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Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses

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ABSTRACT

Objectives: The pathophysiology of bipolar disorder is likely to involve both genetic and environmental risk factors. Our study aimed to provide a systematic search of environmental risk factors for BD. In addition, we assessed possible hints of bias in this literature, and identified risk factors supported by high epidemiological credibility.

Methods: We searched the Pubmed/MEDLINE, EMBASE and PsycInfo databases up to October 7th, 2016 to identify systematic reviews and meta-analyses of observational studies that assessed associations between putative environmental risk factors and BD. For each meta-analysis, we estimated its summary effect size by means of both random- and fixed-effects models, 95% CIs (confidence intervals), the 95% prediction interval, and heterogeneity. Evidence of small-study effects and excess of significance bias were also assessed.

Results: Sixteen references met inclusion criteria (7 meta-analyses and 9 qualitative systematic reviews). Fifty-one unique environmental risk factors for BD were evaluated. Six meta-analyses investigated associations with a risk factor for BD. Only, irritable bowel syndrome (IBS) emerged as a risk factor for BD supported by convincing evidence (k=6; OR=2.48; 95% CI=2.35-2.61, $p < 0.001$), and childhood adversity was supported by highly suggestive evidence. Asthma and obesity were risk factors for BD supported by suggestive evidence, and seropositivity to *Toxoplasma gondii* and a history of head injury were supported by weak evidence.

Conclusions: Notwithstanding several environmental risk factors for BD were identified, few meta-analyses of observational studies were available. Therefore, further well-designed and adequately powered studies are necessary to map the environmental risk factors for BD.

KEYWORDS: bipolar disorder, mania; depression; systematic review, meta-analysis, risk factor, mood disorder, psychiatry; aetiology

1 INTRODUCTION

Bipolar disorder (BD) has an estimated lifetime prevalence of 0.6% for type I BD, 0.4% for type II BD, and 1.4% for subthreshold BD across 11 countries.[1] Bipolar disorder is also associated with substantial morbidity and mortality due to a high prevalence of co-occurring medical (e.g., metabolic) and psychiatric conditions, as well as elevated suicide rates.[2-5] Evidence indicates that BD is largely influenced by genetic factors, with an estimated heritability of 58-85%.[6, 7] However, genome-wide association studies indicate that the cumulative impact of many common alleles of small effect may explain only 38% of the phenotypic variance for BD.[8] Furthermore, emerging evidence indicates that complex gene-environment interactions including epigenetic mechanisms may play a significant role in the patho-etiology of BD.[9, 10]

Therefore, the identification of putative modifiable risk factors for BD may ultimately aid in the prevention of this devastating illness. Furthermore, emerging evidence suggests that neurodevelopmental pathways may be involved in the etiopathogenesis of a subset of individuals with BD.[11-13] These data indicate that perinatal and early life insults may contribute to the pathophysiology of BD. Accordingly, previous systematic reviews indicate that perinatal infections (e.g., Influenza and Toxoplasma gondii) may confer a higher risk of BD.[14, 15] In addition, exposure to childhood maltreatment is supposed to increase the risk of BD, and also may have a detrimental impact on several BD-related outcomes.[16, 17] Finally, a previous systematic review indicates that environmental risk factors occurring later in life (e.g., substance abuse) may also be involved in the development of BD.[16]

To further expand the identification of environmental risk factors for BD, the current work aims to conduct an umbrella review of systematic reviews and meta-analyses of environmental risk factors for BD. Similar efforts have been successfully conducted for a range of neuropsychiatric diseases (e.g. Parkinson's disease and dementia).[18, 19] We will follow a similar methodology herein, which may enable the assessment of hints of bias in this literature, and also the identification of environmental risk factors supported by more credible epidemiological evidence.

2 MATERIALS AND METHODS

2.1 Search strategy and study selection

We systematically searched the PubMed/MEDLINE, EMBASE and PsycINFO databases from inception to October 7th, 2016 to identify systematic reviews and meta-analyses of observational studies examining associations of environmental (non-genetic) risk factors with BD. The search strategy used the keywords "bipolar disorder" and "meta-analyses or systematic reviews"

applied to the title/abstract/keywords fields. Two authors (BB and JLC) independently screened the titles/abstracts of retrieved references, and discrepancies were resolved through consensus. If a final decision could not be reached, a third investigator made the decision regarding possible eligibility (AFC or CAK). The full-texts of references selected after title/abstract screening were then reviewed by the same investigators to determine final eligibility. We included systematic reviews and meta-analyses of observational studies (i.e., cross-sectional, case-control and cohort studies) which investigated environmental risk factors for BD. No language restrictions were applied. Systematic reviews and meta-analyses of genetic risk factors, peripheral biomarkers of BD, factors related to recurrence/relapse of BD or intervention studies were excluded. A published umbrella review evaluated possible hints of bias in the literature of peripheral biomarkers for BD.[20] We also included systematic reviews and meta-analyses in which a disease state was investigated as a putative risk factor for BD (except unipolar depression), but we excluded the ones where BD was studied as a risk factor for another disease. In addition, we excluded systematic reviews and meta-analyses that examined personality constructs and prodromal manifestations as putative risk factors for BD. For meta-analyses available only as meeting abstracts, we electronically contacted the authors in at least two separate occasions to provide data. This search strategy was augmented through tracking the citation of included articles in Google Scholar.[21] We followed an a priori defined but unpublished protocol.

