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Abstract

Objectives: To clarify the clinical features preceding the onset of Bipolar disorder (BD) has become a public health priority for the prevention of high morbidity and mortality. BD remains frequently under- or misdiagnosed, and under- or mistreated, often for years. **Methods:** We assessed the predictive value of precursors and prodromes of BD. We assessed precursors of first-lifetime manic or hypomanic episodes with/without mixed features in retrospective and prospective studies. Methods: The task force evaluated and summarized separately assessments of familial risk, premorbid personality traits, retrospective and prospective studies. **Results:** Cyclothymic features, a family history of BD, retrospectively-reported attenuated manic symptoms, prospectively-identified subthreshold symptoms of hypomania, recurrence of depression, panic anxiety and psychotic features, have been identified as clinical precursors of BD. The prodromal symptoms like [hypo]mania often appears to be long enough to encourage early identification and timely intervention. **Conclusions:** The predictive value of any risk factor identified remains largely unknown. Prospective controlled studies are urgently needed for prevention and effective treatment.

Key words: antecedents, bipolar disorder, depression, early onset, hypomania, mania, prodrome, risk factors.

INTRODUCTION

Bipolar disorder (BD) evolved in the mid-20th century from Kraepelin's proposal of a broader manic-depressive illness characterized by recurrences of manic and depressive episodes[1]. Forms of BD recognized in DSM-5 include *type I*, *type II*, *cyclothymia*, and other specified and *unspecified* forms. Prevalence of BD varies with the diagnostic criteria used and the breadth of included subtypes. Rates may reach 5%, particularly if unspecified BD or recurring major depression with hypomanic features are included[2]. In recent years, there has been increased interest in both the earliest stages of BD and subsyndromal manifestations[3]. This growing interest reflects efforts to predict BD or to identify it earlier, based on early psychopathology, or to differentiate BD from symptoms of other coexisting or emerging conditions that may not be risk factors or precursors of BD[4].

BD is highly heritable, a confirmed family history in first-degree relatives is a strong predictor and identifies a high-risk population[5]. Onset of BD is in adolescent or early adult years, but half of patients who eventually meet diagnostic criteria for BD-I or BD-II have had mood symptoms or episodes of major depression in youth as well as nonspecific psychopathology, including anxiety, substance abuse, attention deficit, or behavior disorders[6,7]. As many as half of BD patients diagnosed in adolescence or early adulthood had prior anxiety disorders, clinically significant mood symptoms and sensitivity or high emotionality to stressors[58,107]. Furthermore, in a vast majority of cases, the index mood episode of a BD is depressive often years prior to the first manic episode[11,21,51]. There are reports of mania-like symptoms in very young, pre-pubertal children, often with complex and rapidly shifting admixtures of affective symptoms resembling "[hypo]manic" (manic or hypomanic) and depressive features and behavioral changes that may represent mixed features, as well as psychotic symptoms, and high rates of co-

occurring neurodevelopmental disorders, and may lack a discrete, episodic course - notwithstanding the cross-diagnostic specificity of such symptoms[2,3,22]. Such early cases may differ in some respects from typical, adult BD, and their developmental continuity remains to be proved. However, there is growing evidence that adolescent and adult presentations of BD as considered typical in adults are particularly likely to be followed by life-long, episodic recurrences[11]. Onset of BD before adulthood has been associated with a poorer outcome, frequent recurrences, high rates of co-occurring anxiety disorders and substance abuse, poor treatment response and functional outcome[8,9,10,11]. Increasingly, clinical and research attention has been directed toward earlier identification and treatment of BD with the hope of reducing the long-term burden of illness and disability. It is important to better characterize the psychopathological conditions arising in youth, which precede more typical, adult forms of BD. Such precursor symptoms and syndromes may include complex, changing, and diagnostically poorly specific and confusing admixtures of affective (depressive and [hypo]manic), anxious, and behavioral features[23,44,60]. Research on precursors and prodromes of BD may contribute to predicting onset of first episode mania-like (mania, hypomania, mixed) episodes[10]. Such research and clinical attention clearly are warranted by the frequency, morbidity, disability, and mortality of BD, particularly of early-onset[6,10]. However the early stages of all psychiatric syndromes are diffuse and non-specific prompting some researchers to embrace transdiagnostic approaches to the at-risk period.

Several relatively nonspecific psychopathological presentations have been reported as antecedents to the syndromal onset of BD[39,138]. They include mood-swings, emotional lability, substance abuse, severe or sustained irritability, psychotic features, depressive and activated/hypomanic symptoms, sleep-disturbances, anxiety, impulsivity, aggression, and sometimes cyclothymia or unspecified forms of BD as well as syndromal depression. Such symptoms and syndromes can occur several years before a first major episode of mania or hypomania, as required to support a diagnosis of BD[39,138]. A particular diagnostic challenge is to differentiate early depressive illness that will or will not later meet criteria for BD. Nevertheless, prospective and retrospective studies have also shown that major depression, especially if recurrent, abrupt onset in adolescence and in the context of a positive family history of BD is predictive of developing BD[20].

Based on this background, the International Society of Bipolar Disorders (ISBD) convened a task force of experts charged primarily with the task of identifying factors that support prediction of the later emergence of BD by summarizing the available research evidence. A secondary aim was to identify next steps for research aimed at improving the timely diagnosis of BD. This report summarizes the findings and recommendations of the ISBD task force.

METHODS

The task force primarily aimed to review and summarize clinical evidence, from family-based and other prospective high-risk studies, as well as retrospective and other types of studies, to identify and evaluate

precursors and prodromes to BD, defined as the occurrence of a first-lifetime manic or hypomanic episodes with/without mixed features.

After several conference calls and an inaugural meeting, the task force organised four working groups to address the prediction of BD by: [a] *prospectively identified risk factors*, [b] *symptomatic prodromes of mania*, [c] *family high-risk studies,* and [d] *affective temperaments*. These working groups continued to use conference calls and exchanges of draft documents; their methods of each working group are summarized next.

