The relationship between childhood adversity and bipolar disorder: A systematic review and meta-analysis.

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Running title: Childhood adversity and bipolar disorder.
Abstract:

**Background:** The relationship between childhood adversity and bipolar disorder remains unclear.

**Aim:** To statistically synthesise the available literature in order to understand the size and significance of this effect.

**Method:** Consistent with the protocol (CRD42015017201), search terms relating to childhood adversity and bipolar disorder were entered into Medline, Embase, PsychInfo, and Web of Science. Eligible studies included a sample diagnosed with bipolar disorder, a comparison sample and a quantitative measure of childhood adversity.

**Results:** In 19 eligible studies, childhood adversity was 2.63 times (CI: 2.00 -3.47) more likely to have occurred in bipolar disorder compared to non-clinical controls. The effect of emotional abuse was particularly robust (OR: 4.04, CI: 3.12-5.22), but rates of adversity were similar to psychiatric controls.

**Conclusions:** Childhood adversity is associated with bipolar disorder, which has implications for the treatment of this clinical group. Further prospective research could clarify temporal causality and explanatory mechanisms.

**Declaration of interest:** None

Key words: adversity, abuse, bipolar, mania, review, meta-analysis.
Introduction

Bipolar disorder is characterised by extreme depressive and manic affective states, which are often associated with adverse outcomes, including reduced functioning (1), impaired quality of life (2) and increased risk of death by suicide (3). Response to treatment is limited with high rates of relapse (4). A better understanding of the risk factors for bipolar disorder is vital for refining detection and intervention strategies. Although research has typically focused on the bio-genetic determinants of bipolar symptomatology, environmental risk factors are also increasingly being considered (5). This review and meta-analysis explores the association between bipolar disorder and childhood adversity.

Childhood adversity is associated with a variety of negative outcomes in the general population (6). In individuals with bipolar disorder, it has been linked to increased mood cycling, greater numbers of affective episodes, and the presence of psychosis (7, 8). However, the question of whether childhood adversity relates to the development of bipolar disorder remains unresolved. Previous reviews (9-14) have observed high rates of adversity in many, but not all, bipolar samples. To date, no research has attempted to integrate empirical findings using meta-analytic methods. To do so would provide a more rigorous method for testing the null hypothesis, but also allow for consideration of the size and consistency of the effects.

Authors have proposed that emotional abuse and neglect may convey greater risk of bipolar disorder than other forms of maltreatment (e.g. sexual abuse, physical abuse; 5). Comparison of effect sizes for different forms of adversity may help to clarify whether specific adversity subtypes are more strongly related to bipolar symptomatology. Meta-analytic approaches might also elucidate whether childhood adversity is associated with a
particular form of bipolar disorder. Bipolar I is characterised by periods of mania (i.e. episodes of extremely elated mood, arousal and levels of activity, often in the presence of psychosis), whereas bipolar II only presents attenuated symptoms of mania with limited impact on functioning (i.e. hypomania). Given the evidence for an association between adversity and severe psychopathology, characterised by psychotic symptoms (15), greater levels of childhood adversity may be elevated in bipolar I patients.

Lastly, diagnoses of major depression (16) and schizophrenia (15) appear more likely in individuals with a history of childhood adversity. It is possible that childhood maltreatment is related to one particular form of psychiatric disorder. The final and exploratory aim of this review was therefore to compare rates of childhood adversity in individuals diagnosed with bipolar disorder to those diagnosed with schizophrenia and major depression.

In summary, this review examined three *a-priori* hypotheses: One, rates of childhood adversity would be elevated in samples with bipolar disorder compared to non-clinical controls; two, effect sizes for emotional abuse and neglect would be higher than that of other forms of adversity; and three, rates of childhood adversity would be greater in individuals with bipolar I compared to bipolar II. The authors made no hypotheses regarding the rates of childhood adversity in bipolar disorder compared to the other clinical samples.

Method

*Search strategy*

The review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. A systematic search of four
databases (Medline, Embase, PsychInfo, Web of Science) identified peer reviewed articles published between January 1980 and October 2014. The authors used blocks of search terms pertaining to bipolar disorder (*bipolar, mani*, *cyclothymi*, *manic-depressi* or *hypomani*) and childhood adversity (*child abuse, physical abuse, sexual abuse, psychological abuse, emotional abuse, neglect*, *trauma*, *advers*, *maltreat*, *bully*, *bullied, victim*, or *parental loss*). The search terms were partly adapted from past reviews (10, 11, 15), and, where possible, were ‘exploded’ in the field of Bipolar Disorder. The authors restricted the search in Web of Science to the areas of Psychiatry and Psychology by ‘Field’.