2.2 Data extraction

Two independent investigators (BB and JLC) extracted the following information from each included article: (1) first author name; (2) year of publication; (4) the examined risk factors; (5) number of included studies. If a quantitative synthesis of the evidence was performed, we extracted the summary effect size (ES) estimate (risk ratio [RR], odds ratio [OR], hazard ratio [HR], or incident risk ratio) with the 95% CIs (confidence intervals). Whenever available, we also extracted the individual ES estimate and the sample sizes of individual studies. If a study had several control groups, we prioritized the extraction of the association with a healthy control group. In the articles where a summary synthesis of the evidence was not available, we extracted the main conclusions reached by the authors and the reasons for not performing a meta-analysis. Whenever two references were available for the same risk factor, we considered the one with the largest number of datasets.

2.3 Statistical analysis

For each meta-analysis, we estimated the summary ES and its 95% CI through both fixed and random-effects models.[22] For meta-analyses where individual study data were not available, we considered the summary associations published by the authors. We also calculated the prediction

interval and its 95% CI, which accounts for between-study heterogeneity and estimates the uncertainty of the association that would be expected in a new study examining that same association.[23] For the largest dataset of each meta-analysis, we calculated the standard error (SE) of the ES. If the SE is less than 0.1 then the 95% CI will be lower than 0.20 (i.e., less than the magnitude of a small ES). We calculated the I^2 metric to assess between-study heterogeneity. Values ≥ 50% indicate high heterogeneity and values ≥ 75% suggest very high heterogeneity.[24, 25] To assess evidence for small-study effects (i.e., whether small studies would have inflated ESs compared to larger ones), we used the regression asymmetry test developed by Egger and coworkers.[26] A *p* value < 0.10 in Egger's test and the ES of the largest study being more conservative than the summary ES of the random-effects meta-analysis were considered as indicative of small-study effects.[27] Finally, we assessed whether an excess of significant findings was present by means of the Ioannidis's test.[28] In brief, this test evaluates whether the number of studies with nominally significant results (i.e. with $p < 0.05$) among those included in a meta-analysis is too large considering their power to detect significant effects at α=0.05. First, we estimate the power of each individual study, using a non-central t distribution. The sum of all power estimates provides the expected (E) number of data sets with nominal statistical significance. The actual observed (O) number of statistically significant data sets is then compared to the E number using a χ^2-based test.[28] The larger the difference between O and E, the higher the degree of excess of significance bias. Since the true ES of a meta-analysis cannot be precisely determined, we considered the ES of the largest data set as the plausible true ES. This decision was based on the fact that simulations indicate that the most appropriate assumption is the ES of the largest dataset included in the meta-analysis.[29] Excess significance for a single meta-analysis was considered if $p < 0.10$ in the Ioannidis's test and O > E.

2.4 Classification of the credibility of evidence

The epidemiological credibility of the association of each environmental risk factor with BD was classified using criteria derived from previously published umbrella reviews.[18, 30] We considered the following criteria: (1) convincing evidence (Class I): more than 1,000 cases, significant summary associations ($p < 10^{-6}$) per random-effects calculations, no evidence of small-study effects, no evidence of excess of significance bias, prediction intervals not including the null and not large heterogeneity ($I^2 < 50\%$); (2) highly-suggestive evidence (Class II): significant summary associations ($p < 10^{-6}$) per random-effects calculation, more than 1,000 cases, the largest study with 95% CI excluding the null; (3) suggestive evidence (Class III): more than 1,000 cases, significant summary associations ($p < 10^{-3}$) per random-effects calculations; (4) weak evidence: all other risk factors with $p < 0.05$; (5) non-significant associations: all associations with $p > 0.05$. For risk factors classified as

class I or II evidence, sensitivity analyses were performed limiting the evidence only to prospective studies.

2.5 Methodological quality assessment

Two authors (CAK and AFC) rated the methodological quality of included systematic reviews and meta-analyses with The Assessment of Multiple Systematic Reviews (AMSTAR) instrument.[31] Scores range from 0 to 11 with higher scores indicating greater quality. The AMSTAR scale involves dichotomous scoring (i.e., 0 or 1) of 11 items related to the methodological rigor of systematic reviews and meta-analyses (e.g., comprehensive search strategy, publication bias assessment). AMSTAR scores are graded as high (8–11), medium (4–7) and low quality (0–3).[31, 32]

3 RESULTS

Our search strategy identified 2,327 hits, and following exclusion of duplicates and searching other sources, the titles/abstracts of 1,205 unique references were screened for eligibility. Of 65 references selected for full-text review, 16 references met inclusion criteria. One study of the 65 articles screened at full text was excluded because a more recent publication had re-analyzed the data.[33, 34] Seven of the 16 eligible articles had a quantitative synthesis providing a summary estimate of the association of the risk factor and BD.[15, 35-40] Individual study data was available for 6 references.[15, 36-40] Three articles reported prevalence rates of BD in medical conditions namely endometriosis,[41] fibromyalgia[34] and multiple sclerosis.[42] The remaining 7 references reported only systematic reviews.[14, 16, 41, 43-46] Figure 1 presents the flowchart of study selection, and the reasons for exclusion are summarized in Supplementary Table S1 (see supplement that accompanies the online version of this article). The eligible references evaluated 51 unique risk factors for BD. Seven putative environmental risk factors were assessed in more than one reference. In these cases, we selected the reference that included the highest number of datasets (see Supplementary Table S2).