a) Prospectively identified risk factors

This component followed reported methods[12], updating the search. Briefly, it involved two separate computerized, systematic searches of PubMed, PsycINFO and SCOPUS databases through June 2017, using the following search terms and algorithms: [1] bipolar disorder AND (antecedent* OR predict* OR prodrom* OR prospect* OR risk) AND (diagnosis OR development); [2] bipolar disorder AND (prenatal exposure OR maternal exposure OR trauma OR childhood abuse OR alcoholism OR cannabis OR smoking OR cocaine OR central stimulants OR opioids OR UV light OR pollution OR vitamin D). References in identified reports were hand-searched for additional reports. Articles selected with text or abstract in English and met the following inclusion criteria: [1] prospective, longitudinal observational cohort studies or longitudinal case-control studies; [2] studies of subjects without lifetime BD-I or -II at initial assessment but with BD-I or -II at follow-up; [3] diagnosis could be clinical or based on structured interviews (meeting DSM-III, -IV, or -5, or ICD-9 or 10 criteria). Non-BD diagnoses at intake could include major depressive episode (MDE), major depressive disorder (MDD), dysthymia, cyclothymia, sub-syndromal affective disorders, anxiety disorders, disruptive behavioral disorders, ADHD, or no psychiatric diagnosis. Exclusion criteria were studies with: [1] subjects with a pre-intake lifetime diagnosis of BD; [2] BD outcome combined with other diagnoses; [3] subjects with genetic abnormalities; [4] risk factors based on neuropsychological testing, biological markers or neuroimaging (as this Task Force was charged with focusing specifically on the clinical at-risk stages or "prodromes" of BD, while a separate ISBD Task Force currently addresses the biological risk factors and mechanisms underlying BD); [5] studies of temperaments or personality traits or disorders; [6] cross-sectional studies without longitudinal follow-up; [7] retrospective studies; [8] clinical trials; [9] reviews or case reports; and [10] studies of antidepressant exposure for anxiety or mood disorders. We focused specifically on new diagnoses of BD type-I or -II (and not -NOS) as the outcome of interest.

b) Symptomatic prodromes of mania

Systematic literature reviews were conducted through June 2017, using the PubMed database and the search terms: predict*, prodrom*, "first episode" and "mania," limited to title and abstracts through 2017. Additional reports were identified from previous reviews on the topic[3,13-17]. Among included studies, outcomes considered were limited to first-lifetime episodes of *mania* (not hypomania, as the validity of identifying a prodrome to hypomania was considered questionable). Hence, we excluded reports focusing on BD-II, BD-NOS or broadly

defined "bipolar-spectrum" diagnoses, or with insufficient information to support a DSM-IV (or equivalent) diagnosis of BD-I. Due to the paucity of prospective studies, cross-sectional and retrospective studies of cases with established BD also were included. Identified studies were stratified by quality-ratings based on the presence of controls and of a systematic identification of antecedent or prodromal symptoms.

c) Family high-risk studies

Based on a systematic literature review in PubMed/Medline until June 2017, we reviewed reports from high-risk family studies of the offspring of one or two parents with BD, emphasizing the work of several leading international research groups. We aimed to identify antecedent conditions and describe the early clinical trajectory of BD among offspring considered to be at increased risk given high estimated heritability of BD[18]. Studies included in this review were: the Amish study in the US[58,100]; the Flourish Canadian Bipolar Offspring study[11,19], the Dutch Bipolar Offspring study[20,21], the BIOS Pittsburgh study[22,23], a US-Australian multi-site study[24], and a Swiss study[25,26] (for focus, only the first and one recent paper from these important cohort studies are listed). These six cohort studies were emphasized as representing the largest and most detailed body of evidence with the longest prospective follow-up duration regarding clinical outcomes of the offspring of parents diagnosed with BD.

d) Affective temperaments

A systematic literature search was conducted in the PubMed/Medline, Scopus, BiomedCentral, PsychLit, Scielo, and Cochrane databases, using the search terms "affective temperament* AND depression*, OR mania*, OR bipolar disorder* OR suicide*". The search period was 1980 through June 2017, as 1980 marked the beginnings of modern interest in the assessment of affective temperament. Two investigators (GHV, PS) conducted independent literature searches and pooled findings based on consensus, after screening titles and abstracts, and reviewing full text articles for potentially eligible articles. The electronic search was supplemented by hand searching of reference lists of included and review articles on this topic. Included were prospective, cross-sectional or retrospective studies of subjects without age restriction, with or without a psychiatric diagnosis, currently suffering or not from a psychiatric disorder, which were published in peer-reviewed journals in any language but with an abstract in English.

RESULTS

a) Prospective studies of risk factors

Homotypic risk factors of BD

Homotypic risk factors (i.e., phenomenological expressions overlapping with the diagnostic criteria for BD) (Table 1) reported in prospectively observed samples share characteristics with BD itself. For example, similar to findings in family high-risk studies[4], mood lability predicted later diagnoses of BD-II disorders in young adults in

a community sample[27], and predicted a change of diagnosis to BD-I in adults hospitalized for MDD with psychotic features[28,29]. A history of sub-syndromal depression predicted BD in a community study of adults[30]. Again, similar to family high risk data, lifetime sub-syndromal hypomanic symptoms predicted later development of BD spectrum disorders and recurrent MDD[30], both risk factors for BD. In addition, the combination of subclinical hypomania with subclinical psychosis predicted new diagnoses of BD three-times more often than subclinical hypomania alone[31]. Similarly, in the NESARC study, symptoms of elation or irritability, and especially their combination, significantly predicted later BD within three years of follow-up[32]. MDD with sub-syndromal hypomanic symptoms predicted later diagnosis of BD in both children[33], adolescents[34], adults[35] and in those with psychotic symptoms regardless the age[28,29,36]. MDD with psychotic symptoms has been found to be diagnostically unstable in several prospective studies, and has included relatively high rates of later BD in both adolescents and adults[35-38]. Among hospitalized children and adolescents diagnosed with MDD, high scores for cyclothymic temperament also significantly predicted later diagnoses of BD[37].

Consistent with prospective studies, mood lability or mood-swings preceding the diagnosis of BD have also been described in retrospective analyses of both youths and adults, and can represent a precursor or part of a prodrome evolving into syndromal [hypo]mania[39-41]. Notably, when depression lacked associated hypomanic features, risk of later BD was less than when such features were present[33,42].

Subsyndromal hypomania has predicted BD in only a minority of subjects over relatively short periods of follow-up [4,23,30-32,43]. Fewer than half of youth diagnosed with BD-NOS at intake, particularly those without a family history of BD, met criteria for BD-I or BD-II within five years of follow-up, suggesting that BD-NOS is not necessarily a precursor to better-defined forms of BD[42,44]. In addition, some cases of cyclothymic disorder, BD-NOS or BD-II remained stable and did not develop mania during follow-up[42,44-46], again failing to support a developmental hierarchy of these conditions, although based on possibly inadequate duration of follow-up. On the other hand, rates of progression to full BD in cases of hypomania or cyclothymia are among the highest and even more predictive than having a family history of BD. However, consistent with findings of the Early Developmental Stages of Psychopathology (EDSP) study, hypomanic symptoms increased risk of BD only if they were recurrent or persistent, and especially when associated with other predictors or precursors of BD[23,33,42,47,48]. Taken together, hypomanic symptoms are relatively sensitive, but not necessarily specific, in predicting BD.

Heterotypic risk factors of BD

Heterotypic risk factors (i.e., phenomenological expressions not overlapping with the diagnostic criteria for BD) (Table 2) can precede development of BD, but are not similar to clinical features typical of BD[49]. Examples include anxiety syndromes, sleep disturbances, substance abuse, and behavior disorders[2,4,23,50,51]. Such early phenomena are also likely to be nonspecific, in that they can precede other clinical conditions or even lack of later diagnosable psychiatric illness. They may be relatively sensitive in predicting later BD, but lacking in specificity, which may be increased if there is also a family history of BD[4,49].

