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Epidemiology and risk factors for bipolar disorder

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Abstract: Bipolar disorder is a multifactorial illness with uncertain aetiology. Knowledge of potential risk factors enables clinicians to identify patients who are more likely to develop bipolar disorder, which directs further investigation, follow up and caution when prescribing. Ideally, identifying directly causative factors for bipolar disorder would enable intervention on an individual or population level to prevent the development of the illness, and improve outcomes through earlier treatment. This article reviews the epidemiology of bipolar disorder, along with putative demographic, genetic and environmental risk factors, while assessing the strength of these associations and to what extent they might be said to be 'causative'. While numerous genetic and environmental risk factors have been identified, the attributable risk of individual factors is often small, and most are not specific to bipolar disorder but are associated with several mental illnesses. Therefore, while some genetic and environmental factors have strong evidence supporting their association with bipolar disorder, fewer have sufficient evidence to establish causality. There is increasing interest in the role of specific gene–environment interactions, as well as the mechanisms by which risk factors interact to lead to bipolar disorder.

Keywords: bipolar disorder, epidemiology, risk factors

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Introduction

Bipolar affective disorder (bipolar) is a multicomponent illness involving episodes of severe mood disturbance, neuropsychological deficits, immunological and physiological changes, and disturbances in functioning.[1] It is one of the leading causes of disability worldwide[2] and is associated with high rates of premature mortality from both suicide and medical comorbidities.[3,4]

The aetiology of bipolar is not well understood and research into the disorder lags behind disorders such as psychosis. However, the last decade has seen an expanding evidence into the genetics of the disorder, underlying developmental pathways, risks and vulnerability factors, gene–environment interactions and the putative features of the bipolar prodrome.

This article summarizes the research into demographic, genetic and environmental risk factors for the development of bipolar, with a focus on recent updates and the role of environmental triggers. To identify relevant literature, searches were conducted in PubMed and PsycINFO using the terms 'Bipolar Disorder', combined with 'risk factors' or 'epidemiology'. Results were reviewed with a focus on the most recent evidence and systematic reviews or large prospective studies, and further individual searches were then expanded for each risk factor category identified. A summary of the included studies relating to specific risk factors for bipolar are included in Table 1.

Epidemiology of bipolar disorder

Epidemiological studies have suggested a lifetime prevalence of around 1% for bipolar type I in the general population.[54,55] A large cross-sectional survey of 11 countries found the overall lifetime prevalence of bipolar spectrum disorders was 2.4%, with a prevalence of 0.6% for bipolar type I and 0.4% for bipolar type II.[56] Although findings

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Table 1. Studies investigating specific risk factors for bipolar disorder.

Study	Risk factor examined	Design	*n* (participants/ studies)	Summary of main findings
Genetics				
Craddock and Jones[5]	Familial genetic risk	Review	8 studies	Meta-analysis provided an overall estimate of the risk of bipolar in first-degree relatives of bipolar type I probands, OR = 7 (95% CI 5–10)
			6 studies	Pooled data provided an estimate of probandwise monozygotic concordance for bipolar of 50% (95% CI 40–60%)
Psychiatric GWAS Consortium Bipolar Disorder Working Group[6]	Multiple SNPs	Case-control GWAS data	11,974 bipolar patients 51,792 controls	Genome-wide significant evidence of association for rs4765913 in CACNA1C ($p = 1.52 \times 10^{-8}$, OR = 1.14) and rs12576775 in ODZ4 ($p = 4.40 \times 10^{-8}$, OR = 0.89)
Fan and Sklar[7]	BDNF Val66Met polymorphism	Meta-analysis	14 studies	Meta-analysis shows evidence for the association between Val66Met polymorphism in BDNF and bipolar (OR = 1.13, 95% CI 1.04–1.23, $p = 0.004$)
Cho *et al.*[8]	5-HTTL polymorphic region and intron 2 variable numbers of tandem repeat polymorphisms	Meta-analysis	17 studies	The review revealed significant pooled OR = 1.12 (95% CI 1.03–1.21) for the association between bipolar and 5-HTTL polymorphic region and OR = 1.12 (95% CI 1.02–1.22) for the intron 2 variable numbers of tandem repeat polymorphisms
Aas *et al.*[9]	Gene–environment interaction of childhood trauma and BDNF Val66Met variants	Cross sectional	141 bipolar patients	There was an additive effect between a history of childhood trauma and BDNF Val66Met, with Met carriers with high levels of childhood trauma having the lowest BDNF mRNA levels.
Oliveira *et al.*[10]	Gene–environment interaction of TLR2 polymorphism and early-life stress	Cross sectional	531 bipolar patients	A combined effect of TLR2 rs3804099 TT genotype and reported sexual abuse was observed on determining an earlier age at onset of bipolar (corrected $p = 0.02$)
Oliveira *et al.*[11]	Gene–environment interaction of TLR2 genetic variation and *Toxoplasma gondii* exposure	Case control	138 bipolar patients 167 healthy controls	There was a trend for an interaction between the TLR2 rs3804099 SNP and *T. gondii* seropositivity in conferring bipolar risk ($p = 0.017$, uncorrected)
Hosang *et al.*[12]	Gene–environment interaction of COMT Val^{158} Met polymorphism and stressful life events	Case control	482 bipolar patients 205 healthy controls	The impact of stressful life events was moderated by the COMT genotype for the worst depressive episode using a Val-dominant model (adjusted risk difference 0.09, 95% CI 0.003–0.18, $p = 0.04$)
De Pradier *et al.*[13]	Gene–environment interaction of serotonin transporter gene polymorphism, cannabis and childhood sexual abuse	Case control	137 bipolar patients	The short allele of the 5-HTTLPR polymorphism and cannabis abuse were significantly more frequent among patients with psychotic symptoms than in those without ($p = 0.01$ and $p = 0.004$, respectively), while childhood sexual abuse was not

Table 1. (Continued)

Study	Risk factor examined	Design	*n* (participants/ studies)	Summary of main findings
Prenatal and perinatal factors				
Barichello *et al.*[14]	Perinatal infections	Systematic review	23 studies	Studies investigated exposure to several pathogens namely cytomegalovirus, Epstein–Barr virus, herpes simplex virus-1, herpes simplex virus-2, human herpesvirus 6, *T. gondii*, influenza, and varicella zoster virus; overall, studies provided mixed evidence
Sutterland *et al.*[15]	*T. gondii*	Meta-analysis	11 studies	Significant association of *T. gondii* infection with bipolar, OR = 1.52 (95% CI 1.06–2.18, $p = 0.02$)
De Barros *et al.*[16]	*T. gondii*	Meta-analysis	8 studies	*T. gondii* infection is associated with bipolar (OR = 1.26, 95% CI 1.08–1.47)
Scott *et al.*[17]	Obstetric complications	Meta-analysis	8 studies	The pooled OR for the exposure to obstetric complications on subsequent development of bipolar was 1.15 (95% CI 0.62–2.14)
Childhood trauma				
Watson *et al.*[18]	Childhood trauma	Case control	60 bipolar patients 55 controls	Significantly higher rates of childhood trauma were observed in patients with bipolar compared with controls; logistic regression, controlling for age and sex, identified emotional neglect to be the only significant childhood trauma questionnaire subscale associated with bipolar
Etain *et al.*[19]	Childhood trauma	Case control	260 bipolar patients 94 controls	The Childhood Trauma Questionnaire total score was higher for bipolar than controls; the presence of multiple trauma was significantly more frequent in bipolar than controls (63% *versus* 33%); multiple logistic regression suggested that only emotional abuse was associated with bipolar with a suggestive dose effect
Garno *et al.*[20]	Childhood trauma	Cross sectional	100 bipolar patients	Histories of severe childhood abuse were identified in about half of the sample and were associated with early age at illness onset; abuse subcategories were strongly inter-related; multiple forms of abuse showed a graded increase in risk for both suicide attempts and rapid cycling
Palmier-Claus *et al.*[21]	Childhood trauma	Meta-analysis	19 studies	Childhood adversity was 2.63 times (95% CI 2.00–3.47) more likely to have occurred in bipolar compared with nonclinical controls; the effect of emotional abuse was particularly robust (OR = 4.04, 95% CI 3.12–5.22)

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Table 1. (Continued)