< Please, insert Figure 1 around here >

Meta-analyses provided evidence for seven environmental factors, and included 54 studies in total (median = 8; IQR = 5 – 10). Three were medical comorbidities [asthma,[35] irritable bowel syndrome (IBS)[39] and obesity[40]], and one referred to seropositivity to a typical perinatal pathogen (*Toxoplasma gondii*[15]). The remaining three were childhood adversity[36], head injury,[38] and exposure to obstetric complications.[37] Table 1 presents the risk factors, summary estimates and characteristics of those meta-analyses. The number of cases was greater than 1000 in 5 (71.4%) meta-analyses. All

meta-analyses were based on published data and none had access to individual participant data. The overall AMSTAR quality scores of the included meta-analyses were medium (median = 7; IQR = 4.5–8.5; Supplementary Table S3).

< Please, insert Table 1 around here >

Six (85.7%) of 7 meta-analyses reported effects that were significant at a nominal *p* value of 0.05. Four (57.1%) were significant at p values less than 0.001 under random effects modelling (Table 1): asthma,[35] childhood adversity,[36] IBS,[39] and obesity.[40] The 95% prediction interval rule under random-effects modelling did not include the null value only in the meta-analysis of IBS.[39] The meta-analysis which investigated the prevalence of BD in individuals with asthma[35] did not provide information to calculate prediction intervals.

The results of the largest study were more conservative than the summary result in the meta-analyses of childhood adversity,[36] IBS,[39] and obesity[40], and in the meta-analysis of exposure to obstetric complications[37] it was in the reverse direction. In 2 meta-analyses, the SD of the largest study was less than 0.10. Two meta-analyses had large heterogeneity ($I^2 \geq 50\%$, childhood adversity,[36] and *T. gondii* infection[15]) and one had very large heterogeneity ($I^2 \geq 75\%$, obesity[40]). The meta-analyses that assessed exposure to obstetric complications[37] and obesity[40] as risk factors for BD had evidence for small-study effects, which provides an indication of publication bias. The largest individual study had either a more conservative effect size than the random-effects summary effect size estimates for the meta-analyses of childhood adversity, IBS and obesity. In the meta-analysis of exposure to obstetric complications the effect size of the largest study was in reverse direction compared to the summary effect size calculated through random-effects modelling. Assuming that the effect size in the largest study represented the true effect of the meta-analysis, only the meta-analysis of obesity[40] had a significant difference between the number of observed and expected 'positive' (i.e., statistically significant) studies providing evidence for excess of significance bias. The meta-analysis that investigated obesity included only cross-sectional studies.[40] The meta-analyses that investigated childhood adversity,[36] exposure to obstetric complications[37] or *T. gondii* infection[15] included only case-control studies. The meta-analyses that investigated asthma[35] and head injury[38] included cross-sectional and case-control studies. Only the meta-analysis that investigated IBS as a risk factor for BD included only retrospective cohort studies.[39]

The assessment of the 7 meta-analyses is presented in Table 2. Only the meta-analysis of IBS[39] was nominally significant at a *p* level less than 10^{-6} per random-effects calculation and had no evidence of small-study effects, had no evidence for excess significance bias, did not have large

heterogeneity, the prediction interval excluded the null and had over a 1000 cases. Therefore, IBS was classified as having Class I evidence as a risk factor for BD. The meta-analysis of childhood adversity[36] was significant at a *p* level less than 10^{-6} per random-effects calculation, more than 1,000 cases, and the largest study with 95% CI excluding the null. Therefore, childhood adversity was classified as Class II evidence. The meta-analyses which evaluated asthma[35] and obesity[40] as possible environmental risk factors for BD met criteria for Class III evidence, and the meta-analysis of head injury[38] and *T. gondii* infection[15] met the criteria for weak evidence. Exposure to obstetric complications provided no evidence of association as a risk factor for BD.[37]

< Please insert Table 2 around here >

Three references reported prevalence rates of BD.[34, 41, 42] The meta-analysis of Stubbs[34] included case-control and retrospective cohort studies, and found that patients with fibromyalgia had a 15.2% prevalence rate of BD (95%CI = 5.3% – 36.3%; n = 806 patients with fibromyalgia). The systematic review of cross-sectional studies conducted by Marrie et al.,[42] reported that in patients with multiple sclerosis, lifetime prevalence of BD ranged from 0% to 16.2% (k = 12 studies), and in the only study that was population based, the prevalence of BD was 5.8%. A systematic review reported a BD prevalence rate of 16.7% in patients with endometriosis when pooling together the 3 included studies.[41] The overall AMSTAR scores of included meta-analyses were medium (median = 6.5; IQR 3.75-7.75). Individual AMSTAR scores for included meta-analyses are provided in Table S3 (available online).