In addition to articles identified through the systematic search, the authors screened the reference lists of the included manuscripts and previous reviews (5, 9-14, 17). The authors also examined journal articles citing at least one of the included studies. In cases where the relevant information from which to assess eligibility or calculate an effect size was unavailable, the authors requested further information from the corresponding author of the manuscript.

Eligibility criteria

The review included case control (comparing two existing groups distinguished by a defining outcome i.e. bipolar status vs. control) and epidemiological (prospective and cross sectional) studies where a quantitative measure of childhood adversity was administered to individuals with a formal diagnosis of bipolar disorder according to the Diagnostic and Statistical Manual (DSM-III, DSM-IIIR, DSM-IV, DSM-IV-TR & DSM-V) or the International Classification of Diseases (ICD-9 or ICD-10). The authors defined childhood adversity as
experiencing neglect, abuse, bullying or the loss of parents before the age of 19. Studies exploring loss through separation (e.g. divorce of parents), expressed emotion, and/or stressful life events occurring in adulthood (i.e. after the age of 18) were not included. The authors excluded relatively high frequency parenting practices (e.g. spanking, shouting), as these were assumed to be subject to cultural variability. They also excluded case notes reviews that opportunistically assessed, rather than systematically measured, childhood adversity due to the increased likelihood of response bias. In cases where the 12-month and lifetime diagnoses were provided, the latter was selected for effect size extraction (18). Only articles published in peer review English language journals were included in the analysis.

The authors only included studies with at least one eligible control sample. Controls were defined *a priori* as healthy individuals without an identified DSM or ICD diagnosis (in the epidemiological studies, this was defined as respondents known to be free of the outcome of interest, i.e. bipolar disorder), and individuals with a DSM or ICD diagnosis of major depression or non-affective psychosis (e.g. schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder).

*Screening and data extraction*

The lead author (JPC) screened articles in three stages: i) the title level, ii) the abstract level, and iii) the article level. One third (33.4%; n=1800) of titles were double rated by a separate postgraduate researcher with adequate levels of agreement (94.6%; $k = .65$). All of the abstracts (n=446) were double rated with similarly high levels of agreement
The majority of discrepancy due to the primary coder (JPC) being overly inclusive.

Two authors extracted data and calculated effect sizes using a data spreadsheet. The intra-class correlation between the two sets of effect sizes indicated high levels of agreement (ICC: .98; \( p < .001 \)). For the four cases where the primary authors were in disagreement, the wider team arbitrated. Extracted data included study and effect size descriptors. When possible, the authors extracted binary (e.g. frequency tables, percentages), as opposed to d-family (e.g. means, standard deviations), effect sizes based on the use of odds ratio (OR) as the overall metric.

**Methodological quality**

Methodological quality was explored using the Newcastle Ottawa Quality Assessment Scale (NOQAS; 19), which assesses the selection and comparability of the samples, and the suitability of the adversity exposures (see online material). Gender was selected as the most important covariate or matching criteria given the studies showing greater levels and impact of childhood adversity in women compared to men (20). Quality ratings were based on the effect sizes of interest, rather than other analyses reported in the papers. Independent quality ratings by a blind postgraduate researcher demonstrated good inter-rater reliability with the lead author (ICC: .83, \( p < .001 \)).

**Statistical analysis**
The authors used comprehensive Meta-Analysis (V2) to compute the effect sizes and conduct the analyses. All effect sizes were converted to ORs in order to aid the interpretation of the results. Effects were integrated using random-effects meta-analysis. Visual inspection of funnel plots and regression tests of funnel plot asymmetry (Egger’s test) established the presence of publication and selection bias. In analyses where selection bias was deemed likely, Duval and Tweedie’s trim and fill method was employed to identify and correct for hypothetically missing effects.

