TECHNICAL COMMENTARY

Behavioural disturbances & psychopathology

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Introduction

Subtle deviations in various developmental trajectories during childhood and adolescence may foreshadow the later development of bipolar disorder. Clinical psychopathology in childhood and adolescence may also be precursors to bipolar disorder. Studies exploring these deviations are ideally based on representative, population-based samples that follow the cohort from birth through childhood and adolescence to adulthood.

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 reviews assessing the same topic were found, only the most recent and/or 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 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 six systematic reviews that met our inclusion criteria[3-8].

- Moderate quality evidence suggests there may be an increased risk of developing bipolar disorder in adulthood if there is a childhood history of attention problems, aggressive behaviour (but not irritability), internalising or externalising behaviour, social isolation, or peer rejection.
- Moderate quality evidence finds the prevalence of bipolar disorder in children and youth with ADHD is around 10%. This represents a large increase in risk of bipolar disorder in children and youth with ADHD

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

compared to children and youth without a psychiatric disorder.

- Moderate quality evidence suggests a higher risk of bipolar disorder with prior behavioural problems/disorders (conduct, oppositional, disruptive, criminal, impulsivity), and anxiety disorders (generalised, separation, panic, PTSD).
- Moderate quality evidence suggests a higher risk of bipolar disorder in people with a history of mood swings, subclinical depression or mania, cyclothymic disorder, higher frequency and loading of depression, and early onset of depression disorders or episodes.
- Moderate to low quality evidence suggests the cumulative rate of conversion from unipolar depression to bipolar disorder increases from 3.78% at 1 year assessment to 12.87% at 10-year assessment. The yearly rate of conversion from unipolar depression to bipolar disorder decreases from 3.83% at 1 year assessment to 0.78% at 10-year assessment.
- Moderate to low quality evidence suggests there may also be a higher risk of bipolar disorder in people with a history of psychotic symptoms, particularly if accompanied by depression.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Brancati GE, Perugi G, Milone A, Masi G, Sesso G

Development of bipolar disorder in patients with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis of prospective studies

Journal of Affective Disorders 2021; 293: 186-96

View review abstract online

Comparison	**Rates of bipolar disorder in children and youth with ADHD vs. children and youth without a psychiatric disorder.** **Age ranged from 6 to 18 years. Data is gained from longitudinal, prospective studies, with follow-up between 4 and 33 years.**
Summary of evidence	**Moderate quality evidence (large sample size, some inconsistency, imprecise, direct) finds the prevalence of bipolar disorder in children and youth with ADHD is around 10%. This represents a large increase in risk of bipolar disorder in children and youth with ADHD compared to children and youth without a psychiatric disorder.**
Bipolar disorder in ADHD	
Overall prevalence of bipolar disorder in youth and children with ADHD; 10 studies, N = 1,248, prevalence = 10%, 95%CI 0.6% to 15%, I^2 = 82% *A large, significant effect of greater risk of bipolar disorder in children and youth with ADHD than in children and youth without a psychiatric disorder;* 6 studies, N = 1,124, RR = 8.97, 95%CI 4.26 to 18.87, $p < 0.0001$, $Qp = 0.9014$ There were no moderating effects of age, gender, or follow-up duration.	
Consistency in results‡	Consistent for control analysis, inconsistent for prevalence.
Precision in results§	Imprecise
Directness of results‖	Direct

Faedda GL, Serra G, Marangoni C, Salvatore P, Sani G, Vazquez GH, Tondo L, Girardi P, Baldessarini RJ, Koukopoulos A

Clinical risk factors for bipolar disorders: a systematic review of prospective studies

Journal of Affective Disorders 2014; 168: 314-21

View review abstract online

Comparison	**Non-depressive psychopathology prior to the onset of bipolar disorder.**
Summary of evidence	**Moderate quality evidence (direct, appears consistent, unable to assess precision, large samples) suggests a higher risk of bipolar disorder with prior ADHD, behavioural problems/disorders (conduct, oppositional, disruptive, criminal, impulsivity), and anxiety disorders (generalised, separation, panic, PTSD).**