Study	Risk factor examined	Design	*n* (participants/ studies)	Summary of main findings
Agnew-Blais and Danese[22]	Childhood trauma and outcomes in bipolar	Meta-analysis	30 studies	Patients with bipolar and history of childhood maltreatment had greater severity of mania, depression and psychosis, higher risk of comorbidity, earlier age of onset, higher risk of rapid cycling, greater number of manic or depressive episodes, and higher risk of suicide attempt compared with those with bipolar without childhood maltreatment
Daruy-Filho *et al*.[23]	Childhood trauma and outcomes in bipolar	Systematic review	19 studies	Childhood maltreatment predicted worsening clinical course of bipolar; childhood maltreatment can be strongly associated with early onset of disorder, suicidality, and substance abuse disorder in patients with bipolar
Upthegrove *et al*.[24]	Childhood trauma and psychosis in bipolar	Cross-sectional	2019 bipolar patients	There was no relationship between childhood events or abuse and psychosis; childhood events were not associated with an increased risk of persecutory or other delusions; significant associations were found between childhood abuse and auditory hallucinations, strongest between sexual abuse and mood-congruent or abusive voices
Psychological stressors				
Lex *et al*.[25]	Life events prior to relapse	Meta-analysis	42 studies	Patients with bipolar reported more life events before relapse compared with euthymic phases; they also experienced more life events relative to healthy individuals and to physically ill patients; no significant difference in the number of life events was found comparing bipolar to unipolar depression and schizophrenia
Kessing *et al*.[26]	Life events and first admission for mania	Case-control	1565 bipolar patients 31,300 controls	Suicide of a mother or of a sibling was associated with increased risk of first psychiatric admission with mania/mixed episode; death of a relative by other causes was not associated with increased risk of admission; recent unemployment, divorce, or marriage also showed moderate effects
Koenders *et al*.[27]	Life events and mood episodes	Prospective cohort	173 bipolar patients	Negative life events were significantly associated with subsequent severity of mania and depressive symptoms and functional impairment, whereas positive life events only preceded functional impairment due to manic symptoms and mania severity; for the opposite temporal direction, mania symptoms preceded the occurrence of positive life events, and depressive symptoms preceded negative life events

Table 1. (Continued)

Study	Risk factor examined	Design	*n* (participants/ studies)	Summary of main findings
Substance misuse				
Gibbs *et al*.[28]	Cannabis	Meta-analysis	6 studies (2 in meta-analysis)	Studies support an association between cannabis use and the exacerbation of manic symptoms in those with previously diagnosed bipolar; furthermore, a meta-analysis of 2 studies suggests that cannabis use is associated with an approximately threefold (OR = 2.97, 95% CI 1.80–4.90) increased risk for the new onset of manic symptoms
Henquet *et al*.[29]	Cannabis	Prospective cohort	4815 (general population)	Use of cannabis at baseline increased the risk for manic symptoms during follow up (adjusted OR = 2.70, 95% CI 1.54–4.75), adjusted for age, sex, educational level, ethnicity, marital status, neuroticism, use of other drugs, use of alcohol, depressive symptoms and manic symptoms at baseline
Tijssen *et al*.[30]	Cannabis	Prospective cohort	705 (general population)	Onset of manic symptoms was associated with cannabis use (OR = 4.26, 95% CI 1.42, 12.76; $p < 0.01$)
Van Laar *et al*.[31]	Cannabis	Prospective cohort	4681 (general population)	After adjustment for strong confounders, any use of cannabis at baseline predicted an increase in the risk of first bipolar episode (OR = 4.98; 95% CI 1.80–13.81)
Feingold *et al*.[32]	Cannabis	Prospective cohort	34,653 (general population)	Weekly to almost daily cannabis use was associated with increased incidence of bipolar (adjusted OR for weekly to daily use = 2.47, 95% CI 1.03–5.92); daily use was not (adjusted OR = 0.52, 95% CI 0.17–1.55)
Marwaha *et al*.[33]	Cannabis	Prospective cohort	3370 (general population)	Cannabis use at least two to three times weekly was associated with later hypomania (OR = 2.21, 95% CI 1.49–3.28) after adjustment; there was a dose–response relationship (any use *versus* weekly); cannabis use mediated the association of both childhood sexual abuse and hypomania, and male sex and hypomania
Schepis and Hakes[34]	Opioids, tranquilizers, stimulants and sedatives	Prospective cohort	34,653 (general population)	Lifetime and past year nonmedical use of prescription medications (NUPM) increased risk for new onset of psychopathology with particular risk for non-NUPM substance use and bipolar
Schepis and Hakes[35]	Opioids, tranquilizers, stimulants and sedatives	Prospective cohort	34,653 (general population)	Incidence of bipolar was related to opioid NUPM, evidenced in a stepwise risk progression, based on the NUPM frequency
Kenneson *et al*.[36]	Substance use disorders	Cross sectional	5217 (general population)	Substance dependence was associated with higher odds of mood disorders than was abuse; among the specific mood disorders, the increased odds of developing bipolar were particularly high among individuals with drug dependence

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Study	Risk factor examined	Design	*n* (participants/ studies)	Summary of main findings
Anthony and Petronis[37]	Cocaine	Nested case control	42 manic patients 164 controls	Subjects reporting cocaine use during follow up were 5.5 times more likely to experience the mania syndrome ($p = 0.006$)
Medical comorbidities				
Forty *et al*.[38]	Medical comorbidities	Cross sectional	1720 bipolar patients	There were significantly increased rates of several medical illnesses in bipolar; a high medical illness burden was associated with a history of anxiety disorder, rapid cycling, suicide attempts and mood episodes with a typically acute onset
Faedda *et al*.[39]	Clinical risk factors	Systematic review	16 studies	Despite heterogeneity in methods, findings across studies were consistent; clinical risk factors of bipolar were early-onset panic attacks and disorder, separation anxiety and generalized anxiety disorders, conduct symptoms and disorder, ADHD, impulsivity and criminal behaviour
Tseng *et al*.[40]	Irritable bowel syndrome (IBS)	Meta-analysis	6 studies	The prevalence rate of bipolar was significantly higher in the IBS patients than in the controls (OR = 2.48, 95% CI 2.35–2.61, $p < 0.001$)
Wu *et al*.[41]	Asthma	Meta-analysis	4 studies	There were significantly higher prevalence rates of bipolar in asthmatic patients than in healthy controls (OR = 2.12, 95% CI 1.57–2.87, $p < 0.001$)
Zhao *et al*.[42]	Obesity	Meta-analysis	9 studies	Meta-analysis suggests that obesity is associated with increased prevalence of bipolar (OR = 1.77, 95% CI 1.40–2.23, $p < 0.001$)
Fornaro and Stubbs[43]	Migraine	Meta-analysis	14 studies	The overall pooled prevalence of migraine in bipolar was 34.8% (95% CI 25.54–44.69).
Perry *et al*.[44]	Traumatic brain injury (TBI)	Meta-analysis	3 studies	A random-effects meta-analysis revealed a significant association of prior TBI with subsequent neurologic and psychiatric diagnosis, including bipolar (OR = 1.85, 95% CI 1.17–2.94, $p < 0.01$)
Liang and Chikritzhs[45]	Asthma	Retrospective cohort	8841 (general population)	Participants who had a history of asthma that lasted 6 months or more were at higher risk of panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, bipolar, mania and hypomania
Wei *et al*.[46]	Asthma	Prospective cohort	49,804 (general population)	The atopic cohort had an increased risk of developing bipolar (HR 2.51, 95% CI 1.71–3.67) compared with the nonatopic cohort
Carta *et al*.[47]	Multiple sclerosis (MS)	Case control	201 MS patients 804 controls	Compared with controls, MS patients had a higher lifetime prevalence of MDD ($p < 0.0001$), bipolar type I ($p = 0.05$), bipolar II ($p < 0.0001$) and cyclothymia ($p = 0.0001$)

Table 1. (Continued)

