Transitioning to bipolar disorder: A systematic review of prospective high-risk studies

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Purpose of review
Bipolar disorder is a highly heritable condition, which can progress from an asymptomatic period in at-risk individuals to a potentially debilitating illness. Identifying individuals who are at a high risk of developing bipolar disorder may provide an opportunity for early intervention to improve outcomes. The main objective of this systematic review is to provide an overview of prospective studies that evaluated the incidence and predictors of transitioning to bipolar disorder among high-risk individuals.

Recent findings
Twenty-three publications from 16 cohorts were included in the final review. Most studies focused on familial high-risk groups, while others either used clinical or a combination of clinical and genetic risk factors. The follow-up length was from 1 to 21 years and the rate of conversion to bipolar disorder was between 8 and 25% among different studies. Overall, the results suggest that a combination of genetic and clinical risk factors; namely, subthreshold (hypo)manic symptoms and elevated depressive symptoms, may be required to optimally predict conversion to bipolar disorder.

Summary
The concept of high-risk for bipolar disorder is still in its infancy. Further discussions are needed to work towards an expert consensus on the high-risk criteria for bipolar disorder, taking into account both clinical and genetic risk factors.

Keywords
bipolar disorder, high-risk, predictors, prospective studies, systematic review

INTRODUCTION

Bipolar disorder is psychiatric condition characterized by episodic mood changes, that is major depression and (hypo)manic episodes. According to the proposed 'clinical staging model', bipolar disorder is a progressive illness that evolves through successive stages: an asymptomatic period in at-risk individuals, nonspecific and subclinical hypo(manic) symptoms (prodromal) with or without syndromal depressive episodes, first threshold hypo(manic) episode, followed by a subsequent pattern of remission and recurrences and, in some patients, refractory phases [1,2]. Over the past two decades, there has been growing interest in early identification and early intervention strategies in bipolar disorder to improve outcomes and mitigate the negative consequences associated with illness progression [3]. However, data from these early intervention programmes suggest that even when evidence-based interventions are initiated shortly after the diagnosis of bipolar disorder is established, the outcomes remain far from ideal as a large subset of patients experience recurrences of mood episodes [3,4], persistent subsyndromal symptoms as well as functional disability [5] even during periods of euthymia. In addition, once the diagnosis of bipolar disorder is established, many patients have already developed significant cognitive impairment in various domains such as executive function, memory and attention [6,7] as well as gross structural abnormalities in prefrontal and subcortical limbic brain areas [8–10]. These discouraging findings highlight the need to focus on the earliest stages of bipolar

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KEY POINTS

- This systematic review provides an overview of prospective studies that evaluated the incidence and predictors of transitioning to bipolar disorder among high-risk individuals.
- Our findings suggest that a combination of familial and clinical risk factors may be required to optimally predict conversion to bipolar disorder.
- Further discussions are required to establish an expert consensus on the high-risk criteria for bipolar disorder.

disorder by identifying those individuals who are at high genetic and/or clinical risk of developing bipolar disorder.

Although a few attempts have been made to operationalize at-risk populations [11], to date, no consensus criteria exist to define high-risk states for bipolar disorder. In this systematic review, we aim to provide an overview of prospective studies that evaluated the rate and predictors of conversion to bipolar disorder among individuals who are at clinical or genetic risk of developing bipolar disorder and to discuss potential clinical implications and future directions.

MATERIALS AND METHODS

Search strategy

We conducted an electronic search on Ovid Medline search on 16 July 2021 using the following search terms: ('mania' OR 'manic' OR 'bipolar') AND ('high risk' OR 'at risk' OR 'offspring*' OR 'prodrome' OR 'prodromal') AND ('prospective' OR 'longitudinal'). We placed no restriction on language, publication type or date of publication.

Selection criteria

Prospective studies that met the following criteria were included in this review: Studies that identified individuals who are at genetic and/or clinical high risk for bipolar disorder with or without a control group; minimum follow-up duration of 1 year; and reported on the rate or predictors of conversion to bipolar disorder. If multiple studies used the same cohort to examine the same corelates relevant to this review, only the most recent and comprehensive study was included. Two authors (K.K. and G.S.) independently inspected titles and abstracts of retrieved studies and selected which texts to examine in full. Full texts of potentially eligible studies were then evaluated by the same reviewers to determine if they met the inclusion criteria. Any disagreement between the reviewers was resolved by consensus.

