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Title: Child and adolescent anxiety as a risk factor for bipolar disorder: A systematic review of longitudinal studies

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract

Objectives

Several studies have suggested that anxiety disorders in childhood and adolescence often precede the onset of bipolar disorder. We therefore systematically reviewed the relationship between child and adolescent anxiety and later bipolar disorder.

Methods

Online databases (Medline (for Ovid), EMBASE and PsychINFO) were searched for original, peer-reviewed studies examining the relationship between child and adolescent anxiety and later bipolar disorder. Studies in both community samples and bipolar offspring samples were included.

Results

A total of 16 studies were included in the review. Results were broadly consistent and revealed that child and adolescent anxiety disorders are associated with later bipolar disorder in community samples. In bipolar offspring, child and adolescent anxiety disorders are a marker of increased risk and predict the onset of bipolar disorder and other major mood disorders.

Conclusions

There is evidence that anxiety disorders in childhood and adolescence increase the risk of later bipolar disorder. Anxiety disorders may be a useful target for early intervention in those at high-risk of bipolar disorder.

Keywords: Bipolar disorder, anxiety, risk factor, childhood, adolescence

1. Introduction

Bipolar disorder is a serious mental health condition and the sixth leading cause of disability among people aged 15-44 worldwide [1]. It typically emerges in early adulthood with 50-75% of individuals reporting the onset of symptoms before the age of 18 [2]. However, the heterogeneity of early symptoms makes timely and accurate diagnosis challenging and means that effective treatment is often delayed resulting in a more severe illness course and a poorer treatment response [3,4]. Better understanding the early course of bipolar disorder is therefore a crucial part of improving early detection, developing primary prevention strategies, and designing novel early intervention approaches. To this end, there is a growing focus on risk factors and early signs of illness with recent studies attempting to identify and characterize clinical risk factors that are present prior to the onset of affective symptoms. These risk factors may be valuable targets for early intervention that could prevent or delay the onset of major mood disorders like bipolar disorder and improve overall functioning.

Given that bipolar disorder has an estimated heritability of between 60- 85% [5-7], one promising approach to identifying those most at risk has been to study the offspring of bipolar parents. Several longitudinal prospective studies of these high-risk offspring now clearly suggest that there are recognisable clinical indicators present before that onset of bipolar disorder including anxiety disorders, sleep problems, behavioural disorders and minor mood disturbances (e.g. subclinical hypomanic symptoms) [8-10]. These findings have also been validated by a number of cross-sectional [11] and retrospective [12] studies and there is now a broad consensus that these clinical presentations likely form part of a developmental trajectory into bipolar disorder. Several studies have attempted to synthesise these results into developmental staging models of bipolar [13,14], all of which emphasise childhood and adolescence as a key risk period for the emergence of affective symptoms. These studies also suggest that potentially targeting risk factors through early intervention may have particular value at this stage in development given

the progressive nature of bipolar disorder and the importance young people being able to attain developmentally normative psychosocial milestones [15].

Anxiety disorders are of particular interest for several reasons: (1) There is already well established evidence that anxiety in childhood is a robust risk factor for other mood disorders in adulthood, for example major depressive disorder (MDD) [16,17] (2) Retrospective studies of adults with bipolar disorder suggest that anxiety is exceedingly common before the onset of bipolar disorder and is commonly experienced as one of several early prodromes including sleep disturbances and mood lability that are experienced in childhood and adolescence before the onset of mood problems [18]. (3) There are strikingly high rates of comorbid anxiety amongst adults with bipolar disorder meaning that anxiety persists even after the onset of affective symptoms; recent research suggests a lifetime prevalence of 44% amongst those with bipolar [19]. (4) It is widely recognised that comorbid anxiety worsens the course bipolar disorder, negatively impacts treatment outcomes and reduces overall wellbeing and functioning [20]

However, questions remain about whether clinically significant anxiety in childhood and adolescence could be a specific marker of risk for later bipolar disorder or an indicator of a more general vulnerability to future psychopathology. Indeed, childhood anxiety predicts the emergence of a range of psychiatric outcomes in adulthood including adult anxiety disorders, substance use disorders and other major mood disorders [21]. However, given bipolar offspring are at a high risk of developing both bipolar disorder and other major mood disorders in adulthood, it may be that anxiety has particular significance for this group as a risk factor for broad affective outcomes. Early intervention targeting anxiety may prevent or delay the emergence of affective symptoms and improve global functioning amongst bipolar offspring