Study	Risk factor examined	Design	*n* (participants/ studies)	Summary of main findings
Nabavi *et al*.[48]	Anxiety disorders	Meta-analysis	52 studies	The rate of lifetime comorbidity was as follows: panic disorder 16.8% (95% CI 13.7–20.1), generalized anxiety disorder 14.4% (95% CI 10.8–18.3), social anxiety disorder 13.3% (95% CI 10.1–16.9), post-traumatic stress disorder 10.8% (95% CI 7.3–14.9), specific phobia 10.8% (95% CI 8.2–13.7), obsessive compulsive disorder 10.7% (95% CI 8.7–13.0) and agoraphobia 7.8% (95% CI 5.2–11.0); the lifetime prevalence of any anxiety disorders in bipolar was 42.7%
Large studies investigating multiple risk factors				
Tsuchiya *et al*.[49]	Demographic factors, perinatal factors, personal background, recent stressful life events, family dysfunction, parental loss, history of medical comorbidities	Systematic review	Around 100 studies	Suggestive findings have been provided regarding pregnancy and obstetric complications, winter–spring birth, stressful life events, traumatic brain injuries and multiple sclerosis with a later risk for bipolar; however, evidence is still inconclusive; childbirth is likely to be a risk factor
Marangoni *et al*.[50]	Maternal influenza during pregnancy, indicators of foetal development, cannabis, cocaine, opioids, tranquilizers, stimulants, sedatives, parental loss, adversities, abuses, brain injury	Systematic review	22 longitudinal studies	Only preliminary evidence exists that exposure to viral infection, substances or trauma increases the likelihood of bipolar
Bortolato[51]	51 environmental risk factors	Umbrella review	16 studies	Only irritable bowel syndrome emerged as a risk factor for bipolar supported by convincing evidence, and childhood adversity was supported by highly suggestive evidence; asthma and obesity were risk factors for bipolar supported by suggestive evidence, and seropositivity to *T. gondii* and a history of head injury were supported by weak evidence
Gilman[52]	Demographic factors, characteristics of depression, prior psychopathology, childhood trauma	Prospective cohort	6214 cases of MDD	Demographic risk factors for the transition from MDD to bipolar included younger age, black race/ethnicity, and less than high school education; clinical characteristics of depression were not associated with diagnostic conversion; prior psychopathology was associated with the transition to bipolar: history of social phobia (OR = 2.20, 95% CI 1.47–3.30) and generalized anxiety disorder (OR = 1.58, 95% CI, 1.06–2.35); environmental stressors that predicted the transition to bipolar include: history of child abuse (OR = 1.26, 95% CI 1.12–1.42) and past-year problems with social support group (OR = 1.79, 95% CI 1.19–2.68)

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Table 1. (Continued)

Study	Risk factor examined	Design	*n* (participants/ studies)	Summary of main findings
Mortensen *et al.*[53]	Family history, urbanicity of birth place, season of birth, birth order, influenza epidemics during pregnancy, and early parental loss	Prospective cohort	2.1 million (general population) 2299 bipolar patients	Those with a first-degree relative with bipolar had a 13.63-fold increased risk (95% CI 11.81–15.71); children who experienced maternal loss before their fifth birthday had a 4.05 (95% CI 1.68–9.77) increased risk of bipolar; no other consistent associations were found

ADHD, attention deficit hyperactivity disorder; BDNF, brain-derived neurotrophic factor; bipolar, bipolar disorder; CI, confidence interval; COMT, Catechol-*O*-methyltransferase; 5-HTTL, serotonin system gene; 5-HTTLPR, serotonin-transporter-linked polymorphic region; GWAS, genome-wide association study; HR, hazard ratio; MDD, major depressive disorder; mRNA, messenger ribonucleic acid; OR, odds ratio; SNP, single nucleotide polymorphism; TLR2, toll-like receptor 2.

varied across different countries, this suggested a lower prevalence of bipolar type I and II than previous studies,[55,57] while the prevalence of bipolar type I in USA was found to be 1%, slightly higher than the other countries. It is unclear whether differences were due to more stringent diagnostic criteria used in this study, or true differences in rates of bipolar across countries and ethnic groups. In one of the very few epidemiological investigations in England, the recent Adult Psychiatric Morbidity Survey 2014 found lifetime prevalence of likely bipolar was 2%. The measurement method suggests that this was an underestimate, but the study did not distinguish bipolar subtypes.[58] A recent meta-analysis of 25 studies found a pooled lifetime prevalence of 1.06% and 1.57% for bipolar type I and II, respectively, although the majority of the included studies were from North or South America.[59] Nevertheless, a similar prevalence has been found in the UK, Germany and Italy,[60] and a lifetime prevalence between 0.1–1.83% was found in a systematic review of studies from African countries.[61]

The reason for international variations in the prevalence of bipolar is not entirely clear, and ethnicity,[49] cultural factors[62] and variations in diagnostic criteria and study methodology[59] may each have an impact. The evidence for differing rates of bipolar in different ethnicities is conflicting, with some studies showing higher rates in Caucasians[63,64] and others in nonwhite populations.[65] A systematic review found no clear evidence for differences across ethnic groups, and suggested individual study differences may be related to cultural factors, migration and higher rates of misdiagnosis of black ethnic groups as having schizophrenia rather than bipolar.[49] With regards to sex, several studies report equal distribution in bipolar,[49] while others have identified a higher prevalence of manic episodes and bipolar type I in males and higher rates of bipolar type II in females.[56] Overall, the evidence is not sufficiently strong to deviate from the view that bipolar appears to have a roughly equal distribution across sex and ethnicity.

The mean age of onset for bipolar appears to be in the early twenties,[56] although findings vary between 20–30 years.[55] A bimodal distribution of the incidence of bipolar has been suggested,[66] supported by a large population-based cohort study, which found two peaks in age of onset at 15–24 years and at 45–54 years.[67] However, age of onset estimates are very difficult to define accurately for bipolar, given the long periods of untreated illness, when symptoms can be nascent or apparent without individuals accessing services, which is often used as the measure of onset in many studies.[68] Moreover, there appear to be differences in the presentation and clinical course of bipolar depending on age of onset,[69] with higher rates of psychiatric and medical comorbidities such as suicidality and vascular disease in later-onset mania.[70]

A number of studies have investigated rates of bipolar according to sociodemographic variables, with generally inconsistent findings.[49] There is some evidence of higher rates in low income, unemployed and unmarried groups,[49] although the social disruption caused by severe mental illness giving rise to such associations cannot be ruled out.[54] Conversely, an interesting finding among some studies is that higher socioeconomic status and higher occupational level, as well as

creativity,[54,71] are associated with increased risk of bipolar,[72,73] which is opposite to that of unipolar depression and schizophrenia.[54] However, these studies are limited by small sample sizes and a lack of replication.[74] Explanations for this association include the possibility of referral bias for those with higher socioeconomic status, while some have suggested that those with high-functioning creative traits may confer a genetic risk of bipolar.[54]

There is also emerging evidence for an association between urban environments and increased rates of bipolar.[49] While the evidence is stronger for schizophrenia, where there have been multiple suggested explanations,[75] the reason for the association between urbanization and bipolar is less clear. However, a cohort study found that there was a strong association between urban residence and the incidence of psychotic bipolar, but no association for bipolar without psychosis.[76] This may suggest that urban residence is a transdiagnostic risk factor for psychotic illness rather than bipolar *per se*.

Genetics and gene environment interactions

The contribution of genetic factors to bipolar has long been identified, with evidence from twin studies suggesting monozygotic concordance of between 40–70%, and lifetime risk in first-degree relatives is 5–10%; around seven times higher than the general population risk.[5] However, relatives of patients with bipolar are more likely to develop unipolar depression than bipolar themselves, suggesting the genetic risk transcends diagnostic categories.[5] There is also evidence of shared genetic risk between bipolar, schizophrenia and autism.[77,78] Nonetheless, bipolar clearly does not follow a Mendelian pattern of inheritance, and linkage studies have not identified individual genes with a strong association with the disorder.[79] The genetic risk for bipolar in part is likely due to multiple single nucleotide polymorphisms, which are highly prevalent in the general population and confer a very small increased risk individually.[80] Technological advances have allowed for genome-wide association studies that have pooled data and identified multiple genetic loci associated with bipolar patients, suggesting aggregated polygenic risk.[6]

Whilst many important genetic loci have been identified, how these translate to risk of illness is a second frontier of discovery. Studies have identified polymorphisms in genes coding for brain-derived neurotrophic factor (BDNF) to be associated with bipolar.[7] BDNF is suspected to be involved in the pathogenesis of bipolar as well as being a potential biomarker of disease activity.[81] Associations with catechol-*O*-methyl transferase (COMT) and monoamine transporters have also been observed.[8,82] Genes for voltage-gated calcium channel subunits such as CACNA1C are located near to single nucleotide polymorphisms that have an association with bipolar, as well as proteins involved in cell signalling such as ODZ4,[6] and genes encoding for gamma-aminobutyric acid (GABA) receptor subunits.[83] The fact that many of the medications used as prophylactic agents in bipolar act on calcium channels or GABA receptors[84] suggests these proteins may be involved in the neurobiology of the disorder, and this evidence is guiding the search for new therapeutic targets.[85]

However, it is clear that the effect size of each single nucleotide polymorphism is very small. For example, the odds of having bipolar in those with the polymorphism around CACNA1C is 1.14, and the majority of those with this polymorphism do not go on to develop the disorder.[6,80] There has therefore been increasing interest in the role of how gene–environment interactions contribute to the onset of bipolar, although this remains an under-researched area, compared with schizophrenia.[86,87] Nevertheless, interaction between childhood abuse and BDNF gene polymorphisms have been shown in several studies,[9,86] while toll-like receptor 2 polymorphisms may interact with stressful life events and *Toxoplasma gondii* infection to increase the risk of bipolar.[10,11] A COMT polymorphism has been found to interact with stressful life events for bipolar depressive episodes,[12] while serotonin transporter genes have interactions with cannabis use on the presence of psychotic symptoms in bipolar.[13] With the increasing ability of genome-wide association studies to identify polymorphisms conferring a very small increased risk, further study of how these genes interact with environmental factors to trigger bipolar is required.

