See commentary by Weissman

Review and Meta-Analysis of Epidemiologic Studies of Adult Bipolar Disorder

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ABSTRACT

Objective: To test whether rates of bipolar disorder (BD) have changed over time or vary across geographic regions after adjusting for design features meta-analyzing epidemiologic studies reporting BD prevalence in adults worldwide.

Data Sources: Searches in PubMed and PsycINFO using the terms (*epidemiology OR community OR prevalence*) *AND* (*mania OR "bipolar disorder" OR cyclothymi**) *AND adult* and backward searches from published reviews were conducted.

Study Selection: Eighty-five epidemiologic studies published in English from 1980 onward that reported prevalence rates for BD or mania for subjects ≥ 18 years old were included.

Data Extraction: We coded BD prevalence, method of data collection, diagnostic criteria, year of study, country, and quality of study design and data reporting. Meta-regression tested whether sample characteristics influenced prevalence rates using the metafor package in R.

Results: Eighty-five effect sizes, from 44 countries, from studies spanning the years 1980–2012, included 67,373 people with BD. Lifetime prevalence for BD spectrum was 1.02% (95% CI, 0.81%–1.29%). Prevalence was moderated by the inclusion of BD not otherwise specified ($P = .009$) and by geographic region; rates from Africa and Asia were less than half of those from North and South America. Rates did not change significantly over 3 decades after controlling for design features.

Conclusions: The overall prevalence rate is consistent with historical estimates, but rates vary significantly across studies. Differences in methodology contribute to the perception that rates of BD have increased over time. Rates varied markedly by geographic region, even after controlling for all other predictors. Research using consistent definitions and methods may expose specific factors that confer risk for BD.

J Clin Psychiatry 2017;78(9):e1259–e1269
https://doi.org/10.4088/JCP.16r11165

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Bipolar disorder (BD) is a leading cause of burden worldwide[1] and contributes significantly to premature death: the suicide risk in BD subjects is up to 30 times higher than the general population,[2] with 1 in 4 or 5 people attempting suicide.[3] Moreover, people with BD are at high risk for physical illness.[4–6] Comorbid psychiatric illnesses are also common, including alcohol and other substance use disorders that are likely to increase impairment and medical costs.[7–9] Obesity, heart disease, and cancer are not uniformly distributed around the world, due to both differences in biological risk, such as genetic epidemiology, and variations in diet and environmental factors. Psychiatric genetic epidemiology is revealing that some of the high risk single-nucleotide polymorphisms are relatively recent mutations not uniformly distributed around the world,[10,11] and differences in the prevalence of BD worldwide have sparked interest in omega-3 fatty acids and other nutrients as potential modifiers of risk and course.[12,13] For all these reasons, it would be valuable to compare rates of BD systematically across different regions of the world.

Rates of clinical diagnoses of BD have varied substantially over time,[14] raising questions about whether the disease is becoming more common,[14–18] versus correcting for past underdiagnosis[19] or representing a misguided bubble in diagnostic practice driven by marketing and fashion.[20] Both clinical and community studies offer important information about the prevalence of BD; the clinical prevalence of BD provides an estimate of cases sick enough—and with enough resources—to receive treatment,[21,22] whereas epidemiologic studies may offer a more accurate estimate of the true prevalence of BD, independent of treatment-seeking behavior or access to mental health care. Increasing rates of clinical diagnoses have led to interest in whether epidemiologic rates of BD have also increased, which would indicate a concerning shift in risk rather than a change in diagnostic practices. Vignette studies and ratings of recorded interviews reveal that a large amount of variance in diagnostic practices is due to differences in training and case formulation—clinicians interpret exactly the same clinical presentation as reflecting different diagnoses or substantially different severity of manic symptoms.[23,24] Differences in prevalence can also be attributed to investigators' idiosyncratic use of *DSM* or *ICD* criteria.[25,26] For example, higher rates of BD in the National Comorbidity Survey were attributed to the inclusion of cases based on irritability, rather than elated mood.[27] Thus, it is crucial to use consistent interview methods and definitions, or at least to calibrate them, before meaningful trends in clinical and/or epidemiologic prevalence can be discerned. Importantly, efforts have been made to standardize the recruitment and diagnostic methods in recent international collaborations,[3] but this remains the exception, rather than the rule.

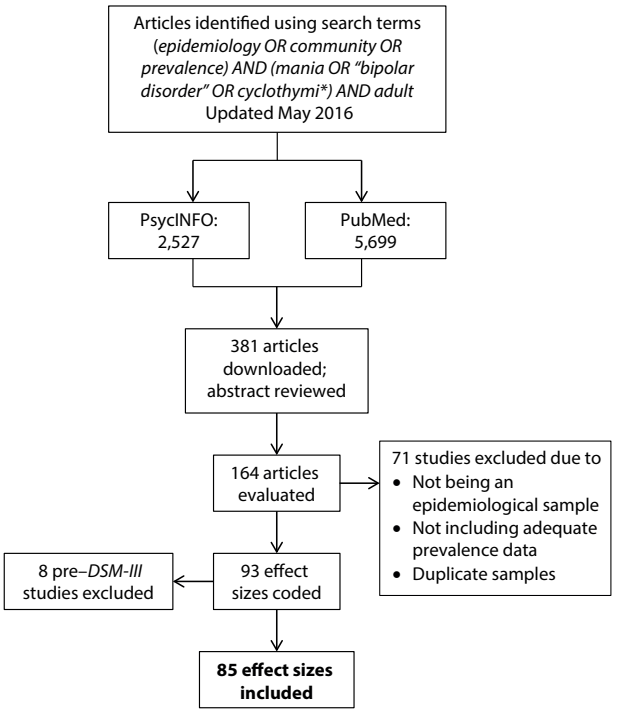
Clinical Points

- In spite of popular perception, the prevalence of bipolar spectrum disorders has not increased over time. However, the prevalence of bipolar spectrum disorders does vary significantly by geographic region.
- Research using consistent diagnostic definitions and methods is important to identify specific factors that confer risk for BD.