High-risk youth, that is those who have a parent with bipolar disorder, provide an excellent opportunity to study risk factors before the onset of major mood disorders. These studies

provide a prospective view of the emergence of affective and non-affective symptoms, allowing for temporal examination of problems and the exploration of potential causal relationships. However, there are a limited number of these cohorts available, and there are significant methodological differences between studies (e.g. assessment tools, recruitment methods) which complicates cross-cohort comparisons. Furthermore, sample sizes are smaller owing to the challenges of recruiting this population in longitudinal studies. Therefore for the current review, we chose to also include data from observational population cohort studies to enhance our understanding of the relationship between childhood anxiety and later bipolar disorder. These prospective studies have far greater statistical power owing to their large sample sizes and generally have longer follow-up periods to allow for more accurate detection of any emerging mood disorders. However, prospective studies also introduce potential bias with regard to missing data and higher drop-out rates. Furthermore, many register-based studies involve pre-determined assessments meaning that meaningful information regarding confounders may be missing (e.g. family history). Combining large scale population studies with smaller high-risk cohorts of bipolar offspring allows us to balance the respective strengths and limitations.

Our aims, therefore were (1) To investigate whether in the general population, a diagnosis of an anxiety disorder in childhood or adolescence is associated with an increased risk of developing bipolar disorder in adulthood and (2) To examine the relationship between anxiety and subsequent affective disorders including transition to bipolar disorder in high-risk bipolar offspring. Cross sectional studies are not reviewed here due to the bias introduced following exposure to bipolar disorder. To our knowledge, this is the first review to systematically examine child and adolescent anxiety as a marker of increased vulnerability to bipolar disorder in adulthood.

2. Methods

2.1 Search strategy

Conducting and reporting of the systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search using EMBASE (1974 to September 2022), PsychINFO (1806 to September 2022) and Medline (1946 to September 2022) was conducted to identify peer-reviewed papers using the search terms: (child* or adoles* or youth) AND anx* AND risk AND (bipolar or "bipolar disorder" or mani*) and longitudinal.

2.2 Study selection and data extraction

Reports were included if they were published in a peer review journal between 1974 and September 2022 and reported (i) a baseline, age-appropriate measure of anxiety disorders or symptoms using either a validated assessment tool or a thorough clinical assessment conducted by appropriately trained clinician (ii) a longitudinal observational design or case-control study within a longitudinal design (iii) recognised clinical assessment of either a) bipolar disorder diagnostic status based on either the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria b) bipolar disorder symptoms (i.e. depression and (hypo)mania) or c) severity of bipolar disorder as evidence by number of bipolar disorder episodes at follow up . Papers were excluded if (i) they evaluated the treatment of anxiety in children and young people, for example cognitive behavioural therapy (CBT) for anxiety or selective serotonin reuptake inhibitors (SSRI's) (ii) they included anxiety solely related to specific populations (i.e., pre-operative anxiety) and (iii) they were a systematic review and/or meta-analysis. This review included papers reporting on child and adolescent obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) because of the core phenomenological experience of anxiety.

Figure 1 outlines the search strategy. Report titles and abstracts were screened by two researchers independently using inclusion and exclusion criteria and any inconsistencies were resolved by discussion. Full texts were then screened by the lead author and checked by the second researcher. The following data were extracted from included reports: study name, year, author, sample characteristics, assessment tools, results and a brief narrative summary. All reports were assigned to one of two groups, 1) those that involved a population cohort 2) those that involved a high-risk cohort of bipolar offspring. Forward and backward citation searches were then conducted on eligible papers.

We followed published guidelines [22] to deal with multiple data sources and overlapping data. In cases where multiple reports were published on the same study, papers were linked to their source study and a main report for each study was identified using the following rules (i) the most recent follow up report for each cohort was chosen if more than one was available that met inclusion criteria (i.e. priority was given to papers with the longest follow up duration) (ii) when separate reports from the same study met inclusion criteria but had different research questions (e.g. reports examining individual anxiety disorders, reports utilising dimensional measures of anxiety instead of categorical measures), a main report was identified and data were extracted from the other sources. Priority was given to reports using (i) using the entire study cohort over subsamples (ii) diagnostic categories over symptom measures.