Environmental risk factors

Prenatal and perinatal factors

Prenatal viral infections have been implicated in a number of mental illnesses, including bipolar.[88–90] A recent review by Barichello and colleagues[14]

investigated associations between bipolar and 10 infectious agents. Findings between studies were generally inconsistent, and no association was found for Epstein-Barr virus, human herpesvirus 6 or varicella zoster virus. Five of the eleven studies investigating cytomegalovirus found an association between antibody levels and bipolar, while two studies found an association between maternal influenza infection and bipolar with psychosis,[91,92] although other studies found no association.[93–95] None of these studies were prospective or longitudinal and it is uncertain whether these infections occurred during pregnancy or subsequently. Therefore, the evidence for maternal viral infection as a risk factor for bipolar remains weak, overall.

However, there is stronger evidence for an association between bipolar and seropositivity for *T. gondii* infection, demonstrated in two recent meta-analyses.[15,16] The first included 11 studies and demonstrated overall increased odds of having bipolar in those with immunoglobulin G (IgG) to *T. gondii*, with an odds ratio of 1.52 (95% confidence interval 1.06–2.18).[15] A second meta-analysis of eight studies also found a significant association between bipolar and *T. gondii* seropositivity, with an odds ratio of 1.26 (95% confidence interval 1.08–1.47).[16] However, the included studies were not prospective and it remains uncertain when *T. gondii* exposure occurred. Notwithstanding, there is preclinical evidence suggestive of a relationship between *T. gondii* and development of mental illness, with studies showing behavioural changes in mice[96] and humans.[97,98] Moreover, there is evidence that infection with *T. gondii* causes changes in dopamine metabolism leading to increased dopamine production,[99] similar to that suggested as a potential mechanism for manic episodes in bipolar.[100] Furthermore, there is evidence that following *T. gondii* infection, the local inflammatory response leads to alteration in cytokines,[101] such as IL-6,[102] which have been implicated in mental illness and bipolar specifically,[103] and may be related to cognitive deterioration in this patient group.[102]

Evidence regarding other prenatal exposures such as maternal smoking and severe psychological stressors are inconsistent, with only a small number of studies investigating these factors.[50] Obstetric complications have generated interest as a risk factor for later development of bipolar,[104] but a meta-analysis found no significant evidence for this association,[17] and bipolar patients were less likely to have experienced obstetric complications than those with schizophrenia. A systematic review by Marangoni and colleagues[50] identified prospective studies which suggested extreme prematurity (less than 32 weeks' gestation) conferred a significant risk of developing bipolar.

In general, the evidence for prenatal and perinatal factors as an independent risk factor for developing bipolar is relatively weak and inconsistent, and such factors appear to confer greater risk for developing other mental disorders, such as schizophrenia.[17] The evidence for *T. gondii* infection is more substantial, while maternal CMV and influenza infection warrant further investigation as to their associations with bipolar.

Postnatal factors

Childhood maltreatment. Childhood maltreatment is a well-studied environmental risk factor with high-quality evidence that it confers a risk for later development of bipolar,[51] although it is also associated with behavioural problems and other mental illnesses.[105,106] When investigating specific subtypes of abuse, several studies have identified a link between emotional abuse or emotional neglect and the later the development of bipolar,[18,19] while emotional abuse appears to be the most frequent subtype of abuse experienced in bipolar patients.[20] A recent high quality meta-analysis of childhood adversity in bipolar patients compared with healthy controls found significant associations between development of bipolar and prior physical, sexual and emotional abuse, and physical and emotional neglect.[21] The largest association was for emotional abuse which was four times more likely to have occurred in bipolar patients than in controls.[21] Moreover, higher rates of childhood adversity were found in patients with bipolar compared with unipolar depression, although rates were similar to schizophrenia.[21] Gilman and colleagues[52] also found that a history of childhood abuse increased the risk of transitioning to bipolar following a depressive episode. This suggests that abuse and neglect during childhood confer some specific risk to more severe forms of mental illness.

As well a risk factor, childhood maltreatment appears to be associated with poorer clinical outcomes in bipolar, with more severe and more frequent mood episodes,[22] earlier onset, increased risk of suicide and comorbid substance misuse.[23] The relationship between childhood abuse and

the severity of bipolar adds further weight to its position as a potential causative factor for the disorder. Notwithstanding, childhood maltreatment does not appear to be specifically related to psychotic symptoms or a diagnosis of bipolar type I over type II.[21,24]

Whilst it seems likely that childhood traumatic events increase the risk of bipolar, why or how they do this remains unclear but is the focus of ongoing research. Traumatic events are linked to increased levels of affective instability or emotional dysregulation more generally in people with bipolar and this represents one possible mechanism of action.[107] Other dimensions of psychopathology such as hostility and impulsivity, along with affective instability have been shown to mediate the association between childhood maltreatment and outcomes in bipolar,[108] while alterations in the hypothalamic–pituitary–adrenal (HPA) axis,[109] increased levels of BDNF and inflammatory cytokines[110] and reduced limbic grey matter volume[111] represent possible neurobiological underpinnings of the effect of childhood trauma and how this may lead to later psychopathology and bipolar, in particular.

It should be noted that there is difficulty in determining to what extent childhood maltreatment is a cause or consequence of the predisposition to develop bipolar, as parental psychopathology may confer a genetic risk of the disorder, as well as increased risk of childhood maltreatment.[112] The retrospective nature of these studies introduces the possibility of recall bias with regard to childhood adversity, and at present, there are few prospective studies investigating the association between childhood maltreatment and bipolar.

Psychological stressors. Recent stressful life events are known to affect the course of bipolar,[113] although their relationship with the onset of the disorder has been less extensively investigated compared with unipolar depression.[49] A systematic review by Tsuchiya and colleagues[49] identified four studies investigating stressful life events prior to the onset of bipolar, the three largest of which found an increased risk of onset within 6 months of such events. A meta-analysis found that patients experience more life events prior to relapses into either manic or depressive episodes than during euthymic periods, although the rate of significant life events prior to the onset of bipolar was similar to unipolar depression.[25] Other studies have supported the association between life events and the onset of bipolar, including a large case-control study which found that stressful life events were associated with a first hospitalization for a manic episode, particularly suicide of a first-degree relative, but also recent marriage, divorce, disability or unemployment.[26] There are a number of confounders to these associations, particularly with regard to suicide of a first-degree relative, where genetic factors play a significant role, as death due to other causes was not associated with hospitalization.[26] A bidirectional relationship has also been suggested for stressful life events in bipolar, as there is evidence that these events occur both prior to and following mood episodes.[27]

There is also evidence for specific life events conferring a risk for bipolar, such as early parental loss and childbirth. The systematic review by Tsuchiya and colleagues[49] found that only 3 of the 10 studies investigating parental loss identified an association with bipolar, although it is noteworthy that one of these was a very large cohort study which adjusted for a number of confounders, including family history of mental illness.[53] A meta-analysis found that childbirth specifically increased the risk of mood episodes in patients with bipolar, more so than relapses in unipolar depression or schizophrenia.[25] Tsuchiya and colleagues[49] identified only three studies investigating onset of bipolar following childbirth, but each found an association with subsequent bipolar diagnosis within 12 months. This is perhaps unsurprising, considering the association between puerperal psychosis and bipolar,[114] but it is unclear whether the reason for the association is genetic, hormonal or related to childbirth as a life event.