The qualitative systematic reviews found in 7 references evaluated a total of 37 unique risk factors with at least 2 individual studies. The median number of studies across these 37 systematic reviews was 3 (IQR 3–7). From the 7 references, 1 included only case-control studies,[46] 2 included mixed cross-sectional and case-control studies,[14, 41] 1 included mixed prospective cohorts and nested case-control studies[16] and the remaining included mixed study designs (cross-sectional, cohorts and case-controls).[43-45] The overall AMSTAR quality scores of the qualitative systematic reviews were low (median = 2; IQR = 1.5–2.5; Table S3, available online). The factors were divided among socio-demographic factors (n = 10), family-related factors (n = 4), medical comorbidities (n = 4), infections (n = 8), pregnancy- and birth-related factors (n = 5), individual factors (n = 3), and medications/substance use (n = 3). Table 3 presents each risk factor with the summary of the evidence. Five risk factors were investigated by a single study, with a median sample size of 26.5 participants (Supplementary Table S4). For the socio-demographic factors, the largest body of evidence was provided for gender (k = 14), and most studies found no significant association with

BD.[43] Evidence for ethnicity[43] and place of residence[43] was conflicting, and most studies suggested either only a trend or no association with BD. For family-related factors, the largest body of evidence was provided for parental loss (k = 10), but there were conflicting results (5 studies suggested no association, 3 studies suggested an association and the remaining 2 provided inconclusive results i.e. a non-significant trend).[43] Regarding medical comorbidities, the overall number of studies was low, with the inclusion of ≤ 5 studies . The studies reviewed across these qualitative systematic reviews are heterogeneous regarding classifications of exposures and do not provide directly comparable associations. For infectious diseases, the largest number of studies were found for CMV perinatal infection (k = 11),[14] *Toxoplasma gondii* perinatal infection (k = 9)[14] and HSV-2 perinatal infection (k = 7).[14] For these three factors, the evidence was inconclusive or suggestive of no association with BD. For CMV perinatal infection[14] and *T. gondii* perinatal infection[14], only approximately half the studies suggested an association. The influenza virus perinatal infection[14] was potentially associated with BPD, as 2 out of 3 studies pointed to an association. Regarding pregnancy- and birth-related factors, birth seasonality[43] was the factor with largest number of studies (k = 9). Only small sample sized studies suggested an association of winter-spring birth and increased risk for BD, whereas the largest studies suggested no association. For the 7 studies assessing pregnancy and birth complications (PBCs)[43] evidence was inconclusive, with different methods of assessment of PBCs. One nested case-control study suggests that pre-term birth (< 37 weeks) may increase the risk of BD in females[47], while a cohort study provided evidence that pre-term birth (32-36 weeks) increased by 3-fold the risk of BD in both genders.[48] For the individual factors, 3 of 4 studies (n = 31–50) showed that exposure to recent stressful events occurring within a short period prior to the first onset (e.g. within 6 months)[43] was associated with an increased risk for BD. Finally, reviewed studies on medications and substance use suggested an association of cannabis[16] or opioid use[16] with BD (k = 2–3). Meta-analyses were not performed due to high heterogeneity.[16]

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4 DISCUSSION

We provide a systematic assessment of putative environmental risk factors for BD across published systematic reviews and meta-analyses by applying pre-defined methodological criteria. To the best of our knowledge, this represents the first effort to synthesize available evidence considering potential biases in this literature. Compared to previous similar efforts conducted in a range of neuropsychiatric disorders[18, 19, 30], our data indicate that the search for environmental risk factors for BD has been thus far a relatively under-studied area of investigation. One of the most relevant roles

of umbrella reviews and other systematic approaches to integrate evidence is to identify areas where further research efforts should be directed.[49]

We identified seven meta-analyses that investigated associations of environmental risk factors for BD. Irritable bowel syndrome was the only risk factor for BD that met criteria for class I evidence, and exposure to childhood adversity met criteria for class II evidence. Obesity and asthma were risk factors which met criteria for class III evidence, while a history head injury and seropositivity to *Toxoplasma gondii* were supported by weak evidence. Bipolar disorder is associated with high rates of co-morbid medical conditions which at least in part may be due to shared environmental risk factors and pathophysiological pathways, and this co-occurring medical conditions may play a significant contribution to the decreased life expectancy observed among individuals with BD.[3, 50, 51] For example, an increase in peripheral inflammation observed in individuals with IBS[52], may contribute to neuroinflammation, which is thought to be a relevant pathophysiological event in BD.[53, 54] Furthermore, stressful life events may precipitate the onset of both BD (as observed in the systematic review conducted by Tsuchiya et al.,[43]) and IBS[55]. Likewise, several mechanistic pathways including but not limited to immune dysfunction and genetic polymorphisms and abnormalities in the circadian system may contribute to a higher prevalence of BD in obese individuals.[56, 57] Notwithstanding, we found that weak evidence supports asthma as a putative risk factor for BD, a recent large prospective study found that asthma and other atopic diseases may increase the risk of BD.[58]

A history of traumatic brain injury was associated with BD in a meta-analysis that included three studies, which followed either cross-sectional or case-control designs.[38] However, this recent meta-analysis did not include at least two large-scale prospective studies which found evidence that traumatic brain injury may increase the risk of BD.[59, 60] Therefore, clearly the incorporation of these and future studies may require an up-dated synthesis of available evidence in the near future.

