Youngstrom E, Ronsaville DS, Martinez PE, Gold PW, et al. Long-term outcomes of youth who manifested the CBCL-Pediatric Bipolar Disorder phenotype during childhood and/or adolescence. J Affect Disord. 2009;113(3):227-35.

37. Wilens TE, Martelon M, Anderson JP, Shelley-Abrahamson R, Biederman J. Difficulties in emotional regulation and substance use disorders: A controlled family study of bipolar adolescents. Drug Alcohol Depend. 2013.

38. Mbekou V, Gignac M, MacNeil S, Mackay P, Renaud J. The CBCL dysregulated profile: an indicator of pediatric bipolar disorder or of psychopathology severity? J Affect Disord. 2014;155:299-302.

39. Peyre H, Speranza M, Cortese S, Wohl M, Purper-Ouakil D. Do ADHD children with and without child behavior checklist-dysregulation profile have different clinical characteristics, cognitive features, and treatment outcomes? J Atten Disord. 2015;19(1):63-71.

40. Dölitzsch C, Kölch M, Fegert JM, Schmeck K, Schmid M. Ability of the Child Behavior Checklist-Dysregulation Profile and the Youth Self Report-Dysregulation Profile to identify serious psychopathology and association with correlated problems in high-risk children and adolescents. J Affect Disord. 2016;205:327-34.

41. Joshi G, Wozniak J, Fitzgerald M, Faraone S, Fried R, Galdo M, et al. High Risk for Severe Emotional Dysregulation in Psychiatrically Referred Youth with Autism Spectrum Disorder: A Controlled Study. J Autism Dev Disord. 2018.

42. Yule A, Fitzgerald M, Wilens T, Wozniak J, Woodworth KY, Pulli A, et al. Further Evidence of the Diagnostic Utility of the Child Behavior Checklist for Identifying Pediatric Bipolar I Disorder. Scand J Child Adolesc Psychiatr Psychol. 2019;7(1):29-36.

43. Holtmann M, Buchmann AF, Esser G, Schmidt MH, Banaschewski T, Laucht M. The Child Behavior Checklist-Dysregulation Profile predicts substance use, suicidality, and functional impairment: a longitudinal analysis. J Child Psychol Psychiatry. 2010;52(2):139-47.

44. Ayer L, Althoff R, Ivanova M, Rettew D, Waxler E, Sulman J, et al. Child Behavior Checklist Juvenile Bipolar Disorder (CBCL-JBD) and CBCL Posttraumatic Stress Problems (CBCL-PTSP) scales are measures of a single dysregulatory syndrome. J Child Psychol Psychiatry. 2009;50(10):1291-300.

45. Goldstein BI, Birmaher B, Carlson GA, DelBello MP, Findling RL, Fristad M, et al. The International Society for Bipolar Disorders Task Force report on pediatric bipolar disorder: Knowledge to date and directions for future research. Bipolar Disord. 2017;19(7):524-43.

46. Havens JF, Marr MC, Hirsch E. Editorial: From Bipolar Disorder to Disruptive Mood Dysregulation Disorder: Challenges to

Diagnostic and Treatment Specificity in Traumatized Youths. J Am Acad Child Adolesc Psychiatry. 2022;61(3):364-5.

47. Faraone SV, Rostain AL, Blader J, Busch B, Childress AC, Connor DF, et al. Practitioner Review: Emotional dysregulation in attention-deficit/hyperactivity disorder - implications for clinical recognition and intervention. J Child Psychol Psychiatry. 2019;60(2):133-50.

48. Biederman J, DiSalvo M, Vaudreuil C, Wozniak J, Uchida M, Woodworth KY, et al. Disentangling the heterogeneity of emotional dysregulation in referred youth using the Child Behavior Checklist attending to age and sex effects. J Affect Disord. 2022;309:259-65.

49. Marangoni C, De Chiara L, Faedda GL. Bipolar disorder and ADHD: comorbidity and diagnostic distinctions. Curr Psychiatry Rep. 2015;17(8):604.