However, life events are relatively nonspecific in relation to mental and physical illness, and appear to be associated not only with the onset of bipolar disorder and unipolar depression, but also psychosis,[115] anxiety disorders,[116] ischaemic stroke[117] and circulatory disorders.[118] While gene–environment interactions have been identified between life events and the onset of specific disorders,[12] the use of checklists to identify life events in such studies has been criticized as lacking sufficient detail with regard to the severity and context of such events.[119] These methodological issues make it difficult to establish causation between life events and development of bipolar.

Substance misuse. Bipolar is frequently comorbid with misuse of substances, including cannabis,

opioids, cocaine, sedatives and alcohol,[50,52] and causality has been suggested in both directions.[120] While the high level of comorbidity is undeniable, causality it much harder to ascertain as there is often difficulty in establishing the temporal relationship between substance misuse and the onset of mental illness. This is compounded by the relative lack of prospective, longitudinal studies examining the relationship between substance misuse and bipolar.[121]

There is increasing evidence that cannabis use can act as a risk factor for the development of bipolar as well as psychotic disorders. A recent systematic review by Gibbs and colleagues[28] identified several studies supporting a link between cannabis use and subsequent relapse of manic symptoms. This review also included a meta-analysis of two large prospective cohort studies[29,30] which found that cannabis use almost trebled the risk of new-onset subthreshold manic symptoms after adjusting for potential confounding factors. A further large prospective cohort study found cannabis use increased the risk of first episode bipolar by a factor of 5 after adjusting for confounders, and demonstrated evidence of a dose–response relationship.[31] Other studies were more equivocal, finding increased risk of bipolar only in those with weekly to daily cannabis use and no dose–response relationship,[32] or increased risk only in those with a past year episode of depression.[52] Recently, a prospective analysis has demonstrated cannabis use at age 17 is associated with hypomania in young adulthood independent of psychotic symptoms and other important confounders. Further path analysis indicated cannabis use is one mechanism by which childhood abuse translates to increased risk of bipolar symptoms.[33]

Other substances of abuse are also important in the risk of bipolar. Prospective studies have linked opioid use to an increased risk of developing bipolar, which is greater than other mood disorders.[34,35] A further study found that alcohol and drug abuse or dependence before the age of 25 increased the odds of developing subsequent bipolar, although differences between specific drugs were not examined.[36] Cocaine use has also been implicated, although is less well studied,[37] and as stimulant use can precipitate mania or similar symptoms,[120] this may lead to inappropriate diagnosis of bipolar,[122] rather than act as a causative factor.

There are significant confounding factors to associations between bipolar and substance misuse, which remain despite attempts at adjustment within the studies. It has been suggested that cannabis may serve as self medication for bipolar illness,[123] and therefore may be used by those with subthreshold symptoms prior to the onset of bipolar. Furthermore, there is evidence that shared genetic factors confer risk for developing both substance misuse disorders and bipolar,[124,125] while childhood maltreatment is also associated with both disorders.[20,22,113]

Medical comorbidity

Bipolar is known to be comorbid with a number of medical and psychiatric conditions.[51,38,39] There are multiple reasons for this, including shared genetic and environmental vulnerabilities, consequences of treatment, recognition bias on the part of clinicians as well as the potential for a direct causal relationship in either direction.

There is strong evidence for the association between bipolar and irritable bowel syndrome (IBS)[51] highlighted in a recent large meta-analysis of retrospective cohort studies.[40] However, potentially important confounders, such as antidepressant use, were not adjusted for. There is also evidence that both disorders may share inflammatory[51,126,127] and stress-related aetiologies,[25,128] which could give rise to this association.

Similarly, recent meta-analyses have shown asthma,[41] obesity,[42] migraine[43] and head injury[44] are associated with bipolar. The evidence for these associations is mediated by the relatively small number of studies included, most of which were cross sectional and lacked data to adjust for confounding factors. However, for asthma, a retrospective cohort[45] and large prospective study[46] also support the association, which may be mediated by shared inflammatory pathways[126,127] or the use of corticosteroids during early childhood.[38,45] Medication and lifestyle factors significantly confound the association with obesity, for which there are few prospective studies and weak evidence for a directly causal relationship, while the association with traumatic brain injury is potentially confounded by 'accident proneness' or physical abuse.[129] There is evidence of increased prevalence of bipolar in patients with multiple sclerosis (MS)[47,130] which cannot be completely accounted for by steroid-induced mania, and in some instances, psychiatric symptoms may predate the diagnosis of MS.[131] However, other studies have not supported this association.[38]

A meta-analysis reported high lifetime prevalence of anxiety disorders in bipolar patients,[48] while ADHD, conduct disorders, aggression and impulsivity also appeared to increase risk of developing bipolar.[39]

Prodromal features and bipolar at-risk criteria

It is becoming increasingly recognised that bipolar, like schizophrenia, has a prodromal phase which can be identified prior to development of the full illness.[132,133] However, one issue with research into this area is the potential conflation of the concepts of a prodrome for bipolar, referring to symptoms that can be retrospectively identified as preceding the onset of the disorder, and a 'risk syndrome' consisting of clinical features, comorbidities and risk factors which increase the risk of later developing bipolar.[134] At present, neither prodrome nor risk syndrome has been fully defined, although the bipolar at-risk (BAR) assessment tool has demonstrated predictive validity and reliability for identifying those at risk of bipolar, with around 23% of those identified transitioning to mania or hypomania.[135] A study using the BAR assessment tool criteria found that cyclothymia had the best overall clinical utility for case finding and screening when focusing on depressed youths with an early transition to bipolar. The clinical utility profile of subthreshold mania, antidepressant emergent elation, family history of bipolar and atypical depression suggested they were better for screening out noncases.[136] However, other studies have questioned the associations between clinical characteristics of depression and transition to bipolar.[52]

The low positive predictive value of these precursors reduces their usefulness, and of the significant proportion of those 'at risk' who do not go on to develop bipolar there is limited understanding of what factors are protective against this transition, or how this group differs from those who do develop bipolar.[134] Future research should focus on identifying differences in this group, while continuing to refine screening tools for prodromal identification and risk syndromes in prospective studies. Focusing on transition to first-episode mania may have greater reliability in identifying cases.[134]

First-episode bipolar mania has an annual incidence of around 5 per 100,000 of population,[137] and peak incidence occurs between 21–25 years.[138] Although the incidence of first-episode mania is equal between males and females,[137] studies have found that age of onset is around 5 years earlier for men.[139] A meta-analysis of longitudinal studies of first-episode mania found that 87.5% of patients achieve syndromal recovery within the first year, meaning they no longer meet criteria for diagnosis. However, the symptomatic recovery rates (essentially defined as being symptom free) were 62.1% within the first year, while 41% experience a recurrence of a manic, mixed or depressed episode over the same period.[140] Considering the relatively poor outcome in such patients, the potential to identify a risk syndrome or prodromal phase of bipolar in those presenting with a depressive illness offers the opportunity to intervene at an earlier stage, leading to improved outcomes.[68]

Conclusion

Risk factors for bipolar are numerous, both genetic and environmental, but low attributable risk, inconsistency of results, inability to identify the temporality of the relationship, lack of a clear biological mechanism and the nonspecific nature of many risk factors means that causation is difficult to assign in an individual patient. Studies of environmental risk were also unable to completely adjust for confounding. However, there is evidence that severity of bipolar is related to childhood emotional abuse and the degree of cannabis misuse, suggesting a dose–response relationship. The association with *T. gondii* is also strong, with some evidence of biological plausibility, although concerns remain about temporality. Bipolar is associated with medical comorbidities such as IBS and asthma, which may point towards shared inflammatory pathophysiology of the disorders, while other psychiatric disorders and clinical features that predate the onset of bipolar may point towards an identifiable 'risk syndrome'. Future research into these risk factors should focus on establishing temporality, whether the severity of bipolar is linked to the risk factor, and identifying potential neurobiological and environmental mechanisms to explain the associations. Finally, research into gene–environment interactions is required to link existing evidence on genetic and environmental risks.