ADHD and behavioural disorders

ADHD

A significant, medium-sized effect suggests ADHD in young adults (>18 years) was associated with an increased risk of bipolar I disorder (3-year follow-up);

1 study, N = 34,653, OR = 2.60, $p < 0.01$

A significant effect suggests ADHD in children (6-17 years) was associated with an increased risk of bipolar disorder (4-year follow-up);

1 study, N = 260, 12% conversion rate, $p < 0.01$

A significant effect suggests ADHD in children (6-17 years) with or without conduct/oppositional defiant disorder was associated with an increased risk of bipolar disorder (10-year follow-up);

1 study, N = 260, OR = not reported, $p < 0.05$

Conduct/oppositional defiant disorders

A significant, medium-sized effect suggests conduct/oppositional defiant disorders in children and adolescents (age not reported) was associated with an increased risk of bipolar disorder (23-year follow-up);

1 study, N = 976, OR = 2.50, p not reported

A significant, medium-sized effect suggests conduct disorder in adolescents (15-20 years) was associated with an increased risk of bipolar disorder (15-year follow-up);

1 study, N = 1,505, OR = 3.90, $p = 0.05$

A significant, small effect suggests conduct disorder in adults (>18 years) was associated with an increased risk of bipolar disorder (3-year follow-up);

1 study, N = 34,653, OR = 1.72 to 2.04, p not reported

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Disruptive behaviour disorder

A significant, medium-sized effect suggests disruptive behaviour disorder in children and adolescents (>5 years) was associated with an increased risk of bipolar disorder (9-year follow-up);

1 study, N = 717, OR = 2.75, $p < 0.05$

A significant, large effect suggests disruptive behaviour disorder in adolescents and young adults (14-24 years) was associated with an increased risk of bipolar disorder (7.3-10.6 year follow-up);

1 study, N = 1,902, OR = 5.29 to 7.82, $p \leq 0.05$

Criminal behaviour

A significant, small effect suggests criminal behaviour in adolescents and young adults (14-24 years) was associated with an increased risk of subclinical bipolar disorder (7.3-10.6 year follow-up);

1 study, N = 2,210, OR = 1.68, $p = 0.05$

Impulsivity

A significant, medium-sized effect suggests impulsivity in adults (>18 years) was associated with an increased risk of bipolar disorder (3-year follow-up);

1 study, N = 34,653, OR = 3.19, $p < 0.05$

A significant, small effect suggests impulsivity in young adults (18-24 years) with or without a family history of bipolar disorder was associated with an increased risk of bipolar disorder (4-5 year follow-up);

1 study, N = 57, OR = 1.10, $p = 0.008$

Anxiety

Any anxiety disorder

A significant, medium to large effect suggests any lifetime anxiety disorder in adolescents and young adults (14-22 years) was associated with an increased risk of bipolar disorder (9-year follow-up);

1 study, N = 717, OR = 4.69, $p < 0.01$

Generalised anxiety disorder

A significant, medium-sized effect suggests generalised anxiety disorder in adults (>18 years) with elation and/or irritability was associated with an increased risk of bipolar disorder (3-year follow-up);

1 study, N = 2,755, OR = 2.10, $p < 0.001$

Separation anxiety

Significant, large effects suggests separation anxiety disorder in adolescents and young adults (14-27 years) was associated with an increased risk of bipolar disorder I or II (4 year follow-up);

1 study, N = 1,090, HR = 6.2 to 9.9, p not reported

Panic attacks/disorder

A significant, medium-sized effect suggests panic attacks in young adults (>18 years) are

associated with an increased risk of bipolar disorder (3-year follow-up); 1 study, N = 34,653, OR = 2.39, $p < 0.001$ <u>Post-traumatic stress disorder</u> *A significant, medium-sized effect suggests post-traumatic stress disorder in young adults (>18 years) was associated with an increased risk of bipolar disorder (3-year follow-up);* 1 study, N = 34,653, OR = 2.40, $p < 0.01$

Consistency in results	Appears consistent, although no measure of consistency is reported.
Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