[Figure 1: PRISMA Flow diagram for systematic review of the relationship between child and adolescent anxiety disorders and later bipolar disorder]

2.4 Quality Assessment Tool

The Newcastle-Ottawa Scale (NOS) for cohort studies was used to assess the quality of included studies. The tool evaluates studies based on three domains, the selection of the exposed cohort (anxiety disorders), the comparability of cohorts (exposed and non-affected or control) and the assessment of outcome. Studies can score a maximum of four stars on the selection domain, two stars on the comparability domain and three stars on the outcome domain giving a total maximum score of 9 points. Total NOS scores can be converted into one of three categories which correspond to the Association of Health Research Quality standards; good (3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain), fair (2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain) and poor (0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain. All included studies were evaluated independently by two researchers; any discrepancies were resolved by discussion.

3. Results

789 reports were identified through databases of which 74 had their full text reviewed. Of these, 13 studies were identified and included in the current review using 18 reports. A further three studies were identified through citation searches of the initial 13 included studies bringing the total to 16 studies comprising 21 reports. Seven studies were in population samples while nine studies were in high risk cohorts, that is samples of bipolar offspring.. Key study characteristics are presented in Table 1. The characteristics of studies are detailed in Table 1. The studies involved 2,433,761 participants from ten countries.

[Table 1: Summary of studies examining the relationship between child and adolescent anxiety and later bipolar disorder]

3.1 Quality Assessment Tool

All studies were subject to a risk of bias assessment. (see Table S1). Studies scored between 6 and 9 out of 9. Twelve studies were classified as good and four were classified as fair.

3.2 Anxiety as a risk factor for bipolar disorder in population cohorts

Of the seven studies using population cohorts, two examined individual anxiety disorder diagnoses whilst the remaining five grouped all anxiety disorders into a single risk factor. The majority of studies (N=5) found a significant association between child and adolescent anxiety and later bipolar disorder.

3.2.1 Individual anxiety disorders

The Early Developmental Stages of Psychopathology Study, a prospective cohort study of 3021 young people aged between 14-24 followed for 10 year investigated the link between several different anxiety disorders in adolescence and later bipolar disorder[23-25]. OCD [25] and specific phobia[24] predicted the onset of subsequent bipolar disorder. The risk of developing bipolar was increased by 590% and 120% respectively. In fact, the increase in risk for bipolar disorder associated with OCD was higher than for any other subsequent adult disorder measured, including other anxiety disorders, MDD and eating disorders. However, the number of OCD cases was low (n=55) and OCD onsets were combined to include retrospective age of onset at timepoint 0 and any subsequent cases that occurred during the follow up period, meaning that some cases will have emerged in adulthood. This study also found a significant relationship between separation anxiety disorder (SAD) and later bipolar disorder in a subsample of 1019 younger adolescents between the ages of 14-17 and followed up for four years. The study found

that adolescents with a history of childhood SAD had an 7-fold increased risk of bipolar disorder when compared with controls. Supplementary prospective analysis excluding all participants who already met criteria for bipolar disorder at timepoint 0 and showed that childhood SAD also predicted the first onset of bipolar-II. This association was specific to bipolar disorder and not to MDD.

A recent study from Brazil[26] utilised machine learning algorithms to identify risk factors for bipolar disorder in a large birth cohort of 3778 assessed at 11, 15, 18 and finally 22 years of age. 255 participants developed bipolar disorder by the final follow up. The authors found that at 18 years of age, GAD was the second most important who would develop bipolar disorder after suicidality.A further study followed a sample of 90 community-based adolescents with hypomania spectrum episodes who were assessed at the age of 16-17 and followed up 15 years later to investigate early risk factors for transition to bipolar disorder. Results showed that panic disorder (PD) and generalised anxiety disorder (GAD) were risk factors for subsequent bipolar disorder.[27] The presence of either anxiety disorder meant a 12-times greater likelihood of developing bipolar disorder. This suggests that anxiety may provide additional predictive value as a risk factor for bipolar in combination with other well-known antecedents such as subthreshold hypomania.

