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Systematic Review or Meta-Analysis

Anxiety disorders comorbidity in pediatric bipolar disorder: a meta-analysis and meta-regression study

Yapıcı Eser H, Taşkıran A.S., Ertınmaz B, Mutluer T, Kılıç Ö, Özcan Morey A, Necef I, Yalçınay M, Öngür D. Anxiety disorders comorbidity in pediatric bipolar disorder: a meta-analysis and meta-regression study.

Objective: Anxiety disorders (AD) are known for its comorbidity and negative impact on the course of adult bipolar disorder (BD). However, there is limited research on AD comorbidity in pediatric BD (PBD). Here, we aimed to conduct a meta-analysis and meta-regression study about the comorbidity and covariates of AD and PBD.
Method: We systematically searched relevant articles published until May 2019, as defined in PRISMA guidelines. Variables for associated features and prevalence of AD were extracted.
Results: Thirty-seven articles represented data for the analysis. Lifetime any AD comorbidity was 44.7%; panic disorder (PD) was 12.7%; generalized anxiety disorder (GAD) was 27.4%; social phobia was 20.1%; separation anxiety disorder (SAD) was 26.1%; and obsessive–compulsive disorder (OCD) was 16.7%. Childhood-onset studies reported higher GAD and SAD comorbidity, while adolescent-onset studies reported higher PD, OCD, and social phobia. Age of onset, gender, comorbidity of ADHD, substance use, oppositional defiant disorder and conduct disorder affected each anxiety disorders' comorbidity with PBD differently.
Conclusion: Anxiety disorders are highly comorbid with PBD. Early-onset PBD increases the risk of AD. Biopsychosocial aspects of this comorbidity and its course needs to be evaluated further.

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Key words: anxiety; bipolar; obsessive; pediatric; separation

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Summations

- Anxiety disorders are highly comorbid with pediatric bipolar disorder.
- Childhood-onset studies report higher generalized anxiety and separation anxiety disorder comorbidity, while adolescent-onset studies reported higher panic disorder, obsessive–compulsive disorder, and social phobia.

Limitations

- There are low number of studies assessing anxiety disorder comorbidity in pediatric bipolar disorder, compared with the number of studies conducted in adults.
- Diagnostic methods used in the included studies are based on DSM-III and DSM-IV criteria.

Introduction

Pediatric bipolar disorder (PBD) is a challenging and controversial diagnosis for clinicians. Episodic presentations of irritability, tantrums, mood instability, free-floating anxiety, impulsivity, or depressed mood, which do not fulfill the criteria of

major manic or depressive episodes, are common in pediatric samples and the increased goal-directed activity criteria of BD may present differently compared with adults (1). PBD also has a complex clinical presentation of a rapid cycling phenomenon and high psychiatric comorbidity (2). There may even be differences between its presentation in childhood versus adolescence. Additionally, the likely similarity of the presenting symptoms to those of other neurodevelopmental disorders such as attention deficit hyperactivity disorder complicates differential diagnosis.

Despite the fact that the phenomenology and comorbidities of PBD are more complex (1) and that the prognosis is worse (3), there are fewer studies on PBD than there are on adults with BD. The number of published studies on PBD has increased lately, but this has not resolved quandaries of phenomenology and variations in PBD (4). Most of our knowledge about bipolar disorder comes from studies on adults, which limits the understanding of pediatric bipolar disorder and early-onset BD. Better understanding of comorbidities in different age groups and clinical presentations are needed to assist clinicians working with pediatric age groups, and for better guidance throughout their longitudinal follow-up, as even childhood and adolescent-onset PBD may have different clinical presentations. Furthermore narrow and broad definitions of PBD may present different comorbidities (5).

The most common comorbid psychiatric disorders of PBD are anxiety disorders (AD), attention deficit hyperactivity disorder (ADHD), and disruptive behavior disorders (6). A systematic review, that used keywords such as 'youth' and 'pediatric' in its search strategy, found around 10 articles on anxiety comorbidity, and reported a range of 41–80% of AD-PBD comorbidity (7). Furthermore, family studies have consistently shown higher rates of anxiety disorders in children of parents with BP (2). Adult studies also support these findings by showing that earlier onset increases the risk of anxiety disorder comorbidity (8, 9).

Anxiety comorbidity in BD is important and thus significantly affects the course of BD and its outcomes (10). Characteristics of the adult comorbidity of anxiety disorders with bipolar disorder are well known for its negative effects as the increased number of hospitalizations, increased number of mood episodes, earlier onset of depressive episodes, and decreased number of manic episodes (8, 11). AD-PBD comorbidity is also shown to increase the risk for substance abuse, completed suicide, and forensic problems (12, 13). There is also limited evidence of a genetic prevalence of anxiety endophenotype in bipolar disorder (14). However, the effect of AD on early-onset bipolar disorder is less known and current studies usually have the limitation of small sample sizes. In PBD patients, anxiety comorbidity explains some of the heterogeneity observed in attention and working memory (15). PBD patients with AD comorbidity have more severe impairment and are admitted to the hospital more often (16–18). Additionally, anxiety symptoms are among the fairly common (25–50%) prodromal symptoms of PBD and AD are suggested to be assessed prospectively for a mood episode emergence (19–21). Anxiety disorders are also suggested to imply important etiologies such as childhood maltreatment (22) and family conflict (23) when comorbid with bipolar disorder, and therefore may present as a target for psychosocial treatments in patients. The association between PBP and comorbid AD is also of clinical importance since one of the management methods for AD is antidepressant pharmacotherapy (6), and having a PBD diagnosis may limit the use of antidepressants because of the risk of a manic switch and increased suicidal behavior. Despite this fact, 24% of children who were newly diagnosed with PBD were found to be on antidepressant monotherapy (24).