Although *DSM* and *ICD* have generally described rates of bipolar disorder as being fairly consistent globally, epidemiologic studies from western countries generally find rates between 1% and 4% for the bipolar spectrum,[3,28–31] whereas studies from Asian and African countries tend to be somewhat lower, ranging between 0.09%[32] and 1.26%[3] in Asia and between 0%[33] and 5.36%[34] in Africa. However, these studies were done during different decades, under the purview of different versions of nosologic criteria. Since its introduction in the second edition of the *DSM*[35] as *manic depressive illness*, the criteria and subtypes for BD have changed, meaning that a wider range of symptom presentations meet diagnostic criteria today than would have in 1968.[36,37] The number of subtypes of bipolar disorder has increased, with *DSM-III-R* moving bipolar II to the main section and *DSM-IV* adding "not otherwise specified" (NOS). NOS has been substantially more common than bipolar I in epidemiologic and clinical samples, while also amassing substantial evidence of associated impairment. Including NOS in the operational definition of BD can double or triple the estimate, confounding the timing of the study with the definition used (only more recent studies could include NOS, though not all recent studies do). The methods used to make diagnoses have also changed over time and can vary from study to study; structured clinical interviews may lead to different results than unstructured interviews or self-report measures.[38,39] Considering symptoms across the lifespan, rather than just in the past year, will also affect rates.[40] For the epidemiologic literature to address fundamental questions such as whether there are regional differences in rates of BD, or whether the rates of BD have changed over time, it is crucial to adjust for differences in methodology and definition.

Our primary aim was to determine the overall prevalence rate of bipolar spectrum disorders across adult samples, as well as specific rates for BD I, BD II, BD I and II combined, and BD NOS, for lifetime, 12 months, and other time periods. A second aim of our study was to test whether rates have changed significantly over time after adjusting for methodological factors. Another aim was to test whether there were significant regional differences in rates of BD after adjusting for definitions and methodological characteristics. Predictors of interest included (1) whether the full spectrum of BD subtypes was included in the study; (2) year of data collection, as there has been debate about secular trends increasing the rate of BD; and (3) geographic region (dummy codes with North America as the reference group). Additionally, we evaluated (1) whether the study used *DSM* or *ICD* criteria as written, because idiosyncratic criteria can narrow or expand the number of cases considered BD; (2) whether a structured interview was used—structured interviews provide both more reliable and more accurate diagnoses[38–41]; (3) whether diagnoses were based on lifetime symptoms, considering that symptoms over the whole lifespan are likely to yield higher—and arguably more accurate—estimates, given the episodic nature of BD; and (4) design and reporting quality, coded via the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist[42] scores, as studies reporting more complete information and less subject to biases may be associated with different rates.

Figure 1. Flow Diagram of Literature Search



METHODS

Search Strategy

Searches of PubMed and PsycINFO used the terms (*epidemiology OR community OR prevalence*) *AND* (*mania OR "bipolar disorder" OR cyclothymi**) *AND adult*. Reference lists from related articles and chapters were combed for other relevant studies. Epidemiologic studies published in English after 1980 (coinciding with *DSM-III*) that reported prevalence rates for BD or mania for subjects ≥ 18 years old were included. Authors made a consensus decision about any study with ambiguity about inclusion; see Figure 1. Some articles reported on more than 1 site of data collection; in such cases, all reported effect sizes (prevalence rates) were included in the meta-analysis. When more than 1 study reported on the same sample, we chose the effect size associated with the most recent and/or complete data from a given study. The search was updated May 2016.