Faedda GL, Marangoni C, Serra G, Salvatore P, Sani G, Vazquez GH, Tondo L, Girardi P, Baldessarini RJ, Koukopoulos A

Precursors of bipolar disorders: a systematic literature review of prospective studies

Journal of Clinical Psychiatry 2015; 76: 614-24

View review abstract online

Comparison	**Affective psychopathology prior to the onset of bipolar disorder.**
Summary of evidence	**Moderate quality evidence (direct, appears consistent, unable to assess precision, mostly large samples) suggests a higher risk of bipolar disorder in people with a history of mood swings, subclinical depression or mania, cyclothymic disorder, higher frequency and loading of depression, and early onset of depression.** **Moderate to low quality evidence (appears inconsistent) suggests there may also be higher risk of bipolar disorder in people with a history of psychotic symptoms, particularly if accompanied by depression.**

Mood swings
A large effect suggests adolescents and adults (average age 18.5 years) who report frequent ups and downs have an increased risk of developing bipolar disorder than those without frequent ups and downs (15-year follow-up);

1 study, N = 591, OR = 14.3, *p* not reported *The presence of mood swings in adults (18-75 years) with major depressive disorder and psychotic symptoms was associated with an increased risk of bipolar disorder (0.5-9 year follow-up);* 1 study, N = 591, Chi-sq = 4.85, *p* not reported *The presence of mood swings in adults (>17 years) with major depressive disorder was associated with moderate sensitivity and good specificity in predicting bipolar disorder (2-11 year follow-up);* 1 study, N = 559, Sensitivity = 42%, Specificity = 86%
Subclinical depression
A large effect suggests subclinical depression in adolescents and young adults (14-24 years) was associated with an increased risk of bipolar disorder (7.3-10.6 year follow-up); 1 study, N = 976, OR = 5.20, *p* not reported *Lifetime subclinical depression in high-risk adults (18-64 years) predicted bipolar disorder (3-year follow-up);* 1 study, N = 976, LR = 3.30, *p* not reported *Subclinical depression in adults (17-65 years) was associated with later bipolar disorder (3-4 year follow-up);* 1 study, N = 100, no statistics reported
Subclinical mania
Transient hypomania in children (8-11 years) with depressive symptoms was associated with bipolar disorder (1.5 year follow-up) compared to children with depressive symptoms and no hypomania; 1 study, N = 33, 48% vs. 12.5%, *p* not reported *A small effect suggests subclinical hypomania in adults (>17 years) with major depressive disorder was associated with an increased risk of bipolar disorder (1-31 year follow-up);* 1 study, N = 550, HR = 1.34, *p* not reported *A medium-sized effect suggests mood disturbances and change in functioning in adolescents and young adults (14-24 years) are associated with an increased risk of bipolar disorder (7.3-10.6 year follow-up);* 1 study, N = 2,210, OR = 4.25, *p* not reported *Elation and/or irritability in adults (>18 years) with subclinical hypomania was associated with an increased risk of bipolar disorder (3-year follow-up);* 1 study, N = 33, OR = 2.60 to 4.60, *p* not reported *Subclinical hypomania in adults (18-75 years) with major depressive disorder and psychotic symptoms was associated with an increased risk of bipolar disorder (0.5-9 year follow-up);* 1 study, N = 49, Chi-sq = 4.76, *p* not reported

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Subclinical hypomania in high-risk adults (18-64 years) was associated with an increased risk of bipolar disorder (3-year follow-up);

1 study, N = 4,638, LR = 25.40, *p* not reported

This finding was greatest in people who also had psychotic symptoms.