Because of a lack of sufficient literature, how subtypes of anxiety disorders are distributed in PBD groups and the variables that moderate their comorbidity in PBD is not known. Assessing subtypes of AD in PBD may assist in uncovering a better phenomenological and clinical description of PBD.

In order to answer the above-mentioned clinical questions, our first aim with this study was to reach an estimation of the prevalence of any anxiety disorder and subtypes of anxiety disorders comorbidity in PBD, by meta-analysis. Second, we investigated the prevalence of anxiety disorder in subcategories of childhood-onset and adolescent-onset PBD and narrow or broad defined PBD, via meta-analysis. Our final aim was to explore the moderators of AD comorbidity in BPD for a better phenomenological understanding, via meta-regression analysis.

Methods

Search strategy

The methodology of this study is a follow-up of the previously published study by Yapici Eser et al (8). This study was designed and conducted in accordance with the MOOSE (25) and PRISMA (26) guidelines. Detailed information about search

strategy can be found in the study by Yapici Eser et al (8). In summary, it was a systematic review, which used the search database Pubmed to identify articles with the keywords 'bipolar disorder' or 'affective psychosis' with 'anxiety disorder', 'generalized anxiety disorder', 'panic disorder', 'social phobia', or 'obsessive–compulsive disorder' in the 'Title/Abstract', and included the ones that were published before September 2015 in English. Articles excluded from the previous study for being conducted on child and adolescent samples have been evaluated and included in this study. In addition, references of the reviews and published articles were also reviewed and relevant articles that could include data about anxiety disorder comorbidity in childhood and adolescent samples of bipolar disorder were detected and evaluated. On May 30, 2019, this search strategy has been updated by a search in PubMed for articles published after September 2015. 'Bipolar' and anxiety, panic, obsessive, or phobia has been used as keywords to search in the title and abstract. New articles conducted on child and adolescent samples were screened and new references of the reviews and published articles were also reviewed for inclusion.

Study selection and data extraction

Selection criteria for inclusion of a study were to report either establishing all diagnosis based on DSM- or ICD-based criteria by an expert clinician or to report the use of a structured clinical interview for the diagnosis of anxiety disorder and bipolar disorder. Structured clinical interviews for diagnosis included the K-SADS, the Structured Clinical Interview for DSM-IV (SCID-4), and Diagnostic Interview for Children and Adolescents-Revised (DICA-R) (6). Studies that only reported a 'multiple anxiety disorder' diagnosis without reporting specific anxiety disorder diagnoses included, were excluded from the total anxiety disorder comorbidity calculations.

The age range of the research samples was expected to be lower than 18 years of age. A flow diagram of the research strategy can be found in Figure 1. All articles were read carefully to identify data related to the hypotheses and relevant information was extracted by authors (BE, TM, IN, OK, MY, AO, and HYE). All extracted data were recontrolled by HYE, BE, and AST. Extracted data included the following: article title, names of the authors, publication year, journal/publication title, country, types of bipolarity in the sample (narrow or broad), types of onset of bipolar disorder (childhood or adolescent onset), sample size, prevalences of any anxiety, panic disorder, OCD, social phobia, GAD and SAD in the sample, in addition to mean age of the sample, female ratio of the sample, method of sampling, diagnosis method of bipolar disorder, percentage of the patients with psychotic features in the sample, diagnosis method of anxiety disorders, index episode of the patients, mean age of onset of BD, family history of anxiety disorder, whether the patients are inpatients or outpatients, ADHD prevalence in the sample, oppositional defiant disorder (ODD), conduct disorder (CD), and substance use prevalence in the sample.

After extracting the relevant information, studies from the same research groups, same cities, and same collaborations were carefully checked to identify any involving similar participant pools. Data from retrospective chart reviews were also included in case they reported to use DSM-IV criteria for screening of all psychiatric diagnosis. Studies using the same sample as COBY study sample or from the same research group were carefully assessed for overlapping data and shared participants. In case of an overlapping sample, data from the most recent and larger sample size were included.

The childhood-onset group defined age of onset before 12 years of age and adolescent onset defined age of onset between 13 and 18 years of age.

Both narrow and broad criteria for BD were extracted. Articles that reported to include narrow phenotype stated exclusion of irritability only, without elevation or expanded mood (27) or reported diagnosing patients based on DSM criteria with structured clinical interviews. Broad phenotype included individuals with non-episodic chronic irritability, without elevation of mood or grandiosity (28) as suggested by Leibenluft et al (29).

