Updated Meta-Analysis of Epidemiologic Studies of Pediatric Bipolar Disorder

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ABSTRACT

Objective: Research on pediatric bipolar disorder (PBD) has grown substantially in the past 7 years; updating a 2011 meta-analysis of PBD prevalence could improve understanding of factors that influence prevalence.

Data Sources: A literature review of papers published in English was updated in 2018 using PubMed and PsycINFO. Search terms included *pediatric, child, "bipolar disorder," bipolar, mania, prevalence, epidemiology, community, adolescent,* and *youth*.

Study Selection: Inclusion criteria were (1) youth epidemiologic sample, (2) number of youth with bipolar spectrum disorders reported, and (3) prevalence rates for youth differentiated from prevalence for those over age 21 years (if both included). Of 2,400 articles retrieved, 44 were evaluated and 8 new were included.

Data Extraction: Prevalence rates for each bipolar subtype were recorded as reported; hypothesized moderators (eg, study characteristics, environmental factors) were also coded.

Results: Eight additional studies resulted in a total sample of 19 studies, tripling the sample size to N = 56,103 and n = 1,383 with bipolar disorder. Seven studies were from the United States, and 12 were from South America, Central America, or Europe. Weighted average prevalence of bipolar spectrum disorders was 3.9% (95% CI, 2.6%–5.8%). There was significant heterogeneity across studies ($Q = 759.82$, $df = 32$, $P < .0005$). The pooled rate of bipolar I was 0.6% (95% CI, 0.3%–1.2%); these rates were also heterogeneous ($Q = 154.27$, $df = 13$, $P < .0001$). Predictors of higher bipolar spectrum disorder prevalence were the use of broad bipolar criteria ($P < .0001$), older minimum age ($P = .005$), and lifetime prevalence ($P = .002$). Newer studies were associated with *lower* rates ($P < .0001$).

Conclusions: The updated meta-analysis confirms that rates of bipolar spectrum disorders are not higher in the United States than in other Western countries, nor are rates increasing over time. Nonstandard diagnostic criteria result in highly variable prevalence rates, as does focusing on narrow definitions of PBD to the exclusion of the full spectrum. Consistent application of validated criteria could help to settle questions regarding PBD prevalence. Studies from non-Western countries are needed to refine understanding of international prevalence and risk factors.

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The field of pediatric bipolar disorder (PBD) has weathered significant debate on topics ranging from the validity of the diagnosis itself[1] to concern about perceived differences in diagnostic practices internationally.[2] Through the early 21st century, relatively little was written about PBD, with 99 publications per year, on average, between 1980 and 2000 (PubMed query December 28, 2018). Since then, interest in this diagnosis has grown (more than 300 publications per year, on average, since 2001), with a number of studies investigating the phenomenology,[3,4] course,[5,6] and treatment[7–9] of bipolar disorder in youth. The resulting accumulation of knowledge has helped resolve some issues in the field[10] but has also led to new questions, particularly regarding presentations of subclinical manic symptoms.[11,12]

One of the main points of debate regarding PBD has been due to conflicting reports regarding the prevalence of the illness. A report by Moreno et al[13] indicated a 40-fold increase in outpatient diagnoses of PBD in the preceding decade; naturally, this caused concern, but also speculation (particularly in the popular press) that the diagnosis was not valid or that clinicians—perhaps under the influence of "Big Pharma"—were overdiagnosing the illness.[14,15] A related issue has been the perception that PBD is primarily an "American problem"[16] and that, rather than differences in training and diagnostic practices,[2,17] there might be environmental[18,19] or biological[20] reasons for higher prevalence rates in the United States.

In response to the contentious questions regarding increasing prevalence over time and differences in the prevalence of PBD due to geography, a previous meta-analysis of epidemiologic studies of PBD[21] found a weighted prevalence rate of 1.8% for bipolar spectrum disorders (mixing PBD subtypes), with no differences internationally and no difference based on year of data collection, after accounting for other moderator variables. Although rates internationally were largely consistent, the rates between individual studies were highly heterogeneous; in addition to geographic location (United States yes/no) and year of data collection, other hypothesized moderators were tested, including use of strict *DSM*/*ICD* diagnostic criteria, quality of the reporting, range of participant ages, the type of interview used, quality of study design for assessing bipolar diagnosis, whether both caregiver and child were interviewed, and whether the rater was a clinician. In multivariate meta-regression models, sample minimum age (younger samples had lower prevalence) and the use of broad, non-*DSM* criteria (higher prevalence) were the only sample characteristics significantly associated with

Clinical Points

- The prevalence of pediatric bipolar disorder in the community has been relatively constant over time.
- The prevalence of pediatric bipolar disorder is not higher in the United States than it is in other countries.
- Knowledge about the community prevalence of pediatric bipolar disorder is limited by the lack of studies from non-Western countries, the inconsistency in measurement across studies, and the small number of studies that include prepubescent youth.

prevalence. Higher quality of study reporting, based on the Strengthening the Reporting of Observational Studies in Epidemiology guidelines,[22] also predicted higher prevalence rates, after controlling for broad criteria and minimum age.