Table 1. Studies Included in Meta-Analysis

Lead Author	Year of Publication	Year of Data Collection	Rate of Bipolar Spectrum Disorders	Total N	Location	Diagnostic Criteria	Criteria Used as Written (Y/N)	Structured Interview (Y/N)	Lifetime Rates Reported (Y/N)	Spectrum Included (Y/N)	Quality Score
Aalto-Setälä[47]	2001	1995	0.62%	647	Finland	*DSM-IV*	Yes	Yes	No[a]	Yes	59
Abou-Saleh[48]	2001	1997	0.36%	1,394	UAE	*ICD-10*	Yes	Yes	Yes	No	61
Alhasnawi[49,b]	2009	2006	0.20%	4,332	Iraq	*DSM-IV*[c]	Yes	Yes	Yes	No	58
Almeida-Filho[50,d]	1997	1991	1.10%	2,345	Brazil	*DSM-III*	No	No	Yes	No	47
Almeida-Filho[50,d]	1997	1991	1.12%	1,742	Brazil	*DSM-III*	No	No	Yes	No	47
Almeida-Filho[50,d]	1997	1991	2.99%	2,384	Brazil	*DSM-III*	No	No	Yes	No	47
Angst[51]	2005	1978–1999	3.10%	4,547	Switzerland	*DSM-IV*	No	Yes	No[e]	No	52
Ansseau[b,52]	2004	1999	1.90%	2,316	Belgium	*ICD-9*	Yes	No	Yes	No	48
Baruffol[53]	1993	1990	1.70%	235	Belgium	*DSM-III*	Yes	Yes	Yes	No	52
Beesdo[54]	2009	2005	6.59%	3,021	Germany	*DSM-IV*	Yes	Yes	Yes	Yes	50
Calvo-Perxas[55]	2015	2011	2.96%	5,068	Spain	*DSM-5*	Yes	Yes	Yes	Yes	51
Canino[56]	1987	1984	0.53%	1,513	Puerto Rico	*DSM-III*	Yes	Yes	Yes	No	59
Chen[57]	1993	1985	0.15%	7,229	Hong Kong	*DSM-III*	No	Yes	Yes	No	55
Faravelli[58]	2006	2000	5.50%	2,363	Italy	*DSM-IV*	No	Yes	Yes	Yes	53
Fassassi[59]	2014	2006	2.77%	3,719	Switzerland	*DSM-5*	Yes	Yes	Yes	Yes	62
Fekadu[60]	2004	1998	1.83%	1,691	Ethiopia	*ICD-10*	Yes	Yes	Yes	No	55
Fogarty[61]	1994	1984	0.71%	3,258	Canada	*DSM-III*	No	Yes	Yes	No	47
Fones[62,f]	1998	1992	0.59%	339	Singapore	*ICD-10*	Yes	Yes	No[g]	No	39
Ford[63]	2007	2002	0.96%	837	US	*DSM-IV*	Yes	Yes	Yes	No	58
Ghanem[64]	2009	2003	0.18%	14,640	Egypt	*DSM-IV*	No	Yes	Yes	Yes	54
Ghubash[65]	1992	1989	1.33%	300	UAE	*ICD-9*	Yes	Yes	No[h]	No	61
Grant[66]	2005	2001	3.30%	43,093	US	*DSM-IV*	Yes	Yes	Yes	No	58
Gureje[33]	2006	2002	0.00%	4,984	Nigeria	*DSM-IV*	Yes	Yes	Yes	No	60
Hsu[67]	2015	2005	0.24%	764,759	Taiwan	*ICD-9*	No	No	No[h]	No	43
Hwu[68]	1989	1984	0.36%	11,004	Taiwan	*DSM-III*	Yes	Yes	Yes	No	57
Jacobi[69]	2004	1999	1.00%	4,181	Germany	*DSM-IV*	Yes	Yes	Yes	No	56
Jaju[70,b]	2009	2005	1.01%	1,682	Oman	*DSM-IV*	Yes	Yes	Yes	No	55
Jansen[71]	2011	2006	7.46%	1,569	Brazil	*DSM-IV*	Yes	Yes	Yes	No	40
Jonas[72]	2003	1991	1.60%	7,667	US	*DSM-III*	No	Yes	Yes	No	46
Judd[25]	2003	1997	6.43%	18,252	US	*DSM-III*	Yes	Yes	Yes	Yes	42
Karam[73,b]	2008	2003	2.14%	2,857	Lebanon	*DSM-IV*	Yes	Yes	Yes	No	55
Kawakami[74]	2004	1998	0.10%	1,029	Japan	*DSM-III-R*	Yes	Yes	Yes	No	54
Kennedy[75]	2005	1999	0.25%	100,000	UK	*DSM-IV*	Yes	No	No[h]	No	56
Keqing[76]	2008	2004	0.31%	20,716	China	*DSM-IV*	Yes	Yes	Yes	Yes	56
Kessler[30]	1994	1991	1.61%	8,098	US	*DSM-III-R*	Yes	Yes	Yes	No	61
Kim-Cohen[77]	2003	1998	2.98%	973	New Zealand	*DSM-III*	Yes	Yes	No[g]	No	63
Kringlen[78,i]	2001	1995	1.60%	2,066	Norway	*DSM-III-R*	Yes	Yes	Yes	No	54
Kringlen[79,i]	2006	1998	0.20%	1,080	Norway	*DSM-III-R*	Yes	Yes	Yes	No	55
Lee[80]	1990	1984	0.41%	3,134	Korea	*DSM-III*	Yes	Yes	Yes	No	45
Levav[81]	1993	1982	0.57%	4,914	Israel	*RDC*	Yes	No	No[g]	No	56
Levinson[82]	2007	2003	0.66%	4,859	Israel	*DSM-IV*	Yes	Yes	Yes	No	56
Lewinsohn[83]	2000	1996	8.73%	893	US	*DSM-IV*	Yes	Yes	Yes	Yes	63
McConnell[84]	2002	1993	0.11%	923	Ireland	*ICD-10*	Yes	Yes	No[g]	No	55
McDonald[85]	2015	2012	1.44%	25,113	Canada	*DSM-IV*	Yes	Yes	Yes	No	41
Medina-Mora[86,b]	2005	2002	1.10%	2,362	Mexico	*DSM-IV*	Yes	Yes	No[g]	No	60
Merikangas[9,b]	2007	2002	4.40%	9,282	US	*DSM-IV*	Yes	Yes	Yes	Yes	55
Merikangas[3,b,j]	2011	2003	2.60%	4,426	Colombia	*DSM-IV*	Yes	Yes	Yes	Yes	54
Merikangas[3,b,j]	2011	2004	0.17%	2,992	India	*DSM-IV*	Yes	Yes	Yes	Yes	54
Merikangas[3,b,j]	2011	2004	0.59%	7,134	Japan	*DSM-IV*	Yes	Yes	Yes	Yes	54
Merikangas[3,b,j]	2011	2005	0.17%	5,037	Bulgaria	*DSM-IV*	Yes	Yes	Yes	Yes	54
Merikangas[3,b,j]	2011	2005	1.53%	5,318	Romania	*DSM-IV*	Yes	Yes	Yes	Yes	54
Merikangas[3,b,j]	2011	2006	1.26%	2,357	China	*DSM-IV*	Yes	Yes	Yes	Yes	54
Merikangas[3,b,j]	2011	2006	1.95%	3,417	Brazil	*DSM-IV*	Yes	Yes	Yes	Yes	54
Mitchell[87]	2004	1998	0.50%	10,641	Australia	*DSM-IV*	Yes	Yes	No[g]	No	52
Mohammadi[88]	2005	1999	0.15%	25,180	Iran	*DSM-IV*	Yes	Yes	Yes	No	60
Moreno[89]	2005	1999	8.33%	1,464	Brazil	*DSM-III-R*	No	Yes	Yes	Yes	39
Negash[90]	2005	1999	0.43%	68,378	Ethiopia	*DSM-IV*	Yes	Yes	Yes	No	32
Oakley Browne[91,b]	2006	2003	3.79%	12,992	New Zealand	*DSM-IV*	Yes	Yes	Yes	Yes	56
Paaren[92]	2013	2007	1.09%	2,300	Sweden	*DSM-IV*	Yes	Yes	Yes	No	55
Pakriev[93]	1998	1995	0.12%	855	Russia	*ICD-10*	Yes	Yes	Yes	No	59
Phillips[94]	2009	2003	0.46%	16,577	China	*DSM-IV*	Yes	Yes	Yes	Yes	62
Pratt[95]	2012	2007	1.65%	23,393	US	*DSM-IV*	No	No	Yes	No	46
Preville[96]	2008	2006	0.64%	2,798	Canada	*DSM-IV*	Yes	Yes	No[g]	No	62
Ritchie[97]	2004	2000	1.20%	1,863	France	*DSM-IV*	Yes	Yes	Yes	No	55
Santos[98]	2006	2001	1.23%	326	Brazil	*ICD-10*	Yes	Yes	Yes	No	52
Sareen[99]	2005	1990	0.80%	8,116	Canada	*DSM-III-R*	Yes	Yes	No[g]	No	42
Schaffer[100]	2006	2002	2.30%	36,984	Canada	*DSM-IV*	No	Yes	Yes	No	56
Scully[101]	2004	1996	0.36%	29,542	Ireland	*DSM-III-R*	Yes	Yes	No[g]	No	58
Shen[102]	2006	2001	0.10%	5,201	China	*DSM-IV*	Yes	Yes	No[g]	No	57

(continued)

Table 1 (continued).