In a community study, any anxiety disorder in adolescence was a significant risk factor for later BD[52]. In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study, generalized anxiety disorder (GAD) in association with irritability or mild elation predicted the onset of BD in adulthood[32], as did a history of separation anxiety[53], panic attacks[54], and post-traumatic stress disorder (PTSD)[55,56]. However, these precursors lacked specificity and were associated with later conditions as diverse as to include anxiety disorders, MDD, alcohol dependence, and chronic pain[32,53-56].

An association of early anxiety disorders with prospectively observed BD is supported by several studies[32,52-56]. This predictive association parallels the high rates of co-occurrence of anxiety disorders in adults with BD[57]. The association of anxiety disorders, especially early in youth, with later BD also is supported by prospective studies of the offspring of patients with BD[4,21,50,58]. Anxiety disorders may be markers of general psychopathology, and often precede disruptive behavior, mood disorders including major depression, and substance-use disorders in youth[59].

In both the EDSP community study[47,48] and the NESARC study[55], adolescent behavior disorders or impulsive behavior often preceded BD by 8–9 years, and the association was even stronger given a family history of BD[4,23]. Again, however, these behavioral disorders also were followed by anxiety, depression, substance abuse, or a cluster B personality disorder[49,60,61].

Risk of BD appears to be increased following a range of conduct symptoms or disorders in childhood or adolescence, including runaway behavior, truancy, fighting, bullying, and other forms of aggression or violence[39,47-49,60-62]. Childhood ADHD and behavioral difficulties have been found prospectively to predict later BD, but also other mood disorders, disruptive behavior disorders, sleep disorders, and specific phobias[63,64]. Interestingly, however, an association between disruptive behavior disorders and later BD was not found in prospective studies of at-risk children of parents with BD in whom ADHD and disruptive behavioral disorders were uncommon, perhaps suggesting different developmental pathways to BD[4,21,23,50,58]. Early violence and criminal behavior also have been associated with later BD; however, such behaviors, too, are likely to precede a range of psychopathology, including alcohol and substance abuse, and personality disorders[34,65]. For all of the preceding, proposed heterotypic risk factors of BD, many studies not only lack specificity for BD, but also lack comparison or control groups with which to estimate rates of sensitivity and specificity in predicting BD[4,23].

Perinatal and juvenile exposure-related risk factors

We identified several conditions (Table 3) that can be considered perinatal_stressors or otherwise serve as risk factors that have been associated with later BD. The Northern California Birth Cohort study has found an approximately twice-greater risk of later BD in offspring of mothers who smoked during pregnancy[66].

Premature birth or low birth-weight_were found to precede BD either in female offspring only[67], or in both sexes[68], with approximately three-fold increase of risk of future BD. Unsurprisingly, the specificity of prematurity as a predictor is limited, as it can precede depression, eating disorders, and non-affective psychotic disorders[67,68]. Among several other perinatal factors, including antenatal uterine bleeding, birth presentation type, induced labor,

and neonatal APGAR score, only planned delivery by cesarean section was associated statistically with increased risk of future BD, but the association is almost certainly not specific for BD[69].

Studies using data from the Northern California Birth Cohort examined the relationship between prenatal infection and BD. One found a four-fold increased risk of BD after exposure to influenza at any time during pregnancy, and a six-fold increase after exposure during the third trimester[70]. Another found that prenatal exposure to maternal influenza significantly increased risk of BD with psychotic features[71]. However, similar associations have been reported for other neuropsychiatric disorders, including schizophrenia[72] and autism[73]. In general, prenatal exposure to infection usually is viewed as a non-specific vulnerability factor for neurodevelopmental disorders, and not disease-specific [74].

At least two studies found that early head injury was associated with increased risk of BD, but also for other neuropsychiatric disorders, including MDD, schizophrenia, and organic mental disorders[75,76].

Prenatal exposure to war during the first trimester of pregnancy was reported to be followed by an excess risk of BD, but also for MDD and other mood disorders[77]. Parental loss within the first few years of life was found to increase risk for later BD by 2–4-fold, but the effect tended to attenuate with increasing ages of the children involved[78], and specificity of the association seems improbable. In subjects with MDD, early physical or sexual abuse, as well as social or economic distress have been associated with increased risk of later BD[79]. Nevertheless, adverse life events and stressors during perinatal or early life appear to lack specificity for predicting later BD. The findings in a Danish register study regarding childhood adverse events as risk factors for later BD do not exclude early-life events as possible risk factors, but challenge the concept of adversities as important independent determinants of BD in genetically vulnerable individuals. Parental mental disorder was by far the strongest risk factor for BD[80].

Several studies found associations between early exposure to prescribed and illicit drugs and later BD, including cocaine[81], cannabis[82,83], opioids[84,85] and clinically prescribed stimulants, tranquilizers or sedatives, particularly when more than one substance was involved[86]. In these studies, risk for later BD was increased by 2–5-fold, but early substance abuse was also associated with later MDD, anxiety disorders, and substance-use disorders.

In summary, a solid and increasing body of evidence suggests that homotypic risk factors along the symptomatic dimensions of (hypo)mania are among the most specific clinical features preceding a full expression of (hypo)mania. Among the most predictive symptoms are attenuated mania-like symptoms and co-occurring symptom constellations, such as increased energy and goal directed behavior, racing thoughts, overtalkativeness and decreased need for sleep, which are all part of the diagnostic criteria for a manic episode, but also prominently mood lability, which is not captured by mania criteria. Frank hypomania, as well as MDD with psychosis or MDD with mania-like symptoms also seem to be a relevant clinical risk states for BD. Heterotypic risk factors may either indicate a more severe psychopathological state due to multiple comorbidities that precede (hypo)mania or overlap with the symptom expressions of (hypo)mania, such as in externalizing disorders during childhood, cluster C personality disorders or substance use disorders. Finally, perinatal and juvenile exposure-related risk factors may be additional “hits” that increase the likelihood of illness expression, but are likely less

specific than heterotypic clinical risk factors, with the highest specificity being observed for homotypic clinical risk factors.

b) Symptomatic prodromes of mania

There are several findings of retrospectively or prospectively described symptoms that emerged prior to overt clinical manifestations of diagnosable BD. Prediction of later BD by preceding hypomanic symptoms was described in the 1970s[87]. More broadly, the search for prodromal features preceding first syndromal episodes of various psychotic disorders gained momentum since then[88]. This effort includes prospective studies of subjects at high familial risk for BD[18] as well as retrospective studies of preceding clinical histories in patients with BD[3,41], as well as prospective studies of subjects not selected based on BD family history. We divided the identified studies into three types: [a] descriptive studies without controls, [b] descriptive studies with structured assessments, and [c] controlled studies (Table 4), to test the hypothesis that prodromal features of first-lifetime [hypo]manic episodes can be characterized systematically.