Outcomes

The main outcomes were the rate of conversion to bipolar disorder among high-risk individuals and clinical factors that predicted the conversion.

Data extraction and management

We examined full texts of selected publications to determine whether they met our inclusion criteria and to extract relevant data such as specific measures or criteria that were used to define high-risk populations, number of participants and their demographic information, length of follow-up, the rate and predictors of conversion to bipolar disorder and how the diagnosis of bipolar disorder was established.

RESULTS

Of the 599 citations retrieved through electronic database search, 91 abstracts were reviewed. Of these, 52 texts were reviewed in full and included 23 publications from 16 cohorts in the final review. Flow diagram of the study selection process has been provided in Fig. 1. The characteristics of the included studies including demographic information, sample sizes, criteria for defining high-risk status, and their main findings are summarized in Table 1. Some studies reported latest findings from well established high-risk cohorts including Pittsburgh Bipolar Offspring Study (BIOS), Longitudinal Assessment of Manic Symptoms (LAMS), the Dutch Bipolar Offspring study, Lausanne–Geneva high-risk study, Flourish Canadian high-risk study and Course and Outcome of Bipolar Youth (COBY). All included studies were published after 2005 except for one which was published in 1985 [12]. Duration of follow-ups ranged from 1 to 21 years. Fifteen studies primarily focused on familial high-risk groups, and these included 14 studies of offspring of parent with bipolar disorder [13▪,14–26] and one study that included both offspring and siblings of patients with bipolar disorder [12]. Four studies used clinical variables to identify high-risk individual [27,28▪,29,30], and an additional four studies used a combination of clinical and genetic risk factors [27–30], and additional four studies used a combination of clinical and genetic risk factors [31–34]. There was significant variation among studies with respect to the age groups: although some studies prospectively followed individuals as young as 2–

