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%s; k = .65). All of the abstracts (n=446) were double rated with similarly high levels of agreement

(87.4% *k* =.71). 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.

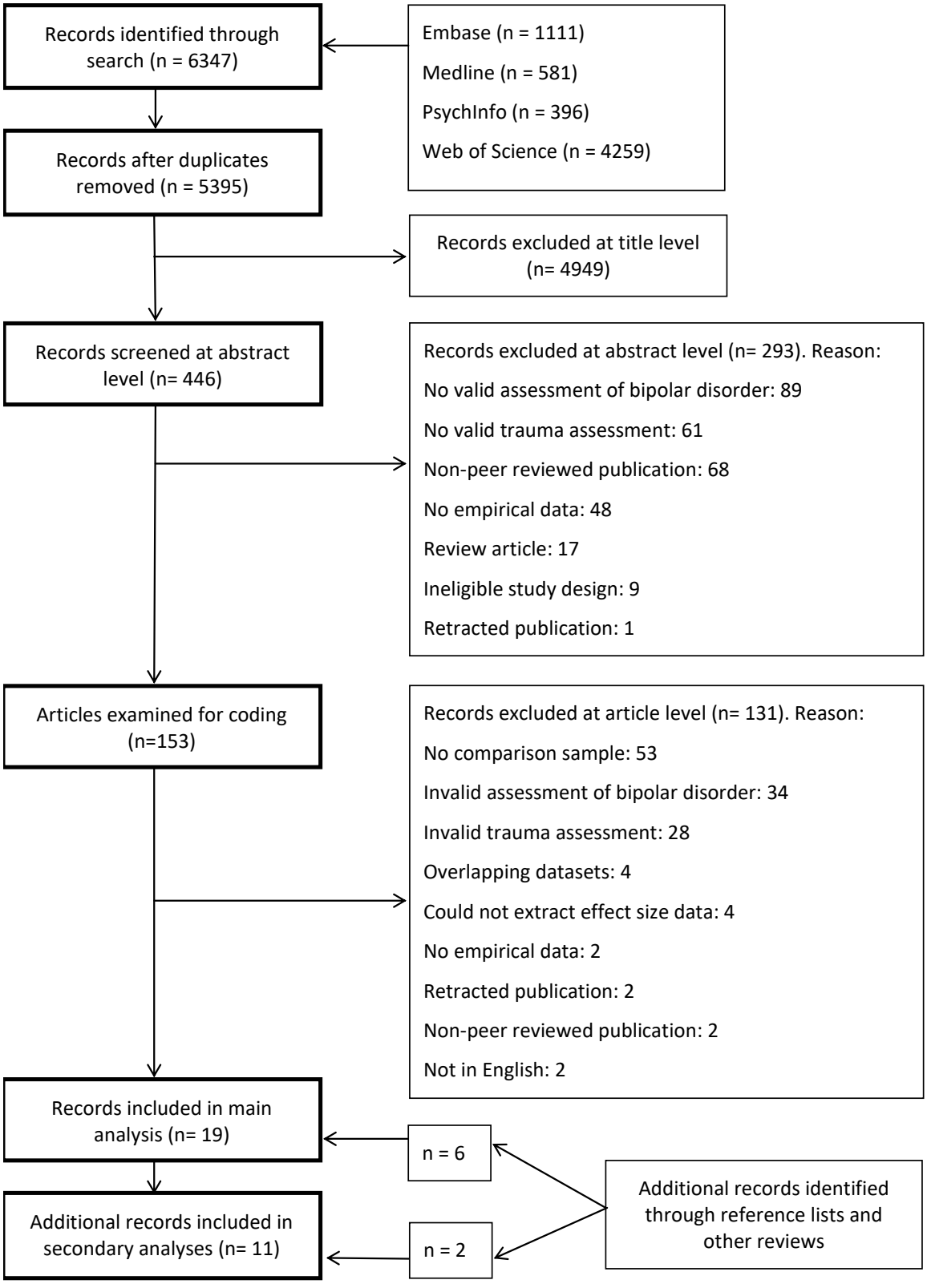

Figure 1. Flow chart detailing the literature screening at the different phases of the review.

Table 1. The characteristics of studies included in the main analysis.