Descriptive studies without controls

A large survey of 600 members of the Depression and Manic-Depression Association (DMDA) found that 70% of participants had at least one manic symptom prior to diagnosis of BD-I[89]. In another retrospective, questionnaire-based study of 240 participants with BD or schizoaffective disorder, depressive or manic symptoms and mood-swings were reported 3–6 years prior to a first manic episode[90].

Descriptive studies with structured assessments

In a cross-sectional study of BD-I participants based on semi-structured interviews, 6/20 subjects reported having had mood-swings before developing BD, and these correlated with a family history of affective disorders and with cyclothymic or irritable temperament[91]. Similarly, a retrospective study examined participants with first episodes of psychotic mania or bipolar-type schizoaffective disorder using structured questionnaires to assess diagnosis, prodromal symptoms, and temperament[92]. The duration of apparent prodromes, consisting of mood symptoms, sleep disruption and functional decline, had a bimodal distribution: ≤10 weeks in 50%, and 24–49 weeks in the other half [92].

A semi-structured interview (Bipolar Prodrome Symptom Scale-Retrospective [BPSS-R]) was developed to examine prodromal symptoms of BD retrospectively[13]. Initial evaluation of this instrument among 52 children and adolescents with BD-I and a first episode of mania at age 13.4±3.3 years found that 26.9% of first episodes of mania occurred before puberty[93]. A proposed *mania prodrome*, based on identifying ≥3 manic features with or without depressive or other symptoms, was present for ≥4 months in 65.4% of subjects, and occurred 10.3 [CI: 6.30–14.4] months before a first-lifetime manic episode[93]. Symptoms identified in >50% of samples prior to mania included subsyndromal hypomanic features, as well as depressed mood and decreased concentration.

Controlled studies

Parents of 82 postpubertal adolescents with BD, ADHD, or no psychiatric illness reported antecedent symptoms in preschool, latency or adolescent periods[94]: compared with the healthy controls or those with ADHD, adolescents with BD more often were reported to have had elevated or irritable mood lasting >6 hours/day for >2 days during earlier adolescence as well as depressed mood lasting >6 hours/day during ages 6–12. A retrospective study evaluated early symptomatic differences between subjects diagnosed with ADHD or early-onset BD based on parental ratings of yearly symptoms[95]. In those with BD, brief (41% vs. 5%) and extended mood elevations (59% vs. 18%) and decreased sleep (44% vs. 9%) were significantly more prevalent than with ADHD. In a 16-year prospective study of 115 Amish-American children with a BD-I parent and 106 children of parents without BD, a total of nine developed BD: 8/115 [6.96%] with and 1/106 [0.94%] without a family history of BD (a 7-4-fold risk difference; $\chi^2 = 5.11$, p=0.02). Prior to onset, parents of all nine juvenile subjects later diagnosed with BD also reported such nonspecific features such as "a sensitive nature," anxiety or worries, obsessive-compulsive symptoms, low energy, somatic complaints, decreased sleep, minor depression, mood changes, or features of ADHD[58].

Another prospective, community-based study of Dutch adolescents used ratings with the Child Behavior Checklist (CBCL) at ages 11–16 years to predict psychiatric diagnoses at age 19[96]. Scores on a composite of CBCL items selected to represent DSM-IV symptoms of [hypo]mania were higher among 56 participants later diagnosed with BD-I compared with those with MDD (p=0.002) or GAD (p=0.004), but did not differ from those later diagnosed with ADHD or oppositional defiant disorder[96].

Another approach combined multiple risk factors as "bipolar-at-risk" (BAR) criteria in youth aged 15–25 years[97]. The authors considered first-degree family history of BD, cyclothymic features, and sub-threshold depressive or manic symptoms as risk factors. In a prospective, controlled evaluation over 12 months[98], participants who fulfilled BAR criteria were significantly more likely to develop BD during follow-up (11.4%: BD-I 2.9%%, BD-II 8.6%) compared with help-seeking psychiatric controls (0.0%). In addition, having a baseline history of alcohol abuse (75% vs. 8%, p<0.001) or a family history of substance-use disorder (67% vs. 12.5%, p=0.01) were associated with development of BD[99].

Relative prevalence of prodromal symptoms

In a meta-analysis of 11 studies (1078 subjects), involving broadly defined BD, the weighted average latency from prodromal symptoms to an initial manic episode was 10.6±10.9 months (range=3.1–18.8 months) in the five studies (178 subjects) providing such information[3]. The most common prodromal symptoms ranked: excessive energy (87%), excessive talkativeness (60%), racing thoughts (59%), elated mood (59%), racing thoughts (59%), decreased need for sleep (57%), irritable mood (54%), hyperactive behavior (50%), and over-productive goal-directed (50%) behavior [3].

In summary, prodromal symptoms of mania can be studied systematically and prospectively with structured methods of assessment, including psychiatric as well as healthy controls. Subjects-of-interest have been identified

in various ways, including those with current mood symptoms or disorders, a family history of BD, or those who had already developed BD. Subthreshold symptoms of hypomania, occurrence of depression and symptoms including anxiety or psychotic features, have been identified as clinical precursors of a manic episode. The duration of clinical prodromes before overt expression of [hypo]mania often appears to be long enough to encourage early identification and timely intervention. Targeting youth entering the typical range of onset-ages for BD, especially those with a family history of probable BD, and focusing on attenuated mania-like symptoms that have a new onset or that are worsening, may improve the accuracy of predicting BD.

c) Family high-risk studies

There are a growing number of prospective, longitudinal, high-risk studies of the children of at least one patient with BD[11,19-26,58,100]. Implications and gaps of these studies have been recently discussed[18]. Most have reported findings that are similar in regards to the clinical trajectories of developing BD despite using different methods of recruitment and assessment. Main convergent findings include: [a] a relatively low rate of BD diagnoses in offspring at confirmed familial risk, in some cases from highly penetrant multigenerational families (9%–22%), although not all of the at-risk subjects had passed the age of highest risk for BD (to at least age 30 years); [b] onset of the first diagnosable [hypo]manic episode arose at ages 13–20 years; [c] depression predominated the early course of emerging BD (in 67%–88% of cases eventually diagnosed as BD); [d] with the exception of the BIOS study, there was little evidence of pre-pubertal [hypo]mania as has been described in studies of clinically referred cohorts[101]; [e] there was increased lifetime risk of a broad range of childhood psychopathological conditions compared to the general population or low-risk controls; [f] anxiety, sleep, and some behavioral disorders were significant predictors (around 2.5-fold increased risk) of subsequent mood disorders in high-risk offspring[50].

Most familial risk studies did not find elevated rates of conduct or neurodevelopmental disorders in association with BD. Further, in the BIOS study, an elevated rate of ADHD in high-risk offspring did not survive adjustment for family-related factors such as the psychosocial milieu and parental psychopathology, suggesting ADHD was not a specific antecedent of BD, at least in the families studied[102]. The Canadian study found that neurodevelopmental disorders in high-risk offspring were increased selectively in a particular psychotic subtype of familial BD, characterized by a poor response to lithium treatment[103].