3.2.2. Any anxiety disorder

When collapsing all anxiety disorders into one category of "any anxiety disorder", one study found that in a sample of 717 participants assessed at 14, those with anxiety disorders had a four times greater likelihood of subsequently developing bipolar disorder.[28] Although adolescent depressive disorders and disruptive disorders were also associated with an increased likelihood of subsequent bipolar disorder in early adulthood, only anxiety disorders remained a significant predictor of both full and subthreshold bipolar disorder when adolescent manic

symptoms were controlled for. This suggests that adolescent anxiety disorder have unique predictive value for bipolar disorder that cannot be explained by overall psychiatric comorbidity or psychiatric disorders

Similar results were reported in a large-scale birth cohort, which found that a prior anxiety disorder increased the risk of adult-onset bipolar disorder 10-fold compared to those with no diagnosis of anxiety.[29] The risk of adult-onset bipolar disorder was increased further in those with a prior diagnosis of an anxiety disorder and attention deficit hyperactivity disorder (ADHD) suggesting that identifying more than one risk factor for bipolar may improve identification of those at highest risk.

Two studies found weaker associations between anxiety disorders and later bipolar disorder. One study, which measured anxiety symptoms as measured by the Strengths and Difficulties Questionnaire (SDQ), did not find a significant association between adolescent anxiety and later bipolar disorder.[30] However bipolar disorder was categorised with psychotic disorders into a "bipolar/psychosis" group limiting the generalisability of the results. A second follow-back report of a large prospective longitudinal birth cohort (N = 1037) first assessed at age 11 and every 2-3 years until 26, examined which adolescent psychiatric diagnoses preceded adult disorders. Results showed that adolescent anxiety disorders were very common in those diagnosed with mania at 26, however this relationship did not meet statistical significance.[31]

3.3 Anxiety as a risk factor for bipolar disorder in high-risk cohorts

Of the nine high-risk cohort studies included in this review seven were naturalistic observational studies whilst one was a follow up study of high-risk youth who had received family focused treatment for bipolar disorder. Seven studies found a significant temporal association between child and adolescent anxiety and subsequent major mood disorders, including bipolar disorder.

3.3.1. Naturalistic observational studies

The Flourish Canadian high-risk study[32] recruited a large cohort of 279 high-risk offspring aged 5-25 at first assessment and found that the presence of an anxiety disorder in childhood nearly doubled the risk of subsequent major mood disorder. The age-adjusted risk of mood disorder increased from 40-85% in those children with an anxiety disorder. At 12-year follow up, the cumulative incidence of bipolar disorder in offspring was 25% and the cumulative incidence of depressive disorders was 70%, supporting the notion that bipolar offspring are at high risk for a range of affective disorders. When examining males and females separately, the magnitude of increase in risk associated with anxiety disorder was much higher for females compared t males. In an earlier paper published on this cohort, the authors found that GAD and social anxiety disorder were the strongest predictors amongst specific anxiety disorders and that the anxiety disorder preceded the onset of major mood disorder by an average of 8.55 years (SD: 5.29)[33]

The Amish study followed 115 bipolar offspring from childhood for 16-years to measure rates of transition to bipolar disorder. In the nine offspring that went on to develop bipolar disorder, key prodromal symptoms were noted as sensitivity by nature (defined in this study as being persistently "different" from peers with regard to sensitivity from a young age as reported by parents), anxiety/worry and somatic complaints in early childhood. Gender differences in prodromal symptoms were not systematically studied . In these children, anxiety symptoms increased in late childhood and into adolescence, when fearfulness along with sad mood and changes in energy were primary symptoms [34] suggesting that anxiety precedes the onset of mood disturbances and eventually major mood disorder. The more recent Dutch Bipolar Offspring Study found that 13% of their sample (14 out of 108) developed a bipolar spectrum

condition over the follow up period of 12 years and that 53% of these had an anxiety disorder. Gender did not affect any of the study findings. The authors suggest a developmental pathway towards bipolar disorder from early anxiety disorders, through an initial depressive episode culminating in bipolar disorder.[35] In line with this, supplemental analysis of this cohort showed that general anxiety symptoms reported on the K-SADS (i.e. marked feelings of tension, marked feelings of self-consciousness and compulsion) were associated with a first mood disorder onset. [36]

In a recent study of 93 bipolar offspring followed prospectively for 3 years, the presence of an anxiety disorder at baseline was associated with a significantly increased risk of later developing bipolar disorder.[37] Those that converted to bipolar disorder were more likely to be girls and also significantly more likely to have had higher overall exposure to antidepressants used to treat anxiety and depressive symptoms. Similar findings were reported in a longitudinal study of 141 bipolar offspring aged between 12-21.[38] 12 of the bipolar offspring (8.5%) developed a bipolar spectrum disorder compared with zero controls. Although overall rates of anxiety disorders did not differ between high-risk and control offspring, anxiety disorders increased the risk of subsequent major mood disorder in bipolar offspring nearly 3-fold suggesting that the presence of anxiety in young people with a family history of bipolar disorder may indicate a marker of additional risk of developing a major mood disorder.