Accumulating evidence provide increasing support to the notion that neurodevelopmental factors may play a role in the patho-etiology of BD.[13, 61] Seropositivity to *T. gondii* may confer a higher risk for BD although the epidemiological credibility of available evidence is weak, while a recent systematic review suggests that perinatal influenza infection may increase the risk of BD.[14] Exposure to perinatal pathogens may activate immune mechanisms leading to a long-term up-regulation of immune systems, and since immune factors influence neural growth and survival, this may disrupt neurodevelopmental trajectories.[62, 63] A recent study found evidence for a gene-environmental interaction involving the rs3804099 single nucleotide polymorphism (SNP) of the

toll-like receptor 2 (TLR2) gene in BD.[64] This study provides preliminary evidence to the hypothesis that prenatal immune activation due to exposure to pathogens may modulate immune pathways relevant to the pathophysiology of BD. The role of neurodevelopmental factors for BD are further supported by the fact that pre-term birth may be a risk factor for BD although this evidence was supported only by a qualitative systematic review.[16]

Qualitative systematic reviews provide some suggestive clues to several possible environmental risk factors for BD. For example, preliminary evidence indicates that the use of cannabis and opioids may confer a higher risk for BD.[16] In addition, proximal stressful life events (i.e., those occurring 6 months prior to illness onset) may increase the risk of BD.[43]

Some limitations of this umbrella review deserve discussion. First, the assessment of heterogeneity and excess of significance findings provide hints of bias but not proof thereof. Several sources of true heterogeneity are possible. For example, BD is *per se* a heterogeneous phenotype with highly variable illness trajectories.[65, 66] In addition, the multivariable adjustment of potential confounders (e.g. co-occurring metabolic disturbances)[67] could vary across component studies included in eligible meta-analyses, thus providing a possible source of heterogeneity. Second, we did not assess the quality of individual studies included in the systematic reviews and meta-analyses because this was beyond the scope of this umbrella review. This was a primary aim of the systematic reviews and meta-analyses included herein. Third, we collected only putative environmental risk factors which have been evaluated through systematic reviews and meta-analyses. Thus, we might have missed some associations which were not yet been evaluated in systematic reviews and meta-analyses. For example, an unhealthier dietary pattern, exposure to smoking in utero, and exposure to corticosteroids may be putative risk factors for BD which deserve further scrutiny. Fourth, the methodological quality of included meta-analyses was in general medium, whereas the methodological quality of narrative systematic reviews was overall low. Finally, we found no protective environmental factor for BD supported by robust evidence.

Despite these limitations, this umbrella review has important relevant clinical and research implications. First and foremost, BD is a heterogeneous phenotype and several of the environmental risk factors evaluated in this effort seem to cross traditional diagnostic categories. For example, evidence indicates that IBS may be a risk factor for major depressive disorder[68], while exposure to perinatal pathogens could be a non-specific risk factor for several disorders with a neurodevelopmental component (e.g., schizophrenia and autism).[62] Some risk factors may increase the risk of certain subtypes of BD. For example, an increasing body of evidence indicates that early-

onset BD may have some specific pathophysiological mechanisms.[69, 70] Finally, this umbrella review indicates that the fine mapping of putative environmental risk factors for BD deserves further study.

5. CONCLUSIONS

This umbrella review of systematic reviews and meta-analyses identified fifty-one unique risk factors for BD. However, only irritable bowel syndrome (IBS) emerged as a risk factor supported by class I evidence. In addition, relatively few putative environmental risk factors for BD have been evaluated through meta-analyses, and several hints of bias were found in this literature. Recently, efforts have been directed to characterize precursors or even a prodrome of BD. The identification of environmental risk factors for BD require further study, and may further aid in the characterization of individuals at-risk to develop BD, who ultimately may benefit from preventative interventions.

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DISCLOSURE

The authors declare no conflicts of interest relevant to the current work.

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Figure 1. Flowchart of literature search.

	Risk factor	N of primary studies	Total number of cases/ controls	Random effects summary effect size (95% CI)	95% PI	*P* random	*p* fixed	Largest study		I^2	Egger's test *p* value
								Effect size (95% CI)	SE		
Wu et al.,[35]	Asthma[a]	4	50,358/109,218	2.12 (1.57 – 2.87)	N/A	< 0.001	N/A	N/A	N/A	44	0.514
Palmier-Claus et al.,[36]	Childhood adversity[b]	13	1,146/977	2.86 (2.03 – 4.04)	0.90 – 9.14	< 0.001	< 0.001	1.92 (1.39 – 2.64)	0.32	71	0.567
Scott et al.,[37]	Exposure to obstetric complications	8	272/341	1.15 (0.62 – 2.11)	0.23 – 5.81	0.659	0.799	0.58 (0.25 – 1.35)	0.28	49	0.004
Perry et al.,[38]	Head injury	3	313/5,370	1.85 (1.17 – 2.94)	0.09 – 36.95	0.009	0.009	2.18 (1.22 – 3.91)	0.69	0	0.201
Tseng et al.,[39]	Irritable bowel syndrome (IBS)	6	177,117/192,092	2.48 (2.35 – 2.61)	2.30 – 2.66	< 0.001	< 0.001	2.47 (2.34 – 2.61)	0.07	0	0.797
Zhao et al.,[40]	Obesity	9	12,259/615,490	1.77 (1.40 – 2.23)	0.90 – 3.43	< 0.001	< 0.001	1.25 (1.19 –			