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References

1. Marwaha S, Durrani A and Singh S. Employment outcomes in people with bipolar disorder: a systematic review. *Acta Psychiatr Scand* 2013; 128: 179–193.
2. Krahn GL. WHO World Report on Disability: a review. *Disabil Health J* 2011; 4: 141–142.
3. Hayes JF, Miles J, Walters K, *et al.* A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta Psychiatr Scand* 2015; 131: 417–425.
4. Crump C, Sundquist K, Winkleby MA, *et al.* Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. *JAMA Psychiatry* 2013; 70: 931–939.
5. Craddock N and Jones I. Genetics of bipolar disorder. *J Med Genet* 1999; 36: 585–594.
6. Group PGCBDW. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nature Genet* 2011; 43: 977–983.
7. Fan J and Sklar P. Genetics of bipolar disorder: focus on BDNF Val66Met polymorphism. *Novartis Found Symp* 2008; 289: 60–72; discussion 72–63, 87–93.
8. Cho HJ, Meira-Lima I, Cordeiro Q, *et al.* Population-based and family-based studies on the serotonin transporter gene polymorphisms and bipolar disorder: a systematic review and meta-analysis. *Mol Psychiatry* 2005; 10: 771–781.
9. Aas M, Haukvik UK, Djurovic S, *et al.* Interplay between childhood trauma and BDNF val66met variants on blood BDNF mRNA levels and on hippocampus subfields volumes in schizophrenia spectrum and bipolar disorders. *J Psychiatr Res* 2014; 59: 14–21.
10. Oliveira J, Etain B, Lajnef M, *et al.* Combined effect of TLR2 gene polymorphism and early life stress on the age at onset of bipolar disorders. *PLoS One* 2015; 10: e0119702.
11. Oliveira J, Kazma R, Le Floch E, *et al.* Toxoplasma gondii exposure may modulate the influence of TLR2 genetic variation on bipolar disorder: a gene-environment interaction study. *Int J Bipolar Disord* 2016; 4: 11.
12. Hosang GM, Fisher HL, Cohen-Woods S, *et al.* Stressful life events and catechol-O-methyl-transferase (COMT) gene in bipolar disorder. *Depress Anxiety* 2017; 34: 419–426.
13. De Pradier M, Gorwood P, Beaufils B, *et al.* Influence of the serotonin transporter gene polymorphism, cannabis and childhood sexual abuse on phenotype of bipolar disorder: a preliminary study. *Eur Psychiatry* 2010; 25: 323–327.
14. Barichello T, Badawy M, Pitcher MR, *et al.* Exposure to perinatal infections and bipolar disorder: a systematic review. *Curr Mol Med* 2016; 16: 106–118.
15. Sutterland AL, Fond G, Kuin A, *et al.* Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. *Acta Psychiatr Scand* 2015; 132: 161–179.
16. De Barros JL, Barbosa IG, Salem H, *et al.* Is there any association between Toxoplasma gondii infection and bipolar disorder? A systematic review and meta-analysis. *J Affect Disord* 2017; 209: 59–65.
17. Scott J, McNeill Y, Cavanagh J, *et al.* Exposure to obstetric complications and subsequent development of bipolar disorder: Systematic review. *Br J Psychiatry* 2006; 189: 3–11.
18. Watson S, Gallagher P, Dougall D, *et al.* Childhood trauma in bipolar disorder. *Aust N Z J Psychiatry* 2014; 48: 564–570.
19. Etain B, Mathieu F, Henry C, *et al.* Preferential association between childhood emotional abuse and bipolar disorder. *J Trauma Stress* 2010; 23: 376–383.
20. Garno JL, Goldberg JF, Ramirez PM, *et al.* Impact of childhood abuse on the clinical course of bipolar disorder. *Br J Psychiatry* 2005; 186: 121–125.
21. Palmier-Claus JE, Berry K, Bucci S, *et al.* Relationship between childhood adversity and bipolar affective disorder: systematic review and meta-analysis. *Br J Psychiatry* 2016; 209: 454–459.
22. Agnew-Blais J and Danese A. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry* 2016; 3: 342–349.

23. Daruy-Filho L, Brietzke E, Lafer B, *et al*. Childhood maltreatment and clinical outcomes of bipolar disorder. *Acta Psychiatr Scand* 2011; 124: 427–434.
24. Upthegrove R, Chard C, Jones L, *et al*. Adverse childhood events and psychosis in bipolar affective disorder. *Br J Psychiatry* 2015; 206: 191–197.
25. Lex C, Bazner E and Meyer TD. Does stress play a significant role in bipolar disorder? A meta-analysis. *J Affect Disord* 2017; 208: 298–308.
26. Kessing LV, Agerbo E and Mortensen PB. Major stressful life events and other risk factors for first admission with mania. *Bipolar Disord* 2004; 6: 122–129.
27. Koenders MA, Giltay EJ, Spijker AT, *et al*. Stressful life events in bipolar I and II disorder: cause or consequence of mood symptoms? *J Affect Disord* 2014; 161: 55–64.
28. Gibbs M, Winsper C, Marwaha S, *et al*. Cannabis use and mania symptoms: a systematic review and meta-analysis. *J Affect Disord* 2015; 171: 39–47.
29. Henquet C, Krabbendam L, de Graaf R, *et al*. Cannabis use and expression of mania in the general population. *J Affect Disord* 2006; 95: 103–110.
30. Tijssen MJ, Van Os J, Wittchen HU, *et al*. Risk factors predicting onset and persistence of subthreshold expression of bipolar psychopathology among youth from the community. *Acta Psychiatr Scand* 2010; 122: 255–266.
31. Van Laar M, Van Dorsselaer S, Monshouwer K, *et al*. Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction* 2007; 102: 1251–1260.
32. Feingold D, Weiser M, Rehm J, *et al*. The association between cannabis use and mood disorders: a longitudinal study. *J Affect Disord* 2015; 172: 211–218.
33. Marwaha S, Winsper C, Bebbington P, *et al*. Cannabis use and hypomania in young people: a prospective analysis. *Schizophr Bull* Epub ahead of print 28 November 2017. DOI: 10.1093/schbul/sbx158.
34. Schepis TS and Hakes JK. Non-medical prescription use increases the risk for the onset and recurrence of psychopathology: results from the national epidemiological survey on alcohol and related conditions. *Addiction* 2011; 106: 2146–2155.
35. Schepis TS and Hakes JK. Dose-related effects for the precipitation of psychopathology by opioid or tranquilizer/sedative nonmedical prescription use: results from the national epidemiologic survey on alcohol and related conditions. *J Addict Med* 2013; 7: 39–44.
36. Kenneson A, Funderburk JS and Maisto SA. Substance use disorders increase the odds of subsequent mood disorders. *Drug Alcohol Depend* 2013; 133: 338–343.
37. Anthony JC and Petronis KR. Epidemiologic evidence on suspected associations between cocaine use and psychiatric disturbances. *NIDA Res Monogr* 1991; 110: 71–94.
38. Forty L, Ulanova A, Jones L, *et al*. Comorbid medical illness in bipolar disorder. *Br J Psychiatry* 2014; 205: 465–472.
39. Faedda GL, Serra G, Marangoni C, *et al*. Clinical risk factors for bipolar disorders: a systematic review of prospective studies. *J Affect Disord* 2014; 168: 314–321.
40. Tseng PT, Zeng BS, Chen YW, *et al*. A meta-analysis and systematic review of the comorbidity between irritable bowel syndrome and bipolar disorder. *Medicine (Baltimore)* 2016; 95.
41. Wu MK, Wang HY, Chen YW, *et al*. Significantly higher prevalence rate of asthma and bipolar disorder co-morbidity: a meta-analysis and review under PRISMA guidelines. *Medicine (Baltimore)* 2016; 95.
42. Zhao Z, Okusaga OO, Quevedo J, *et al*. The potential association between obesity and bipolar disorder: a meta-analysis. *J Affect Disord* 2016; 202: 120–123.
43. Fornaro M and Stubbs B. A meta-analysis investigating the prevalence and moderators of migraines among people with bipolar disorder. *J Affect Disord* 2015; 178: 88–97.
44. Perry DC, Sturm VE, Peterson MJ, *et al*. Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. *J Neurosurg* 2016; 124: 511–526.
45. Liang W and Chikritzhs T. Asthma history predicts the risk of affective disorders and anxiety disorders. *Health* 2013; 5: 313–319.
46. Wei HT, Lan WH, Hsu JW, *et al*. Risk of developing major depression and bipolar disorder among adolescents with atopic diseases: a nationwide longitudinal study in Taiwan. *J Affect Disord* 2016; 203: 221–226.