Three studies reported mixed results with weaker associations between child and adolescent anxiety and later bipolar disorder. The Lausanne-Geneva high risk study on mood disorders published a recent paper[39] that followed 449 children of parents with major mood disorders (bipolar disorder or MDD) for 13 years (mean age 10.1 at baseline) to study precursors to the onset of major mood disorders. Anxiety disorders frequently preceded (hypo)manic episodes however only predicted the onset of major depression in offspring. SAD, GAD and PD were

particularly relevant. When stratified by parental disorder, no significant associations were found between SAD, GAD or PD and later major mood disorder.

The Pittsburgh Bipolar Offspring Study (BIOS), a large-scale study of 391 high-risk offspring aged between 6-18 followed for on average 6.8 years, found that anxiety disorders were not associated with the onset of (hypo)mania.[8] However, in a follow up study, self-report symptoms of anxiety and depression - were the strongest predictor of a later bipolar disorder.[40] Similarly, the Bipolar Kids and Sibs Study recruited 163 high-risk youth aged between 12-30 who had a first degree relative with bipolar disorder found no relationship between baseline anxiety disorders and a first episode of hypo(mania) over a follow up period of five years.[10] No gender effects were reported.

3.3.2 Studies of high-risk offspring receiving treatment

Findings from a recent study examining the relationship between anxiety and bipolar disorder in 126 high risk offspring aged between 9-17 who had received family focused therapy suggested that anxiety at baseline was associated with more severe mood symptoms (depressive and hypomanic) at follow up.[41] There were no significant gender effects found.

Discussion

We systematically reviewed the literature to examine the relationship between child and adolescent anxiety and later bipolar disorder. The sixteen studies identified included both high-risk cohorts of bipolar offspring as well as population cohorts and assessed whether anxiety disorders in childhood and/or adolescence increase the risk of developing bipolar disorder in adulthood. The review establishes two interesting findings. First, there is evidence from population cohort studies that child and adolescent anxiety significantly increases the risk of later bipolar disorder between 2-12-fold. SAD, GAD and PD appear to have particular clinical relevance. This is in line with the hg\ literature ([16,17,21]) which suggests that anxiety in childhood or adolescence predisposes individuals to a range of poor outcomes in adulthood including anxiety disorders, mood disorders, educational underachievement, and substance use disorders.

Secondly, in high-risk cohorts of bipolar offspring, there is good evidence that child and adolescent anxiety may be a useful marker of those who are more vulnerable to developing a major mood disorder in adulthood. There was mixed evidence about the specificity of anxiety as a risk factor for bipolar disorder. Some studies [34,37,38] found an association between child and adolescent anxiety and later bipolar disorder, however others [36,41,42] found that anxiety increased the risk of later mood disorders but was more predictive of a first depressive episode. This is noteworthy as in all but one of the high-risk cohort studies, the majority of those who developed bipolar disorder initially presented with a depressive episode. There was also some evidence[32,37] that female offspring were more at risk of conversion to bipolar disorder particularly if they experienced anxiety disorders. Two studies found no association between child and adolescent anxiety disorders and later (hypo)mania .