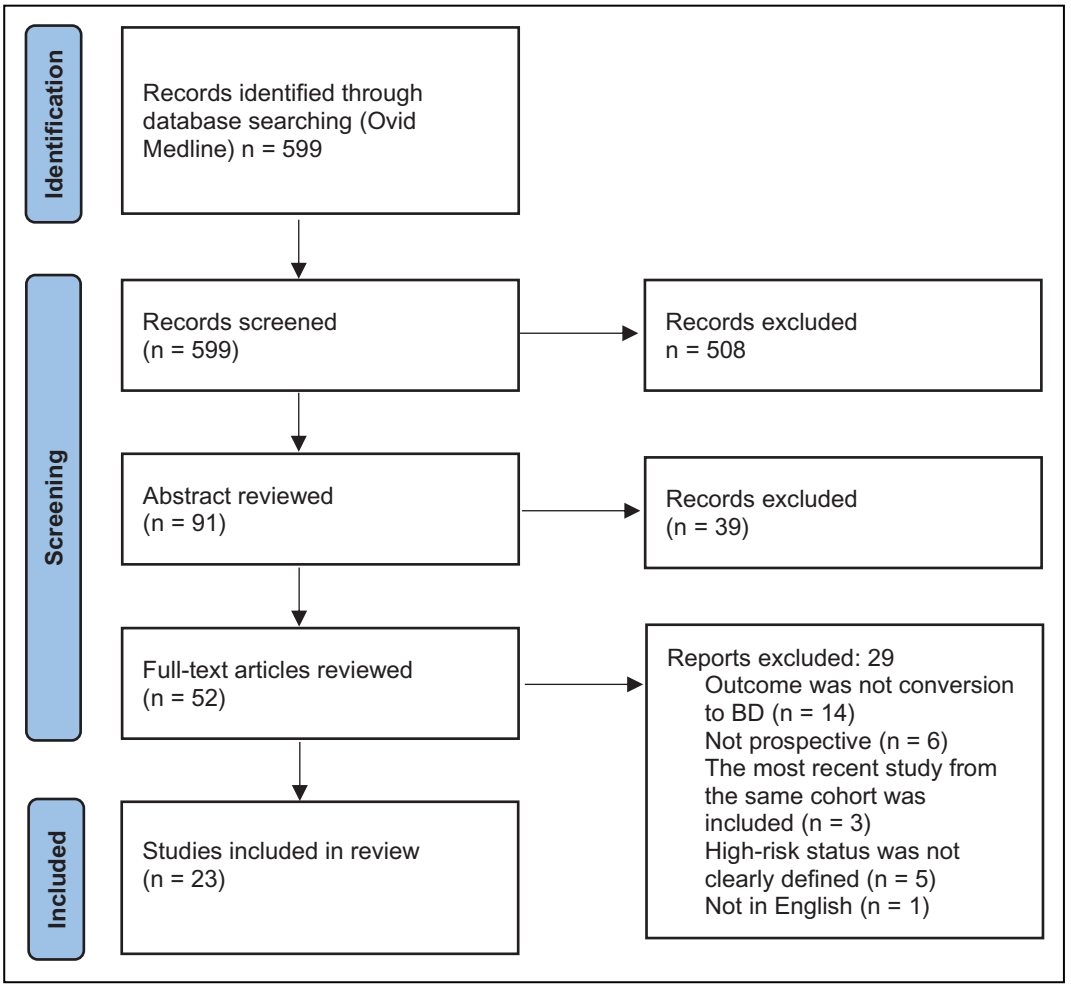

FIGURE 1. Flow diagram of study selection process.

5 years, others included participants up to 35 years of age. Fifteen studies included a control group, while eight studies only included high-risk individuals. All studies that used a control group reported an increased rate of conversion to bipolar disorder in genetically and/or clinically high-risk individuals. Average age at onset of bipolar disorder varied greatly among different studies (from as early as 7 years to early 20 s).

DISCUSSION AND FUTURE DIRECTIONS

This review of studies examining rates and predictors of conversion to bipolar disorder yielded four findings with respect to the literature for bipolar disorder high-risk states. First, there was significant heterogeneity in how high-risk states were defined (further discussed in the following section), with no standard operationalized criteria in use. Second, most studies used one or two criteria to identify youth at high risk, with only three studies (see below) using multivariate models to generate estimates of risk. Third, high-risk criteria appeared to be sensitive predictors of bipolar disorder conversion, as the vast majority of individuals who developed bipolar disorder were in the high-risk group. These high-risk criteria were however lacking in specificity; despite the elevated conversion rates, the majority of high-risk youth did not develop bipolar disorder. Lastly, replicated baseline predictors of conversion included (hypo)manic symptom severity, depressive symptoms/major depressive episode and early onset of parental mood disorders.

Criteria could broadly be categorized into those that identified high-risk youth by family history and those that identified high-risk youth by clinical criteria. A minority of studies used clinical criteria, such as the presence of subthreshold manic or hypomanic symptoms, to identify high-risk youth [25,28▪,29,30]. Rates of conversion from studies