Lead Author	Year of Publication	Year of Data Collection	Rate of Bipolar Spectrum Disorders	Total N	Location	Diagnostic Criteria (*DSM*, *ICD*)	Criteria Used as Written (Y/N)	Structured Interview (Y/N)	Lifetime Rates Reported (Y/N)	Spectrum Included (Y/N)	Quality Score
Slade[103]	2009	2007	1.80%	8,841	Australia	*ICD-10*	Yes	Yes	Yes	No	57
Smith[104]	2013	2008	1.31%	123,000	UK	*DSM-IV*	No	Yes	Yes	No	47
Song[105]	2015	2009	0.67%	8,141,033	Sweden	*ICD*	No	No	Yes	No	44
Stefansson[106]	1991	1987	0.23%	862	Iceland	*DSM-III*	No	Yes	Yes	No	55
Subramaniam[107,f]	2013	2009	1.41%	6,616	Singapore	*DSM-IV*	Yes	Yes	Yes	No	41
Suvisaari[108]	2009	2004	1.83%	546	Finland	*DSM-IV*	Yes	Yes	Yes	Yes	64
Szadoczky[109]	1998	1995	5.05%	2,953	Hungary	*DSM-III-R*	Yes	Yes	Yes	No	61
ten Have[110]	2002	1996	2.23%	7,076	The Netherlands	*DSM-III-R*	Yes	Yes	Yes	Yes	50
Vazquez-Barquero[111]	1986	1980	0.08%	1,223	Spain	*DSM-III*	No	Yes	Yes	No	38
Vega[112]	1998	1992	1.66%	3,012	US	*DSM-III-R*	Yes	Yes	Yes	No	60
Vicente[113]	2006	1995	1.90%	2,978	Chile	*DSM-III-R*	Yes	Yes	Yes	No	49
Wells[114]	1989	1986	0.73%	1,498	New Zealand	*DSM-III*	No	Yes	Yes	No	57
Yamamoto[115]	1993	1983	0.49%	815	Peru	*DSM-III*	Yes	Yes	Yes	No	58
Zutshi[116,k]	2011	1998	0.53%	3,010	Australia	*DSM-IV*	Yes	Yes	No[h]	No	38
Zutshi[116,k]	2011	2004	0.96%	3,015	Australia	*DSM-IV*	Yes	Yes	Yes	No	38
Zutshi[116,k]	2011	2008	1.49%	3,014	Australia	*DSM-IV*	Yes	Yes	Yes	No	38

[a]One-month prevalence reported.
[b]Part of the World Mental Health Survey Initiative.
[c]The criteria for bipolar disorders did not change between *DSM-IV* and *DSM-IV-TR*, both versions are listed as *DSM-IV*.
[d]These rates were reported in the same article but constitute different samples.
[e]Cumulative prevalence over 20 years.
[f]Part of the Singapore Mental Health Study; samples drawn from different years.
[g]Twelve-month prevalence reported.
[h]Incidence.
[i]Studies used similar design, on samples that were drawn from different parts of Norway.
[j]These rates were reported in the same article, but constitute different samples.
[k]Zutshi et al reported 3 independent samples gathered in different years in a single publication.
Abbreviations: UAE = United Arab Emirates, UK = United Kingdom, US = United States.

Study Coding

Data extraction and coding followed the same methods as a previous meta-analysis of the prevalence of pediatric BD,[26,43] capturing data on prevalence of BD subtypes, sample demographic data, method of attainment, quality of design and of reporting, and country variables. Quality of design and reporting was evaluated using the STROBE checklist.[42] The first and second authors coded all studies. Reliability was calculated using κ for categorical and intraclass correlation for absolute agreement for continuous variables; reliability coefficients ranged from 0.86 to 1.00, with a median of 1.00.

Meta-Analysis

The prevalence of bipolar spectrum cases was based on the number of cases of BD (depending on subtype) out of the full sample size for each study. We used the metafor package in R[44] to meta-analyze the data. Prevalence rates were transformed using logit transformation,[45] in order to normalize the data distribution, with inverse variance weighting. A random effects model estimated the average weighted prevalence for overall bipolar rate,* in addition to BD I, BD II, BD combined,† and BD NOS, for lifetime, 12-month, and < 12-month time periods. We chose not to estimate separate prevalence rates for cyclothymic disorder; even though this is a prevalent illness associated with serious functional impairments, only 3 studies reported Ns that could be meta-analyzed. We also calculated prevalence rates for geographic regions separately. Cochran *Q* statistic assessed whether prevalence rates were homogeneous across samples, and the I^2 statistic measured the percentage of variability in prevalence rates that was due to true heterogeneity.[46] Mixed-effects meta-regression tested whether prevalence of BD changed over time or across regions, controlling for definitions used and other design features.

RESULTS

The search netted a total of 85 effect sizes from 44 different countries, from studies conducted from 1980 to 2012, covering 67,373 cases with BD, out of a total of 9,696,193 participants. This suggests a raw prevalence of 0.7% (ie, 67,373/9,696,193), but that would be biased either as an estimate of BD I (because it includes other bipolar diagnoses) or as a bipolar spectrum estimate (because many studies focused only on bipolar I). Table 1 lists all the studies included in the analyses. Funnel plots and Egger test indicated publication bias, with a tendency to omit studies with higher rates (see Figure 2).