Due to the relatively small number of studies in the previous meta-analysis, it was not possible to explore moderators related to location or culture. For example, there is evidence that diet may be related to risk for mood disorders, which could explain why the prevalence of bipolar disorder in adults is higher, on average, in Western countries[23]; sugar is associated with risk for depression,[24] possibly due to its contribution to obesity, which is also associated with mood disorders.[25] Diet can also be protective; high consumption of omega-3 fatty acids is thought to reduce risk for bipolar disorder[19] and may explain the lower rates of mania among adults in some Asian countries.[23] Additionally, the results from several small trials evaluating the efficacy of nutritional supplements, including omega-3 fatty acids[26–33] and micronutrients,[34–36] suggest that these may be helpful augmentative therapies for mood disorders. There is also evidence that light exposure impacts circadian function[37,38] and can influence risk for bipolar disorder; as such, prevalence rates may be higher in northern countries with very long summer days[39,40] and in places with large urban populations, where exposure to artificial light is high.[41] Gross domestic product (GDP) offers a consistently measured index of economic development.[42,43] If evidence of these location/cultural moderators were found in epidemiologic studies, it would help to validate the associations previously made in clinical samples and could inform the development of interventions designed to limit risk or to promote protective factors. Observations of epidemiologic differences in the rate of mood disorders helped launch inquiry into the possible role of omega-3 fatty acids,[44] and other studies have worked in the opposite direction, identifying geographical correlates between suicide rate and lithium levels in drinking water, for example.[45]

In the time since the original meta-analysis was published, the number of epidemiologic studies of PBD has increased by 50%, and the number of youth represented has tripled. Additionally, as the diagnosis has gained acceptance, more professionals have experience with it and diagnostic criteria may be more routinely applied, which could lead to prevalence rates becoming more homogeneous. One of the limitations of the previous report was that a quarter of the included studies used criteria that were "off-label" from *DSM* or *ICD*; 2[46,47] of these included youth who did not meet the duration or severity criteria, and 1[48] used a stricter definition requiring full criteria for mania and that the youth "needed treatment" based on evaluation by 2 independent raters. Adding newer studies with strict *DSM*/*ICD*-based diagnoses and higher quality reporting could yield more homogeneous estimates, in turn imparting greater confidence to the weighted average prevalence.

The goal of this meta-analysis was to update the literature on epidemiologic rates of PBD. We hypothesized that the prevalence rates reported by more recent studies (since 2000) would be more homogeneous compared with earlier studies, reflecting the growing consensus in the field and refinement in epidemiologic methodology. Additionally, we expected to find that samples with an older minimum age would have higher rates, that the use of broad criteria would yield higher rates, that there would be no difference in rates between the United States and other countries, that the rate would be stable over time, and that informant (parent, child, or both) would not affect prevalence. We expected that studies reporting lifetime estimates would have higher rates than studies with shorter reference periods. We also tested whether certain environmental factors, hypothesized to be related to health outcomes, affected rates. These included per capita sugar consumption—associated with obesity and putatively playing a direct role in metabolic pathways contributing to mood problems,[24] percent of population living in urban areas,[41] GDP per capita—a measure of national development,[42,43] absolute value of latitude—indicating seasonal fluctuations in light exposure with potential sleep and mood effects,[39,40] obesity rate—a direct measure of metabolic outcomes,[49] and fish consumption per capita.[19]

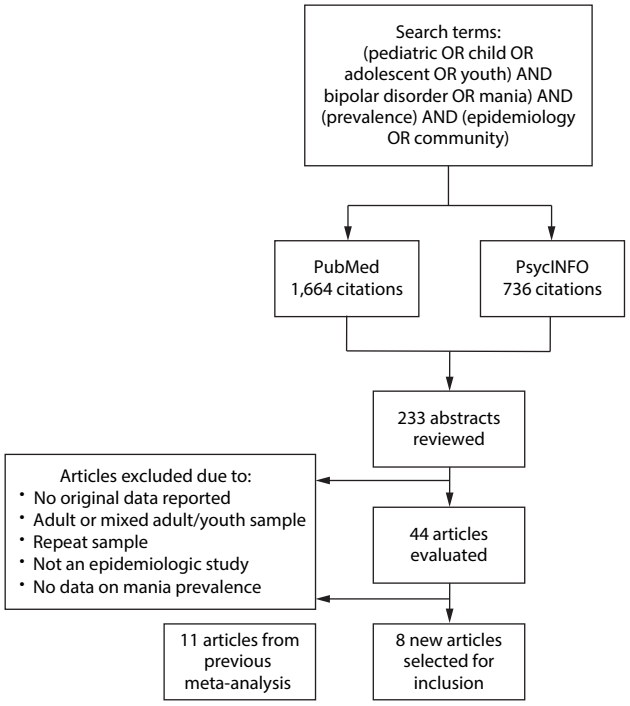
METHODS

The literature review was updated in December 2018 and was conducted using PubMed and PsycINFO.[21] Search terms included *pediatric, child, "bipolar disorder," bipolar, mania, prevalence, epidemiology, community, adolescent,* and *youth*. Additionally, reference lists were checked and a search was done to look at published studies that cited the 2011 meta-analysis.

The searches yielded over 2,000 articles. Of these, 233 abstracts were read, and 44 articles were selected for closer examination. Eight new studies met the inclusion criteria of (1) epidemiologic sample, (2) number of youth with bipolar spectrum disorders reported, and (3) prevalence rates for youth differentiated from prevalence for those over 21 (if both included); see Figure 1.

