TECHNICAL COMMENTARY

Childhood adversity

Introduction

Childhood adversities encompass a range of childhood experiences, including loss of a close relative, bullying, physical abuse, sexual abuse, emotional abuse, and neglect. The nature, timing, severity, and duration of exposure are likely to influence mental health outcomes.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Due to the high volume of systematic reviews, we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most comprehensive review was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found three systematic reviews that met our inclusion criteria[3-5].

- Moderate quality evidence finds a small, increased risk of bipolar disorder after exposure to any childhood adversity. There were higher rates of childhood adversity in people with bipolar disorder compared to people without bipolar disorder or people with major depression. No differences in rates of childhood adversity were found between bipolar disorder and schizophrenia.

- Moderate quality evidence suggests childhood adversity in people with bipolar disorder is associated with more symptom episodes and severity, rapid cycling, psychosis, anxiety, post-traumatic stress disorder, substance use, suicides, and an earlier age at onset.

NeuRA

Discover. Conquer. Cure.

BIPOLAR DISORDERS LIBRARY

Agnew-Blais J, Danese A

Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: A systematic review and meta-analysis

The Lancet Psychiatry 2016; 3: 342-9

View review abstract online

Comparison	Clinical outcomes in people with bipolar disorder and childhood maltreatment vs. people with bipolar disorder and no childhood maltreatment.
Summary of evidence	Moderate quality evidence (mostly inconsistent, imprecise, direct, large samples) suggests small effects of more mania and depression episodes, greater symptom severity, more rapid cycling, more psychosis symptoms, more anxiety disorders, more post-traumatic stress disorder (medium effect), more substance use, more suicide and an earlier age at onset in people with bipolar and a history of childhood maltreatment than in people with bipolar and no history of childhood maltreatment.

Symptoms
Patients with bipolar disorder and history of childhood maltreatment had greater symptom severity than those with bipolar disorder without childhood maltreatment (all small effects);
Mania: 6 studies, N = 780, OR = 2.02, 95%CI 1.21 to 3.39, *p* = 0.008, I² = 70.8%, *p* = 0.004
Mania episodes: 7 studies, N = 3909, OR = 1.26, 1.09 to 1.47, *p* = 0.003, I² = 0%, *p* = 0.581
Depression: 8 studies, N = 1007, OR = 1.57, 95%CI 1.25 to 1.99, *p* = 0.0001, I² = 0%, *p* = 0.055
Depressive episodes: 8 studies, N = 4025, OR = 1.38, 95%CI 1.07 to 1.79, *p* = 0.013, I² = 49.3%, *p* = 0.004
Rapid cycling: 8 studies, N = 3010, OR = 1.89, 1.45 to 2.48, *p* < 0.0001, I² = 38.9%, *p* = 0.120
Psychosis: 7 studies, N = 1494, OR = 1.49, 95%CI 1.10 to 2.04, *p* = 0.011, I² = 8.6%, *p* = 0.618
Anxiety disorders: 7 studies, N = 5091, OR = 1.90, 1.39 to 2.61, *p* < 0.0001, I² = 72.8%, *p* = 0.229
There was a medium-sized effect for post-traumatic stress disorder;
8 studies, N = 2494, OR = 3.60, 2.45 to 5.30, *p* < 0.0001, I² = 50.4%, *p* = 0.049
Authors report that these results were not subject to publication bias or variation in study quality.

Substance use
Patients with bipolar disorder and history of childhood maltreatment had greater risk of substance misuse than those with bipolar disorder without childhood maltreatment (small effects);
Substance misuse disorders: 11 studies, N = 5469, OR = 1.84, 1.41 to 2.39, *p* < 0·0001, I² = 61%, *p*

NeuRA | Childhood adversity

February 2021

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au

Page 2

= 0.004 Alcohol misuse disorder: 8 studies, N = 5040, OR = 1.44, 1.13 to 1.83, p = 0.003, I² = 47.1%, p = 0.067	
Age at onset	
Patients with bipolar disorder and history of childhood maltreatment had an earlier age at onset than those with bipolar disorder without childhood maltreatment (small effect); 14 studies, N = 5733, OR = 1.85, 1.43 to 2.40, p < 0.0001, I² = 69.7%, p < 0.0001	
Suicide	
Patients with bipolar disorder and history of childhood maltreatment had a greater risk of suicide than those with bipolar disorder without childhood maltreatment (medium-sized effect); 13 studies, N = 3422, OR = 2.25, 1.88 to 2.70, p < 0.0001, I² = 0%, p = 0.479	
Consistency in results‡	Inconsistent for mania symptoms, depressive episodes, PTSD, substance use, and age at onset.
Precision in results§	Imprecise, apart from mania episodes.
Directness of results‖	Direct