Statistical analysis

The software program used to analyse the data for meta-analysis and meta-regression was Comprehensive Meta-Analysis software version 2, licensed to Koç University. We conducted publication bias analysis for any anxiety disorder in children with bipolar disorder and inspected the Funnel plots, and conducted the Egger's test (30) and calculated the Begger-Mazumdar Kendall's tau (31). I^2 and Q statistics were used for each analysis to determine heterogeneity of the studies. Heterogeneity represents to what extend the results of the studies are consistent and the variation in study outcomes between studies. I^2 value higher than 75% represented high heterogeneity whereas I^2 lower than

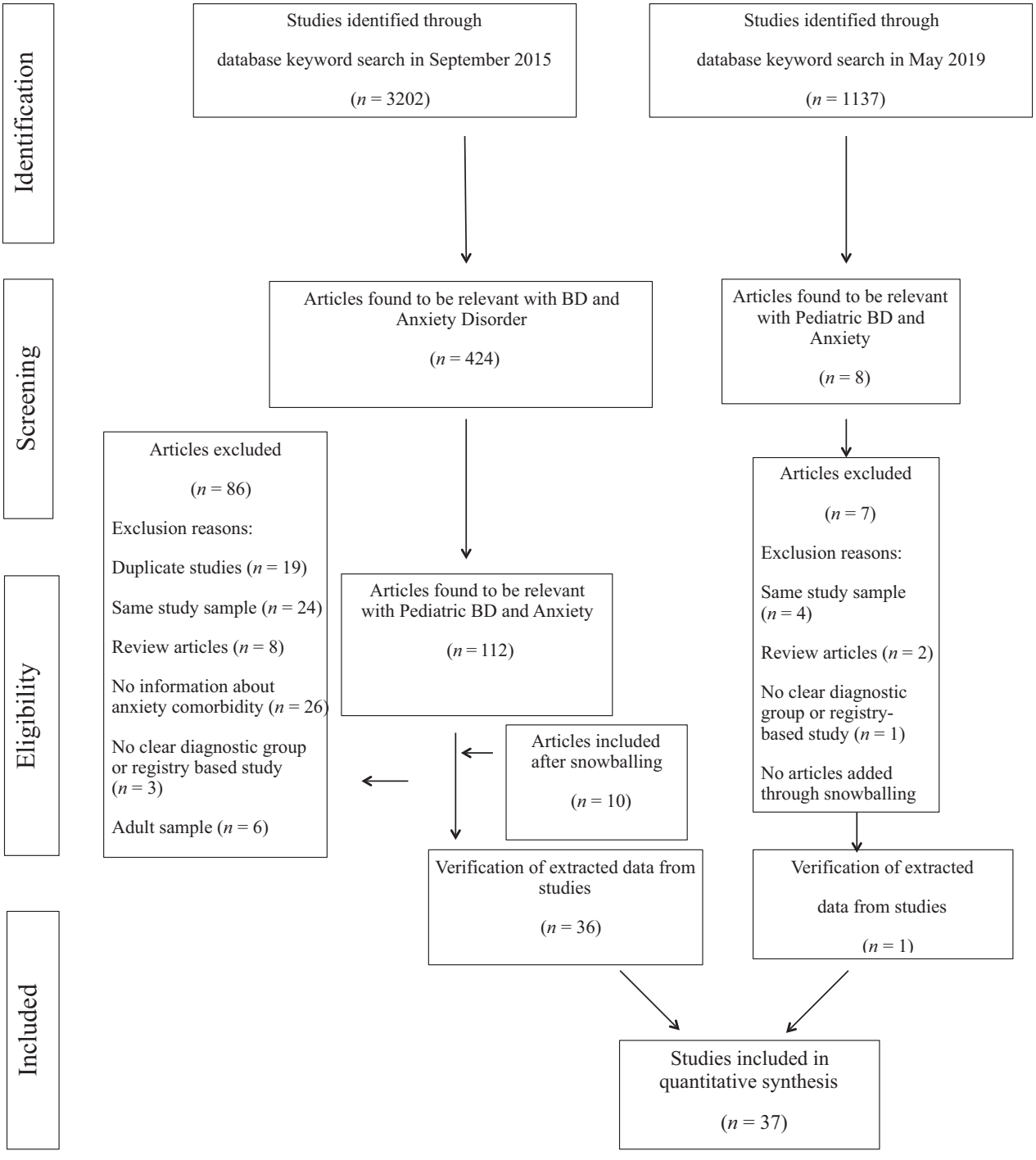

Fig. 1. PRISMA flow diagram for meta-analysis on prevalence of anxiety disorders comorbidity in pediatric bipolar disorder.

25% represented small heterogeneity. The prevalence of these anxiety disorders in childhood-onset bipolar disorder and adolescent-onset bipolar disorder was analyzed separately with a random effects model and compared with each other using the chi-squared test. Considering that use of narrow or broad diagnostic criteria could influence anxiety disorder comorbidity, the prevalence of these anxiety disorders in narrow and broad diagnosed bipolar disorder was also analyzed with a random effects model and compared with each other using the chi-square test.

Lastly, since studies showed a great level of heterogeneity, moderating variables with a possible impact on anxiety disorder comorbidity in bipolar disorder were extracted and a meta-regression analysis using mixed-effect regression (unrestricted maximum likelihood) was conducted for the effects of mean age of

the sample, % of females in the sample, % of the patients with a history of psychosis, % of patients with index episode of mania, mean age of onset, % of patients with ADHD, % of patients with ODD, % of the patients with CD, and % of the patients with substance use. Data of the studies that did not clearly identify the episodes as mania, depression, or mixed were not included in the variable for index episode. Only the studies with the prevalence data of lifetime comorbidity of ADHD, psychosis, ODD, and CD diagnosis were used for the regression analysis for these variables. The substance use variable was defined as alcohol or drug use. Data from studies that presented prevalence of ODD and CD as one variable were not included in the calculation of these variables. Because of the multitude of comparisons, $P < 0.001$ has been considered significant at this level.