Interpretation of the findings from high-risk family studies should consider limitations that include differences in study methods and designs, including variable intake-age and length of follow-up of high-risk offspring, recruitment and assessment strategies, parental differences, differences in other risk factors, and the BD subtypes encountered (Table 5). It is also very important to the goal of early detection of BD to realize that most cases eventually diagnosed as BD debuted with a depressive episode, often years prior to the first diagnosable [hypo]manic episode. The Dutch Bipolar Offspring study found that subthreshold manic experiences proved the strongest predictor of BD conversion in those offspring with a depressive mood episode[51]. Some differences in onset-age and risk of an initial major depressive episode may reflect such factors as heterogeneity of the parental

BD, risks of general psychopathology in the families, sex of the offspring, and psychosocial influences as reflected in family socioeconomic status, as well as substance abuse in the family[104]. In a recent study, the rates of psychopathology in the Pittsburgh BIOS study and the Dutch Bipolar Offspring Study were compared systematically[105]. BIOS offspring displayed significantly more non-affective psychopathology, but the two studies did not differ in risk of BD (13% in BIOS and 14% in the Dutch study at a mean age of 19 years). Parental reports indicated similar levels of dimensional psychopathology in both studies.

In the Canadian Flourish cohort, childhood anxiety disorders in offspring at risk for BD were associated with a 2.5-fold greater risk of subsequent major mood disorders of various types, compared to controls[50]. This association was replicated by Nurnberger and colleagues[24]. Further, clinically significant hypomanic symptoms but not self-reported symptoms differentiated high-risk offspring from low-risk controls and predicted recurrent mood disorders[43]. The Pittsburg BIOS study reported that parent-reported internalizing symptoms and offspring-reported affective lability at baseline were strong predictors of new-onset BD-like disorders in the at-risk offspring, whereas hypomanic symptoms were more proximal predictors of BD[4]. Both findings had been anticipated earlier in the Amish high-risk study[58,100] and are concordant with more recent findings from both the Canadian and Dutch studies[43,51].

In addition to clinical risk factors, the Canadian study found that perceived neglect by mothers during childhood and longer exposure to active BD in the affected parent was associated with a significantly greater risk of diagnosable psychopathology in the children, whereas exposure during the first two years of life was significantly associated with later emergence of mood disorders[106]. Both the Dutch and Canadian studies have independently reported that stressful life events and personality characteristics (high sensitivity or emotionality and low risk-taking or avoidant) were independent risk factors that predicted onset of mood disorders in at-risk offspring[107,108].

Based on findings from high-risk studies, Duffy and colleagues proposed a model describing the trajectory of emerging BD that considered the important issue of heterogeneity of BD[11], as well as proposing associated psychological risk processes and factors. In addition, these authors and others have discussed points of similarity and differences in the clinical trajectory of BD compared to schizophrenia[109]. Such syntheses can be helpful in identifying important knowledge gaps and highlighting directions for future risk research that should investigate different psychological risk processes and factors, and trajectories.

In summary, the findings underscore the critical importance of considering family history of psychiatric disorders in evaluating clinical syndromes in children and adolescents, and support closer monitoring of youth with a family history of BD, especially in those presenting with anxiety and mood symptoms**[110]**. Whether or not the clinical antecedents of BD reflect a general risk trajectory or a specific predisposition to BD or other mood disorders in the immature nervous system of at-risk children, requires further systematic research. Taking a developmental prospective approach to both research and diagnosis can powerfully advance understanding and differentiation of emerging trajectories of psychiatric illness, improve early detection of emerging syndromal illnesses, and identify specific targets for early intervention.

d) Affective Temperaments

Temperaments are permanent variations of personality that play a crucial role in determining emotional reactions and affective resonance, and that have been related to mood disorders[111]. According to Akiskal and colleagues[112], affective temperaments are subclinical, sub-affective, trait-like manifestations that may or may not be associated with mood disorders. This concept was introduced by Kraepelin in presenting his broadly defined group of manic-depressive disorders, ranging from traits (so-called fundamental states) to mild cyclothymia, through severe depression with or without mania or hypomania, and is supported by family, genetic, biological and clinical studies[112-118]. In short, affective temperaments, as attenuated manifestations or precursors of mood disorders, are often conceived to be part of the non-pathological end of the spectrum reaching into the normal domain of mental functioning, with potentially important contributions to predicting, diagnosing and subtyping affective illnesses[119-121]. Affective temperaments may play a moderating role, probably influencing the emergence and clinical evolution of mood disorders and important disease characteristics, including predominant polarity, symptomatic expression, neurocognitive performance[112-124], long-term course and outcome, as well as response and adherence to treatment[119]. Temperament may also mediate such features of BD, such as impulsivity, suicidal risk, and functional capacity[125].

Affective temperaments are found in psychiatric disorders other than BD and MDD[126], as well as in 13%–20% of the healthy general population, depending on the definition of the dominant temperament-type[120]. In mood disorder patients, dominant forms of affective temperaments are much more prevalent than in the healthy general population [120]. Notably, a recent meta-analytic study found that *cyclothymic, depressive, irritable* and *anxious* temperament scores with the TEMPS-A scale were significantly higher (p<0.0001) among patients with BD than in healthy controls, whereas *hyperthymia* ratings were significantly lower (p=0.004) in BD subjects compared to healthy controls[127].

Affective temperaments show a characteristic sex-distribution, with depressive and anxious temperaments being more common among females and hyperthymic temperament being more frequent among males[120]. In clinical samples, depressive temperament has been especially prevalent in MDD patients[119,128], whereas hyperthymic[128] and cyclothymic temperaments are characteristic of patients with BD, whereas irritable temperament is less prevalent and found in both unipolar and bipolar mood disorders[119,128,129]. In a prospective study, 35% of subjects with cyclothymic temperament developed hypomanic, manic or depressive episodes within three years, and one-third of the offspring and siblings of BD patients had dysthymic, cyclothymic, or hyperthymic temperaments[129]. Cyclothymic temperament in MDD patients also has been associated with atypical features, such as hypersomnia and hyperphagia, which are common in bipolar depression[119,129]. In patients with recurrent MDD, higher ratings for cyclothymic temperament also have been associated with earlier age of onset, a greater number of previous depressive episodes, more psychotic and melancholic features, and more suicidal ideation and attempts[125]. Such features also are predictive of bipolarity among patients with recurrent MDD[130]. These findings support the suggestion that assessment of particular temperament-types may have prognostic value, including anticipation of BD.