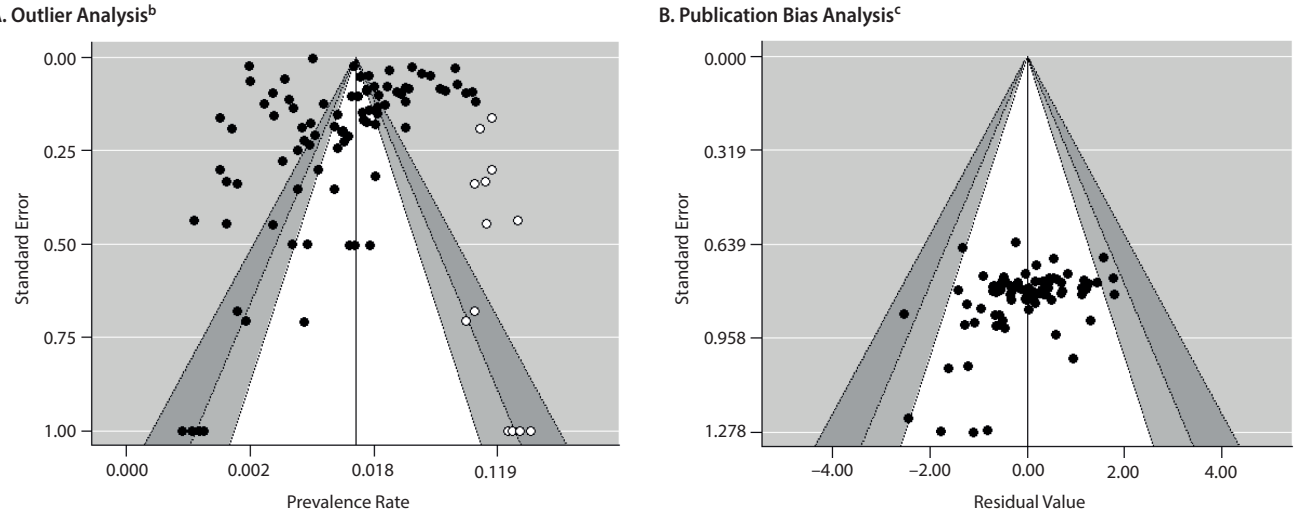
What Is the BD Spectrum Prevalence Worldwide?

The overall prevalence for bipolar spectrum disorders across studies, based on a random effects model, was

*The overall BD rate is the total number of BD cases—regardless of subtype or time period reported—divided by the total sample size for the study.

†Rather than reporting BD subtypes separately, some studies reported a combined rate for BD I and BD II.

Figure 2. Funnel Plot to Look for Outliers and Evidence of Publication Bias[a]



[a]Gureje et al (2006)[33] excluded from both plots.
[b]White dots are the imputed points for the trim and fill. Points in the light gray bands exceeded the 95% threshold, and in the dark gray band, the 99% threshold, for being extreme observed rates.
[c]Shows the discrepancy between the observed and predicted rate based on the meta-regression.

Table 2. Bipolar Disorder Prevalence by Subtype and Time Period

Bipolar Disorder	*k*	Prevalence	95% CI	*Q*	I^2
Lifetime					
BD Spectrum all[a]	85	1.02	0.81–1.29	22,553.41*	99.67
BD I	45	0.62	0.44–0.86	3,330.56*	99.13
BD II	27	0.36	0.23–0.55	451.96***	98.14
Combined BD I & II	41	0.87	0.63–1.19	4,212.28*	99.49
BD NOS	22	0.96	0.56–1.63	1,665.39*	99.26
12-Month					
BD I	22	0.49	0.32–0.78	746.48*	97.89
BD II	13	0.14	0.08–0.26	147.75*	89.13
Combined BD I & II	25	0.58	0.32–1.04	7,423.49*	99.00
BD NOS	9	0.34	0.17–0.71	109.52*	96.42
Other time period					
BD I	11	0.25	0.14–0.45	89.50 *	93.01
BD II	4	0.16	0.06–0.46	22.60*	81.66
Combined BD I & II	8	0.53	0.29–0.94	46.30*	88.57
BD NOS	4	0.26	0.07–1.00	39.58*	88.55

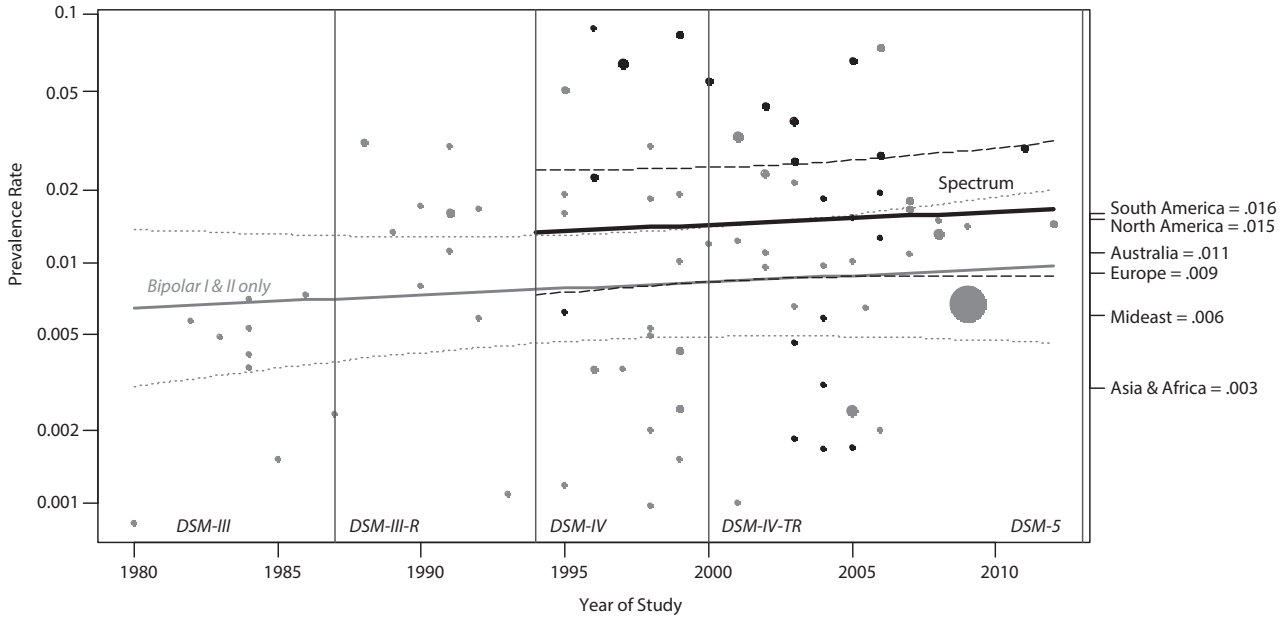
[a]This rate collapses some studies reporting only BD I with others that report combinations of BD I, BD II, cyclothymic disorder, and BD NOS, as noted in the Results.
*$P < .0001$, all based on random effects models.
***$P < .0005$.
Abbreviations: BD I = bipolar I disorder, BD II = bipolar II disorder, BD NOS = bipolar disorder not otherwise specified.