Results

Description of the Included Studies

The search strategy of this study was conducted in two steps. First search through Pubmed was completed in 2015 as described in Yapici-Eser et al (8). This study's search strategy resulted in 3202 articles, 112 of which were found to be relevant with PBD and anxiety disorder comorbidity. Each of the relevant articles was read by at least two authors, and 80 of articles were excluded from the study. Ten articles were included in the study after reference catching from the read articles (snowballing). A total of 36 articles were included in the final analysis, as a result of the first search.

In the second search, among the 1137 articles that were identified, 11 of them were found to be relevant with our hypothesis in the screening step. Eight articles were screened for eligibility. Four articles included samples that were used in the first search with no new data. One study was excluded for being a registry-based study. Two articles were reviews; therefore, only one study could be included from the updated search. In total, 37 articles were used for the analysis. Summary characteristics of the included studies can be found in Table S1.

Sample sizes of the included studies ranged from 10 to 446. Mean ages of the studies ranged from 7.9 to 16. The PRISMA flow of the selection process and exclusion criteria are presented in Figure 1.

Risk of bias and quality assessment

The distribution of the included studies in the Funnel plot indicated no publication bias. In addition, no publication bias was detected according to the results of the Egger's regression test [intercept: −0.52 (−3.7, 2.64), *P*-value: 0.73] and Kendall's tau with continuity correction test (tau: 0.078, *P*-value: 0.61). The heterogeneity of the included studies in lifetime anxiety disorder comorbidity in pediatric bipolar disorder analysis were all significant and highly heterogeneous ($I^2 > 87\%$). In both subgroup analyses, childhood-/adolescent-onset subgroups and narrow/broad subtypes of bipolar disorders, most of the studies showed moderate heterogeneity ($I^2 > 83\%$) and 4 analysis results showed small heterogeneity in total, in adolescent onset of PBD and broad definition of PBD (Table 1).

Prevalence of anxiety disorders in PBD

The analysis resulted that the prevalence of any anxiety disorder in pediatric bipolar disorder is 44.7%, GAD is 27.4%, OCD is 16.7%, panic disorder is 12.7%, SAD is 26.1% and social phobia is 20.1% (Table 1). The analysis of the childhood-onset and adolescent-onset PBD subgroup analysis is presented in Table 2. The chi-squared test to compare each anxiety disorders' comorbidity in childhood- and adolescent-onset PBD showed higher any anxiety disorder ($P < 0.000000001$), generalized anxiety disorder ($P = 0.046$) and separation anxiety disorder in childhood-onset bipolar disorder ($P < 0.000000001$) and higher obsessive–compulsive disorder, panic disorder and social anxiety disorder in adolescent-onset bipolar disorder ($P < 0.000001$, for OCD, PD, and social phobia).

The prevalence of any anxiety disorder in narrow and broad subtypes is represented in Table 3. Patients diagnosed as bipolar disorder with broad criteria reported significantly higher anxiety disorders (for all anxiety disorders, $P < 0.0001$, chi-squared test). The prevalence of any anxiety disorder in narrow and broad subtypes is represented in Table 3.

Meta-regression analysis

A univariate mixed-effect regression (unrestricted maximum likelihood) was applied to estimate the effects of moderator variables on anxiety disorder-BD comorbidity. The results showed that none of the variables that we extracted were associated with the heterogeneity of any anxiety disorder comorbidity in PBD (Table 4). However, the heterogeneity of GAD and SAD was correlated with most of the variables. The mean age of the population was associated with the prevalence of GAD [*Z*: −2.55, *P*: 0.001] and SAD [*Z*: −2.93, *P*:

Table 1. Lifetime comorbidity of anxiety disorders in pediatric bipolar disorder

Lifetime comorbidity	No of studies	No of patients	Prevalence % (CI)	Heterogeneity I^2	Cochran Q (*P*-value)	References
Any anxiety disorder	22	2233	44.7 (37–52,7)	90.97	232.46 ($P < 0.0001$)	(10, 13, 16, 28, 43, 44, 54, 56, 60–73)
Generalized anxiety disorder	21	2349	27.4 (21.1–34.7)	90.79	217.30 ($P < 0.0001$)	(13, 16, 28, 44, 52, 54–56, 62, 65–67, 69, 70, 74–80)
Obsessive–compulsive disorder	23	2363	16.7 (11.4–23.8)	92.63	298.45 ($P < 0.0001$)	(13, 16, 28, 44, 52–54, 56, 60, 62, 67–70, 75–83)
Panic disorder	23	2933	12.7 (9.2–17.2)	87.3	173.31 ($P < 0.0001$)	(13, 16, 28, 44, 52–56, 62, 66–69, 71, 75–81, 83)
Separation anxiety disorder	22	2351	26.1 (19.9–33.5)	91.04	234.55 ($P < 0.0001$)	(13, 16, 28, 52, 54–56, 60, 62, 65–70, 74–80)
Social phobia	22	2534	20.1 (15.4–25.9)	88.27	179.04 ($P < 0.0001$)	(13, 16, 28, 44, 52–56, 66–70, 75–81, 83)