Table 1. Characteristic of the included studies in the systematic review

Citation	Cohort	High risk definition/criteria used	Control (Y/N)	Participants	Length of follow up	Findings
DeGeorge *et al.* [29]	University of North Carolina at Greensboro	Students enrolled in introductory psychology courses scoring at least 1.5 SD above the mean on the Hypomanic Personality Scale	N	$N=112$ (76 female) university students enrolled in introductory psychology courses. Mean age = 19.5 years, SD = 2.5 years at baseline.	3 years	Twelve participants (11%) qualified for a DSM-IV-TR BD (two with BD-I, seven with BD-II and three with BDNOS)
Nery *et al.* [14]	University of Cincinnati	9–20 years old and at least one biological parent with BD-I	N	$N=93$ (49 girls) mean age = 13.7, SD = 2.9 years (at baseline).	Mean = 140.6 weeks (range = 1–407, SD = 88.7)	Seven participants (7.53%) develop a manic or mixed episode.
Papachristou *et al.* [30]	TRacking Adolescents' Individual Lives Survey (TRAILS)	Latent class analysis was used to identify subthreshold manic symptom at age 11 years based on CBCL-MS	Y	N = 1429, age = 11 years	8 years	Three classes (asymptomatic, mildly symptomatic and highly symptomatic) were identified. Children assigned to the mildly (HR = 2.01) and highly symptomatic (HR = 5.02) classes had a significantly increased risk of BD.
Birmaher *et al.* [13▪]	Pittsburgh Bipolar Offspring Study (BIOS) Preschool sample	2–5 years old offspring of parents with DSM-IV BD-I/II	Y	$N=116$ (60 female, mean age at intake = 3.8, SD = 1.3) preschool offspring of parents with BD (BDI = 53, BD-II = 25) and $N=98$ preschool offspring of 79 controls.	Mean = 9.6 years, SD = 2.8.	Only offspring of BD parents developed. BD-I/II: 3.4% ($n=4$) and BD-NOS: 11.2% ($n=13$), with mean onset ages 11.4 and 7.4, respectively.
Hafeman *et al.* [16]	Pittsburgh Bipolar Offspring Study (BIOS)	6–18 years old offspring of parents with DSM-IV BD-I/II	N	$N=412$ (202 girls) mean visit age = 12 years, SD = 3.5	Median = 9.5 years	54 (13.1%) participants Developed new-onset BPSD (nine BD-I, nine BD-II, and 36 BDNOS). Univariate predictors of developing BPSD were dimensional measures of mania, depression, anxiety and mood lability; psychosocial functioning; and parental age at mood disorder.
Levenson *et al.* [17]	Pittsburgh Bipolar Offspring Study (BIOS)	6–18 years old offspring of parents with DSM-IV BD-I/II	Y	$N=612$ (307 women) Mean age at their first School Sleep Habits Survey (SSHS) assessment = 12.81 years (SD = 2.25)	Mean = 3.63 years (SD = 1.63, range = 0.94–7.35).	Thirty-six participants (5.88%) converted to BD during the study, with an average age of BD onset of 17.23 years. Latent transition analysis identified three groups of good, poor and variable sleepers. Those in the poor sleep group had almost twice the odds of developing BD as those in the good (OR = 1.99) and variable sleep group (OR = 2.03).

Table 1 (*Continued*)

Citation	Cohort	High risk definition/criteria used	Control (Y/N)	Participants	Length of follow up	Findings
Levenson *et al.* [15]	Pittsburgh Bipolar Offspring Study (BIOS)	6–18 years old offspring of parents with DSM-IV BD-I/II with and without BD at intake.	Y	*N* = 47 (26 girls) offspring of parents with BD diagnosed with BD at intake. Mean age = 11.7 (SD = 3.3). N = 386 (194 female) offspring of parents with BD without BD at intake. Mean age = 11.4 (SD = 3.6). and *N* = 301 (157 female) offspring of matched control parents who did not have BD. Mean age = 11.0 (SD = 3.5).	Mean = 7.5 years SD = 1.6) for convertors Mean = 6.2 years, SD = 2.4 for nonconvertors.	Parent-reported extreme evening, frequent night-time waking, insufficient sleep, and time to fall asleep as well as child-reported time to fall asleep on weekends and frequent night-time waking predicted conversion to BD.
Axelson *et al.* [18]	Pittsburgh Bipolar Offspring Study (BIOS)	6–18 years old offspring of parents with DSM-IV BD-I/II	Y	*N* = 391 (191 female) High-Risk offspring. Mean age at intake = 11.9 years (SD = 3.7). *N* = 248 (134 female) comparison offspring. Mean age = 11.8 years (SD = 3.6).	Mean = 6.8 years (SD = 2.2) for High-Risk offspring. Mean =6.9 years (SD = 2.0) for comparison offspring.	The cumulative rate of BPSD at age 21 was 23.0% and 3.2% in the High-Risk and control groups respectively. Restricting the analysis to the 344 high-risk offspring with prospective follow-up data showed 6.1% conversion rate (*N* = 21, eight had manic and 13 had hypomanic episodes). In the high-risk offspring, subthreshold (hypo)manic episodes (HR = 2.29), MDE (HR = 1.99) and disruptive behaviour disorders (HR = 2.12) were linked to manic, mixed, or hypomanic episodes. Restricting the analysis to prospective data showed only subthreshold (hypo)manic episodes (HR = 7.57) as significant.
Reichart *et al.* [20]	The Netherland study	11–21 years old offspring of parents with BD-I/II	N	*N* = 129 (60 female). Mean age at follow up = 20.8 (S.D. = 2.8)	5 years	General Behavior Inventory (GBI) was used at baseline. 4 had BD at baseline. 31 had unipolar disorder (7 converted to BD), 23 nonmood diagnosis (1 converted) and 71 no diagnosis (1 converted). The OR (1.13) but not for the hypomanic/ biphasic scale.