Temperament also may be a major factor influencing the clinical evolution of BD. For example, affective temperaments have been associated with an earlier age at onset of BD[131]; higher scores for depressive versus hyperthymic temperaments have been associated with relatively more depressive than manic recurrences[132]. Among BD-I patients, depressive temperament has been associated with predominant depressive polarity, whereas hyperthymic temperament has been associated with predominantly [hypo]manic polarity[119,132] (Table 6). BD patients with cyclothymic or hyperthymic temperaments are reported to differ significantly in several important clinical and course features, including sex differences, predominant episode polarity, greater episode-frequency, more hospitalization, higher suicidal risk, and co-occurring anxiety and personality disorders[133-135]. Furthermore, hyperthymic temperament was associated with psychotic features during major affective episodes in both BD-I and BD-II patients[128]. Spontaneous and antidepressant-induced mood switches into [hypo]mania have been more common in BD patients with a hyperthymic temperament[136].

In summary, BD-I can be associated with various temperaments, but there has been a relatively high ratio of hyperthymic/depressive temperament ratings. BD-II is more selectively associated with cyclothymic temperament[137] and hyperthymic temperament was correlated with fewer depressive episodes and with seasonal features[138]. Finally, cyclothymic temperament is also associated with progression from MDD to BD[37].

DISCUSSION

Prevention and early identification and treatment of BD are preeminent clinical goals. The body of research reviewed above points to the fact that BD is often preceded by homotypic or heterotypic precursors, as well as symptoms, syndromes, and disorders that require clinical attention themselves as well as have some predictive value for identifying patients likely to be diagnosed with BD later. However, the nonspecific nature and uncertain predictive value of many of these antecedents call for research aimed at identifying more specific risk characteristics and constellations, as well as effective ways to intervene at different stages of BD.

Various sources of information were considered relevant for evaluating manifestations prior to the full clinical expression of BD. We considered clinical risk factors as well as identifying a prodrome for mania, prospective studies of the offspring of BD patients, and investigations of temperament in BD patients. We emphasized prospective studies of subjects followed to full expression of BD, but included some, largely consistent, retrospective findings from studies of cases of established BD. Prospective studies of this type are preferred since recall may be biased in retrospective studies and by the failure to recognize some antecedent conditions prior to first-lifetime episodes of [hypo]mania.

Information about homotypic, heterotypic and other risk factors for BD, derived from prospective as well as retrospective studies are clearly important, especially when considered together[12]. Individual risk factors seem to be insufficiently specific to predict BD reliably. Particularly challenging is to predict BD when early manifestations have been mainly depressive for months or years before a first episode of [hypo]mania[4,13,18,21]. Combinations of risk factors may be more important than any single measure.

Retrospective and prospective information about a symptomatic prodrome to developing syndromal mania, is marked particularly by attenuated hypomanic features[3,93,98]. Converging evidence suggests that mood lability and mood swings are a core feature of the clinical prodrome to (hypo)mania. This is relevant, as mood lability s also part of the illness itself and poorly captured by the diagnostic criteria for BD. Mood lability is however also part other mood and anxiety disorders as well as emerging borderline and related personality disorders, and these are major differential diagnoses. In contrast, depressive symptoms are more often prodromal to depressive episodes or a mixed state as defined in DSM-IV [3]. A Bipolar Prodrome Symptom Interview and Scale-Prospective (BPSS-P) has been developed and validated for use in identifying and scoring symptoms that may be part of the prodome to mania[93].

In studies of subjects at increased risk for BD due to having a parent with BD, rates of prospectively observed development of BD have been surprisingly small, and other forms of psychopathology have been quite prevalent, possibly owing to the unusual nature of such uncommon at-risk families, and insufficiently prolonged years of follow-up. Nevertheless, in offspring studies mood-swings and attenuated but worsening hypomanic symptoms in youth were especially strongly associated with later diagnosis of BD or related disorders[138]. Studies of affective temperaments appear to be helpful in identifying traits that may underlie risk for developing BD[37,107,112,118,130]. However, the limited specificity of temperamental expressions, as with many other factors found to precede BD, restrict the utility of assessing temperament as a means of enhancing prediction of future BD[120]. For all of these several approaches to establishing sensitive and specific predictors of BD, limitations arise from selecting possibly non-representative samples, incomplete or inaccurate recording of past events, insufficient follow-up through the years of risk for BD (especially ages 15–30 years), and the low diagnostic specificity of most individual, identified predictive factors. Prospective studies can address some of these issues, but are difficult and costly to carry out. Finally, a limitation of this report is that each of the four work groups used somewhat different databases for their identification of the evaluated evidence. However, all used at least PubMed/Medline as the overlapping, large data source. Nevertheless, despite these limitations of the review and the reviewed literature, converging evidence from the four types of studies reviewed here suggests that some factors and especially in combinations, can contribute to improving prediction of new onset or worsening of attenuated hypomanic symptoms [3,4,18,22,43,44,47,98]. These findings encourage better-designed clinical studies aimed at improving prediction of new [hypo]mania. Importantly, comparison or control groups, ideally with other psychiatric disorders as outcomes, should be included to increase the chance to identify clinically useful, sufficiently sensitive, and specific predictors of BD risk. Indeed, the sensitivity and specificity of most identified predictors of BD has not been adequately evaluated and requires further study. Finally, with growing data from prospective studies with harmonized assessment of risk factors, emerging risk calculators for the development of BD are likely going to become relevant for clinical care.

In conclusion, based on the review of pertinent research findings and their critical discussion, among its members, this Taskforce makes the following recommendations:

1. More prospective studies of well-characterized clinical and/or familial high-risk individuals that focus on identifying precursors and prodromes of BD are needed to pursue efforts to identify individuals at risk for emergence of first lifetime episodes of [hypo]mania.
2. We recommend development of a consensus about a minimal and optimal set of methods for clinical and biomedical assessments in order to generate a sharable pool of data related to prediction and early recognition of BD.
3. We suggest that studies should assess the many risk and predictive factors enumerated above, with the hope that this International Society of Bipolar Disorders Taskforce Report on precursors and prodromes in BD will help clinicians and investigators to more efficiently address prediction and early recognition of BD, with the aim of improving treatment and outcomes.

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Table 1. Homotypic risk factors for BD.