1.02% (95% CI, 0.81%–1.29%). Simple trim and fill adjustment suggested that the rate would rise to 1.34% with imputation of the "missing" studies implied in the funnel plot. There was significant heterogeneity between studies ($Q = 22{,}553.41$, $df = 84$, $P < .0001$; $H^2 = 301.98$, $I^2 > 99\%$); see Table 2. Mixed effects meta-regression tested whether hypothesized moderators influenced the overall bipolar spectrum disorder prevalence rate. The inclusion of bipolar subtypes other than BD I and II was associated with higher prevalence rates ($P = .009$; 95% CI, $B = 0.17$ to 1.20). The other design features (STROBE score, lifetime prevalence, use of structured interview, following strict nosologic definitions) did not account for unique incremental heterogeneity when included together in the meta-regression ($Qm = 3.86$, $df = 4$, $P = .425$). We also used a meta-analysis multivariate model to test whether prevalence was influenced by the fact that some studies were nested within collaborative projects[3,25] and, consequently, shared a majority of design features; the amount of variance accounted for within consortia was not significant.

After controlling for design features, there was no significant association between study year and rate of BD ($z = 0.71$, $P = .479$). Had we not adjusted for design features, there would seem to be a trend for rates to increase ($B = 0.03$, $z = 1.79$, $P = .074$). However, the apparent trend could be attributed to the introduction of NOS as a category, resulting in significantly higher rates in studies that included NOS; see Figure 3.

In contrast, regional differences in rates accounted for large amounts of heterogeneity between studies, even after adjusting for year, definition of BD, and other design features ($Qm = 34.56$, $df = 6$, $P < .00005$). The full meta-regression explained 37% of the variance in rates across studies, with regional differences accounting for 27% of the variance and the other predictors, for 10%. Table 3 presents the regional rates for BD I and II, as well as the rates including BD NOS, controlling for design features. The rates for Asia and Africa are significantly lower than almost all other regions, and North and South America and Australia have the highest rates, with most differences between regions remaining significant after post hoc correction. Regional estimates also appear at the bottom of the forest plot shown in Figure 4. Residual heterogeneity was significant ($Q_E = 2{,}731.76$, $df = 72$, $P < .0001$; $H^2 = 69.0$, $I^2 = 98.6\%$), suggesting that there are important moderators

Figure 3. Prevalence Rates for Bipolar I and II Disorders (gray) and the Bipolar Spectrum Disorder (adding NOS, black) as a Function of Year of Study[a]



[a]The change in rates of bipolar I and II disorders or bipolar spectrum disorder is not significant over time. Vertical reference lines show the publication dates for revised classification systems. Data collection for studies often straddled the publication of the closest *DSM* version. Circle size indicates the weight due to sample size and precision of estimates; black circles include bipolar disorder not otherwise specified (NOS) in the estimates.

Table 3. Lifetime Prevalence Rates by Geographic Region[a,b]

			BD I & II		Adding BD NOS	
Region	Samples	N Total	Prevalence	(95% CI)	Prevalence	(95% CI)
North America	16	194,671	1.5	(0.6–3.7)	2.9	(1.2–6.7)
South America	10	23,086	1.6	(0.5–4.7)	3.0	(1.1–8.0)
Australia	8	43,984	1.1	(0.4–3.1)	2.1	(0.8–5.8)
Europe	25	8,448,239	0.9	(0.4–2.2)	1.7	(0.8–3.8)
Middle East	8	45,518	0.6*	(0.2–1.7)	1.1*	(0.4–3.2)
Africa	4	89,693	0.3**	(0.1–1.3)	0.7**	(0.2–2.3)
Asia	14	851,002	0.3***	(0.1–0.7)	0.5***	(0.2–1.3)

[a]Mixed-model meta-regression prevalence estimates based on maximum quality reporting (STROBE total), using a structured interview, following the formal diagnostic criteria, for lifetime estimates. Gureje et al (2006)[33] was a potential outlier based on visual inspection of forest and funnel plots, as well as standardized residual. Rates for Africa did not change in the first two reported decimal places with this study excluded.

[b]For the statistically significant comparisons of regional rate to North American rate: *$P < .05$, **$P < .01$, ***$P < .0005$. Three regions—Africa, Asia, and the Middle East—showed significantly lower rates than North America, even after Holm step-down Sidak correction for multiple comparisons. Europe's rate ($P < .068$) was nearly statistically significant compared to North America. After post hoc correction, Asian rates were lower than every region. Rates for Africa and the Middle East ($P = .054$) were lower than North America, South America, and Australia, again robust to post hoc correction.

Abbreviations: BD I & II = bipolar I and II disorders combined, BD NOS = bipolar disorder not otherwise specified, STROBE = Strengthening the Reporting of Observational studies in Epidemiology.

of BD prevalence beyond those measured in the study. Examination of standardized residuals, Cook *d*, and other regression diagnostics found no influential outliers. Gureje et al[33] was a borderline outlier; excluding it did not change any of the results to the second decimal place due to its low weight.