Prevalence rates for all new studies were coded; rates were coded separately for bipolar spectrum (bipolar I, bipolar II, cyclothymic disorder, and bipolar not otherwise specified [NOS]), bipolar I, and undifferentiated bipolar I and II (12 studies reported results in a way that precluded differentiating bipolar I and II, eg, combining manic and

Figure 1. Study Selection Process



hypomanic episodes). Additionally, potential moderator variables were coded, including the year(s) of data collection, geographic location of the study, informant interviewed (parent, child, or both), age range (minimum at time of assessment), whether diagnostic criteria were applied as defined by *DSM*/*ICD*, and whether lifetime or some other prevalence period was reported.

The environment-related moderator variables were drawn from gapminder.org/data to match the country and year of data collection for each sample. Gapminder anthologizes data from the World Bank, World Health Organization, and other international sources (technical details available at www.gapminder.org/).

All analyses were performed using the metafor package 2.0 in R (version 3.3.2).[50] Prevalence rates were transformed using logit transformation[51] with inverse variance weighting. Random effects models estimated the average weighted prevalence for the bipolar spectrum, bipolar I, and undifferentiated bipolar I and II separately.

Additionally, we used multivariate parameterization[52,53] to test whether including multiple effect sizes from individual studies would affect prevalence. For example, some studies report prevalence for bipolar I disorder as well as bipolar disorder NOS. If these 2 rates used nonoverlapping cases, they could be summed to create a total N for bipolar cases, but the rates for more inclusive definitions typically included the bipolar I cases again. Other studies contribute only 1 rate, which could be for bipolar I disorder or bipolar disorder NOS or all subtypes (ie, bipolar I and II, cyclothymic disorder, and bipolar NOS combined). Additionally, we estimated prevalence rates for bipolar subtypes separately, rather than combining all effect sizes, allowing the heterogeneity within each subtype to be different.[53] These are technical advances on our prior study.

Each hypothesized moderator was evaluated individually; those that were significant were included in a mixed-effects model with multivariate parameterization. Hypothesized moderators of prevalence rate included year of data collection, whether the sample was from the United States, informant, minimum age, whether diagnostic criteria were applied as written in the *DSM*/*ICD* or were more loosely interpreted (broad criteria), and whether rates were lifetime estimates. Models testing hypothesized environmental factors controlled for the significant design variables.

RESULTS

The 8 new studies[54–61] represent 31,140 youth, including 422 youth with bipolar disorder. The total meta-analysis sample now includes 19 studies* with 56,103 youth, 1,383 of whom met criteria for bipolar spectrum disorders[46,47,54,56–58,60–71] (see Table 1).

The weighted average prevalence rate of bipolar spectrum disorders was 3.9% (95% CI, 2.6%–5.8%). Although this rate is higher than the prevalence rate reported in the original meta-analysis, the confidence intervals overlap (1.8% prior weighted average; 95% CI, 1.1%–3.0%). In addition, the previous meta-analysis combined rates of bipolar I, bipolar II, and bipolar NOS to estimate an average prevalence rate; the rate of 3.9% estimates the rate of bipolar spectrum disorders, not a mix of definitions. We compared model fit between a model including separate random effects for each PBD subtype versus with a single, shared random variance estimate; the model allowing for heterogeneity between subtypes and between studies fit better (likelihood ratio test = 180.50, $P < .0001$). There was significant heterogeneity across studies ($Q_E = 759.82$, $df = 32$, $P < .0005$), even after accounting for variance due to subtype, which was also significant ($Q_M = 103.16$, $df = 2$, $P < .00005$; the bipolar spectrum disorder rate was significantly higher than the rate of bipolar I); see Figure 2.

In addition to bipolar subtype, other moderators of prevalence included year of data collection (newer studies had lower rates; $P < .0001$); the use of broad, non-*DSM*/*ICD* criteria (higher rates; $P < .0001$); age (older minimum age associated with higher rates; $P = .005$); and lifetime rates (higher, $P = .002$). When we included each of these moderators, along with bipolar subtype in a multivariate model, the moderators accounted for a significant portion of variance ($Q_M = 243.24$, $df = 6$, $P < .0001$). Only use of broad criteria ($P = .026$) and lifetime rates ($P = .003$) remained significant at the individual level. Significant heterogeneity in

*The previous meta-analysis included 1 study (Kim-Cohen et al[62]) that we decided not to retain because the pediatric bipolar disorder rate was based on retrospective report about childhood onset using interviews with adults; thus, the retrospective period varied in length and typically spanned decades.

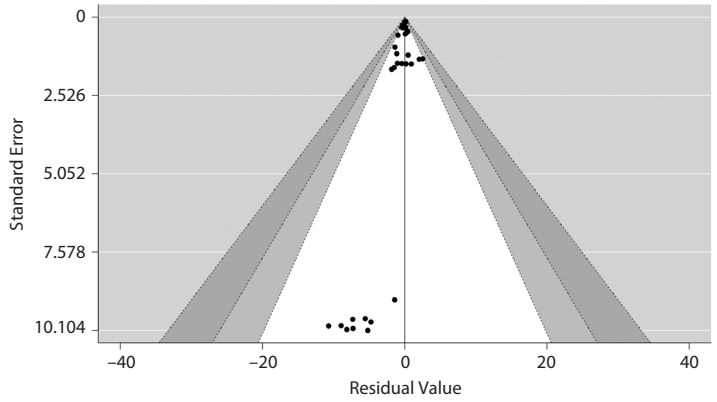
Table 1. Studies Included in the Updated Meta-Analysis