47. Carta MG, Moro MF, Lorefice L, *et al*. The risk of bipolar disorders in multiple sclerosis. *J Affect Disord* 2014; 155: 255–260.

48. Nabavi B, Mitchell AJ and Nutt D. A lifetime prevalence of comorbidity between bipolar affective disorder and anxiety disorders: a meta-analysis of 52 interview-based studies of psychiatric population. *EBioMedicine* 2015; 2: 1405–1419.

49. Tsuchiya KJ, Byrne M and Mortensen PB. Risk factors in relation to an emergence of bipolar disorder: a systematic review. *Bipolar Disord* 2003; 5: 231–242.

50. Marangoni C, Hernandez M and Faedda GL. The role of environmental exposures as risk factors for bipolar disorder: a systematic review of longitudinal studies. *J Affect Disord* 2016; 193: 165–174.

51. Bortolato B, Kohler CA, Evangelou E, *et al*. Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. *Bipolar Disord* 2017; 19: 84–96.

52. Gilman SE, Dupuy JM and Perlis RH. Risks for the transition from major depressive disorder to bipolar disorder in the national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry* 2012; 73: 829–836.

53. Mortensen PB, Pedersen CB, Melbye M, *et al*. Individual and familial risk factors for bipolar affective disorders in Denmark. *Arch Gen Psychiatry* 2003; 60: 1209–1215.

54. Bebbington P and Ramana R. The epidemiology of bipolar affective disorder. *Soc Psychiatry Psychiatr Epidemiol* 1995; 30: 279–292.

55. Pini S, De Queiroz V, Pagnin D, *et al*. Prevalence and burden of bipolar disorders in European countries. *Eur Neuropsychopharmacol* 2005; 15: 425–434.

56. Merikangas KR, Jin R, He JP, *et al*. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry* 2011; 68: 241–251.

57. Bauer M and Pfennig A. Epidemiology of bipolar disorders. *Epilepsia* 2005; 46(Suppl. 4): 8–13.

58. Marwaha S, Sal N and Bebbington P. *Chapter 9: bipolar disorder*. 2016. Leeds: NHS Digital.

59. Clemente AS, Diniz BS, Nicolato R, *et al*. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. *Rev Bras Psiquiatr* 2015; 37: 155–161.

60. Fajutrao L, Locklear J, Priaulx J, *et al*. A systematic review of the evidence of the burden of bipolar disorder in Europe. *Clin Pract Epidemiol Ment Health* 2009; 5: 3.

61. Esan O and Esan A. Epidemiology and burden of bipolar disorder in Africa: a systematic review of data from Africa. *Soc Psychiatry Psychiatr Epidemiol* 2016; 51: 93–100.

62. Johnson KR and Johnson SL. Cross-national prevalence and cultural correlates of bipolar I disorder. *Soc Psychiatry Psychiatr Epidemiol* 2014; 49: 1111–1117.

63. Marquez C, Taintor Z and Schwartz MA. Diagnosis of manic depressive illness in blacks. *Compr Psychiatry* 1985; 26: 337–341.

64. Blanco C, Compton WM, Saha TD, *et al*. Epidemiology of DSM-5 bipolar I disorder: results from the national epidemiologic survey on alcohol and related conditions - III. *J Psychiatr Res* 2017; 84: 310–317.

65. Kessler RC, Rubinow DR, Holmes C, *et al*. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychol Med* 1997; 27: 1079–1089.

66. Kessing LV. Diagnostic subtypes of bipolar disorder in older versus younger adults. *Bipolar Disord* 2006; 8: 56–64.

67. Kroon JS, Wohlfarth TD, Dieleman J, *et al*. Incidence rates and risk factors of bipolar disorder in the general population: a population-based cohort study. *Bipolar Disord* 2013; 15: 306–313.

68. Joyce K, Thompson A and Marwaha S. Is treatment for bipolar disorder more effective earlier in illness course? A comprehensive literature review. *Int J Bipolar Disord* 2016; 4: 19.

69. Leboyer M, Henry C, Paillere-Martinot ML, *et al*. Age at onset in bipolar affective disorders: a review. *Bipolar Disord* 2005; 7: 111–118.

70. Cassidy F and Carroll BJ. Vascular risk factors in late onset mania. *Psychol Med* 2002; 32: 359–362.

71. Johnson SL, Murray G, Fredrickson B, *et al*. Creativity and bipolar disorder: touched by fire or burning with questions? *Clin Psychol Rev* 2012; 32: 1–12.

72. Weissman MM and Myers JK. Affective disorders in a US urban community: the use of research diagnostic criteria in an epidemiological survey. *Arch Gen Psychiatry* 1978; 35: 1304–1311.

73. Petterson U. Manic-depressive illness. A clinical, social and genetic study. *Acta Psychiatr Scand Suppl* 1977; 56: 1–93.

74. Der G and Bebbington P. Depression in inner London. A register study. *Soc Psychiatry* 1987; 22: 73–84.

75. Krabbendam L and Van Os J. Schizophrenia and urbanicity: a major environmental influence–conditional on genetic risk. *Schizophr Bull* 2005; 31: 795–799.

76. Kaymaz N, Krabbendam L, de Graaf R, *et al.* Evidence that the urban environment specifically impacts on the psychotic but not the affective dimension of bipolar disorder. *Soc Psychiatry Psychiatr Epidemiol* 2006; 41: 679–685.

77. Lichtenstein P, Yip BH, Bjork C, *et al.* Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* 2009; 373: 234–239.

78. Sullivan PF, Magnusson C, Reichenberg A, *et al.* Family history of schizophrenia and bipolar disorder as risk factors for autism. *Arch Gen Psychiatry* 2012; 69: 1099–1103.

79. Badner JA, Koller D, Foroud T, *et al.* Genome-wide linkage analysis of 972 bipolar pedigrees using single-nucleotide polymorphisms. *Mol Psychiatry* 2012; 17: 818–826.

80. Craddock N and Sklar P. Genetics of bipolar disorder. *Lancet* 2013; 381: 1654–1662.

81. Fernandes BS, Molendijk ML, Kohler CA, *et al.* Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. *BMC Med* 2015; 13: 289.

82. Craddock N and Sklar P. Genetics of bipolar disorder: successful start to a long journey. *Trends Genet* 2009; 25: 99–105.

83. Craddock N, Jones L, Jones IR, *et al.* Strong genetic evidence for a selective influence of GABAA receptors on a component of the bipolar disorder phenotype. *Mol Psychiatry* 2010; 15: 146–153.

84. Sigitova E, Fisar Z, Hroudova J, *et al.* Biological hypotheses and biomarkers of bipolar disorder. *Psychiatry Clin Neurosci* 2017; 71: 77–103.

85. Cipriani A, Saunders K, Attenburrow MJ, *et al.* A systematic review of calcium channel antagonists in bipolar disorder and some considerations for their future development. *Mol Psychiatry* 2016; 21: 1324–1332.

86. Misiak B, Stramecki F, Gaweda L, *et al.* Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: a systematic review. *Mol Neurobiol* 2017: 1–26.

87. Uher R. Gene-environment interactions in severe mental illness. *Front Psychiatry* 2014; 5: 48.

88. Kim DR, Bale TL and Epperson CN. Prenatal programming of mental illness: current understanding of relationship and mechanisms. *Curr Psychiatry Rep* 2015; 17: 5.

89. Brown AS. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. *Dev Neurobiol* 2012; 72: 1272–1276.

90. Simanek AM and Meier HC. Association between prenatal exposure to maternal infection and offspring mood disorders: a review of the literature. *Curr Probl Pediatr Adolesc Health Care* 2015; 45: 325–364.

91. Canetta SE, Bao Y, Co MD, *et al.* Serological documentation of maternal influenza exposure and bipolar disorder in adult offspring. *Am J Psychiatry* 2014; 171: 557–563.

92. Parboosing R, Bao Y, Shen L, *et al.* Gestational influenza and bipolar disorder in adult offspring. *JAMA psychiatry* 2013; 70: 677–685.

93. Machon RA, Mednick SA and Huttunen MO. Adult major affective disorder after prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* 1997; 54: 322–328.

94. Mortensen PB, Pedersen CB, McGrath JJ, *et al.* Neonatal antibodies to infectious agents and risk of bipolar disorder: a population-based case-control study. *Bipolar Disord* 2011; 13: 624–629.

95. Gerber SI, Krienke UJ, Biedermann NC, *et al.* Impaired functioning in euthymic patients with bipolar disorder–HSV-1 as a predictor. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; 36: 110–116.