Table 2 and Figure 5 report prevalence rates for BD I, BD II, BD I and II combined, and BD NOS (lifetime, 12 month, <12 month other time period). Again, rates were highly heterogeneous; *P* values < .0001.

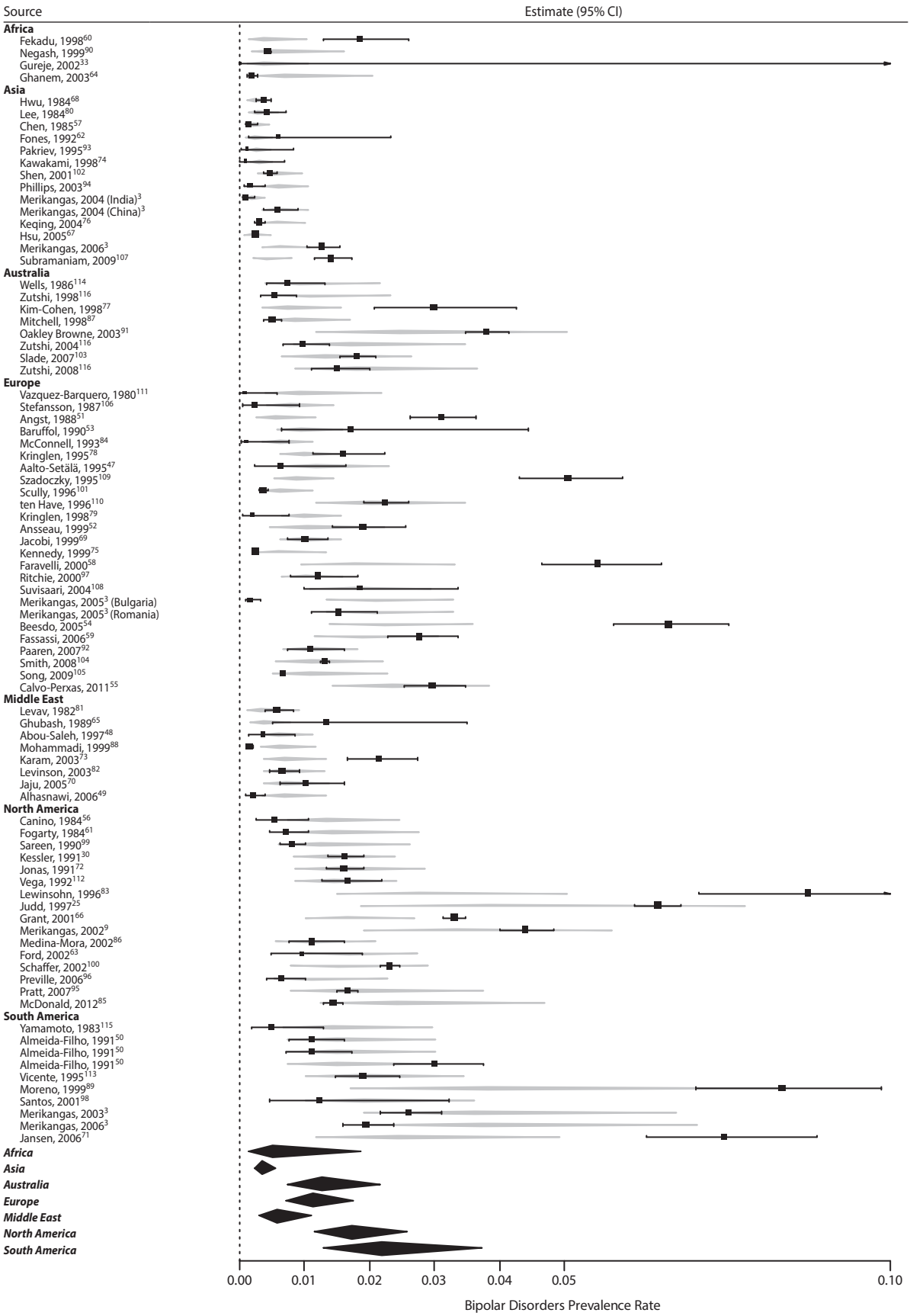
DISCUSSION

The goal of the present study was to use meta-regression to determine the influence of key design features on the epidemiologic prevalence rates of bipolar disorder, including operational definition of bipolar disorder and interview type, and then to test whether the rates of BD were changing significantly over time or whether they varied regionally. The inclusion of BD NOS was the most important design feature, accounting for significantly higher prevalence estimates. After accounting for design features, there was no significant time trend in the rates of BD. However, there were large regional differences in rates of BD.

International Prevalence of BD

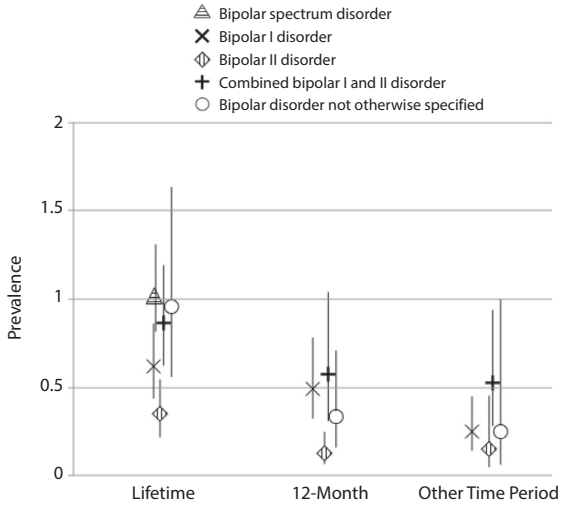
The results show that rates of BD vary widely internationally. The 7 regions fell into roughly 3 groups. High prevalence regions included North and South America and Australia; Asia and Africa were low prevalence regions, and the Middle East and Europe were moderate. The differences were substantial, with the high prevalence regions having rates of both BD I/II or BD spectrum (including NOS) that doubled the low prevalence regions. These differences remained after controlling for design features and after post hoc correction. Our results were

Figure 4. Forest Plot of Prevalence by Study, Sorted by Geographic Region and Year of Data Collection[a]



[a]Polygons indicate predicted prevalence based on meta-regression adjusting for design characteristics, study year, and geographic region.