Table 1 (*Continued*)

Citation	Cohort	High risk definition/criteria used	Control (Y/N)	Participants	Length of follow up	Findings
Hillegers *et al.* [19]	The Netherland study	12–21 years old offspring of parents with BD-I/II	N	*N* = 129 (60 female). Mean age at follow up = 20.8 (S.D. = 2.7)	5 years	K-SADSPL was used at baseline. Twelve participants converted from depressive disorder, with a mean age at onset of 13.4 years (SD 4.2), to BD with a mean age at onset of 18.4 years (SD 2.9).
Bechdolf *et al.* [31]	Orygen Youth Health clinical program (OYH)	15–24 years old help-seeking individuals who met the Bipolar At Risk (BAR) criteria of at least one of three at-risk groups: sub-threshold mania (Group I), depression and cyclothymic features (Group II), depression plus genetic risk (Group III)	Y	*N* = 35 (29 female) BAR group. Mean age = 19.2 years (SD = 3.1). *N* = 35 (27 female) non-BAR group. Mean age = 19.1 (2.7)	12 months	Five BAR group participants (14.3%) converted to BD (1 BD-I, 3 BD-II and 1 BDNOS) with no conversion in the non-BAR group.
Ratheesh *et al.* [32]	Orygen Youth Health clinical program (OYH)	15–24 years old help-seeking individuals with one or more baseline DSM-IV diagnoses—of MDD, anxiety disorder or SUD. Three risk clusters were identified including Bipolar At-Risk (BAR) and the Bipolarity Index and the Ultra-High Risk assessment for psychosis.	Y	*N* = 52 (44 female). Mean age = 19.7 years (SD = 2.8).	12 months	Four participants (7.7%) developed BD within 1 year of follow up. Baseline predictors of developing BD were having an alcohol use disorder or a family history of SUD. Subthreshold (hypo)manic symptoms at baseline were associated with development of BD.
Van Meter *et al.* [28▪]	Longitudinal Assessment of Manic Symptoms (LAMS)	6–12 years old help-seeking youth who were experiencing elevated symptoms of mania (ESM) as indicated by a score of > 12 on the Parent General Behavior Inventory 10-Item Mania scale (PGBI-10M)	Y	*N* = 473 (141 female). Mean age at intake = 9.3 (SD = 1.9). *N* = 86 demographically matched youths with no manic symptoms.	5 years	During the follow-up period, 65 participants (13.74%) met criteria for BPSD (19 BD-I, 5, BD-II and 40 BPNOS, and 1 Cyclothymia). Converters had significantly higher PGBI-10M, Mania Rating Scale, and Depression Rating Scale scores than nonconverters. The original risk calculator identified youths who developed BPSD only moderately well.
Findling *et al.* [27]	Longitudinal Assessment of Manic Symptoms (LAMS)	6–12 years old help-seeking youth who were experiencing elevated symptoms of mania (ESM) as indicated by a score of > 12 on the Parent General Behavior Inventory 10-Item Mania scale (PGBI-10M)	Y	*N* = 703 (226 female) Mean age = 9.4 years (SD = 1.9), among which 162 had BPSD at baseline.	24 months	During the follow-up period, 42 participants (7.76%) converted from nonbipolar to BD (14 BD-I and 28 BPSD), while 22 converted from BPSD to BD-I.