The analysis consisted of four stages. In stage one, the authors considered the overall effects from studies comparing bipolar and non-clinical samples on measures of childhood adversity. This analysis focused on the association between childhood adversity and bipolar disorder regardless of adversity type, and considered both single (e.g. sexual abuse) and multiple (e.g. sexual abuse, emotional abuse etc.) exposures. When extracting data in the presence of more than one measure of adversity, the authors used the most global or wide reaching assessment (e.g. total levels of adversity). In cases where this information was unavailable, the authors contacted the corresponding author of the primary manuscript to request information regarding an aggregated effect. In the absence of this information, they calculated separate effect sizes for each type of adversity, which they then aggregated in the main analysis.

In the second stage of analysis, the authors examined independent associations between different types of exposures and bipolar disorder. In the third stage, overall effects were extracted for studies that compared childhood adversity between bipolar I and bipolar II disorder. Finally, the authors independently examined differences in childhood adversity between bipolar disorder and other psychiatric groups (major depression, schizophrenia).
In some cases, manuscripts contained both the results to the unadjusted analyses and those adjusting for covariates. In order to increase comparability amongst the eligible studies, the authors included the unadjusted results in the main analyses and then conducted a sensitivity analysis with the adjusted effects. In the presence of multiple levels of adjustment, the authors included the analysis with the largest number of demographics and/or clinical covariates. The majority of the aforementioned analyses explored the impact of childhood adversity generally, rather than the specific effects of adversity subtypes over and above the other forms of adversity. Therefore, we did not include effects that examined the impact of exposures whilst controlling for other types of childhood adversity (e.g.21).

The full review protocol is available online (http://www.crd.york.ac.uk/PROSPERO/; CRD42015017201).
Results

Description of identified research

The authors summarise the screening procedure in Figure 1 and the characteristics of the included articles in Table 1. Eleven authors provided clarification or further information from which to generate an effect size. Only 11 studies reported the exact prevalence of childhood adversity within bipolar samples, which ranged from 7.7% (22) to 77.1% (23), with a weighted average exposure of 10.5%. This estimate includes parental loss (n=4), sexual abuse (n=3), and composite adversity measures (n=4).