Authors	Country	Bipolar sample characteristics	Diagnostic system	Sample sizes (n)					Measure	
				Total	BD	NC	MD	SCZ	Adversity (type)	Diagnosis
Case control studies										
Agid et al., 1999 (28)	Israel	Bipolar patients	DSM-III-R	158	79	79	79	76	University Database Questionnaires (PL)	SCID
Furukawa et al., 1999 (29)	Japan	Bipolar patients	DSM-III-R	195	73	122	570		PISA or TOSHI (PL)	PISA
Rucklidge et al., 2006 (30)	New Zealand	Bipolar NOS, I & II adolescent outpatients	DSM-IV-TR	63	24	39			CBC, KSADS-PL & WASHU-K-SADS (SA, PA, N, EA)	KSADS
Grandin et al., 2007 (31)	USA	Bipolar NOS, I & cyclothymic patients	DSM-IV	310	155	155			Childrens Life Events Scale (maltreatment)	General Behaviour Inventory & SADS-L
Savitz et al., 2008 (32)	South Africa	Bipolar I & II patients	DSM-IV	133	68	65	44 / 33*		CTQ (SA, PA, EA, EN, PN)	SCID

Etain et al., 2010 (33)	France	Bipolar I & II patients	DSM-IV	300	206	94		CTQ (SA, PA, EA, EN, PN)	DIGS
Horesh & Iancu, 2010 (34)	Israel	Bipolar outpatients	DSM-IV	90	30	60		Child Life Events List (PL)	SCID
Fowke et al., 2012 (23)	England	Bipolar patients	ICD-10	70	35	35		CTQ (SA, PA, EA, EN, PN)	From service
Konradt et al., 2013 (35)	Brazil	Bipolar I & II patients	DSM-IV	149	54	95	82	CTQ (SA, PA, EA, EN, PN)	MINI & SCID
Aas et al., 2014 (36)	Norway	Bipolar NOS, I & II patients	DSM-IV	66	42	14		CTQ (SA, PA, EA, EN, PN)	SCID
Chen et al., 2014 (37)	Taiwan	Bipolar I & II	DSM-IV	531	329	202		CIDI (PA)	CIDI
Watson et al., 2014 (38)	UK & New Zealand	Bipolar I & II outpatients	DSM-IV	115	60	55		CTQ (SA, PA, EA, EN, PN)	SCID
Janiri et al., 2015 (39)	Italy	Bipolar I & II outpatients	DSM-III-R	207	104	103		CTQ (SA, PA, EA, EN, PN)	SCID

Epidemiological studies

Molnar et al., 2001 (25)	USA	Bipolar disorder	DSM-III-R	5866				Items from the CTS (SA)	CIDI
Laursen et al., 2007 (22)	Denmark	Bipolar disorder	ICD-8 & ICD-10	2.1M	4490	31752	13297	Cause of Death Register (PL)	Danish Psychiatric Central Register
Scott et al., 2010 (18)	New Zealand	Bipolar disorder	DSM-IV	2144				Child protection agency status (maltreatment)	CIDI
Stikkerlbroak et al., 2012 (21)	Netherlands	Bipolar disorder	DSM-III-R	7076				Item on parental death (PL)	CIDI
Afifi et al., 2014 (24)	Canada	Bipolar disorder	DSM-IV	23395				Items from CEVQ (SA, PA)	CIDI
Gilman et al., 2014 (26)	USA	Bipolar I disorder	DSM-IV	33379				Items from CTQ & CTS (maltreatment, SA)	AUDADIS-IV
Studies included in comparisons with major depression and schizophrenia (stage four of analysis)									
Alnaes & Torgersen, 1993 (40)	Norway	Bipolar and cyclothymic patients	DSM-III	156	59	97		Anamnestic interview (PL)	SCID
Darvez-Bornoz et al., 1995 (41)	France	Bipolar patients	DSM-III-R	89	25		64	Interview (SA)	Psychiatrist rated against criteria

Hlastala & McClellan, 2005 (42)	USA	Bipolar I	DSM-IV-TR	49	22		27	PTSD module of SCID (SA, PA, N)	SCID
Hyun et al., 2000 (43)	USA	Bipolar patients	DSM-IV	333	142	191		Semi-structured interview (SA, PA)	Diagnostic interview
Watson et al., 2007 (44)	UK	Bipolar patients	DSM-IV	40	30	10		CTQ (SA, PA, EA, EN, PN)	SCID
Angst et al., 2011 (45)	Switzerland	Bipolar disorder	Broad DSM-IV	287	104	183		Unclear (SA)	SCL-90-R
Alvarez et al., 2011 (46)	Spain	Bipolar patients	DSM-IV	92	40		52	Items from TLDEQ (SA, PA)	Unclear
Parker et al., 2013 (47)	Australia	Bipolar I & II patients	DSM-IV	352	138	214		Unclear (SA, PA)	MINI
Perna et al., 2014 (48)	England	Bipolar I & II patients	DSM-IV	74	47	27		CTQ (SA, PA, EA, EN, PN)	Clinical inteview (unspecified)

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; DIGS, Diagnostic Interview for Genetic Studies; MINI, Mini International Neuropsychiatric Interview; CIDI, Composite International Diagnostic Interview; CTS, Confict 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).