Table 1 (*Continued*)

Citation	Cohort	High risk definition/criteria used	Control (Y/N)	Participants	Length of follow up	Findings
Rudaz *et al.* [21]	Lausanne–Geneva high-risk study	6–17 years old offspring of inpatients and outpatients with BD-I/II as well as schizoaffective-BD, MDD and SUD.	Y	*N* = 449 (229 female) including offspring pf parents with BD (*N* = 163), MDD (*N* = 128), SUD (*N* = 35) and medical controls (*N* = 123). Mean age at intake 10.1	Mean = 13.2 years	At the end of the follow-up, 18 participants met lifetime criteria for at least one manic, and 28 for a hypomanic episode (without a manic episode). The breakdown of conversion rates according to parental diagnosis: BD (*N* = 163), 10 (6.2%) mania and 17 (10.4%) hypomania; MDD (*N* = 128), three (2.3%) mania and five (3.9%) hypomania; SUD (*N* = 35), one (2.9%) mania and four (11.4%) hypomania; and medical controls (*N* = 123), four (3.3%) mania and two (1.6%) hypomania. Within the whole cohort of offspring, MDE (HR = 4.44), CD (HR = 3.31) and SUD (HR = 2.54) predicted the onset of (hypo)manic episodes.
Preisig *et al.* [22]	Lausanne–Geneva high-risk study	6–17 years old offspring of inpatients and outpatients with BD-I/II as well as schizoaffective-BD, MDD, and SUD.	Y	*N* = 372. Offspring of patients with BD: *N* = 145 (74 female) mean age = 10.4 years (SD = 4.3). Offspring of patients with MDD: *N* = 115 (59 female) mean age = 10.1 years (SD = 3.8). Offspring of medical controls: *N* = 112 (51 female) mean age = 9.3 years (SD = 4.8)	Mean= 10.6 years	Offspring of parents with early onset BD < 21 years) showed an elevated risk of BD (HR = 7.9), while offspring of parents with late onset BD had no elevated risk (HR = 0.9).
Duffy *et al.* [24]	Flourish Canadian high-risk study	5–25 years old offspring of patients with BD	Y	*N* = 279 (167 female) high-risk offspring mean age at baseline = 16.48 years (SD = 6.26). *N* = 87 (51 female) controls mean age = 14.71 years (S = 2.24)	1–21 years (mean=7.72, SD = 5.28)	BD was observed only in the high-risk group. The cumulative incidences of BPSD in the high-risk group was 37 (24.5%): 11 BP-I, 13 BD-II, 12 BDNOS and one cyclothymia. The cumulative incidence of subthreshold hypomanic symptoms were 22.01% and 1.69% in high-risk and control groups respectively. Median onset of BD was 20.73 years (range= 12.37–30.25), with no incidence of full criteria being met in a child under age 12.

Table 1 (*Continued*)

Citation	Cohort	High risk definition/criteria used	Control (Y/N)	Participants	Length of follow up	Findings
Mesman *et al.* [23]	Dutch Bipolar Offspring Study	12–21 years old offspring of patients with BD-I/II	N	*N*=108 (50 female) Mean age at baseline = 16.5 years (SD=2.0)	12 years	During the follow-up period, 17 offspring (13%) developed BPSD (4 BD-I, 11 BD-II, one schizoaffective BD, one cyclothymia). Median age at onset for hypomania was 17.3 and for mania was 20.2 years. None of the participants had a prepubertal hypomanic or manic episode.
Birmaher *et al.* [25]	Course and Outcome of Bipolar Youth (COBY)	7–18 years youth with BDNOS	N	*N*=140 (55 female) Mean age at baseline = 11.9 years (SD=3.2)	Median = 11.5 years (range 0.5–15.3 years)	During the follow-up period, 75 patients (53.6%) converted from BPNOS to BD-I (*N*=27) or BD-II (*N*=48). Of the 75 who converted, 57 (76.0%) did so within 5 years (median time to conversion 2.7 years, range 0.5–11.2 years). Earlier onset of BPNOS, familial (hypo)mania, and high mania, anxiety, and mood lability symptoms predicted conversion to BD.
Fusar-Poli *et al.* [34]	Clinical High Risk For Psychosis (CHR-P) study	15–35 years old individuals who met criteria of at least one of the six Bipolar At Risk State (BARS) criteria: Group 1: Sub-threshold mania Group 2: Depression plus Cyclothymic features Group 3: Depression plus Genetic risk Group 4: Cyclothymic features and Genetic risk Group 5: Sub-threshold mixed Episode Group 6: Mood swings	Y	*N*=71	Mean= 531 days (SD=409.13)	During the follow-up period, 5 participants developed BD (2 BD-I and 3 BD-II), all of them in the BARS+ group. Median time to conversion was 539 days. Point estimate risk of transition to BD in individuals who met the BARS criteria at 24 months 0.234.