Table 2. Lifetime comorbidity of anxiety disorders in childhood-onset and adolescent-onset subtypes of pediatric bipolar disorder

Lifetime comorbidity	Onset	No of studies	No of patients	Prevalence % (CI)	Heterogeneity I^2	Cochran Q (*P*-value)	References
Any anxiety disorder	Childhood Onset	5	712	37.3 (23.8–53)	93.19	58.77 ($P < 0.0001$)	(43, 54, 70, 73, 84)
	Adolescent Onset	4	287	30.3 (24–37.5)	36.25	4.70 ($P < 0.0001$)	(10, 16, 68, 84)
Generalized anxiety disorder	Childhood Onset	8	733	25.6 (14.3–41.4)	92.15	89.12 ($P < 0.0001$)	(54, 67, 70, 74–76, 84, 85)
	Adolescent Onset	5	274	14.5 (6.7–28.6)	80.91	20.95 ($P < 0.0001$)	(16, 67, 74, 84, 85)
Obsessive–compulsive disorder	Childhood Onset	7	719	13.9 (6–29.2)	92.98	85.44 ($P < 0.0001$)	(54, 67, 70, 75, 76, 84, 85)
	Adolescent Onset	7	474	23.6 (12.3–40.5)	90.50	63.13 ($P < 0.0001$)	(16, 67, 68, 81, 83–85)
Panic disorder	Childhood Onset	6	604	9 (0.3–19.5)	86.31	36.53 ($P < 0.0001$)	(54, 67, 75, 76, 84, 85)
	Adolescent Onset	7	474	18 (8.6–34)	90.32	61.97 ($P < 0.0001$)	(16, 67, 68, 81, 83–85)
Separation anxiety disorder	Childhood Onset	8	733	27.8 (20.3–36.8)	78.34	32.32 ($P < 0.0001$)	(54, 67, 70, 74–76, 84, 85)
	Adolescent Onset	6	354	13.4 (9.4–18.8)	25.44	6.71 ($P < 0.0001$)	(16, 67, 68, 74, 84, 85)
Social phobia	Childhood Onset	7	719	15.1 (8.3–25.9)	86.95	45.98 ($P < 0.0001$)	(54, 67, 70, 75, 76, 84, 85)
	Adolescent Onset	7	474	23.8 (14.3–36.7)	83.70	36.80 ($P < 0.0001$)	(16, 67, 68, 81, 83–85)

0.003] significantly. The percentage of the females was associated with the heterogeneity of GAD [*Z*: −2.19, *P*: 0.029], SAD [*Z*: −3.36, *P*: 0.0008], and social phobia [*Z*: −1.97, *P*: 0.048]. History of psychotic features was associated with the heterogeneity of GAD [*Z*: −3.23, *P*: 0.001] and panic disorder [*Z*: 2.18, *P*: 0.03]. Additional details for association of other variables as manic index episode, age of onset, % of patients with ADHD in the sample, % of patients with ODD in the sample, % of patients with CD in the sample, and % of substance use in the sample are reported in Table 4. The reference list of articles used for the calculation of each variable is presented in supplementary reference Table S2.

Discussion

Prevalence of anxiety disorders in pediatric BD

We found that AD comorbidity is very high in PBD patients. Almost half of the patients reported at least one of the anxiety disorders. The most common comorbidity is generalized anxiety, followed by separation anxiety. When all relevant studies regardless of adolescent- and childhood-onset PBD were pooled for the analysis of comorbid AD in pediatric BD, the comorbidity of any anxiety disorder, social phobia, generalized anxiety, separation anxiety, and obsessive–compulsive disorder is also higher than the comorbidity found in adult cases when compared to the results of a recent meta-analysis (8). Only the comorbidity of panic disorder is lower than the comorbidity of panic disorder in adult BD patients (8). This finding also replicates that earlier onset of BD increases the risk of anxiety comorbidity. It may also imply a more anxiety dominant phenotype of early-onset BD compared with adult onset.

The high comorbidity of anxiety disorders in PBD may have multiple reasons. First of all, being diagnosed with one of the DSM categories may reduce the number of symptoms required for other DSM categories, because of overlapping symptoms that may occur in more than one disorder. Additionally, anxiety disorders may also be comorbid with each other and patients may be diagnosed with multiple anxiety disorders (32). So, our finding may be the result of a phenomenological similarity. One study reported that 65 % of youth with rapid cycling PBD have a comorbid anxiety disorder (32). Prodromal and residual symptoms of apparent mood episodes may share anxiety phenotypes and increase the diagnosis of AD. Second, PBD patients also report higher somatic symptoms (33), especially higher cardiac and respiratory medical disorders (34, 35). Altered interoceptive awareness in PBD, because of these somatic symptoms and distorted perceptions of interoceptive signals, may lead to AD diagnosis (13). Third, shared

Table 3. Lifetime comorbidity of anxiety disorders in narrow and broad subtypes of pediatric bipolar disorder