	Year of Data Collection	Country	Bipolar I, %	Undifferentiated Bipolar I and II, %	Bipolar Spectrum, %	Total N	Diagnostic Criteria	Interview	Subtypes Included	Informant	Percent Male	Age Range, y	Lifetime Rate
Non-US Studies													
Anselmi et al, 2010[54]	2004	Brazil	0	…	…	4,448	*DSM-IV* or *ICD-10*	DAWBA	Mania	Youth and caregiver	50	11–12	No
Benjet et al, 2009[67a]	2005	Mexico	2.0	…	2.5	3,005	*DSM-IV*	CIDI	Bipolar I, spectrum	Youth	48	12–17	No
Canals et al, 1997[65a]	1994	Spain	…	0[b]	…	290	*DSM-III-R*	SCAN	Hypomania	Youth	48	17–18	No
Kozloff et al, 2010[57]	2002	Canada	2.0	…	…	1,360	*DSM-IV*	CIDI	Mania	Youth	44	15–18	Yes
Lynch et al, 2006[66a]	2002	Ireland	0	0	0	723	*DSM-IV*	KSADS	Mania, hypomania, cyclothymia	Youth and caregiver	47	12–15	Yes
Pääre n et al, 2013[71]	1992	Sweden	0.04	…	4.0	2,300	*DSM-III-R*	DICA	Bipolar I, spectrum	Youth	47	16–17	Yes
Pan et al, 2014[56]	2010	Brazil	…	0.2	1.8	2,503	*DSM-IV*	DAWBA	Bipolar I/II, NOS	Youth	53	6–12	Yes
Stringaris et al, 2010[68a]	2004	UK	…	0.1	1.2[c]	5,247	*DSM-IV*	DAWBA	Bipolar I/II, NOS	Youth and caregiver	50	8–19	No
Tijssen et al, 2010[58]	1994	Germany	…	2.7	14.3	1,395	*DSM-IV*[d]	DICA	Bipolar I/II, spectrum	Youth	53	14–17	Yes
Verhulst et al, 1997[64a]	1993	The Netherlands	1.2[e]	1.2[e]	…	780	*DSM-III-R*	DISC	Mania, hypomania	Youth and caregiver	…	13–18	No
Vizard et al, 2018[60]	2017	UK	0.1	…	…	9,117	*ICD-10*	DAWBA	Mania	Youth	…	5–19	Yes
Karacetin et al, 2018[61]	2014	Turkey	0	0	0	5,842	*DSM-IV*	KSADS	Bipolar spectrum	Caregiver	52	8–10	Yes
US Studies													
Andrade et al, 2005[63a]	1994		…	1.5	…	611	*DSM-III-R*	DISC	Mania-hypomania	Youth	47	13–21	Yes
Costello et al, 1996[70a]	1994		0	0.1	…	1,015	*DSM-III-R*	CAPA	Mania, hypomania	Youth and caregiver	…	9–13	No
Gould et al, 1998[69a]	1996		1.2	…	…	1,285	*DSM-III-R*	DISC	Mania	Youth and caregiver	53	7–18	No
Kashani et al, 1987[48a]	1986		0.7	…	…	150	*DSM-III*	DICA	Mania[f]	Youth and caregiver	50	14–16	Yes
Kessler et al, 2009[47a]	2003		0.5	2.3	6.6	10,148	*DSM-IV*[d]	CIDI	Bipolar I, II, NOS	Youth and caregiver	…	13–17	Yes
Lewinsohn et al, 1995[46a]	1988		0.1	0.8	6.7	1,709	*DSM-III-R*[d]	KSADS	Bipolar I, II, spectrum	Youth	46	14–18	Yes
Roberts et al, 2007[59]	2000		0.4	1.2	…	4,175	*DSM-IV*	DISC	Mania, hypomania	Youth	51	11–17	No

[a]Included in the original meta-analysis.
[b]Canals et al reported rates separately based on *DSM-II-R* and *ICD-10* criteria. To be more consistent with other studies, we chose to include the rate associated with *DSM* . The *ICD-10* rate was 2.4%.
[c]Stringaris et al reported rates separately for parent and youth report. We chose to include the parent-reported rate. The youth-reported rate was 1.7%.
[d]Broad, non-*DSM*/*ICD* criteria used.
[e]Verhulst et al reported rates separately for parent and youth report. We chose to include the parent-reported rate. The youth-reported rate was 1.8%.
[f]Kashani et al used narrow criteria, requiring treatment-seeking for a diagnosis of mania.
Abbreviations: CAPA = Child and Adolescent Psychiatric Assessment, CIDI = Composite International Diagnostic Interview, DAWBA = Development and Well-Being Assessment, DICA = Diagnostic Interview for Children and Adolescents , DISC = Diagnostic Interview Schedule for Children, KSADS = Kiddie Schedule for Affective Disorders and Schizophrenia, NOS = not otherwise specified, SCAN = Schedules for Clinical Assessment in Neuropsychiatry.
Symbol: … = not reported.

Figure 2. Forest Plot of Prevalence by Bipolar Subtype, Sorted by Location and Year of Publication

Figure 3. Funnel Plot Indicating Bias for Lower Prevalence Rates in Larger Samples



prevalence remained ($Q_E = 371.59$, $df = 28$, $P < .0001$) (Supplementary Table 1).