Table 1 (*Continued*)

Citation	Cohort	High risk definition/criteria used	Control (Y/N)	Participants	Length of follow up	Findings
Frankland *et al.* [33]	Bipolar Kids and Sibs Study	12–30 years old individuals with a first-degree relative with a diagnosis of BD-I/II 'Probabilistic Approach to Bipolar Depression' (cut-off of four or more features): hypersomnia, increased weight/appetite, psychomotor retardation, psychotic features and/or pathological guilt, other atypical features, mixed features, onset before age 25, and at least five lifetime MDEs.	Y	*N* = 163 (89 female) High-Risk. Mean age= 19.2 (SD = 5.8) *N* = 124 controls (65 female). Mean age = 21.5 (SD = 4.6)	Median = 5 years	Eight High-Risk participants (4.9%) converted to BD-I (*N* = 4) and BD-II (*N* = 4) and 11 (6.7%) developed subthreshold hypo(manic) episodes. The median ages at which threshold and subthreshold criteria were met were 23 and 20 years, respectively. One participant in the control group developed a subthreshold episode. High-risk participants with a lifetime MDE at baseline were more likely to convert to BD (HR = 13.9). Psychomotor retardation at baseline (OR = 41.7), 5 MDEs or more prior to baseline (OR = 117.2) and the presence of 4 or more probabilistic features compared with < 3 (OR = 14.5), were associated with a BD diagnosis. Behavioural disorders only predicted conversion to subthreshold BD whereas anxiety and substance use disorders did not predict either threshold or subthreshold (hypo)mania.
Egeland *et al.* [26]	Amish Study	Offspring of parents with BD	Y	*N* = 115 offspring of parents with BD-I. *N* = 106 offspring of well parents.	16 years	Nine children were diagnosed with BD-I. Eight belong to the high-risk and one to the control sample. Average age of onset was 15 years (range= 13–29).
Akiskal *et al.* [12]		Offspring or siblings of patients with BD	N	*N* = 68 (29 female)	3 years	16% of participant developed an acute manic (*N* = 8) or mixed (*N* = 3) episode. All full-blown manic/mixed episodes occurred after age 13.

BD, Bipolar Disorder; BD-I, Bipolar Disorder I; BD-II, Bipolar Disorder II; BDNOS, Bipolar Disorder Not Otherwise Specified; CBCL, Child Behavior Checklist; CBCL-MS, Child Behavior Checklist-Mania Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; HR, hazard ratio; MDE, major depressive episode; OR, odds ratio; SD, standard deviation; SUD, substance use disorder.

using clinical criteria ranged from 8 to 11% over 2–3 years of follow-up [27,29]. Higher (hypo)manic and depressive symptoms were identified as predictors of conversion in those at high risk by these clinical criteria [28▪]; further supporting the association between elevated (hypo)manic symptoms and increased risk was data from the COBY study, in which over half of individuals meeting criteria for BD-NOS converted to BDI or BDII over 0.5–15.3 years of follow-up (median = 11.5 years) [25]. There was significant variability in how high risk was identified clinically, with different scales and cut-offs used to establish subthreshold (hypo)mania.

The majority of studies examined youths at genetic high risk. These studies tended to show a higher rate of conversion to bipolar spectrum disorder (BPSD), ranging from 13 to 25%, than clinical high-risk cohorts (although this might be an artifact of long follow-up durations – up to 21 years – in some of the genetic high-risk studies). However, most genetically high-risk individuals did not develop even broadly defined BPSD. Some studies attempted to identify clinical features, which could enhance prediction in those at genetic high risk. Subthreshold baseline (hypo)manic symptoms, and elevated depressive symptoms/past or current major depressive episode (MDE) were some replicated predictors of conversion [16,18,19,33]. Although the features of MDEs that predict the development of bipolar disorder is of great clinical interest, there was relatively little examination of this in genetic high-risk groups, with two studies relating psychomotor retardation, psychotic features and multiple previous MDEs with increased risk [24,33]. Earlier onset of parental bipolar disorder /mood symptoms, believed to reflect heavier genetic loading, was also associated with a higher risk of conversion in a number of studies [13▪,16,22]. Increased severity of anxiety symptoms [16,24], presence of behavioural disorders or ADHD [13▪,18,33], substance use disorders [21,22] and sleep disruption in children at genetic high risk [15,24] were variously found to be associated with conversion to bipolar disorder.