Palmier-Claus JE, Berry K, Bucci S, Mansell W, Varese F

Relationship between childhood adversity and bipolar affective disorder: Systematic review and meta-analysis

British Journal of Psychiatry 2016; 209: 454-9

[View review abstract online](#)

Comparison 1	Rates of childhood adversity in people with bipolar disorder vs. non-clinical controls.
Summary of evidence	**Moderate quality evidence (direct, inconsistent, imprecise, large sample) suggests a medium-sized effect of higher rates of childhood adversity in people with bipolar disorder compared to controls.**
All childhood adversities	
A significant, medium-sized effect of more childhood adversity in people with bipolar disorder than controls; 19 studies, N > 2 million, OR = 2.63, 95%CI 2.00 to 3.47, p < 0.001, I² = 77%, p < 0.001	

NeuRA | Childhood adversity   February 2021

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au   Page 3
To donate, phone 1800 888 019 or visit www.neura.edu.au

Effect sizes were similar in case-control and population studies, and in studies of bipolar I and bipolar II disorder.	
Emotional abuse showed a larger effect size (OR = 4.04) than physical abuse (OR = 2.86), sexual abuse (OR = 2.58), physical neglect (OR = 2.26), emotional neglect (OR = 2.62) or parental loss (1.16; not significant).	
There was no evidence of publication bias, and authors report that study quality was mostly adequate.	
Comparison 2	**Rates of childhood adversity in people with bipolar disorder vs. other psychiatric disorders.**
Summary of evidence	**Moderate to high quality evidence (direct, consistent, precise, large sample) suggests a small effect of higher rates of childhood adversity in people with bipolar disorder than in people with major depression, with no difference in the comparison with schizophrenia.**
All childhood adversities	
A significant, small effect of more childhood adversity in people with bipolar disorder than in people with major depression;	
11 studies, N = 38,533, OR = 1.24, 95%CI 1.02 to 1.50, *p* = 0.031, I² = 22.08%, *p* = 0.233	
Authors report possible publication bias.	
There were no significant differences in the comparison between bipolar disorder and schizophrenia.	
Consistency in results	Inconsistent in the control comparison, consistent in the depression comparison.
Precision in results	Imprecise in the control comparison, precise in the depression comparison.
Directness of results	Direct

Rodriguez V, Alameda L, Trotta G, Spinazzola E, Marino P, Matheson SL, Laurens KR, Murray RM, Vassos E

Environmental Risk Factors in Bipolar Disorder and Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies

[View review abstract online](#)

Comparison	**Risk of bipolar disorder after exposure to any childhood adversity (any trauma, parental death or separation) vs. no**

NeuRA | Childhood adversity   February 2021

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au   Page 4
To donate, phone 1800 888 019 or visit www.neura.edu.au

Childhood adversity

	exposure.
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) finds a small increased risk of bipolar disorder after exposure to childhood adversity.**
Childhood adversity	
A small effect of increased risk of bipolar disorder with exposure to childhood adversity; 4 studies, N = 9,469, OR = 1.46, 95%CI 1.22 to 1.76, $p < 0.05$, I^2 = 96%	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant)

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[6].

---

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large treatment effect[6].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[7]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Childhood adversity

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I² is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[8].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

NeuRA | Childhood adversity

February 2021

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au

Page 7

Childhood adversity

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Agnew-Blais J, Danese A (2016): Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: A systematic review and meta-analysis. *The Lancet Psychiatry* 3: 342-9.
4. Palmier-Claus JE, Berry K, Bucci S, Mansell W, Varese F (2016): Relationship between childhood adversity and bipolar affective disorder: Systematic review and meta-analysis. *British Journal of Psychiatry* 209: 454-9.
5. Rodriguez V, Alameda L, Trotta G, Spinazzola E, Marino P, Matheson SL*, et al.* (2021): Environmental Risk Factors in Bipolar Disorder and Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies. *Schizophrenia Bulletin*: https://doi.org/10.1093/schbul/sbaa197.
6. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
7. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
8. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*

NeuRA | Childhood adversity

February 2021

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au To donate, phone 1800 888 019 or visit www.neura.edu.au

Page 8