Our hypothesis that studies conducted after 2000 would yield more homogeneous rates was not supported; the 20 effect sizes from studies conducted after 2000 were more heterogeneous ($Q_E = 508.87$, $df = 17$, $P < .0001$) than the 15 effect sizes from studies conducted before 2000 ($Q_E = 154.92$, $df = 12$, $P < .0001$). Relatedly, the average bipolar spectrum rate from studies conducted after 2000 was lower than the rate from studies conducted before 2000.

We opted to further explore how the other significant moderators affected prevalence rates; the studies that used broad criteria ($k = 3$) had an average bipolar spectrum rate of 8.6% (95% CI, 5.2%–14.1%), whereas those that did not use broad criteria ($k = 16$) had an average bipolar spectrum rate of 2.6% (95% CI, 2.0%–3.3%). Older minimum sample age was also associated with higher rates; studies with a minimum sample age over 12 years ($k = 9$) had a bipolar spectrum disorder rate of 8.3% (95% CI, 5.8%–11.8%), whereas studies with a minimum age of 12 or younger ($k = 10$) had an average bipolar spectrum disorder rate of 1.7% (95% CI, 1.3%–2.3%). The 11 studies that reported lifetime prevalence rates had a bipolar spectrum disorder rate of 6.4% (95% CI, 3.9%–10.3%), and studies that reported on a shorter time period had an average prevalence of 1.7% (95% CI, 1.1%–2.8%).

Fourteen studies reported on the rate of bipolar I disorder. Of these, 4 reported zero cases, and 3 reported just 1 or 2 cases. The pooled rate of bipolar I was 0.6% (95% CI, 0.3%–1.2%). These rates were also heterogeneous ($Q = 154.27$, $df = 13$, $P < .0001$). Mixed-effects models investigated whether any of the hypothesized moderator variables influenced rates of bipolar I disorder; none of the individual variables were significant, nor did the set of moderators explain variance in the rates of bipolar I disorder ($Q_M = 4.35$, $df = 6$, $P = .630$) (Supplementary Table 2).

The rate for undifferentiated bipolar I and II (reported by 12 studies) was 0.7% (95% CI, 0.4%–1.3%); rates were heterogeneous across studies ($Q = 122.91$, $df = 11$, $P < .0001$). Older minimum age was associated with higher rates ($P < .0001$) in a single predictor model. When all of the design moderators were included as a set, they explained the bulk of the heterogeneity in rates ($Q_M = 115.89$, $df = 6$, $P < .0001$) (residual heterogeneity $Q_E = 7.02$, $df = 5$, $P = .219$) (Supplementary Table 3).

We also tested whether the effects of design variables differed significantly across the bipolar definitions; there were no significant findings.

After including the significant design moderators (year of data collection, use of broad criteria, minimum age, lifetime estimate), we evaluated the hypothesized environmental factors. Significant moderators included sugar consumption (higher rates; $P = .033$), fish consumption (lower rates; $P = .0002$), percent urban population (lower rates; $P < .0001$), and latitude (lower rates; $P = .009$). As a block, the environmental moderators were significant ($Q_M = 13.27$, $df = 6$, $P = .039$), even after controlling for design factors (Supplementary Table 4).

Funnel plots (Figure 3) and Egger test, conducted on the model including all predictors, indicated bias; larger samples reported lower-than-expected prevalence rates.

DISCUSSION

The goal of this meta-analysis was to extend previous work on the prevalence and correlates of PBD.[21] Results indicated that the prevalence rate of pediatric bipolar spectrum disorders is relatively stable; the inclusion of an additional 39,881 youth, roughly tripling the sample, resulted in a prevalence rate of 3.9% for broad bipolar spectrum disorders. Although this is higher than the result of the previous meta-analysis of 1.8%, the current study uses more advanced statistical methods that account for the fact that some studies report rates for multiple bipolar subtypes, whereas other studies may report a rate for bipolar I (or NOS) only. In the 2011 analysis, only 1 effect size from each study was included, and we did not distinguish rates for bipolar I, undifferentiated bipolar I and II, and bipolar NOS in the main analysis. This would result in an underestimate of the bipolar spectrum because most older studies did not assess for subtypes other than bipolar I or II.

Results show that epidemiologic rates of bipolar disorder are not increasing over time; in fact, more recent studies were associated with *lower* prevalence rates. The bulk of the studies gathered data more than 10 years ago (range, 1986–2009), but the newest studies[60,61] both have very low rates, suggesting that, in spite of increasing clinical diagnoses, rates in the community are not growing. It is also unlikely that rates are actually declining; Egger test suggested evidence of bias among large studies (including the most recent two). Because the bias related to sample size is confounded with year of data collection, the decrease over time should be interpreted with

caution. Finding evidence of bias is unusual in studies that report descriptive statistics, like prevalence, rather than the outcome of a clinical trial or other experiment. However, it could be related to methodology; very large studies may rely on more structured diagnostic methods and lay raters that are more likely to miss cases of PBD, resulting in a pattern of lower-than-expected rates.