Hyperenergenic activity in young adults (>17 years) with major depressive disorder was associated with later bipolar disorder (2-11 year follow-up);

1 study, N = 559, no statistics reported

Subclinical hypomania in adults (31-33 years) with hypomanic personality was associated with later bipolar disorder (13-year follow-up);

1 study, N = 67, no statistics reported

Cyclothymic disorder or bipolar disorder not otherwise specified

Cyclothymic temperament in children and adolescents (7-17 years) with major depressive disorder was associated with later bipolar disorder, suicide, and suicide attempts (2-4 year follow-up);

1 study, N = 80, statistics not reported

Cyclothymic disorder in adolescents and adults (15-45 years) was associated with later bipolar disorder (2-3 year follow-up);

1 study, N = 46, 35% developed bipolar disorder (7% bipolar I, 28% bipolar II)

Hypomania and mania in adolescents and young adults (14-24 years) were associated with bipolar disorder (7.3-10.6 year follow-up);

1 study, N = 154, 64.1% developed bipolar disorder (16.5% bipolar I, 47.6% bipolar II)

Bipolar disorder not otherwise specified in children and adolescents (7-17 years) was associated with later bipolar disorder (0.5-8.3 year follow-up);

1 study, N = 140, 45% developed bipolar disorder (23% bipolar I, 22% bipolar II)

A small effect suggests behavioural reward and fun seeking in young adults (18-24 years) was associated with an increased risk of later bipolar disorder (0.5-8.3 year follow-up);

1 study, N = 57, OR = 1.40, *p* not reported

Psychotic symptoms in people with major depression

Psychotic symptoms in children and adolescents (13-17 years) with major depressive disorder predicted bipolar disorder (2-year follow-up) compared to major depressive disorder with no psychotic symptoms;

1 study, N = 58, 8.6% vs. 0% developed bipolar disorder

Cyclothymic temperament with psychotic symptoms in children and adolescents (7-17 years) with major depressive disorder is associated with bipolar disorder (2-4 year follow-up) compared to children and adolescents with major depressive disorder without cyclothymic temperament and psychotic symptoms;

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1 study, N = 80, 57.4% vs. 6.1% developed bipolar disorder
Small to medium-sized effect suggests severity of psychotic systems in adults (>17 years) with major depressive disorder is associated with an increased risk of later bipolar disorder (1-31 year follow-up);
1 study, N = 550, HR = 1.97 (bipolar I) to 3.54 (bipolar II), *p* not reported
Psychotic symptoms in adults (31.7 years) with major depression were associated with greater conversion to bipolar disorder than psychotic symptoms alone;
1 study, N = 198, 20.7% vs. 10.7% developed bipolar disorder
Mixed states and hypomania in children and adults (10 to 82 years) with major depressive disorder and psychotic symptoms were associated with later bipolar disorder (4-year follow-up);
1 study, N = 107, statistics not reported
Decreased psychotic and negative symptoms in adolescents and adults (15 to 60 years) with major depressive disorder was associated with later bipolar disorder (10-year follow-up);
1 study, N = 80, statistics not reported
Psychotic symptoms in adolescents and adults (15-75 years) with major depressive disorder was not specifically associated with later bipolar disorder (1-2 year follow-up);
1 study, N = 157, 9% developed bipolar disorder I, 4% developed bipolar disorder II
Schizotypy and psychosis
A small effect suggests schizotypal features in adolescents (18.5 years) are associated with later bipolar disorder (27-year follow-up);
1 study, N = 335, OR = 1.57, *p* not reported
Psychosis not otherwise specified in children (10-12 years) was associated with later bipolar disorder (4-8 year follow-up);
1 study, N = 32, 38% developed bipolar disorder
Psychotic disorder in children and adolescents (9-17 years) was not specifically associated with later bipolar disorder (2-year follow-up);
1 study, N = 70, 10% developed bipolar disorder
Age at onset of major depression
Age of onset of major depression episode or disorder under 25 years was associated with good sensitivity and specificity in predicting bipolar disorder (1-9 year follow-up);
1 study, N = 206, Sensitivity = 71%, Specificity = 68%, Positive Predictive Value = 69%
Early onset depression (<17 years) was associated with later bipolar disorder II (2-11 year follow-up);
1 study, N = 559, *t* = 2.79, *p* not reported
Early onset depression (<17 years) was associated with later bipolar disorder (7.3-10.6 year follow-

up); 1 study, N = 976, 9% vs. 1-2% developed bipolar disorder
Frequency and loading of affective symptoms
Loading of lifetime major depressive episodes and hypomania in high-risk adults (18 to 64 years) were associated with later bipolar disorder (3-year follow-up); 1 study, N = 4,628, LR = 2.7 to 16.4 *Duration of depressive symptoms, recurrence and duration of episodes in high-risk adolescents and young adults (14 to 24 years) were associated with later bipolar disorder (7.3-10.6 year follow-up);* 1 study, N = 1,902, no statistics reported