Lifetime comorbidity	Narrow/ Broad	No of studies	No of patients	Prevalence % (CI)	Heterogeneity I^2	Cochran Q (*P*-value)	References
Any anxiety disorder	Narrow	16	1582	42.9 (33.6–52.8)	91.52	177.03 ($P < 0.0001$)	(10, 13, 16, 28, 43, 44, 54, 61–63, 65, 66, 68, 71, 73, 85)
	Broad	2	581	57 (42.3–70)	92.09	12.64 ($P < 0.0001$)	(56, 72)
Generalized anxiety disorder	Narrow	11	1182	20,5 (12.3–32.1)	92.45	132.38 ($P < 0.0001$)	(13, 16, 28, 44, 54, 55, 62, 65, 66, 74, 78)
	Broad	5	553	41.9 (30.5–54.1)	83.19	23.79 ($P < 0.0001$)	(56, 75–77, 79)
Obsessive–compulsive disorder	Narrow	9	1015	13 (5.5–27.6)	95.05	161.86 ($P < 0.0001$)	(13, 16, 28, 44, 54, 62, 68, 78, 83)
	Broad	6	635	22.4 (13.5–34.8)	88.26	42.59 ($P < 0.0001$)	(56, 75–77, 79, 82)
Panic disorder	Narrow	12	1603	9.4 (5–16.9)	91.95	136.72 ($P < 0.0001$)	(13, 16, 28, 44, 54, 55, 62, 66, 68, 71, 78, 83)
	Broad	5	553	14.6 (11.2–18.8)	24	5.27 ($P = 0.0001$)	(56, 75–77, 79)
Separation anxiety disorder	Narrow	11	1174	20.1 (12–31.7)	92.99	142.78 ($P < 0.0001$)	(13, 16, 28, 54, 55, 62, 65, 66, 68, 74, 78)
	Broad	5	553	40.6 (29.5–52.8)	83.25	23.88 ($P < 0.0001$)	(56, 75–77, 79)
Social phobia	Narrow	10	1278	14.4 (7.9–24.8)	93.12	130.97 ($P < 0.0001$)	(13, 16, 28, 44, 54, 55, 66, 68, 78, 83)
	Broad	5	553	27.8 (24.2–31.6)	<0.0001	2.207 ($P < 0.0001$)	(56, 75–77, 79)

Table 4. Meta-regression analysis of the variables that affect the heterogeneity of lifetime anxiety disorder comorbidity in pediatric bipolar disorder

	Any anxiety disorder		Generalized anxiety disorder			Obsessive–compulsive disorder		Panic disorder		Separation anxiety disorder			Social phobia	
	†	*P*	†	*P*	*z*	†	*P*	†	*P*	†	*P*	*z*	†	*P*
Mean Age	19	0.87	19	*0.001*	−2.55	22	0.94	22	0.38	20	*0.003*	−2.93	21	0.59
% of females	18	0.52	20	0.029	−2.19	22	0.61	22	0.66	21	*0.0008*	−3.36	21	0.048 ($z = -1.97$)
% with a history of psychosis	8	0.25	11	*0.001*	−3.23	11	0.28	12	0.03 ($z = 2.18$)	11	0.05	−1.92	12	0.09
Manic index episode	7	0.13	7	0.009	−2.59	8	0.54	7	0.03 ($z = -2.17$)	6	*0.0001*	−3.85	6	0.57
Age of onset	12	0.93	19	*<0.00001*	−4.6	18	0.55	18	0.81	18	*<0.00001*	−5.05	17	0.22
%of patients with ADHD	16	0.89	18	*0.001*	3.3	17	0.79	18	0.43	19	*0.001*	3.2	17	0.46
%of patients with ODD	15	0.63	16	0.032	2.14	14	0.29	15	0.49	17	*0.0018*	3.12	14	0.24
%of patients with CD	14	0.77	17	*0.0013*	3.22	15	0.2	16	0.09	18	*0.00003*	4.18	15	*0.0056 ($z = 2.76$)*
% of substance use	5	0.51	7	0.89	0.14	6	0.02 ($z = 2.37$)	7	0.099	7	0.21	1.26	6	0.014 ($z = 2.46$)

†Number of studies, *P*, *P*-value, *z*, *z* value.

Italic values represent statistically significant results.

genetic factors may lead individuals to be prone to both AD and PBD (14). Lastly, environmental factors as early life adversities could play a role in changing ventromedial prefrontal cortex, insula and amygdala functions, and cause both PBD and various subtypes of AD (36). A recent registry-based study from Norway also shows that anxiety disorder diagnosis may both precede and follow the onset of BD diagnosis in almost equal prevalences (37).

Effects of childhood onset and adolescent onset of BD on comorbidity with anxiety disorders

The numbers of studies on childhood-onset and adolescent-onset PBD data were almost equal in this study; however, most of the studies included both groups. For childhood-onset PBD, any AD comorbidity was comparable to that is found in adult cases, but for adolescent-onset PBD diagnosis, any AD comorbidity was found lower than that found in adult cases, when compared using the results of a recent meta-analysis (8). However, for the AD subgroups as OCD, GAD, and SAD, both childhood- and adolescent-onset groups were found to show higher comorbidity than that found in adult cases, when compared using the results of a recent meta-analysis (8). Any anxiety disorder comorbidity was found to be higher in childhood onset, compared with adolescent onset, but when we analyzed the subcategories of anxiety comorbidity for their comorbidities with PBD using chi-squared test, childhood-onset studies reported higher GAD and SAD comorbidity, while adolescent-onset studies reported higher panic disorder, OCD, and social phobia (Table 2). This finding may imply that child- and adolescent-onset PBD have different phenotypes and that childhood-onset PBD is more prone to anxiety disorders. A large sample study also supports that childhood-onset PBD has higher comorbidities including those with anxiety disorders, higher familial load, and worse prognosis (3). Additionally, this finding may show an overlap with the age of onset for different psychiatric disorders. Mean age of onset for separation anxiety is around 7 years of age; however, for OCD, social anxiety, and panic disorder, age of onset is usually after adolescence (38, 39).