Comparing results from population offspring cohorts, there are several points to note. Firstly, although both found a significant relationship between child and adolescent anxiety and later

mood disorders including bipolar disorder, population cohorts reported a greater increase in risk compared to bipolar offspring cohorts. This can be explained by the fact that population cohorts are much larger and do not account for family history, the most well-established risk factor for bipolar disorder while at the same time, high-risk studies may also be underpowered to detect effects and have shorter follow-up periods that may not have followed all participants through the peak age of onset risk.Although family history is the most potent risk factor, the presence of an anxiety disorder among bipolar offspring appears to delineate a subgroup of offspring most vulnerable to developing major mood disorders including bipolar disorder.. Secondly, although population studies have greater power to detect effects, the high-risk studies here provide a finer-grain look at the progression from early childhood problems through to later bipolar disorder as a result of the more frequent and numerous follow ups and the more diverse range of assessment measures used, for example dimensional measures of anxiety [36,40]. For example, while population cohorts did not demonstrate gender effects, two offspring studies here provided tentative evidence that females may be particularly vulnerable to transitioning from non-mood disorders like anxiety to major mood disorders compared to males. The majority of offspring studies agreed that offspring who do develop bipolar disorder likely progress through a recognisable set of stages from non-mood disorders like anxiety in childhood, through minor mood disturbance, an initial depressive episode and finally hypo(mania). Offspring studies, therefore perhaps suggest that that child and adolescent anxiety has most importance as a predictor of who will move along this developmental trajectory towards bipolar disorder through a depressive episode, which has a greater significance in those with a genetic risk of bipolar disorder.

There was greater agreement amongst population studies about the relationship between child and adolescent anxiety and later bipolar disorder, however amongst the offspring cohorts three

large, comprehensive studies failed to find a specific relationship between anxiety and later (hypo)mania. This may be because anxiety is more predictive of an initial depressive episode. However discrepant findings may also be explained by methodological differences. In one study that reported no relationship between anxiety and later (hypo)mania[10], participants were older at baseline (mean 19.1) and the majority had already experienced a major depressive episode meaning they were most likely already experiencing a major mood disorder at baseline. This limits the ability of this study to truly examine the relevance of anxiety as risk factor prior to illness onset. In the second study [8], the sample had a mean age at baseline of 11 and a mean follow up duration of 6.8 years meaning that most participants would not yet have reached the highest-risk period of transition to bipolar disorder. In addition, the much higher rates of pre-puberal mania in this sample compared to other studies underscores the differences in the diagnosis and conceptualisation of paediatric bipolar disorder across cohorts and countries. Given the unique age of onset patterns seen across anxiety disorders, differences in age at recruitment could affect the detection rates of anxiety disorders or introduce recall bias.

There were also significant differences in recruitment strategies and inclusion criteria across high-risk studies. Five studies recruited participants through larger ongoing genetic or imaging studies, while three used advertising and recruitment through clinical services. These distinct recruitment methods may have resulted in differences in parent samples given the differences in how reliably diagnostic status was obtained. Furthermore, there may be differences in parents recruited by self-referral compared to those recruited through specialist clinical services for bipolar disorder. Despite this, there were sufficiently large sample sizes and adequate follow up periods reported in most studies as well as adequate retention rates and well described case and control samples. There are already several other large-scale offspring studies ongoing[43-45] which may provide more insight into the role of anxiety as a clinical predictor of bipolar disorder in high-risk youth. The Danish high-risk study[45] has already published data from an

initial four year follow up and found higher rates of anxiety disorder in bipolar offspring compared to controls. Further follow up papers will be able to assess the rates of transition to mood disorder and the importance of anxiety as a risk factor.

Overall, the results from this review are in line with other studies which suggest that anxiety that clinically significant anxiety, particularly in young people with a familial risk of bipolar disorder may increase the risk of major mood disorders including bipolar disorderand delineates a subgroup of vulnerable high-risk youth that warrant additional monitoring. It is reasonable to tentatively suggest that early interventions for bipolar disorder that focus on anxiety could be beneficial in preventing or delaying the emergence of major mood symptoms in this population. Furthermore, anxiety disorders significantly impair functioning, and recent evidence suggests that high functional impairment in bipolar offspring is prospectively associated with higher expression of both depressive and manic symptoms. There are of course inherent ethical considerations associated with preventative early interventions which have been discussed in detail elsewhere, particularly with regard to psychotic disorders[46]. The dilemma central to all preventative approaches including those aimed at reducing the impact of bipolar disorder, is how to weigh up the possible benefits of individual treatment, versus the potential stigma and negative impact of interventions in the context of each service users' right to choose. However anxiety disorders, relatively common place occurrences in childhood and adolescence, may in fact be an ideal treatment target in high-risk youth. Future research is urgently needed to identify the mechanisms that may drive the relationship between anxiety and mood instability in high-risk youth to elucidate potential processes which could be targeted through intervention.