Thirteen case control and six epidemiological studies were included in the main analysis. The case control studies included 1259 cases and 1118 controls, whereas the epidemiological studies surveyed over 2.1 million respondents. The epidemiological research included three population based cross-sectional design studies (21, 24, 25), two retrospective cohort design studies (18, 22), and one quasi-prospective study (26). The latter examined childhood adversity as a predictor of transition to psychosis over a three-year period in adulthood. The quasi-prospective design studies linked data on current diagnosis to registers on parental loss (22) and child protection status (18). The most commonly used assessment of adversity in the case control studies was the Childhood Trauma Questionnaire (N=7; (27)), which is a 28-item self-report measure of emotional and physical abuse, emotional and physical neglect, and sexual abuse. Measures of childhood adversity in the epidemiological studies were generally single items derived from validated measures.
Figure 1. Flow chart detailing the literature screening at the different phases of the review.
Table 1. The characteristics of studies included in the main analysis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Bipolar sample characteristics</th>
<th>Diagnostic system</th>
<th>Sample sizes (n)</th>
<th>Measure</th>
<th>Adversity (type)</th>
<th>Diagnosis</th>
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<tr>
<td><strong>Case control studies</strong></td>
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<td>Agid et al., 1999 (28)</td>
<td>Israel</td>
<td>Bipolar patients</td>
<td>DSM-III-R</td>
<td>158</td>
<td>BD: 79; NC: 79; MD: 79; SCZ: 76</td>
<td>University Database Questionnaires (PL)</td>
<td>SCID</td>
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<tr>
<td>Furukawa et al., 1999 (29)</td>
<td>Japan</td>
<td>Bipolar patients</td>
<td>DSM-III-R</td>
<td>195</td>
<td>BD: 73; NC: 122; MD: 570</td>
<td>PISA or TOSHI (PL)</td>
<td>PISA</td>
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<tr>
<td>Grandin et al., 2007 (31)</td>
<td>USA</td>
<td>Bipolar NOS, I &amp; cyclothymic patients</td>
<td>DSM-IV</td>
<td>310</td>
<td>BD: 155; NC: 155</td>
<td>Childrens Life Events Scale (maltreatment)</td>
<td>General Behaviour Inventory &amp; SADS-L</td>
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<td>Savitz et al., 2008 (32)</td>
<td>South Africa</td>
<td>Bipolar I &amp; II patients</td>
<td>DSM-IV</td>
<td>133</td>
<td>BD: 68; NC: 65; SCZ: 44 / 33*</td>
<td>CTQ (SA, PA, EA, EN, PN)</td>
<td>SCID</td>
</tr>
<tr>
<td>Reference</td>
<td>Country</td>
<td>Type of Patients</td>
<td>Diagnostic Manual</td>
<td>N</td>
<td>M</td>
<td>SD</td>
<td>CTQ</td>
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<td>DSM-IV</td>
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<td>94</td>
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<tr>
<td>Horesh &amp; Iancu, 2010 (34)</td>
<td>Israel</td>
<td>Bipolar outpatients</td>
<td>DSM-IV</td>
<td>90</td>
<td>30</td>
<td>60</td>
<td>Child Life Events List (PL)</td>
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<tr>
<td>Fowke et al., 2012 (23)</td>
<td>England</td>
<td>Bipolar patients</td>
<td>ICD-10</td>
<td>70</td>
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<td>35</td>
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<td>Konradt et al., 2013 (35)</td>
<td>Brazil</td>
<td>Bipolar I &amp; II patients</td>
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<td>Aas et al., 2014 (36)</td>
<td>Norway</td>
<td>Bipolar NOS, I &amp; II patients</td>
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<td>42</td>
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<td>Chen et al., 2014 (37)</td>
<td>Taiwan</td>
<td>Bipolar I &amp; II</td>
<td>DSM-IV</td>
<td>531</td>
<td>329</td>
<td>202</td>
<td>CIDI (PA)</td>
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<tr>
<td>Watson et al., 2014 (38)</td>
<td>UK &amp; New Zealand</td>
<td>Bipolar I &amp; II outpatients</td>
<td>DSM-IV</td>
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<td>60</td>
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<td>Janiri et al., 2015 (39)</td>
<td>Italy</td>
<td>Bipolar I &amp; II outpatients</td>
<td>DSM-III-R</td>
<td>207</td>
<td>104</td>
<td>103</td>
<td>CTQ (SA, PA, EA, EN, PN)</td>
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**Epidemiological studies**
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Disorder</th>
<th>Diagnostic Manual</th>
<th>N</th>
<th>Cause of Death Register (PL)</th>
<th>Items from the CTS (SA)</th>
<th>DSM-IV CIDI</th>
<th>CIDI</th>
<th>Danish Psychiatric Central Register</th>
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<tr>
<td>Molnar et al., 2001</td>
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<td>Laursen et al., 2007</td>
<td>Denmark</td>
<td>Bipolar disorder</td>
<td>ICD-8 &amp; ICD-10</td>
<td>2.1M 4490</td>
<td>Cause of Death Register (PL)</td>
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<td>Cause of Death Register (PL)</td>
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<tr>
<td>Scott et al., 2010</td>
<td>New Zealand</td>
<td>Bipolar disorder</td>
<td>DSM-IV</td>
<td>2144</td>
<td>Child protection agency status (maltreatment)</td>
<td>CIDI</td>
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<tr>
<td>Stikkeribroak et al., 2012 (21)</td>
<td>Netherlands</td>
<td>Bipolar disorder</td>
<td>DSM-III-R</td>
<td>7076</td>
<td>Item on parental death (PL)</td>
<td>CIDI</td>
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<tr>
<td>Afifi et al., 2014</td>
<td>Canada</td>
<td>Bipolar disorder</td>
<td>DSM-IV</td>
<td>23395</td>
<td>Items from CEVQ (SA, PA)</td>
<td>CIDI</td>
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<td>Gilman et al., 2014</td>
<td>USA</td>
<td>Bipolar I disorder</td>
<td>DSM-IV</td>
<td>33379</td>
<td>Items from CTQ &amp; CTS (maltreatment, SA)</td>
<td>AUDADIS-IV</td>
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Studies included in comparisons with major depression and schizophrenia (stage four of analysis)