Separation anxiety is considered a new diagnosis that is not highly assessed in adults. A recent study on adult patients with panic disorder found that SAD is a manic/hypomanic spectrum component when questioned with a self-report mood questionnaire (40) and when compared to panic disorder patients without SAD, patients with SAD reported higher manic performance scores. This study presents a stronger link between SAD and BD, when compared to PD.

Effects of narrow and broad definitions of PBD on comorbidity with anxiety disorders

We found a higher number of studies using narrow phenotype of PBD, compared with broad phenotype, with narrow phenotype showing lower AD compared with broad phenotype in these studies (Table 3). This finding is controversial to findings of Dickstein 2005 (28), where chronic irritability experiencing broad phenotype patients were diagnosed with less anxiety disorders. On the other hand, use of broad definition criteria for PBD leads to almost 2.5 times higher prevalence for individuals diagnosed with PBD (4). Broad definition of PBD includes chronic irritability and mood lability, but not necessarily apparent mood episodes. Therefore, this definition is criticized for the fact that chronic irritability and mood lability may not always be present in the presentation of hypomania (41) and that it does not exactly overlap with the definition of BD-NOS, but may include the DSM-5 diagnosis of DMDD. The results of narrow definition of PBD might represent the current diagnostic criteria for PBD better and model hypomanic and manic episodes; however, some authors also argue that paying attention to the prodromal and more generalized presentation of mood episodes and mild but significant symptoms during childhood is needed for a better coverage of the bipolar spectrum in youth. In contrast, in one study, 2 years follow-up of chronic rather than episodic irritability did not predict development of episodic mania (42). A recent meta-analysis that aimed to characterize the mania phenotype of BD in youth, found that anxiety disorder comorbidity in BD-I, BD-NOS, and BD-Spectrum was around 24%, 25%, and 23% respectively (41). Since this study focused on the presentation of mania, resulting prevalences lower than those in our study would not be out of the ordinary. In addition, since they did not aim to cover all studies that assessed AD comorbidity in PBD, they did not include as many studies as we are able to (41). Two other studies also found similar AD comorbidity in BD-NOS and BD- I (43, 44). It is therefore possible that our observation of higher AD in broad definition of PBD may stem from including milder symptoms of chronic irritability rather than the inclusion of BD-NOS. A limited number of published studies on DMDD-AD comorbidity also support high AD found in DMDD (45, 46).

Moderator variables of anxiety disorder comorbidity in BD

As moderator variables, we could only include general sociodemographic variables and reported structured clinical interview diagnosis. Unfortunately, none of the moderators that could be assessed were biomarkers related to one disorder.

In our analysis, none of the assessed variables provided an explanation for the heterogeneity of any anxiety, in PBD. Female percentage only affected the heterogeneity of GAD, SAD, and social phobia, negatively (Table 4). Women are known to be more prone to all anxiety disorders, and the female gender is a significant predictor of separation anxiety (47). The role of gender-related hormones in later ages may have lead to our findings. In order to explain the female gender-SAD-PBD relationship, early adverse life events and age-related hormonal changes could be presented as mediating factors for the three courses.

As another finding, GAD and SAD comorbidity were explained by similar variables such as lower mean age, earlier onset, history of psychosis, lower index episode of mania, higher ADHD, ODD, and conduct disorder (Table 4). The finding of association of lower mean age with these disorders also overlaps with the finding that child-onset PBD cases have higher GAD and SAD comorbidity.

Based on our pooled analysis, ADHD also explained the variability in only GAD and SAD. ADHD is known to have high comorbidity with anxiety disorders, but the prevalence of each specific anxiety disorder's comorbidity is not well known in this group (48). 30% of ADHD cases were reported to have GAD diagnosis (49). So our finding of a correlation between GAD and ADHD in PBD could be the result of their shared etiologies. On the other hand, the fidgety symptoms of ADHD may sometimes also be misdiagnosed as GAD and this may lead to higher comorbidity reports. But from the neurobiology perspective, this finding could also be the result of prefrontal dysfunction observed in ADHD, which may lead to less top-down control of anxiety observed in GAD (50). Both ADHD and PBD have impairments in executive functioning (51) and both disorders are related to dysfunctional frontostriatal-basal ganglia circuitry (27), which can lead to preoccupations observed in GAD.

Conduct disorder explained the heterogeneity of the studies for comorbidity of SAD, SP, and GAD in PBD. Conduct disorder is one of the major comorbidities of AD in pediatric samples. Inhibited temperament (38) and emotional dysregulation in CD may share similarities with SAD and GAD.

Substance use, which is an independent predictor of PBD (52), explained the heterogeneity of OCD and social phobia comorbidity in PBD. This finding is in accordance with the results found in adults, where substance use is found to be related to social anxiety (8). However, for this analysis, we could use only data from 6 studies (28, 52–56) and this may limit generalizability of our findings. Also, children and adolescents may not have yet been exposed to substances, in the time of the assessments, which may lead to underestimation of the effect sizes. The adolescent period is very critical for the initiation of substance use (57). Therefore, new studies in different countries involving higher number of participants may show the real impact of substance use on AD comorbidity in PBD.