Unfortunately, standard pharmacological interventions (SSRI's) for anxiety in childhood and adolescence potentially carry the risk destabilising mood in high-risk offspring. Several case studies and two recent prospective studies[47-49] have examined the impact of SSRI use in this

population and found the rates of anti-depressant induced mania-like symptoms (AIMS) was much higher than in similar studies of young people with depression or anxiety but without the family history of bipolar disorder. A recent review concluded that the evidence base suggests antidepressant medication may be poorly tolerated in youth with familial risk of bipolar disorder[50]. Indeed, this is illustrated in one study included here where exposure to SSRI's increased the risk of transition to bipolar disorder.[37] However, effective psychological treatments for child and adolescent anxiety disorders also exist, most notably CBT. CBT interventions do not carry the same risks, have fewer side effects and are generally more acceptable to families particularly within an early intervention context. Some work has already started using psychological therapy to target anxiety in high-risk youth and adults with bipolar disorder and comorbid anxiety [51-53]. For example, one study has evaluated the impact of mindfulness-based cognitive therapy in targeting anxiety in high-risk young people and found reductions in anxiety symptoms. [51]. The authors hypothesise that this type of intervention may be effective through affecting interoception and by changing how young people process internal and external stimuli [54]. It may be helpful to investigate whether other current psychological treatments for child and adolescent anxiety can be adapted effectively to meet the needs of high-risk bipolar offspring.

There are several limitations of the current review that should be noted: (1) The heterogeneity of designs and methodology (e.g. assessment tools, follow up periods, sample characteristics) across studies prevented the use of meta-analysis and limits their comparability (2) Given the small number of studies in this area, it was not possible to address the high rates of anxiety co-morbidity; that is multiple anxiety disorders co-occurring at once and the potential impact this might have on the subsequent risk of later major mood disorders(3) The methods of ascertaining exposure to childhood anxiety were varied across studies, some based on retrospective self-report which may have introduced the issue of recall bias (4) The nature of

longitudinal studies mean that there are inevitable sources of bias introduced through the loss of participants at follow up although most studies had processes in place to minimise this as reflected in satisfactory NOS scores (5) Although studies were included from a range of countries across the world, it should be noted that these are all high-income, western countries whose populations are majority white which limits the generalisability of our results across other cultures, countries and ethnicities.

Nonetheless, this review suggests that anxiety in childhood or adolescence increases the risk of later bipolar disorder and may represent a clinically useful marker of vulnerability to major mood disorders in bipolar offspring. Our results also indicated that future research is warranted to explore the potential clinical utility of child and adolescent anxiety as an early intervention target for those at high risk of developing bipolar disorder.

Other Information

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Table 1. Summary of studies examining the relationship between child and adolescent anxiety and later bipolar disorder

Study no.	Study Name *(if applicable)*, Author & Year	Region	Cohort Type (C=Community; HR= High-risk)	N	Gender (% Female)	Age	Diagnostic Assessment Tool	Risk of Bias Assessment	Length of follow up	Findings
1	EDSP **Hofer et al. (2018)[25]** *Bruckl et al. (2007)[23]; Lieb et al. (2016)[24];*	Germany	C	3021	49.3	14-24	CIDI	Good	10 years	SAD = 7x increase in risk of bipolar disorder (HR= 7.7, 95% CI [2.8-20.8]). Specific phobia = 2x the risk of later bipolar disorder (RR = 2.2, 95% CI [1.10, 4.41]). PAF = 15.49. OCD = Nearly 7x increase risk of bipolar disorder (HR = 6.9, 95% CI [2.9, 17.3]).
2	Paaren et al. (2014)[27]	Sweden	C	287	80%	16-17	DISC	Good	15 years	PD or GAD = 12x greater likelihood of adult bipolar disorder (OR= 12.0, 95% CI [1.39- 103.48])
3	Johnson et al. (2000)[28]	USA (New York)	C	717	51%	14	DISC	Fair	8 years	Any anxiety disorder = 4x greater likelihood of bipolar disorder in early adulthood (OR 4.69, 95% CI [1.78-12.38)
4	Meier et al. (2018)[29]	Denmark	C	2,409,236	57%	<16	ICD-10	Good	>5 years	Prior anxiety disorder increased incidence of bipolar disorder 12x fold (IRR = 12.05, 95% CI [11.30, 12.83])
5	CATSS/NTR Doering et al. (2019)[30]	Sweden & The Netherlands	C	14,106	53%	15	SDQ	Good	7 years	No association between adolescent anxiety scores on subscale of the SDQ and later bipolar/psychotic disorders
6	Pelotas Birth Cohort	Brazil	C	3778	53.4%	11	MINI	Good	11 years	GAD at 18 was the second most important predictor of