Importantly, the results of this meta-analysis suggest that youth in the United States are not more likely to develop bipolar disorder than youth growing up in other countries. One of the primary drivers for doing the 2011 meta-analysis was the international perception that PBD was a creation from the United States—or perhaps that cultural or parenting practices were leading to a generation of out-of-control youth.[16,18] Youth in the United States do not appear to be at higher risk for the development of bipolar disorder. However, there is some evidence from other studies that very early onset is more likely among youth in the United States,[72] and because the majority of youth represented in this study were adolescents, any differences in prevalence among prepubescent youth were not captured.

Consistent with our hypothesis, samples with older participants had significantly higher prevalence rates. Unfortunately, epidemiologic studies do not tend to report age at onset information, but this would be interesting to explore in light of evidence that there may be a bimodal pattern to onset[73,74] and that youth in the United States may be at higher risk for early onset bipolar disorder.[75–77] Relatedly, it is important to note that the typically older sample age limits our knowledge about the prevalence of bipolar disorder in school-aged children. Because early onset bipolar disorder is associated with a more severe course of illness[78] and may be distinct from adolescent onset bipolar disorder in important ways, epidemiologic studies including young children are necessary to better understand the etiology and full developmental course of bipolar disorder.

Environmental Factors Potentially Associated With Rates

We tested 6 potential environmental factors as predictors of bipolar rates. When tested as single predictors after controlling for significant design variables, 4 were significant. As hypothesized, more fish consumption predicted lower rates, and more sugar consumption predicted higher rates. However, higher urbanization and more extreme latitude predicted significantly lower rates, which was the opposite of expectations. GDP and life expectancy were not associated with rates. None of the environmental variables showed incremental significance in an augmented model entering all of them as a set. These should be interpreted cautiously given the modest statistical power, unexpected results, and gaps in sampling. Unfortunately, there are no non-Western cultures represented in our sample, likely restricting the range observed in the putative risk factors and predictors. The fact that sugar and fish consumption were the 2 environmental variables that were consistent with our hypotheses reinforces this point; as globalization spreads, there are fewer differences in the diet and health of people internationally. This may be especially true among youth who, arguably, are growing up in societies more similar across cohorts than those of their parents. In a recent meta-analysis of the prevalence of bipolar disorder among adults,[23] the rates were significantly lower in Asian and African countries. It is important to extend our knowledge of the prevalence of PBD to include Asia and Africa; if there are differences, and these can be explained by environmental factors, it could lead to the development of interventions to help prevent the onset of bipolar disorder.[36]

The fact that greater urban population and higher latitude were associated with lower rates was surprising. There was relatively little variability in the percent of the population living in urban areas (73%–93%) among the studies, and using 1 rate does not accurately capture variability within geographic locations. It may also be that some of the factors thought to drive the higher prevalence of mental health disorders in urban areas (eg, availability of mental health services) influence youth less than adults. Similarly, whereas adults may be susceptible to the effects of long daylight hours at higher latitudes, youth, whose daily schedules tend to be more tightly regulated, may be somewhat protected from the expected circadian disruption. Additionally, the intensity of sun exposure is somewhat independent of daylight hours and may be a stronger driver of circadian function.[39] It also is possible that these are spurious effects due to the ecological fallacy, which can reverse the sign of relationships at the aggregate level.[79]

Effects of Diagnostic Criteria

The rate of bipolar I disorder (0.6%) is lower than the rate reported in the 2011 meta-analysis (1.2%); of the 8 new studies, 6 reported bipolar I separately.[54,55,57,59,60,61] Together, these studies contributed over 27,000 participants, but only 53 cases of bipolar I. Because these are large samples, they carry a strong influence on the weighted average. The rates of bipolar I must also be considered in a developmental context; many youth who initially have subthreshold manic symptoms will go on to develop bipolar I.[6,12] As the youth in these cohorts age, a substantial number may develop a manic episode. This would be consistent with our finding that rates of bipolar spectrum disorders increase through adolescence, with the highest rates found in samples with an older minimum age.

None of the hypothesized moderators of rates of bipolar I were significant, and only age moderated rates of undifferentiated bipolar I and II. This may be related to the relatively small number of studies reporting on bipolar I; with only 13 studies, nearly half of which had rates near zero, important methodological differences might be obscured. It is also important to note that some methodological differences cannot be easily measured. For example, although we coded for the use of structured interviews (all studies reported using one to make diagnoses), diagnostic criteria are not uniformly applied.[80,81] Asking the same questions will not lead to the same diagnoses if participants' responses

are interpreted through different filters. Clinicians' training and work setting will influence their diagnostic decision making,[2] and in the case of interviewers working on epidemiologic studies, heuristics are likely to impact how they interpret responses.[82,83] Unfortunately, data on these factors are not typically reported and, consequently, cannot be meta-analyzed. Relatedly, epidemiologic studies tend to rely on structured diagnostic interviews, administered by lay raters—or even by computer—and although this is a practical approach for studies recruiting hundreds or thousands of people, bipolar disorder is challenging to diagnose, and the skip-outs and rigid questions typical of fully structured interviews are likely to misdiagnose some people.[84]

Diagnostic criteria change over time, which can influence prevalence rates. We are aware of only 1 epidemiologic study[60] that used *DSM-5* criteria; although the changes from *DSM-IV-TR* were minimal, the new criterion requiring a change in energy could affect rates.[85] However, we would not expect the introduction of disruptive mood dysregulation disorder to affect the prevalence of PBD in epidemiologic studies: although this diagnosis was introduced to help correct for the perceived overdiagnosis of pediatric bipolar disorder in clinical settings,[86] manic symptoms persisting more than a few hours a day are an exclusion criterion,[87] so youth who had adequate manic symptoms to meet criteria for bipolar disorder on a structured interview should not be eligible for a diagnosis of disruptive mood dysregulation disorder.