Study name	Design	Adversity	Odds ratio	Lower limit	Upper limit	p-Value
Aas et al., 2014	Case control	Trauma total	5.58	1.67	18.69	0.01
Agid et al., 1999	Case control	Parental loss	2.65	0.89	7.92	0.08
Chen et al., 2014	Case control	Physical abuse	1.92	1.39	2.64	0.00
Etain et al., 2010	Case control	Trauma total	2.94	1.87	4.62	0.00
Fowke et al., 2012	Case control	Trauma total	5.81	2.37	14.28	0.00
Furukawa et al., 1999	Case control	Parental loss	0.68	0.30	1.53	0.35
Grandin et al., 2007	Case control	Maltreatment	2.53	1.68	3.82	0.00
Horesh & Iancu, 2010	Case control	Parental death	0.96	0.44	2.13	0.93
Janiri et al., 2015	Case control	Trauma total	3.60	2.16	5.99	0.00
Konradt et al., 2013	Case control	Trauma total	7.73	4.04	14.78	0.00
Rucklidge et al., 2006	Case control	Trauma total	1.68	0.22	12.80	0.62
Savitz et al., 2008	Case control	Trauma total	4.47	2.28	8.77	0.00
Watson et al., 2014	Case control	Trauma total	4.82	2.17	10.69	0.00
			2.88	2.04	4.06	0.00
Afifi et al., 2014	Epidemiological	Trauma total	4.40	3.29	5.88	0.00
Gilman et al., 2014	Epidemiological	Trauma total	2.74	2.08	3.61	0.00
Laurson et al., 2007	Epidemiological	Parental loss	1.57	1.16	2.12	0.00
Molnar et al., 2001	Epidemiological	Sexual abuse	4.37	1.70	11.22	0.00
Scott et al., 2010	Epidemiological	Maltreatment	1.86	1.00	3.46	0.05
Stikkerlbroak et al., 2012	Epidemiological	Parental loss	0.77	0.38	1.57	0.47
			2.24	1.40	3.57	0.00
			2.63	2.00	3.47	0.00

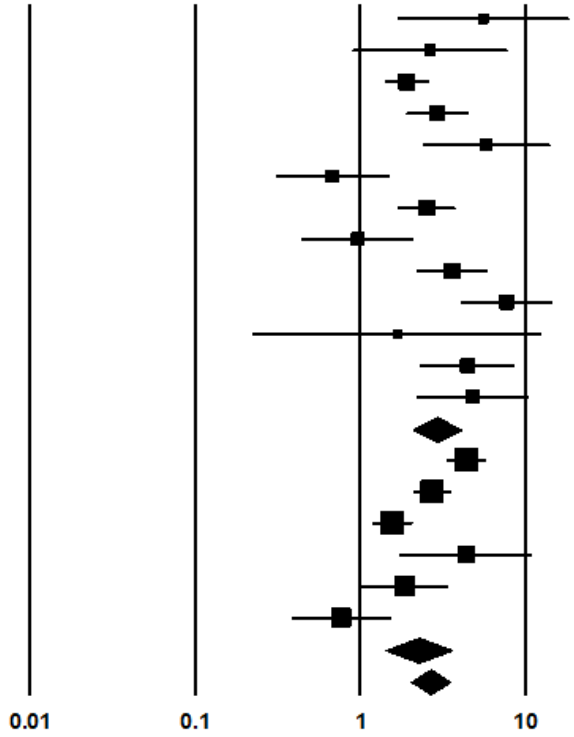

Figure 2. Forest plot of effect sizes.

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.

			Confidence interval			Heterogeneity tests		
Trauma type	*k*	Odds Ratio	Lower	Upper	*p*-value	I^2	Q	*p*-value
Physical abuse	12	2.86	2.22	3.69	<.001	70	36.55	<.001
Sexual abuse	12	2.58	2.08	3.20	<.001	35	16.94	0.109
Emotional abuse	9	4.04	3.12	5.22	<.001	23	10.40	0.238
Physical neglect	7	2.26	1.74	2.93	<.001	0	5.41	0.492
Emotional neglect	7	2.62	2.03	3.38	<.001	0	5.94	0.430
Parental loss	5	1.16	0.75	1.78	0.514	51	8.23	0.084

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 adjusted 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 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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