									1.30)			
Sutterland et al.,[15]	*T. gondii* infection	15	1,163/13,836	1.52 (1.05 – 2.19)	0.48 – 4.76	0.023	< 0.001	2.11 (1.48 – 3.00)	0.39	67	0.896

		Sample size (number of cases)	Significance threshold reached (under the random	95% prediction interval rule	Estimate of heterogeneity[a]	Small-study effects or excess significance		Random-effects summary effect size		Classification[b]	

Table 1. Characteristics, quantitative synthesis, and bias assessment of the 7 meta-analyses of risk factors for bipolar disorder.

Abbreviations: CI = confidence interval; **N/A** = not available; **PI** = prediction interval.

[a] Meta-analysis data was obtained as provided in the published report.

[b] Epidemiological studies were not included in the meta-analysis since they evaluated childhood adversity in a sample of bipolar patients.

		effects model)			bias	(95% CI)	
Asthma[35]	> 1000	< 0.001	N/A	Small	N/A	2.12 (1.57 – 2.87)	III
Childhood adversity[36]	> 1000	$< 10^{-6}$	Including the null value	Large	Neither	2.86 (2.03 – 4.04)	II
Exposure to obstetric complications[37]	< 500	> 0.05	Including the null value	Small	Small-study effects	1.15 (0.62 – 2.11)	Non-significant
Head injury[38]	< 500	> 0.001 but < 0.05	Including the null value	Small	Neither	1.85 (1.17 – 2.94)	Weak
Irritable bowel syndrome[39]	> 1000	$< 10^{-6}$	Excluding the null value	Small	Neither	2.48 (2.35 – 2.61)	I
Obesity[40]	> 1000	$> 10^{-6}$ but < 0.001	Including the null value	Very Large	Both	1.77 (1.40 – 2.23)	III
T. gondii infection[15]	> 1000	> 0.001 but < 0.05	Including the null value	Large	Neither	1.52 (1.05 – 2.19)	Weak

Table 2. Assessment across the 6 meta-analyses of risk factors for bipolar disorder.

[a] Heterogeneity was categorized as not large ($I^2 < 50\%$), large ($I^2 \geq 50\%$ but $I^2 < 75\%$), and very large ($I^2 \geq 75\%$)

[b] Convincing evidence criteria (Class I): more than 1,000 cases, significant summary associations ($p < 10^{-6}$) per random-effects calculations, no evidence of small-study effects, no evidence of excess of significance bias, prediction intervals not including the null and not large heterogeneity ($I^2 < 50\%$); Highly-suggestive evidence criteria (Class II): significant summary associations ($p < 10^{-6}$) per random-effects calculation, more than 1,000 cases, the largest study

with 95% CI excluding the null; Suggestive evidence criteria (Class III): more than 1,000 cases, significant summary associations ($p < 10^{-3}$) per random-effects calculations; Weak evidence criteria: all other risk factors with $p < 0.05$; Non-significant associations: all associations with $p > 0.05$.

Table 3. Evidence across the systematic reviews of risk factors for bipolar disorder.

Study	Environmental factor	N studies	Main findings
Sociodemographical factors			
Tsuchiya et al.,[43]	Education	7	2/7 studies supported an association between a higher educational level and an elevated risk for BD [n = 2,953]. 3 community surveys did not support this association [n = 1,513–4,914]. Two other community surveys suggested an inverse association [n = 6,673–18,572]
Tsuchiya et al.,[43]	Education of parents	2	1/2 studies found an association between a higher educational level of parents and an increased risk for BD [n= 123]. The other study found no association [n= 1709 community adolescent sample]
Tsuchiya et al.,[43]	Ethnicity	8	One study suggested an increased risk for BD in Caribbean born subjects when compared with those born in the UK [n = 2 million registered sample UK]. Other study suggested a non-significant trend for non-whites at higher risk for BD than whites [n = 6,673 community sample, USA]. One survey suggested higher rates of BD in Jews with a father of North African origin than those with a father of European origin [n = 4,914 community sample, Israel]. Three more community surveys in the United States did not support significant differences between Caucasians and other ethnic groups [n = 1,709–18,572], although Asians may be at lower risk only for DSM-defined bipolar I disorder than whites. One study showed an association between black ethnicity and a decreased risk for BPD compared with whites [n = 423,937 first-admitted subjects, USA]. None of the various ethnicities in Ethiopia appeared to show an increased risk for BD [n = 1,420 community sample]