96. Webster JP. The effect of Toxoplasma gondii on animal behavior: playing cat and mouse. *Schizophr Bull* 2007; 33: 752–756.

97. Yagmur F, Yazar S, Temel HO, *et al.* May Toxoplasma gondii increase suicide attempt-preliminary results in Turkish subjects? *Forensic Sci Int* 2010; 199: 15–17.

98. Kocazeybek B, Oner YA, Turksoy R, *et al.* Higher prevalence of toxoplasmosis in victims of traffic accidents suggest increased risk of traffic accident in Toxoplasma-infected inhabitants of Istanbul and its suburbs. *Forensic Sci Int* 2009; 187: 103–108.

99. Prandovszky E, Gaskell E, Martin H, *et al.* The neurotropic parasite Toxoplasma gondii increases dopamine metabolism. *PLoS One* 2011; 6: e23866.

100. Ashok AH, Marques TR, Jauhar S, *et al.* The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. *Mol Psychiatry* 2017; 22: 666–679.

101. Novotna M, Hanusova J, Klose J, *et al.* Probable neuroimmunological link between Toxoplasma and cytomegalovirus infections and personality changes in the human host. *BMC Infect Dis* 2005; 5: 54.

102. Hamdani N, Daban-Huard C, Lajnef M, *et al.* Cognitive deterioration among bipolar disorder patients infected by Toxoplasma gondii is correlated to interleukin 6 levels. *J Affect Disord* 2015; 179: 161–166.

103. Muneer A. The neurobiology of bipolar disorder: an integrated approach. *Chonnam Med J* 2016; 52: 18–37.

104. Buka SL and Fan AP. Association of prenatal and perinatal complications with subsequent bipolar disorder and schizophrenia. *Schizophr Res* 1999; 39: 113–119; discussion 160–111.

105. Verdolini N, Attademo L, Agius M, *et al.* Traumatic events in childhood and their association with psychiatric illness in the adult. *Psychiatr Danub* 2015; 27(Suppl. 1): S60–S70.

106. Schmitt A, Malchow B, Hasan A, *et al.* The impact of environmental factors in severe psychiatric disorders. *Front Neurosci* 2014; 8: 19.

107. Marwaha S, Gordon-Smith K, Broome M, *et al.* Affective instability, childhood trauma and major affective disorders. *J Affect Disord* 2016; 190: 764–771.

108. Etain B, Lajnef M, Henry C, *et al.* Childhood trauma, dimensions of psychopathology and the clinical expression of bipolar disorders: a pathway analysis. *J Psychiatr Res* 2017; 95: 37–45.

109. Schreuder MM, Vinkers CH, Mesman E, *et al.* Childhood trauma and HPA axis functionality in offspring of bipolar parents. *Psychoneuroendocrinology* 2016; 74: 316–323.

110. Bucker J, Fries GR, Kapczinski F, *et al.* Brain-derived neurotrophic factor and inflammatory markers in school-aged children with early trauma. *Acta Psychiatr Scand* 2015; 131: 360–368.

111. Van Dam NT, Rando K, Potenza MN, *et al.* Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. *JAMA Psychiatry* 2014; 71: 917–925.

112. Etain B, Henry C, Bellivier F, *et al.* Beyond genetics: childhood affective trauma in bipolar disorder. *Bipolar Disord* 2008; 10: 867–876.

113. Johnson SL and Roberts JE. Life events and bipolar disorder: implications from biological theories. *Psychol Bull* 1995; 117: 434–449.

114. Jones I and Craddock N. Familiality of the puerperal trigger in bipolar disorder: results of a family study. *Am J Psychiatry* 2001; 158: 913–917.

115. Beards S, Gayer-Anderson C, Borges S, *et al.* Life events and psychosis: a review and meta-analysis. *Schizophr Bull* 2013; 39: 740–747.

116. Spinhoven P, Elzinga BM, Hovens JG, *et al.* Positive and negative life events and personality traits in predicting course of depression and anxiety. *Acta Psychiatr Scand* 2011; 124: 462–473.

117. Guiraud V, Touze E, Rouillon F, *et al.* Stressful life events as triggers of ischemic stroke: a case-crossover study. *Int J Stroke* 2013; 8: 300–307.

118. Renzaho AM, Houng B, Oldroyd J, *et al.* Stressful life events and the onset of chronic diseases among Australian adults: findings from a longitudinal survey. *Eur J Pub Health* 2014; 24: 57–62.

119. Spence R, Bunn A, Nunn S, *et al.* Measuring life events and their association with clinical disorder: a protocol for development of an online approach. *JMIR Res Protoc* 2015; 4: e83.

120. Post RM and Kalivas P. Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation. *Br J Psychiatry* 2013; 202: 172–176.

121. Strakowski SM and DelBello MP. The co-occurrence of bipolar and substance use disorders. *Clin Psychol Rev* 2000; 20: 191–206.

122. Goldberg JF, Garno JL, Callahan AM, *et al.* Overdiagnosis of bipolar disorder among substance use disorder inpatients with mood instability. *J Clin Psychiatry* 2008; 69: 1751–1757.

123. Grinspoon L and Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J Psychoactive Drugs* 1998; 30: 171–177.

124. Carmiol N, Peralta JM, Almasy L, *et al.* Shared genetic factors influence risk for bipolar disorder and alcohol use disorders. *Eur Psychiatry* 2014; 29: 282–287.

125. Lin PI, McInnis MG, Potash JB, *et al.* Clinical correlates and familial aggregation of age at onset in bipolar disorder. *Am J Psychiatry* 2006; 163: 240–246.

126. Rosenblat JD and McIntyre RS. Are medical comorbid conditions of bipolar disorder due to immune dysfunction? *Acta Psychiatr Scand* 2015; 132: 180–191.

127. Leboyer M, Soreca I, Scott J, *et al.* Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord* 2012; 141: 1–10.

128. Hungin AP, Becher A, Cayley B, *et al.* Irritable bowel syndrome: an integrated explanatory model for clinical practice. *Neurogastroenterol Motil* 2015; 27: 750–763.

129. Orlovska S, Pedersen MS, Benros ME, *et al.* Head injury as risk factor for psychiatric disorders: a nationwide register-based follow-up study of 113,906 persons with head injury. *Am J Psychiatry* 2014; 171: 463–469.

130. Schiffer RB, Wineman NM and Weitkamp LR. Association between bipolar affective disorder and multiple sclerosis. *Am J Psychiatry* 1986; 143: 94–95.

131. Murphy R, O'Donoghue S, Counihan T, *et al.* Neuropsychiatric syndromes of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2017; 88: 697–708.

132. Martin DJ and Smith DJ. Is there a clinical prodrome of bipolar disorder? A review of the evidence. *Expert Rev Neurother* 2013; 13: 89–98.

133. Singh MK. Is there validity to the bipolar prodrome? *J Clin Psychiatry* 2015; 76: e655–e656.

134. Geoffroy PA and Scott J. Prodrome or risk syndrome: what's in a name? *Int J Bipolar Disord* 2017; 5: 7.

135. Bechdolf A, Nelson B, Cotton SM, *et al.* A preliminary evaluation of the validity of at-risk criteria for bipolar disorders in help-seeking adolescents and young adults. *J Affect Disord* 2010; 127: 316–320.

136. Scott J, Marwaha S, Ratheesh A, *et al.* Bipolar at-risk criteria: an examination of which clinical features have optimal utility for identifying youth at risk of early transition from depression to bipolar disorders. *Schizophr Bull* 2017; 43: 737–744.

137. Baldwin P, Browne D, Scully PJ, *et al.* Epidemiology of first-episode psychosis: illustrating the challenges across diagnostic boundaries through the Cavan-Monaghan study at 8 years. *Schizophr Bull* 2005; 31: 624–638.

138. Kennedy N, Everitt B, Boydell J, *et al.* Incidence and distribution of first-episode mania by age: results from a 35-year study. *Psychol Med* 2005; 35: 855–863.

139. Kennedy N, Boydell J, Kalidindi S, *et al.* Gender differences in incidence and age at onset of mania and bipolar disorder over a 35-year period in Camberwell, England. *Am J Psychiatry* 2005; 162: 257–262.

140. Gignac A, McGirr A, Lam RW, *et al.* Recovery and recurrence following a first episode of mania: a systematic review and meta-analysis of prospectively characterized cohorts. *J Clin Psychiatry* 2015; 76: 1241–1248.