Overall, these results suggest that a combination of genetic and clinical risk factors is required to optimally predict conversion to BPSD. Three studies created risk calculators to quantify the risk of conversion to bipolar disorder using multiple demographic and clinical risk factors, in cohorts at either genetic or clinical high risk [16,25,28▪]. These models were generally able to discriminate convertors from nonconvertors with good, though not excellent, accuracy. Predictive variables in these three calculators included depressive/manic and anxiety severity and family history of bipolar disorder (in youth at clinical high risk). By providing a percentage risk of conversion over 5 years based on clinical/demographic measures, the concept of such risk calculators provide an easy-to-use and clinically feasible prediction tool, similar to the Framingham Criteria for estimating risk of cardiovascular morbidity. However, improved model performance and further external validation is required. Two groups came up with an operationalized criteria for high-risk groups by combining clinical and genetic risk factors. Bechdolf *et al*. [31] proposed and validated the Bipolar At Risk (BAR) criteria, which includes 15 to 24-year-old individuals with one or more of the followings: sub-threshold mania, depression and cyclothymic features, and depression and genetic risk. During the 1-year follow up period, 14.3% of participants converted to bipolar disorder. More recently, another group modified the BAR criteria by expanding the age range to 15–35 years and including three additional risk criteria, that is cyclothymic features and genetic risk, sub-threshold mixed episode and mood swings. The risk of transition to bipolar disorder at 24 months was estimated to be 23% [34].

Although the extant literature signals the potential benefit of identifying individuals who are at a high risk for developing bipolar disorder, there is a great deal of work to be done to advance this field. First, only a few studies have come up with operationalized criteria or risk calculators by combining genetic and clinical risk variables. Although this is a welcome step in the right direction, no consensus currently exists. This is in contrast to psychotic disorders, which has well delineated clinical criteria for high-risk and ultra high-risk states [35]. Heterogeneity in the literature is also a reflection of variability in primary outcomes, for which studies may have used conversion to broadly defined bipolar spectrum or narrowly defined BD-I, as well as the measures used to establish conversion to bipolar disorder. Furthermore, the baseline age of participants and length of follow-up differed amongst studies, which may impact the detected conversion rate. Despite these limitations, the high-risk bipolar disorder literature does yield useful, clinically relevant data. Clinicians should have a higher index of suspicion for conversion in youths with a combination of genetic risk, high baseline (hypo)manic symptoms and current or previous MDEs. Moreover, most studies show that syndromal manic or mixed episodes are rare in the prepubertal stage. However, many patients who eventually develop bipolar I disorder show subthreshold (hypo)manic symptoms during their early childhood period, lending support to this as a prodromal stage towards bipolar disorder. Lastly, these studies show that genetic or clinically high-risk youth are at a high risk for other types of psychopathology, including major depression, ADHD, anxiety and substance use disorders

[13▪,18]. Thus, clinicians should monitor for non-bipolar disorder psychopathology in youths with family history or suggestive high-risk clinical features, and early intervention strategies need to be framed to optimize mental health outcomes and overall functioning in all high-risk individuals, regardless of whether they develop bipolar disorder specifically.

Compared with the operationalized criteria for Ultra High-Risk for psychosis (UHR) [36], which has been thoroughly validated and widely adopted to identify individuals who are at high risk of developing psychosis [37], the concept of high-risk for bipolar disorder is still in its infancy. Our hope is that this review will inspire further discussions on this issue in order to work towards an expert consensus on the high-risk criteria for bipolar disorder, taking into account both clinical and genetic risk factors.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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