Tsuchiya et al.,[43]	Gender	14	The community surveys have not shown a statistically significant gender difference in lifetime or period prevalence of BD [n=865–18,572]. One study found female predominance in an adolescent sample [age 14–18, n = 1,710]. Findings seem in favor of no association between a specific gender and an increased risk for BD, although the exceptions remain.
Tsuchiya et al.,[43]	Income	2	Two community surveys suggested a weak trend towards an association between lower income and an increased risk for BD
Tsuchiya et al.,[43]	Marital status	7	5/7 studies discussing marital status showed that single persons tend to be associated with an elevated risk for BD compared with married or cohabiting persons. One of the remaining studies suggested that the association is limited to female subjects. The last study (community survey) showed no association.
Tsuchiya et al.,[43]	Occupation	3	1/3 studies supported an association between a higher occupational class and an increased risk for BD [n = 1,500]. 2/3 studies did not support the association.
Tsuchiya et al.,[43]	Place of residence	8	Seven community surveys and register-based studies showed a trend for an association between urban residence and an increased risk for BD [n = 7,301–115,000]. One survey suggested no association of place of residence and BD [n = 3,798]
Tsuchiya et al.,[43]	Socio-economic status (SES)	3	Three studies exploring SES and BD that used a summary score showed inconsistent results. Two of them indicated an association between a higher social class and a slightly increased risk [n = 123–938], whereas one indicated no association [n = 2 million].
Tsuchiya et al.,[43]	Unemployment	4	2/4 community surveys suggested a weak trend towards an association between unemployment and an increased risk for BD, while one suggested such an association limited to male subjects. The last study implied no association.

Family-related factors

Tsuchiya et al.,[43]	Child parent relationship	4	2/4 studies found that a dysfunctional relationship with parents during childhood and adolescence was associated with an increased risk for BD. One study implied a similar association between a father's aggression and BD but not a mother's aggression, but the association disappeared after adjusting for subjects' psychiatric comorbidity. The fourth study did not support the association [n = 19–5,877].
Tsuchiya et al.,[43]	Childbirth	3	2/3 studies suggested that giving birth is associated with an increased risk for BD in women within a 3-month period after the birth [n = 36–50]. Another study has supported this association in women within a 12-month postpartum period [n = 1.2 million admitted female subjects followed up]
Tsuchiya et al.,[43]	Parental occupation	3	2/3 studies suggested an association between higher occupational class of parents and an elevated risk for BPD. 1/3 studies did not support the association.
Tsuchiya et al.,[43]	Parental loss	10	3/10 studies found a statistically significant association between early parental loss (e.g. a death and/or a separation for a long period during childhood and adolescence) and an increased risk for BD [n = 123–2.1 million births followed up]. One study suggested a non-significant trend towards the association [n = 79]. One study indicated that only parental separation but not death had such an association, but the statistical significance disappeared after controlling for other social adversities and parental psychiatric disorders [n = 5,877]. The rest of the studies did not support the association [n = 19–462]
Medical comorbidities			
Vannucchi et al.,[44]	Asperger syndrome	5	In adults with AS, BD comorbidity ranges from 6.0% to 21.4% of the cases. Among ASD patients, a positive family history for affective disorders can be found in the 17% and 13% of the family members of Autistic and Asperger subjects respectively.
Pope et al.,[41]	Endometriosis	3	1/3 studies found that women with pelvic pain related to endometriosis were more likely to have BD diagnosis as compared to women with chronic pelvic pain [n=39]. Another study found no significant differences in prevalence of BD between women with endometriosis as compared to controls [n = 67]. The

			last study reported only a prevalence of 62.7% of BD in women with endometriosis, with no control group to compare [n = 16].
Leo and Singh[45]	Migraine	5	Two clinic-based cross sectional studies found that the weighted mean prevalence of BD in migraine patients diagnosed based in the IHS criteria was 9.0% [n = 1,102] (3.2-fold greater than the 12-month prevalence rates of BPD in the general population). Two epidemiological studies from samples derived from the community found that the weighted mean prevalence of BD in patients diagnosed with the same criteria was 5.9% (2.1-fold greater than the 12-month prevalence rates of BD in the general population). The last study had the sample derived from a Health Maintenance Organization, and found a prevalence of 4.7% type I BD and 3.9% type II BD, and an OR = 4.7 (1.4–15.4) comparing migraine vs. non-migraine patients.
Cirillo et al.,[46]	Premenstrual syndrome or premenstrual dysphoric disorder	3	One study from a community sample, among 201 subjects with subthreshold premenstrual dysphoric disorder, 3.8 % had BD-I (OR= 5.3) and 0.3% had BD-II (OR 0.5). Among 74 PMDD patients, 5.7% had BD-I (OR 7.9) and 4.9% had BD-II (OR 8.1), while 0.8 % of subjects without PMDD [n = 828] had BD-I and 0.6% had BD-II. Another study found a prevalence of BPD prevalence of 9% in controls, 17% across depressed peri-MS women and 15% across non-depressed peri-MS women [n = 247]. The final study found that women with LLPDD (late luteal phase dysphoric disorder) scored higher on measures of hypomania than controls at all menstrual cycle phases (elevated, unstable moods, impulsiveness, overeactivity, irritability) [n = 30]
Infections			
Barichello et al.,[14]	BoDV perinatal infection	2	One of two studies demonstrated an association between BDV and BD, in bipolar patients BoDV circulating immune complexes were significantly elevated (45.3%, p = 0.001). However, Hornig and colleagues performed a case-control study utilizing molecular assays (RT-PCR and PCR) and serologic