Not all studies used *DSM*/*ICD* criteria, which significantly influenced results; broad, non-*DSM*/*ICD* criteria were associated with prevalence estimates nearly 4 times higher than those that adhered to *DSM*/*ICD* criteria. As the field shifts toward a transdiagnostic approach to mental illness,[88] the boundaries between diagnoses are likely to become hazier. Many of the youth with manic symptoms that do not meet criteria for hypomania or mania may never meet *DSM*/*ICD* criteria for bipolar disorder[89] and may not benefit from the same interventions. Distinguishing between clinical cases and those at risk or with subclinical symptoms is important to understanding the societal consequences of these related, but distinct, categories. Furthermore, in order for meta-analysis to be a valuable tool for measuring patterns across time, geography, and development, it is essential that investigators use agreed upon tools and criteria. This does not preclude the addition of other broader groups, but, ultimately, we must have some way of separating the apples from the oranges.[90] In this updated meta-analysis, we used a more sophisticated analytic approach that allowed us to estimate rates for bipolar I, undifferentiated bipolar I and II, and bipolar spectrum separately while also accounting for the nesting of effect sizes within study. However, this is not a substitute for collecting complete diagnostic information from participants in a consistent way.

Effects of Other Study Design Features

As epidemiologists would predict, lifetime estimates tended to be higher than estimates based on shorter reference intervals. We included informant (child alone or caregiver combined with youth) as a potential moderator (NS), but this variable is also likely to be confounded with the age of the sample. Because the majority of samples included only adolescents, differences in how symptoms are interpreted by different informants across development might be obscured. Youth may not consider some behaviors concerning or inappropriate, and caregivers might be unaware of depressed mood or hallucinations that a youth is experiencing.[91] It is possible that this affects rates less in adolescents—who are, arguably, better able to articulate their symptoms than young children. How divergent reports are reconciled has implications for both research and clinical diagnoses. Clinical guidelines recommend interviewing both the youth and the caregiver when possible, then addressing discrepancies in their reports to arrive at a diagnosis that incorporates both perspectives.[92] In cases when only 1 informant is interviewed, whether by necessity or for time/resource reasons, there are likely to be differences not only in the rates reported, but also in the specific individuals who are diagnosed, which will influence sample composition. For example, in the study by Stringaris et al,[68] the prevalence rate was 1.7% according to youth report and was 1.2% according to caregiver report. The κ between caregiver and youth was 0.02, suggesting almost no overlap in the individuals identified as having bipolar disorder (κ for bipolar diagnoses is typically low, ~0.1 among clinicians in a meta-analysis[93]). Similarly, in the Verhulst et al[64] article, rates were reported separately for youth and caregivers, with much higher rates of hypomania reported by youth (0.9% vs 0%), and, although rates of mania were similar (1.1% caregiver, 0.9% youth), the authors report there was "little overlap" between the two groups. Given evidence that caregivers are better at distinguishing symptoms of mania than youth,[94] we chose to include the parent-reported rate in both instances. However, best practice guidelines suggest integrating information from multiple informants.[92] Although resource constraints make it understandable that epidemiologic studies, which tend to be much larger than clinical studies, would interview just 1 informant, doing so comes at significant cost to the validity of the diagnostic findings. Relatedly, the reliance on fully structured diagnostic interviews, common in epidemiologic studies, is likely to result in many people being misdiagnosed; bipolar disorder is challenging to diagnose and clinical judgment is often necessary to establish episodicity and impairment, both of which are important to accurate diagnosis.[84,95] This may be a factor in the bias we found for larger studies to report lower-than-expected prevalence rates.

Limitations

A meta-analysis can be only as good as the data that go into it. Many of the limitations of this study are elaborated above, including the lack of samples from non-Western countries, the relatively old age of most samples, and the lack of variability in some of the constructs we

hypothesized as moderators. Even in the multivariate model with multiple moderators included, significant heterogeneity remained in the rates of PBD. Important factors were not reported in enough detail to be included as moderators, such as how interviewers were trained to interpret participants' responses, diagnostic reliability across raters, whether PBD was an a priori focus of the study, rates of comorbid diagnoses, and information about treatment-seeking. Unfortunately, these variables are rarely reported in community studies, the focus of which tends to be less clinically oriented. We cannot evaluate what was not reported, but our results make clear that there are significant, unmeasured, factors at play. Relatedly, our analyses suggested that larger samples were biased toward reporting lower prevalence rates; because larger studies are weighted more heavily, this likely means that our results are an underestimate of the true prevalence of PBD.