Figure 5. Prevalence of Bipolar Disorder by Subtype and Time Period



consistent with other data suggesting that prevalence rates vary internationally, with western countries reporting higher rates than African or Asian countries.[22,33,117] Myriad variables might influence differences internationally, including cultural differences in the experience of symptoms, stigma against talking about psychological problems, prevalence of risk factors, and access to mental health care. It is possible that, as western culture permeates other cultures, important differences in risk will be eliminated. There is a certain degree of urgency, given rapid globalization, to learn more about the factors that drive these differences in prevalence, in order to determine whether there are protective agents we might be able to capitalize on to reduce the prevalence of BD worldwide.

Influence of Study Design

As expected, those studies that included subtypes of bipolar disorder other than just BD I or II tended to have higher prevalence rates. This is consistent with other studies that have found that the "subthreshold" subtypes—cyclothymic disorder and BD NOS (now "other specified bipolar and related disorder")—are more prevalent than BD I or II.[26,118] Only about a quarter of studies included BD NOS, and only 5% included cyclothymic disorder. This is not surprising, but it does mean that we know the least about the bipolar spectrum subtypes that affect the highest number of people.[119]

We were surprised that our hypothesis that the use of a structured interview would affect the BD prevalence rate was not supported. Previous studies have found higher rates of illness using structured interviews.[27] However, the majority of studies in our sample did use a structured interview (72/85), so lack of variability may have reduced our ability to find an effect. Had we chosen to include studies prior to 1980, when contemporary definitions of bipolar spectrum disorders were introduced, there would have been a greater number of studies that did not use structured interviews. Relatedly, our hypothesis that idiosyncratic use of diagnostic criteria would influence prevalence might have been supported; it is a positive sign that there has been a concerted effort in recent years to establish guidelines[42,120] and to collaborate internationally in order to more accurately map similarities and differences in rates of mental illness.[3]

We had expected that those studies that used lifetime symptoms in determining a diagnosis would report higher prevalence rates, but this hypothesis was not supported. This may be because those studies that did not report on lifetime rates primarily reported on 12-month rates, and most people with BD will experience symptoms over the course of a year. Additionally, the "other" time period category in our study included anything less than a year, which may not have provided the same level of contrast in rates that incidence rates would have, for example.

Strengths of the Study

The present study is the largest meta-analysis conducted on prevalence rates of BD. Eighty-five studies conducted between 1980 and 2012, from 44 different countries, including 9,696,193 people. We were able to explore the prevalence rates for BD II, cyclothymic disorder, and BD NOS as well as BD I. Although many studies focused on BD I, all subtypes can cause considerable impairment, and the "subthreshold" subtypes—BD NOS and cyclothymic disorder—appear at least as prevalent as BD I or II.[26]

The large number of studies included in this meta-analysis allowed us to use mixed-effects meta-regression to test whether hypothesized factors and design features influence prevalence. Importantly, the results of the meta-regression also challenge perceptions that the prevalence of BD has been increasing over time, consistent with a previous meta-analysis of the prevalence of BD in youth.[26] Prior narrative reviews of the literature may not have systematically adjusted for changes in definitions over time and other design features.

Limitations

Meta-analyses can be only as good as the studies they include[43]; although the number of studies we analyzed is a strength, it also introduces wide variability in terms of how BD is defined, the subtypes and time period assessed, the quality of the design, and other potential moderating factors. Meta-regression quantified the influence of sample and design characteristics that were reported, but other important factors were not reported consistently or at all (including demographic characteristics of interest). Additionally, although we had hypotheses about specific design features (ie, type of interview, bipolar definition) and about sample characteristics (ie, date of data collection, location), these attributes were often collinear, obscuring our ability to detect and interpret differences. Substantial heterogeneity remained even after controlling for all measured predictors; without standard recruitment and diagnostic methods across samples, the inferences to be drawn from meta-analyses will remain limited by the "noise" introduced by study variability.

Finally, our sample represents 44 countries, but we included only papers published in English, perhaps limiting our ability to fully represent global epidemiologic data.

Conclusion and Future Directions

The results suggest that the inclusion of BD NOS significantly increases the rate of BD, roughly doubling the estimates. The relatively recent addition of BD NOS to research studies contributes to the perception of higher rates of BD over time, and the time trend was no longer significant after controlling for BD definition and study design features. Most importantly, the meta-analysis confirmed large differences in regional rates of BD, even after adjusting for all other measured factors. Although the difference in rates contradicts earlier generalizations in nosologic systems, it is broadly consistent with emerging findings in psychiatric genetic epidemiology,[9] as well as the epidemiology of cardiovascular disease and obesity[121]: Risky variants of genes and environmental factors are not uniformly distributed globally, nor are the common medical comorbidities that are associated with BD. We hope that newer studies will provide a fuller accounting for the bipolar spectrum in their reports, using consistent definitions and strong methodology, as well as adding information about biological and environmental factors to help unpack the substantial regional differences in risk.

Submitted: August 23, 2016; accepted March 27, 2017.

Published online: November 28, 2017.

Potential conflicts of interest: **Dr Moreira** is currently involved in a Boehringer Ingelheim clinical trial. **Dr Youngstrom** has consulted with Pearson, Janssen, Otsuka, Lundbeck, Joe Startup Technologies, and Western Psychological Services about psychological assessment. The authors report no competing interests.

Funding/support: Dr Moreira was supported by fellowships from Fulbright and the Fundação para a Ciência e a Tecnologia-Portugal (SFRH/BD/38246/2007).

Role of the sponsor: The authors thank the funding institutions for having strongly facilitated the collaboration between Dr Moreira and Drs Van Meter and Youngstrom, which was particularly important in the design and collecting of data for the study.

Previous presentations: Preliminary findings were presented as part of an Expert Workshop at the 10th International Review of Bipolar Disorders in May 2010 in Budapest, Hungary, and at the 18th Annual Conference of The International Society for Bipolar Disorders held jointly with the 8th Biennial Conference of The International Society for Affective Disorders in July 2016 in Amsterdam, The Netherlands.

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