Consistency in results	Appears consistent for mood swings, subclinical depression and mania, cyclothymic disorder, frequency and loading of depression, early onset of depression. Appears inconsistent for psychosis with or without depression.
Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

Kessing LV, Willer I, Andersen PK, Bukh JD

Rate and predictors of conversion from unipolar to bipolar disorder: A systematic review and meta-analysis

Bipolar Disorders 2017; 19: 324-35

View review abstract online

Comparison	**Conversion rates over time from unipolar depression to bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (large sample, direct, unable to assess consistency or precision) suggests the cumulative rate of conversion from unipolar depression to bipolar disorder increases from 3.78% at 1 year assessment to 12.87% at 10-year assessment.** **The yearly rate of conversion from unipolar depression to bipolar disorder decreases from 3.83% at 1 year assessment to 0.78% at 10 year assessment.**

Conversion rates	
11 studies, N = 77,066 *The cumulative risk of conversion increased, and the yearly rate of conversion decreased over time;* 1 year cumulative % = 3.78, 2-year cumulative % = 6.74, 5 year cumulative % = 9.41, 10 year cumulative % = 12.87 1 year rate = 3.85%, 1-2 year rate = 3.13%, 2-5 year rate = 0.97%, 5-10 year rate = 0.78% Authors report no consistent associations between conversion rates and having a family history of bipolar disorder, or younger age a first depression diagnosis. Authors report no evidence of publication bias.	
Consistency in results	No measure of consistency is reported.
Precision in results	Unable to assess.
Directness of results	Direct

Laurens KR, Luo L, Matheson SL, Carr VJ, Raudino A, Harris F, Green MJ

Common or distinct pathways to psychosis? A systematic review of evidence from prospective studies for developmental risk factors and antecedents of the schizophrenia spectrum disorders and affective psychoses

BMC Psychiatry 2015; 15(1): 205

View review abstract online

Comparison	**Behaviour and psychopathology in children and adolescents prior to the development of bipolar disorder.**
Summary of evidence	**Moderate quality evidence (imprecise, direct, large samples, appears consistent) suggests an increased risk of developing bipolar disorder in adulthood if there is a childhood history of attention problems, aggressive behaviour, conduct/oppositional defiant disorder, depression, internalising or externalising behaviour, social isolation, or peer rejection. Moderate to low quality evidence (inconsistent) also suggests they may be an increased risk of bipolar disorder if there is a childhood history of anxiety symptoms.**
Behaviour and psychopathology	

A significant, large effect of more attention problems, aggressive behaviour, anxiety and depression in children aged around 4 years who developed bipolar disorder in adulthood (18 to 28 years old);

1 study, N = 97, OR = 8.75, 95%CI 1.89 to 40.58, $p < 0.01$

A significant, medium-sized effect of more behavioural problems in children aged between 7 and 16 years who developed bipolar disorder in adulthood (16-28 years old);

1 study, N = 261, OR = 2.05, 95%CI 1.01 to 4.15, $p < 0.05$

A significant, medium-sized effect of more attention problems in children aged between 7 and 16 years who developed bipolar disorder in adulthood (>18 years old);

1 study, N = 261, OR = 2.51, 95%CI 1.21 to 5.18, $p < 0.05$

A significant, medium-sized effect of more depressive disorders in children aged between 11 to 15 years and risk of bipolar disorder in adulthood (26 years old);

1 study, N = 939, OR = 3.30, 95%CI 1.20 to 9.20, $p < 0.05$

A significant, small effect of more depressive symptoms in children aged between 11 to 21 years and risk of bipolar disorder in adulthood (15 to 26 years old);