CONCLUSION

This update of an earlier meta-analysis of the prevalence of PBD now includes data from over 50,000 youth. Importantly, the results were consistent with the previous report: the rates of bipolar disorder are not increasing among youth, and the rate is not higher in the United States than the rest of the world. In addition to the inclusion of 3 times as many youth, this update has other strengths; the use of meta-regression with multivariate parameterization allowed us to include nested effect sizes within the same model and to estimate the rates for different subtypes of PBD.[52,53] Additionally, we explored environmental factors that we hypothesized would be related to mental health and to bipolar disorder specifically. Our results reflect increasing globalization in terms of environment but also suggest that significant differences remain in terms of how psychopathology is conceptualized across research groups. To better understand how environment affects risk for bipolar disorder, particularly outside Europe and the Americas, epidemiologic studies from non-Western countries are needed (cf Moreira et al[23]). Despite evidence from clinical studies that prepubescent youth can develop mania (eg, Pan et al,[56] Geller et al,[96] Van Meter et al[97]), most epidemiologic studies focus on adolescents; new studies that include both school-aged children and adolescents are needed to answer questions related to age at onset and could help clarify questions related to diagnostic progression (eg, is hypomania more prevalent in younger children youth and mania more common in adolescents?). Finally, future epidemiologic studies across cultures should use consistent definitions and evaluation methods, not only because it will facilitate more reliable estimates from future meta-analyses, but also because it will provide clearer answers to questions of risk and resilience, enabling more informed efforts to ameliorate the significant consequences of this illness.

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Supplementary Material

Article Title: Updated Meta-Analysis of Epidemiologic Studies of Pediatric Bipolar Disorder

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List of Supplementary Material for the article

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Supplementary Table 1.

Results of the univariate and multivariate mixed meta regression models predicting bipolar spectrum

	Incremental coefficient	Test of moderator significance	Augmented model coefficient	Test of moderator significance
Bipolar I & II (reference Bipolar I)	0.23	0.14	0.29	$Q_M(2)= 72.16^{***}$
Bipolar Spectrum (reference Bipolar I)	2.00^{***}	12.61^{***}	2.00^{***}	
Year of data collection	-0.10^{***}	27.97^{***}	-0.05^{**}	$Q_M(4)= 58.51^{***}$
Use of broad criteria	1.40^{***}	17.48^{***}	0.65^{*}	
Minimum age	0.17^{**}	7.82^{**}	0.04	
Lifetime rate	1.30^{**}	9.63^{**}	0.58	
From the United States	0.05	0.05	-	-
Informant (caregiver & youth)	-0.38	1.99	-	-

Note. Incremental coefficient models test the effect of each moderator controlling only for the bipolar definitions; the augmented model coefficients are the effect of each moderator in a model using block entry, with the 4 *df* testing the effect of the four predictors as a set.
$^{*}p<.05$, $^{**}p<.005$, $^{***}p<.0005$, two-tailed.

SupplementaryTable 2.

Results of the univariate and multivariate meta regression models predicting bipolar I

	Single predictor coefficient	Test of moderator significance	Augmented model coefficient	Test of moderator significance
Year of data collection	-0.01	0.02	0.06	$Q_M(6)=4.35$
Use of broad criteria	-0.76	0.56	-0.41	
Minimum age	0.05	0.13	0.25	
Lifetime rate	-1.22	2.67	-1.72	
From the United States	-0.14	0.03	-0.3	
Informant (caregiver & youth)	0.44	0.23	1.43	

Note. Single predictor coefficient models test the effect of each moderator by itself; the augmented model coefficients are the effect of each moderator in a model using block entry, with the 6 *df* testing the effect of the four predictors as a set.
$^{*}p<.05$, $^{**}p<.005$, $^{***}p<.0005$, two-tailed.

Supplementary Table 3.

Results of the univariate and multivariate meta regression models predicting undifferentiated bipolar I & II

	Single predictor coefficient	Test of moderator significance	Augmented model coefficient	Test of moderator significance
Year of data collection	-0.07	1.35	0.19***	$Q_M(6)=115.89^{***}$
Use of broad criteria	1.29	3.24	-0.26	
Minimum age	0.34***	17.67***	.75***	
Lifetime rate	0.92	1.41	0.01	
From the United States	0.6	0.57	0.11	
Informant (caregiver & youth)	-0.07	0.004	-1.09**	

Note. Single predictor coefficient models test the effect of each moderator controlling only for the bipolar definitions; the augmented model coefficients are the effect of each moderator in a model using block entry, with the 6 *df* testing the effect of the four predictors as a set.
*$p<.05$, **$p<.005$, ***$p<.0005$, two-tailed.

Supplementary Table 4.

Results of the univariate and multivariate mixed meta regression models for environmental moderators

	Single predictor coefficient	Test of moderator significance	Augmented model coefficient	Test of moderator significance
Bipolar I & II (reference Bipolar I)	0.23	0.14	0.92*	$Q_M(2)=28.93^{**}$
Bipolar Spectrum (reference Bipolar I)	2.00***	12.61***	2.58***	
Year of data collection	-0.10***	27.97***	0.11*	
Use of broad criteria	1.40***	17.48***	-0.08	$Q_M(4)=17.50^{*}$
Minimum age	0.17**	7.82**	0.31*	
Lifetime rate	1.30**	9.63**	0.42	
Sugar consumption	0.01*	4.53*	0.03	
Fish consumption	-0.07***	14.09***	-0.02	$Q_M(4)=6.5$
Urban population	-0.16***	83.35***	-0.18	
Latitude	-0.02**	6.90**	0.02	
Obesity rate	-0.05	2.54	-	
GDP	0	0.31	-	

Note. Single predictor coefficient models test the effect of each moderator controlling only for the bipolar definitions; the augmented model coefficients are the effect of each moderator in a model using block entry, with the corresponding 2 or 4 *df* tests of effect of the predictors as a set.
*$p<.05$, **$p<.005$, ***$p<.0005$, two-tailed.