Risk factors	Study	BD risk	Design	Diagnosis	Age (y)	Follow up (y)	Assessment	Notes
Mood lability	Angst et al., 2003[27]	OR=14.3 (4.94–41.6), p<0.001; OR=20.6 (7.0–60.9), p<0.001 for BD-II	C	none	(18.5)	15	Clinical	
	Tohen et al., 2012[28]	χ^2=4.85, p=0.03 for BD-I/NOS	I	MDDP	18–75 (36.3)	0.5–9 (3.9)	SCID	
	Salvatore et al., 2013[29]	RR=1.45, p=0.05 for BD-I/NOS	I	MDDP	10–82 (34.6)	4	SCID	
Subsyndromal depression	Regeer et al., 2006[30]	PP=1.0 (0.7–1.3), LR=3.3 (2.1–5.3)	C	none	18–64 (41.2)	3	CIDI	
Subsyndromal hypomania in MDD	Tohen et al., 2012[28]	χ^2=4.76, p=0.03	I	MDDP	18–75 (36.3)	0.5–9 (3.9)	SCID	
	Fiedorowicz et al., 2011[35]	HR=1.34 (1.17–1.54), p<0.001; HR=1.28 (1.09–1.52), p=0.003 for BD-I; HR=1.23 (1.02–1.17), p=0.03 for BD-II	I	MDD	>17	1–31 (17.5)	SADS	Combined elevated mood+decreased need for sleep+increased energy+increased goal directed activi-ty+grandiosity pre-dicted BD

Risk factors	Study	BD risk	Design	Diagnosis	Age (y)	Follow up (y)	Assessment	Notes
	Zimmer-man et al., 2009[34]	OR=4.25 (1.13–15.9), p=0.03; OR=8.32 (1.49–46.4), p=0.02 for BD-I	C	MDD	14–24	7.3–10.6 (8.3)	CIDI	Mood disturbances or change in func-tioning observable by others signifi-cantly predicted BD
	Salvatore et al., 2013[29]	RR=5.43, p<0.001 for mixed state at intake; RR=10.9, p=0.002 for antecendent hypomanic symptoms; RR=2.08, p=0.01 for hypomanic symptoms at onset	I	MDDP	10–82 (34.6)	4	SCID	
	Nadkarni et al, 2010[33]	Fisher's exact test=8.50, p=0.01	O	MDD or Dysthymia	8–11 (9.9)	1.5	ChIPS-C	Transient hypo-manic symptoms increased risk of BD by 3.8x
Subsyndromal hypomania	Regeer et al, 2006[30]	PP=7.1 (6.4–7.9), LR=25.4 (10.6–60.6)	C	none	18–64 (41.2)	3	CIDI	
	Kaymaz et al, 2007[31]	PP=3.0 (2.5–3.4); PP=9.5 (4.7–14.4) for subjects with subsyndromal psychosis	C	none	18-64 (41.2)	2	CIDI	

Risk factors	Study	BD risk	Design	Diagnosis	Age (y)	Follow up (y)	Assessment	Notes
	Homish et al, 2013[32]	OR=2.8 (2.4–3.2), p<0.001 (elation or irritability); OR=4.6 (3.7–5.8), p<0.001 (elation and irritability)	C	none	>18	3	AUDADIS-IV	
Cyclothymia in MDD	Kochman et al, 2005[37]	63.8% with cyclothymic temperament converted to BD vs, 15.3% without (p<0.0001)	I	MDD	7–17 (12.7)	2–4 (2.2)	SADS	
Psychotic symptoms in MDD	Strober et al, 1993[36]	Psychotic symptoms predicted conversion (p=0.02)	I	MDD	13–17 (15.3)	2	SADS	
	Kochman et al, 2005[37]	57.4% with cyclothymic temperament + psychotic symptoms converted to BD vs.6.1% without psychosis (p<0.001)	I	MDD	7–17 (12.7)	2–4 (2.2)	SADS	
	Fiedorowicz et al, 2011[35]	HR=3.54 (1.85–6.77), p<0.001 for BD-I	I	MDD	>17	1–31 (17.5)	SADS	
	Bromet et al, 2011[38]	AOR 0.45 (0.28–0.71), p<0.001	I	MDD	15–60	10	SCID	Decreased psychotic symptoms predicted BD

Abbreviations: AOR, adjusted odds ratio; AUDADIS, Alcohol Use Disorder and Associated Disability Interview Schedule; BD, bipolar disorder; C, community; ChiPS-C, Children's Interview for Psychiatric Syndromes–Child; CIDI, Composite International Diagnostic Interview; HR, hazard ratio; I=inpatients; LR=likelihood ratio; MDD=major depressive disorder; MDDP=major depressive disorder with psychosis; O=outpatients; PP=post test probability; RR=risk ratio; SCID=Structured Clinical Interview for DSM.

Table 2. Heterotypic risk factors for BD.

Risk factors	Study	BD risk	Design	Diagnosis	Age (y)	Follow up (y)	Assessment	Notes
Anxiety disorders	Johnson et al., 2000[52]	OR=4.69 (1.78–12.38), p<0.01	C	various	14–22	9	DISC	Intake diagnoses: anxiety, depressive, disruptive, personality, & substance disorders
GAD	Homish et al., 2013[32]	OR=2.10 (1.80–2.40), p<0.001	C	none	>18	3	AUDADIS-IV	
PTSD	Grant et al., 2009[55]	OR=2.40 (1.33–4.31), p<0.01 for BD-I	C	none	>18	3	AUDADIS-IV	
	Chou et al., 2011[56]	OR=3.35 (1.03–10.8), p<0.01 for BD-I	C	none	>60	3	AUDADIS-IV	PTSD also predicted MDD, panic disorder, specific phobia & GAD
SA	Brückl et al., 2007[53]	HR=6.20 (1.70–21.6) for BD-I; HR=8.5 (1.6–43.5) for BD-II	C	none	14–24	4	CIDI	retrospectively reported; also predicted PDAG, specific phobia, GAD, OCD, pain disorder & alcohol dependence.

Risk factors	Study	BD risk	Design	Diagnosis	Age (y)	Follow up (y)	Assessment	Notes
Substhreshold SA		HR=8.10 (2.3–27) for BD-II	C	none	14–24	4	CIDI	retrospectively reported; also predicted PDAG, pain disorder and alcohol dependence
SA + subthreshold SA		OR=9.90 (1.10–84.0) for BD-II	C	none	14–24	4	CIDI	prospectively reported; also predicted panic, alcohol dependence, pain disorder.
Panic attacks	Kinley et al., 2011[54]	AOR=2.39 (1.61–3.54), p<0.001 for BD	C	none	>18	3	AUDADIS-IV	also predicted GAD, PD, social phobia, MDD, dysthymia, anxiety disorders & mood disorders
ODD, CD or ADHD	Tijssen et al., 2010[47]	HR=5.29 (2.01–13.9), p<0.001	C	none	14-24 (18.3)	7.3–10.6 (8.3)	CIDI	
CD and/or ODD	Kim-Cohen et al., 2003[49]	AOR=2.50 (1.10–5.40) for BD-I	BC	none	11-26	23	DISC	also predicted anxiety disorders, depression and substance abuse

Risk factors	Study	BD risk	Design	Diagnosis	Age (y)	Follow up (y)	Assessment	Notes
CD	Morcillo et al., 2012[61]	men: AOR=2.04 (1.62–2.57), p<0.05; women: AOR=1.72 (1.23–2.41), p<0.05	C	none	>18	3	AUDADIS-IV	also predicted Axis I & II disorders in both sexes
Subthreshold CD	Shankman et al., 2009[60]	HR=3.90 (1.60–9.40), p<0.05	C	none	14–20	15	SADS	also predicted alcohol & substance abuse & CD
Impulsivity	Chamorro et al., 2012[65]	AOR=3.19 (2.81–3.61), p<0.05	C	none	>18	3	AUDADIS-IV	also predicted other Axis I & II disorders
ADHD	Grant et al., 2009[55]	OR=2.60 (1.14–6.10), p<0.01 for BD-I	C	none	>18	3	AUDADIS-IV	

Abbreviations: AOR, adjusted odds ratio; AUDADIS, Alcohol Use Disorder and Associated Disability Interview Schedule; BC, birth cohort; BD, bipolar disorder; C, community; GAD, generalized anxiety disorder; CIDI, Composite International Diagnostic Interview; HR, hazard ratio; OCD, obsessive compulsive disorder; PDAG, panic disorder with agoraphobia; RR, risk ratio.