			assays (ELISA and IFA) to evaluate the presence of BoDV virus or antibodies. The authors did not find immunoreactivity to He/80, Strain V, No/98, Universal, or Avian BoDV genotypes 1–4 in samples from bipolar patients
Barichello et al.,[14]	CMV perinatal infection	11	5/11 studies showed significant associations between CMV antibody levels and bipolar disorder. In one study, CMV IgG concentrations were higher in bipolar disorder compared to healthy controls. Another study showed that when groups of seropositive and seronegative bipolar disorder patients were compared, there was a decrease in the right hippocampal volume in CMV-positive patients ($p = 0.044$).
Barichello et al.,[14]	HSV-1 perinatal infection	5	2/5 studies showed an association between HSV-1 and bipolar disorder
Barichello et al.,[14]	HSV-2 perinatal infection	7	1/7 studies showed an association between HSV-2 and bipolar disorder
Barichello et al.,[14]	HHV-6 perinatal infection	2	No study demonstrated an association between HHV-6 and bipolar disorder
Barichello et al.,[14]	Influenza virus perinatal infection	3	2/3 studies demonstrated an association between influenza infection and bipolar disorder
Tsuchiya et al.,[43]	Influenza virus prenatal infection	5	One study implied a trend towards statistical significance for an increased risk of an occurrence of BD from exposure during the second trimester [n = 681 births followed up]. The other studies have not supported this trend [n = 525–2.1 million births followed up].
Barichello et al.,[14]	*Toxoplasma gondii* perinatal infection	9	5/9 studies showed an association of perinatal *T. gondii* infection and BD

Pregnancy- and birth-related factors			
Tsuchiya et al.,[43]	Birth seasonality	9	Six of the nine studies supported an association between a winter–spring birth and an elevated risk for BD, compared with general live-birth statistics [n = 294–18,021]. Three other studies did not support this association [n = 220–2.1 million births followed up].
Marangoni et al.,[16]	Indicators of fetal development (gestational age, birth weight, Apgar score)	3	One study found that pre-term birth (<37 weeks) alone, or associated with low birth-weight (<2,500 g) increased the risk of bipolar disorder only in females. A second study found a seven-fold increase in the risk of bipolar disorder in very preterm (<32 weeks), and a three-fold increased risk in preterm (32–36 weeks) of both sexes. The third study found that only planned delivery by c-section increased the risk of BD among several factors (Apgar score, birth presentation, birth type, uterine bleeding, induced labor).
Marangoni et al.,[16]	Physical and emotional stress during pregnancy (famine, war stress)	3	Prenatal exposure to war during the 1st trimester increased the risk for bipolar disorder (1 study). Prenatal famine (1 study) and maternal bereavement (1 study) were not associated with BD.
Tsuchiya et al.,[43]	Pregnancy and/or birth complications (PBCs)	7	3/7 studies suggested an association between a higher score and an elevated risk for BD [n = 110 measured by an early version of Lewis's score; n = 16–30 measured by Mirdal's score]. The other studies have not supported this. Results regarding summary scores of PBCs are conflicting. The inconsistency may result from the varying definitions of PBCs used.
Marangoni et al.,[16]	Smoking during pregnancy	2	In the Northern California Birth Cohort, a 2-fold increased risk of BD in offspring of mother who smoked during pregnancy was detected. In an independent sample this association was not replicated.
Individual factors			

Tsuchiya et al.,[43]	Handedness	2	BD was not associated with handedness [n = 36–88]
Tsuchiya et al.,[43]	Premorbid adjustment	3	1/3 studies indicated that premorbid adjustment [as measured by means of the Premorbid Adjustment Scale] of subjects with BD was poorer than that of normal controls during adolescence, but this was not so during childhood [n = 28]. Another study suggested a similar association by means of the Global Assessment of Functioning score [n = 1,709]. The third study suggested that disciplinary difficulties at school predict BPD [n = 462]
Tsuchiya et al.,[43]	Recent stressful events	4	3/4 studies suggested that an exposure to recent stressful events occurring within a short period prior to the first onset (e.g. within 6 months) was associated with an increased risk for BD [n = 31–50]. This was not supported by another study [n = 14]
Medications/substance use			
Marangoni et al.,[16]	*Cannabis*	3	Three community studies suggested an association with BD. The studies reported an aOR = 1.03 – 4.98
Marangoni et al.,[16]	Opioids	2	Two community studies suggested an association of opioids use and BPD. The first study reported an aOR 2.0 (1.1–3.7), with 1,499 exposed and 33,154 non-exposed. The second study reported an aOR = 2.12 (1.52–2.96) for weekly/daily use, with 461 exposed and 17,011 non-exposed.
Marangoni et al.,[16]	Tranquilizers/sedatives	2	One community study (subjects with lifetime alcohol, substance, MDD, anxiety disorder) found an association with BD [aOR = 1.50 (1.15–1.94); 3 years follow-up; n = 15,329]. Another community study found a non-significant effect of tranquilizers and sedatives [n = 17,405].

Abbreviations: aOR = adjusted odds ratio; **BoDV** = Borna disease virus; **BD** = bipolar disorder; **CMV** = cytomegalovirus; **EBV** = Epstein-Barr virus; **HHV-6** = Human herpes virus-6; **HSV** = herpes simplex virus; **IHS** = International Headache Society; **IQ** = Intelligence Quotient; **MDD** = major depressive disorder; **OR** = odds ratio; **VZV** = varicella-zoster virus