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<tr>
<th>Study</th>
<th>Country</th>
<th>Disorder</th>
<th>Diagnostic Manual</th>
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<th>Cause of Death Register (PL)</th>
<th>Items from the CTS (SA)</th>
<th>DSM-IV CIDI</th>
<th>CIDI</th>
<th>Danish Psychiatric Central Register</th>
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<tr>
<td>Alnaes &amp; Torgersen, 1993 (40)</td>
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<td>Bipolar and cyclothymic patients</td>
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<td>Darvez-Bornoz et al., 1995 (41)</td>
<td>France</td>
<td>Bipolar patients</td>
<td>DSM-III-R</td>
<td>89 25</td>
<td>Interview (SA)</td>
<td>Psychiatrist rated against criteria</td>
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<td>Hlastala &amp; McClellan, 2005 (42)</td>
<td>USA</td>
<td>Bipolar I</td>
<td>DSM-IV-TR</td>
<td>49</td>
<td>22</td>
<td>PTSD module of SCID (SA, PA, N)</td>
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<td>Hyun et al., 2000 (43)</td>
<td>USA</td>
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<td>DSM-IV</td>
<td>333</td>
<td>142</td>
<td>Semi-structured interview (SA, PA)</td>
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<td>Watson et al., 2007 (44)</td>
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<td>Angst et al., 2011 (45)</td>
<td>Switzerland</td>
<td>Bipolar disorder</td>
<td>Broad DSM-IV</td>
<td>287</td>
<td>104</td>
<td>Unclear (SA)</td>
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<tr>
<td>Alvarez et al., 2011 (46)</td>
<td>Spain</td>
<td>Bipolar patients</td>
<td>DSM-IV</td>
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<td>40</td>
<td>Items from TLDEQ (SA, PA)</td>
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<td>Parker et al., 2013 (47)</td>
<td>Australia</td>
<td>Bipolar I &amp; II patients</td>
<td>DSM-IV</td>
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<td>138</td>
<td>Unclear (SA, PA)</td>
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<tr>
<td>Perna et al., 2014 (48)</td>
<td>England</td>
<td>Bipolar I &amp; II patients</td>
<td>DSM-IV</td>
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<td>47</td>
<td>CTQ (SA, PA, EA, EN, PN)</td>
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</tbody>
</table>
Key: BD, Bipolar disorder; NC, Non-clinical controls; MD, unipolar or major depression; SCZ, schizophrenia; UK, United Kingdom; USA, United States of America; DSM, Diagnostic and Statistical Manual; PA, physical abuse; SA, sexual abuse; N, neglect; EN, emotional neglect; PN, physical neglect; EA, emotional abuse; PL, parental loss; ICD, International Classification of Diseases; SCID, Structured Clinical Interview for DSM Disorders; PISA, Psychiatric Initial Screening for Affective Disorders; TOSHI, Time-Ordered Stress and Health Interview; CBC, Child Behaviour Checklist; KSADS-PL, Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; WASHU-K-SADS, Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia; SADS-L, Schedule for Affective Disorders - Lifetime Diagnostic Interview (SADS-L); CTQ, Childhood Trauma Questionnaire; DFGS, Diagnostic Interview for Genetic Studies; MINI, Mini International Neuropsychiatric Interview; CIDI, Composite International Diagnostic Interview; CTS, Conflict Tactics Scales; CEVQ, Childhood Experiences of Violence Questionnaire; AUDADIS-IV, Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV; PTSD, post-traumatic stress disorder; SCL, symptom checklist; TLDEQ, Traumatic Life Events and Distressing Event Questionnaires.
Stage one: Overall association between childhood adversity and bipolar disorder.

Figure 2 shows the ORs for each of the included studies, and the aggregated effects of childhood adversity on bipolar disorder. The analysis showed an overall effect of 2.63 (CI: 2.00 - 3.47, \( p < .001 \)), suggesting that individuals with bipolar disorder are 2.6 times more likely to have experienced childhood adversity when compared to non-clinical controls. Similar effect sizes were observed for the case control (OR: 2.88, CI: 2.04 – 4.06, \( p < .001 \)) and epidemiological studies (OR: 2.24, CI: 1.40 - 3.57, \( p = .001 \)). There was no significant difference (Q (1) = 0.74, \( p = 0.391 \)) in the strength of the effect sizes between the two subgroups.

**Heterogeneity analyses**

Heterogeneity was examined using the Q-test and I-square statistics. Results showed that the strength of the relationship between childhood adversity and bipolar disorder varied considerably across studies (Q (18) = 79.53, \( p < .001 \)), with 77% of the observed dispersion attributable to true statistical heterogeneity. This level of heterogeneity is generally thought to be high and should be considered when interpreting the results.