Finally, it is apparent that the moderators of AD-PBD comorbidities as conduct disorder, ADHD, and substance use also have an interaction with each other, which may have influenced our findings.

Limitations of the study and the current literature

In our search strategy, searching one database could be a limitation. However, in this study, we decided to search PubMed extensively and read all relevant papers' references for finding new articles that were not listed in our identification step after PubMed search. This approach called 'snowballing' is conducted by using the reference list of an article to identify additional articles. We continued this reference catching process until we could not find any more relevant articles. By this 'snowballing' approach in addition to search of PubMed, we believe that we could cover all relevant resources published on this topic.

Since the article database included in this study stems from a previous study (8) conducted with keywords that were not limited to any age groups, we were able to find a higher number of articles compared with the previous systematic review (7) and were able to conduct meta-analysis and meta-regression statistics. We considered that if we had used 'pediatric' as a keyword, we could miss some of the studies that did not use 'pediatric' as a keyword, but used 'childhood', 'adolescent', or 'under 18 years if age' as keywords in the text. Therefore, when we updated our search in 2019, we again did not use 'pediatric' as a keyword with the same apprehension. We believe that our strategy could cover all literature about bipolar-anxiety comorbidity and with focused identification, screening and eligibility steps, we could discriminate studies on pediatric samples, without missing any data.

Even though we did not include 'separation anxiety' as one of the keywords, the keyword 'anxiety' was able to cover this diagnosis on its own. As another strength, here we were able to do analysis separately for individual anxiety disorder categories, child and adolescent onset, and narrow or broad phenotypes, in addition to moderator variables as ADHD, conduct disorder and substance use. Updating the search strategy until 2019 has also helped us to reach a wider coverage of the literature.

As an important finding, our search strategy update for the period between 2015 and 2019 could add only one article relevant to our hypothesis. This low number of studies show a gap of enough number of studies on this area. We believe that this approach will assist in understanding the phenomenology of PBD better and guide more researchers for studying this topic.

On the other hand, this study and the current literature involved, have several limitations. First of all, even though we updated our search for the most recent articles, they were conducted using structured interviews for DSM-III and DSM-IV. Since the publication of the DSM-5 in 2013, criteria for the disruptive mood dysregulation disorder (DMDD) diagnosis have emerged with the aim of decreasing the overdiagnosis of PBD. Thus, the bipolar disorder group in newly published articles may show phenomenological differences. DMDD cases present with chronic, non-episodic irritability and are usually followed by depressive episodes instead of manic episodes (58). The exclusion of OCD from the anxiety disorders category would also limit the generalization of the 'any anxiety disorder' group across the diagnosis. In the present study, we categorized OCD under the anxiety disorder diagnosis since the included studies used the DSM-IV and the 'any anxiety disorder' category still included OCD. Some of the studies included in the present study are based on the DSM-III while others are based on the DSM-IV. The effects of the diagnostic manual used may have effected our findings. Even though we only included studies that used a structured diagnostic interview for their analysis, interview methods used, retrospective recall of the participants and interviewing with presenting parents may have led to variation. Also, narrow or broad definition of PBD may also be

criticized; therefore, we had to strictly investigate articles for their diagnosing methods and criteria for a decision. When conducting the meta-regression analysis, we conducted a univariate analysis; however, the variables we assessed may show collinearity or interaction, so multiple interactions should be assessed in further studies. We could not calculate the effect of duration of illness, number of previous and manic episodes on the comorbidity of AD, because of lack of enough data and therefore, could not make a correlation of PBD severity with anxiety emergence. Family history of AD and BD could also be moderators of AD-PBD comorbidity; however, this variable also could not be calculated in this study. The effect of medication on AD-BPD comorbidity is also of particular interest, but the found studies did not report this effect as a numerical variable. We were not able to find enough data about chronic-episodic presentation. Even though PTSD was categorized under the anxiety disorder diagnosis in DSM-IV, we did not record its subcategory data here. Most of the included studies were conducted on Caucasians. Lastly, because of the small amount of studies, we were not able to conduct a meta-regression analysis on the moderators of AD comorbidity in childhood and adolescence PBD cases in the present study separately.

Future perspectives

Our study also shows that there have only been a limited number of studies published after the present data on pediatric bipolar disorder and anxiety disorder comorbidity. Much of the current literature is also composed of studies with very small sample sizes. It is apparent that more research is needed in this area. Compared with the number of studies on adult bipolar disorder patients, differential diagnosis in pediatric samples is very difficult and prospective studies for the stability of anxiety disorder and bipolar disorder diagnosis are highly needed.

Recognition of anxiety disorder comorbidity with mood disorders could have a significant importance, as depressive episodes of bipolar disorder may have higher anxiety disorder comorbidity and this may assist in forecasting future bipolar disorder in pediatric patients with depressive episode (59). Also, considering the high comorbidity of AD with PBD and limited treatment options when comorbidity is recognized, we suggest that psychosocial treatments for anxiety in this group should be investigated further. Lastly, studies following the trajectory of childhood symptoms up into adulthood and future predictive neurobiological correlates are needed.

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Conflict of Interest

None.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of the characteristics of the 37 studies included in the analysis.
Table S2. The reference list of articles used for the calculation of each variable in meta-regression analysis.