1 study, N = 66, OR = 1.12, 95%CI 1.04 to 3.85, $p < 0.05$

A significant, large effect of more internalising problems in children aged between 5 and 11 years who developed bipolar disorder in adulthood (26 years old);

1 study, N = 662, OR = 22.05, 95%CI 9.67 to 50.27, $p < 0.01$

A significant, large effect of more externalising problems in children aged between 5 and 11 years who developed bipolar disorder in adulthood (26 years old);

1 study, N = 662, OR = 59.89, 95%CI 25.94 to 138.27, $p < 0.05$

A significant, small to medium-sized effect of more social maladjustment/overreacting in children aged 7 years who developed bipolar disorder in adulthood (16-28 years old);

1 study, N = 1,416, OR = 1.96, 95%CI 1.03 to 3.75, $p < 0.05$

A significant, medium-sized effect of more conduct/oppositional defiant disorder in children aged between 11 and 15 years who developed bipolar disorder in adulthood (26 years old);

1 study, N = 939, OR = 2.50, 95%CI 1.10 to 5.40, $p < 0.05$

A significant, large effect of more social isolation in children aged between 5 and 11 years who developed bipolar disorder in adulthood (26 years old);

1 study, N = 662, OR = 243.45, 95%CI 103.04 to 575.17, $p < 0.01$

A significant, large effect of more peer rejection in children aged between 5 and 11 years who developed bipolar disorder in adulthood (26 years old);

1 study, N = 662, OR = 903.18, 95%CI 372.18 to 2191.78, $p < 0.01$

No significant effect of social maladjustment/underreacting in children aged 7 years and risk of bipolar disorder in adulthood (16-28 years old);

1 study, N = 1,416, OR = 1.46, 95%CI 0.76 to 2.78, $p > 0.05$

No significant effect of psychotic symptoms in children aged 11 years and risk of bipolar disorder in adulthood (26 years old);

1 study, N = 761, OR = 0.46, 95%CI 0.06 to 3.59, $p > 0.05$

No significant effect of anxiety disorders in children aged between 11 to 15 years and risk of bipolar disorder in adulthood (26 years old);

1 study, N = 939, OR = 2.10, 95%CI 0.95 to 4.63, $p > 0.05$

No significant effect of ADHD in children aged between 11 to 15 years and risk of bipolar disorder in adulthood (26 years old);

1 study, N = 939, OR = 0.48, 95%CI 0.06 to 4.16, $p > 0.05$

No significant effect of hypomania in children aged between 11 to 21 years and risk of bipolar disorder in adulthood (15 to 26 years old);

1 study, N = 66, OR = 0.44, 95%CI 0.18 to 1.05, $p > 0.05$

No significant effect of irritability in children aged around 14 years and risk of bipolar disorder in adulthood (33 years old);

1 study, N = 631, OR = 1.02, 95%CI 0.39 to 2.69, $p > 0.05$

Consistency in results	Appears consistent, apart from anxiety.
Precision in results	Imprecise

Directness of results	Direct

Vidal-Ribas P, Brotman MA, Valdivieso I, Leibenluft E, Stringaris A

The Status of Irritability in Psychiatry: A Conceptual and Quantitative Review

Journal of the American Academy of Child and Adolescent Psychiatry 2016; 55: 556-70

View review abstract online

Comparison	**Irritability in children and adolescents prior to the development of bipolar disorder.**
Summary of evidence	**Moderate quality evidence (consistent, imprecise, direct, large sample) suggests no relationship between irritability in childhood and bipolar disorder in adulthood.**
Irritability	
No significant effect of irritability in children aged 6-19 years and risk of bipolar disorder in adulthood (< 33 years old); 3 studies, N =1,209 OR = 1.09, 95%CI 0.67 to 1.77, p = 0.739, I^2 = 0%	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, HR = hazard ratio, LR = likelihood ratio, N = number of participants, OR = odds ratio, ns = not significant, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus

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 tath 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[9].

† Different effect measures are reported by different reviews.

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 medium effect, and 0.8 and over represents a large treatment effect[9].

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[10]. 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.

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).

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. I^2 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. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[9];

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

§ 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[11].

‖ 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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