**Selection bias analyses**
Regarding publication bias, funnel plots of standard error by log odds ratios indicated a roughly symmetrical distribution of studies around the mean effect sizes. When combining the case control and epidemiological literature the result to Egger’s test was also non-significant (B: .12, SE: 1.08, \( p = .456 \)) indicating no evidence of publication or selection bias. Duval and Tweedie’s trim and fill found two hypothetical missing studies, which brought the imputed OR to 2.47 (CI: 1.8-3.1).

Sensitivity analysis

One-study removed analysis suggested that the withdrawal of any particular study would not greatly alter the results. Three of the epidemiological studies provided effect sizes adjusted for covariates in addition to unadjusted scores. Repeating the analysis using adjusted scores yielded highly similar results (OR: 2.58, CI: 1.96 - 3.36, \( p < .001 \)), with equivalent levels of statistical heterogeneity (Q (18) = 79.2, \( p < .001 \), \( I^2 = 77.27 \)). This was also true when only including the epidemiological studies in the analysis (OR: 2.14, CI: 1.36-3.39, \( p = .001 \)).
<table>
<thead>
<tr>
<th>Study name</th>
<th>Design</th>
<th>Adversity</th>
<th>Statistics for each study</th>
<th>Odds ratio and 95% CI</th>
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<tbody>
<tr>
<td>Aas et al., 2014</td>
<td>Case control</td>
<td>Trauma total</td>
<td>5.68</td>
<td>1.67</td>
</tr>
<tr>
<td>Agid et al., 1999</td>
<td>Case control</td>
<td>Parental loss</td>
<td>2.65</td>
<td>0.89</td>
</tr>
<tr>
<td>Chon et al., 2014</td>
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<td>1.92</td>
<td>1.39</td>
</tr>
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<td>Etain et al., 2010</td>
<td>Case control</td>
<td>Trauma total</td>
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<td>1.87</td>
</tr>
<tr>
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<td>Case control</td>
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<td>5.81</td>
<td>2.37</td>
</tr>
<tr>
<td>Furukawa et al., 1999</td>
<td>Case control</td>
<td>Parental loss</td>
<td>0.68</td>
<td>0.30</td>
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<td>Grandin et al., 2007</td>
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<td>Maltreatment</td>
<td>2.53</td>
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<tr>
<td>Horesh &amp; Lanco, 2010</td>
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<tr>
<td>Konradt et al., 2013</td>
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<tr>
<td>Ruckridge et al., 2006</td>
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<td>0.22</td>
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<tr>
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<td>2.28</td>
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<td>Trauma total</td>
<td>4.82</td>
<td>2.17</td>
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<tr>
<td>Affi et al., 2014</td>
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<td>Trauma total</td>
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<tr>
<td>Gilman et al., 2014</td>
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<td>Trauma total</td>
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<td>Sexual abuse</td>
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<td>Scott et al., 2010</td>
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<td>Maltreatment</td>
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<td>1.00</td>
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<td>Stikkerbroek et al., 2012</td>
<td>Epidemiological</td>
<td>Parental loss</td>
<td>0.77</td>
<td>0.38</td>
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</table>

Figure 2. Forest plot of effect sizes.
Stage two: Associations between specific adversity subtypes and bipolar disorder.

Table 3 shows the results to the analyses exploring whether specific types of childhood adversity are elevated in bipolar disorder. Grandin (31) and Neeren (49) both report analyses from the Longitudinal Investigation of Bipolar Spectrum Disorders Project. For this analysis, the authors selected information from the Neeren and colleagues’ paper as this study specifically reported effects pertaining to the impact of adversity subtypes. The results of these separate meta-analyses showed significant effects of all childhood adversity subtypes, with the exception parental loss, on bipolar disorder. Emotional abuse showed the strongest effect with an OR of 4.04 (CI: 3.12-5.22, p <.001).
Table 2. The results to the trauma subtype analyses.