	Rabelo-da-Ponte et al. (2020)[26]									who would develop bipolar disorder
7	Dunedin Birth Cohort Kim-Cohen et al. (2003)	New Zealand	C	1037	48%	11	DISC / DIS	Good	15 years	Adult mania often preceded by anxiety disorders, but anxiety not reaching significance as predictor (AOR = 2.1; 95% CI, 0.9-4.8)
8	The Flourish Canadian high-risk study **Duffy et al. (2019)[32]** *Duffy et al., (2013)*	Canada	HR	279	60% (HR) 59% (Control)	16.48	K-SADS	Good	M = 7.72 years (SD = 5.28)	Anxiety disorders = nearly 2x fold increase in risk of later major mood disorder (HR= 1.84, 95% CI =91.24, 2.74). Increased age-adjusted risk from 40% to 85%.
9	The Dutch Bipolar Offspring Study **Mesman et al. (2013)[35]** *Mesman et al. (2017)*	The Netherlands	HR	108	46%	16	K-SADS	Fair	12 years	53% of bipolar offspring that developed bipolar disorder had a lifetime diagnosis of an anxiety disorder
10	The Amish Study Egeland et al. (2012)[34]	USA (Pennsylvania)	HR	115	51%	75% <14	CARE Interview	Fair	16 years	Sensitivity by nature is an early marker of risk**.** risk **in those who develop bipolar disorder.** Anxiety/worry is the most common antecedent in adolescents who later developed bipolar disorder
11	Nery et al. (2020)[37]	USA (Cincinnati)	HR	93	53%	13.7	K-SADS	Good	2.7 years	Anxiety disorders = 4x greater likelihood of (developing major mood

										episode, depressive or hypo(manic) (OR = 3.8, 95% CI [1.1, 12.8])
12	Nurnberger et al. (2011)[38]	USA (Indiana)	HR	141	52% (HR) 47% (Control)	11.06	K-SADS	Fair	Range = 6-15 years	Anxiety disorders = 2x risk of later mood disorder including bipolar disorder (RR = 2.6, 95% CI [1.4-9.0]
13	BIOS **Axelson et al. (2015)[8]** *Hafeman et al. (2016)*	USA (Pittsburgh)	HR	391	49% (HR) 54% (Control)	11.9	K-SADS	Good	6.9 years	Relationship between childhood anxiety and later bipolar disorder approaching significance (HR = 1.86, 95% CI [0.97, 3.50])
14	The Bipolar Kids and Sibs Study Frankland et al. (2018)[10]	Australia	HR	163	55% (HR) 52% (Control)	19.2	K-SADS	Good	Median = 5 years	Adolescent anxiety disorders did not predict first episode of hypomania.
15	Weintraub et al. (2020)[41]	USA (California & Colorado)	HR	126	65%	13.2	K-SADS	Good	1.9 years	Young people with anxiety disorder at baseline were more likely to be significantly symptomatic compared to improving or moderately symptomatic at follow up (X^2 (2) = 8.48, p = 0.01)
16	Lausanne-Geneva High Risk Study on Mood Disorders Rudaz et al. (2021)	Switzerland	HR	163	52%	10.1	K-SADS	Good	Mean = 13.2 years	Anxiety disorders predicts major depression in HR offspring. SAD, panic disorder and GAD are particularly relevant.

For studies with multiple reports, the primary report is highlighted in bold and secondary reports are italicised. HR= high risk, C= community, M= mean, SD= standard deviation, DISC=diagnostic interview schedule for children, DIS = diagnostic interview for children, CIDI=composite international diagnostic interview, K-SDAS = kiddie schedule for affective disorders and schizophrenia, MINI = Mini-International Neuropsychiatric Interview, CARE interview = child and adolescent research and evaluation interview, SDQ= strengths & difficulties questionnaire, ICD-10= international classification of diseases v.10