<table>
<thead>
<tr>
<th>Trauma type</th>
<th>k</th>
<th>Odds Ratio</th>
<th>Confidence interval</th>
<th>Heterogeneity tests</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>12</td>
<td>2.86</td>
<td>2.22</td>
<td>3.69</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>12</td>
<td>2.58</td>
<td>2.08</td>
<td>3.20</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>9</td>
<td>4.04</td>
<td>3.12</td>
<td>5.22</td>
</tr>
<tr>
<td>Physical neglect</td>
<td>7</td>
<td>2.26</td>
<td>1.74</td>
<td>2.93</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>7</td>
<td>2.62</td>
<td>2.03</td>
<td>3.38</td>
</tr>
<tr>
<td>Parental loss</td>
<td>5</td>
<td>1.16</td>
<td>0.75</td>
<td>1.78</td>
</tr>
</tbody>
</table>
Stage three: Differences between bipolar subtypes.

Four identified studies provided data to compare rates of childhood adversity across subtypes of bipolar disorder (32, 38, 39, 47). No significant difference in childhood adversity was observed between bipolar I and bipolar II disorder (OR: 0.93, CI: 0.48 - 1.81, \( p = .0.827 \); Q (3) = 6.91, \( p = .075 \), \( I^2 = 56.58 \)).

Stage four: Differences between bipolar disorder and psychiatric control, major depression and schizophrenia.

Data from 11 studies were used to compare rates of childhood adversity in bipolar and unipolar depression (see online material). The results showed that childhood adversity was significantly greater in bipolar disorder (OR: 1.24, CI: 1.02 - 1.50, \( p = .031 \)), with low levels of statistical heterogeneity (Q (10) = 12.83, \( p = .233 \), \( I^2 = 22.08 \)). However, Egger’s test approached significance (B: .75, SE: 0.43, \( p = .058 \)) indicating the possibility of publication bias. After Duval and Tweedie’s trim and fill adjustment for three hypothetical missing studies, the imputed OR fell to 1.09 (CI: 0.88 - 1.36).

Based on the post-hoc hypothesis that the absence of an effect was due to the types of adversity considered, the authors repeated the analyses removing studies that focused on parental loss (n=4). This elevated the effect size (OR = 1.54, CI: 1.19 - 2.00, \( p < .001 \); Q (6) = 4.30, \( p < .001 \), \( I^2 = 0 \)) showing significantly higher rates of childhood adversity in bipolar disorder when compared to unipolar depression.
No hypothetically missing studies were detected with no indication of publication bias (B: -1.34, SE: 1.25, \( p = .166 \)).

No significant difference in rates of childhood adversity was found when comparing bipolar disorder and schizophrenia in the analysis of five studies (OR = 0.89, CI: 0.79 – 1.01, \( p = .067 \); Q(4) = 2.32, \( p = .677 \), \( I^2 = 0 \); see online material). Egger’s test was non-significant (B: -0.52, SE: 0.42, \( p = .152 \)) and no hypothetically missing studies were estimated.

**Quality assessment**

The NOQAS ratings for the case control studies are displayed online. Generally, the quality of the studies in the main analysis was adequate, with eight studies employing an appropriately matched control group and/or controlling for covariates in the analysis. Only one study failed to substantiate participants’ diagnoses through interview (23). There was a non-significant trend of better study quality producing larger effects (\( b = .22, SE = .12, CI (-.01 \text{ to } .45) \), \( Z = 1.82, p = .066 \)) in the case control studies.

Quality ratings for the case control studies included in the secondary analysis were lower than for those the main analysis. This was largely due to studies not controlling for covariates or employing matching criteria. The majority of the studies included in the secondary analysis employed a rigorous method of ascertaining diagnoses. Epidemiological studies included nationally representative samples with data obtained through structured interviews or record linkage.
Epidemiological studies adequately controlled for a range of covariates in their analyses, including gender.
Discussion

The results of the meta-analysis suggest that individuals with bipolar disorder are 2.63 times more likely to experience childhood adversity when compared to non-clinical controls. This effect did not appear to be the result of study design or bias, and remained robust and significant even when controlling for hypothetically missing studies. The findings should be interpreted in the context of relatively few longitudinal and no prospective cohort design studies, limiting the ability to make causal inferences. Nevertheless, there appears to be a strong and significant association between childhood adversity and bipolar disorder.

We found some variances in the association between adversity and bipolar disorder when specific type of exposures were analysed separately. Emotional abuse was four times more likely to occur in bipolar disorder than healthy controls; an effect seemingly larger than other types of adversity. This is in contrast to a recent meta-analysis that observed roughly equivalent effect sizes for adversity subtypes on psychosis (15). Interestingly, parental loss did not significantly differ between bipolar and non-clinical samples. One explanation is that the impact of losing a parent is highly dependent on the context and stage at which it occurs (5). Indeed, past research has suggested that a younger age at parental loss, maternal loss in particular, and death by unnatural causes are more strongly associated with a bipolar disorder diagnosis (22, 50, 51). Rejecting our initial hypothesis, the effect of childhood adversity on bipolar II disorder, compared to bipolar I disorder, did not reach statistical significance. Although the analysis included only four studies, it is possible that childhood adversity is associated with both the more severe and attenuated bipolar profiles.
Rates of childhood adversity were significantly greater in bipolar disorder when compared to unipolar depression. However, this effect became non-significant when controlling for hypothetically missing studies. The absence of a stronger effect may have been due to the overrepresentation of studies considering parental loss, which did not appear to be elevated in bipolar disorder more generally. When repeating the analysis without effects pertaining to parental loss, individuals with bipolar disorder presented with higher levels of adversity compared to unipolar depression. Nevertheless, it is difficult to draw firm conclusions on the specificity of childhood adversity on bipolar and unipolar depression.

The results showed no significant difference in the rates of childhood adversity between individuals diagnosed with bipolar disorder and schizophrenia. A wealth of research has focused on the role of childhood adversity in the development of psychosis (15). The current findings suggest similar levels of adversity in bipolar disorder. Interestingly, correlational studies have showed associations between childhood adversity and psychotic experiences in bipolar disorder (8). Future research should explore the exact pathways by which specific forms of adversity lead to particular symptom clusters.

The analysis revealed high levels of statistical heterogeneity, which allows for less confidence in the estimated effect sizes, but is not surprising given the methodological and analytic variances in the identified studies. For example, measures of childhood adversity included national registers (18, 22), questionnaires (32, 38), survey items (21, 26) and semi-structured interviews (29, 30). Furthermore, studies differed in terms of diagnostic assessments (e.g. the Structure Clinical Interview for DSM Disorders, the Composite International Diagnostic Interview) and inclusion criteria (e.g. adolescents, adults), with two studies restricting their analysis to bipolar I disorder (26, 42). Although the analyses allowed
for the examination of some potential sources of heterogeneity (e.g. the impact of study
design), the limited number of identified studies prevented the authors from testing the
impact of other methodological differences on effect sizes. In the presence of further
publications, future reviews might wish to explore whether such methodological and clinical
variations moderate the association between childhood adversity and bipolar disorder.

There are some limitations of this meta-analysis and of the research literature more
generally. Recall bias and illness representations may confound retrospective reporting of
childhood adversity (17). In the absence of long-term prospective research, it is impossible
to reach a definitive conclusion on the causal link between childhood adversity and bipolar
disorder. It is feasible that, in some cases, early or prodromal symptoms in childhood may
place greater strain on parenting, which could contribute to dysfunctional relationships.
Therefore, a genetic predisposition to bipolar disorder may increase levels of childhood
adversity. Similarly, we note the absence of studies carefully examining graded (i.e. dose
response) relationships, which in conjunction with the investigation of putative biological
and psychosocial mechanisms might enable the identification of plausible pathogenic
pathways linking adversity to bipolar psychopathology. Lastly, the adversity subtypes were
not statistically independent making it difficult to draw firm conclusions on the specificity of
adversity subtypes on bipolar disorder.

The findings have clinical implications. Given the association between childhood
adversity and bipolar disorder, practitioners should carefully enquire about their clients’
past adverse experiences, including emotional abuse. Read and colleagues (52) have
provided guidance on how clinicians might conduct these conversations and sensitively
respond to and deal with disclosures. Identification of childhood adversity should then lead
to its integration into personalised formulations of clients’ difficulties and the provision of appropriate support and interventions.

In conclusion, childhood adversity appears to be associated with the development of bipolar disorder. Rates of childhood adversity in bipolar disorder appear to be similar to those observed in psychosis and major depression. In the future, researchers should explore the ways in which childhood adversity interacts with cognitive, behavioural, and biological factors. They should also investigate the potential impact of alternative forms of adversity such as bullying and witnessing domestic violence. Further prospective research exploring dose-response and accounting for genetic effects would help to elucidate the nature of the relationship between childhood adversity and bipolar symptomatology. The findings have implications for the study and treatment of bipolar disorder.

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