Table 3. Exposure-related risk factors for BD.

Risk factors	Study	BD risk	Design	Follow up (y)	Cases (n)	Controls (n)	Assessment	Notes
Maternal influenza	Parboosing, 2013[70]	AOR=4.21 (1.60–11.0), p=0.004 (all trimesters); AOR 5.68 (1.07–30.1), p=0.04 for trimester-3	NCC	to 29	BD patients identified through medical databases (92)	Non-BD matched controls identified through medical databases (722)	SCID	
	Canetta, 2014[71]	AOR=4.87, 1.18–20.1, p=0.03 for BD-I with psychosis	NCC	to 29	BD patients identified through medical databases (85)	Non-BD matched controls identified through medical databases (168)	SCID	
Maternal smoking	Talati, 2013[66]	AOR=2.014 (1.48–2.53), p=0.01	NCC	to 29	BD patients identified through medical databases (79)	Non-BD matched controls identified through medical databases (654)	SCID	
Maternal war stress	Kleinhaus, 2013[77]	RR=2.44 (1.00–5.99), p=0.054 for 1st trimester	CS	to 41	Exposed born during the Six Days War (4298)	Unexposed born before or after the Six Day War (85781)	Clinical	also predicts MDD and mood disorders NOS

Risk factors	Study	BD risk	Design	Follow up (y)	Cases (n)	Controls (n)	Assessment	Notes
Gestational age	Øgendahl, 2006[67]	Females only: OR=2.91 (1.10–7.73 p=0.05) for <37 weeks; OR=3.70 (1.35–10.2, p=0.05) for weight <2.5 kg & age <37 weeks	NCC	to 11	BD patients identified through medical databases (196)	Non-BD matched controls identified through medical databases (4900)	Clinical	
Gestational age	Nosarti, 2012[68]	AHR=7.40 (2.70–20.6) p<0.05 for <32 weeks; AHR=2.70 (1.60–4.50), p<0.05 for 32–36 weeks	CS	to 19	Born < 32 or 32–36 weeks gestation (52989)	Born > 37 weeks gestation (1243543)	Clinical	also predicts non affective psychosis, depression, eating disorders
Birth type	Chudal, 2014[69]	AOR=2.51 (1.32–4.78), p<0.01 for planned cesarean	NCC	to 21	BD patients identified in medical databases (724)	Non-BD matched controls from medical databases (1419)	Clinical	
Any substance abuse	Schepis, 2011[86]	AOR=1.33 (1.18–1.51, p<0.001)	C	3	Exposed to any substance abuse (2639)	Not exposed to any substance abuse (12,690)	AUDADIS-IV	Subjects with lifetime alcohol, substance, MDD, anxiety disorders; also predicts alcohol, SUD, depressive & anxiety disorders

Risk factors	Study	BD risk	Design	Follow up (y)	Cases (n)	Controls (n)	Assessment	Notes
Cocaine	Anthony, 1991[81]	OR=11.8, p=0.031 for DSM manic episode; OR=5.5, p=0.006 for mania syndrome	NCC	1	BD (66)	Non-BD (268)	DIS	also predicts panic, depression, psychotic symptoms
Cannabis	van Laar, 2007[82]	AOR 4.98 (1.80-13.81), p<0.01; AOR 8.93 (2.77-28.82), p<0.001 for 1-4 times/week use	C	3	Exposed to cannabis (484)	Not exposed to cannabis (4,197)	CIDI	
	Gilman, 2012[79]	OR=2.12 (1.10–4.08), p<0.05	C	3	Exposed to cannabis (336)	Not exposed to cannabis (2,249)	AUDADIS-IV	Subjects with past-year MDD
	Feingold, 2015[83]	AOR=2.47 (1.03–5.92), p<0.05 for weekly to near-daily use	C	3	Exposed to cannabis (1029)	Not exposed to cannabis (31,577)	AUDADIS-IV	
Opioids	Schepis, 2011[86]	AOR=2.61 (2.03–3.36), p<0.001 for any drug; AOR=2.81 (2.47–3.21), p<0.001 for any past-year drug	C	3	Exposed to opioids (337)	Not exposed to opioids (16,830)	AUDADIS-IV	also predicts SUD, depressive and anxiety disorders

Risk factors	Study	BD risk	Design	Follow up (y)	Cases (n)	Controls (n)	Assessment	Notes
	Schepis, 2011[86]	AOR=1.33 (1.18–1.51, p<0.001) for any drug; AOR=1.50 (1.15–1.94 p<0.002) for tranquilizers	C	3	Exposed to opioids (2639)	Not exposed to opioids (12,690)	AUDADIS-IV	Subjects with lifetime alcohol, substance, MDD, anxiety disorders; also predicts alcohol, SUD, depressive and anxiety disorders
	Martins, 2012[85]	AOR=2.00 (1.10–3.70), p<0.05	C	3	Exposed to opioids (1499)	Not exposed to opioids (33154)	AUDADIS-IV	also predicts MDD, any anxiety disorders and GAD
	Schepis, 2013[84]	AOR=2.12 (1.52–2.96), p<0.001 for weekly/daily user	C	3	Exposed to opioids (461)	Not exposed to opioids (17,011)	AUDADIS-IV	Subjects with lifetime alcohol, substance, MDD, anxiety disorders; also predicts depressive and anxiety disorders
Tranquilizers	Schepis, 2011[86]	AOR=1.50 (1.15–1.94, p<0.002)	C	3	Exposed to tranquilizers (2639)	Not exposed to tranquilizers (12,690)	AUDADIS-IV	Subjects with lifetime alcohol, substance, MDD, anxiety disorders

Risk factors	Study	BD risk	Design	Follow up (y)	Cases (n)	Controls (n)	Assessment	Notes
Head injury	Mortensen, 2003[75]	IRR 1.55 (1.36–1.77), p=0.01	NCC	to 15	BD inpatients identified in medical databases (10242)	Non-BD matched controls identified in medical databases (102420)	Clinical	
	Orlovska, 2014[76]	IRR=1.28 (1.10–1.48), p<0.05	CS	to 23	Exposed to head injury (113,906)	Not exposed to head injury (1,324,433)	Clinical	also predicts schizophrenia, MDD and organic mental disorder
Parental loss	Mortensen, 2003[78]	RR=4.05 (1.68–9.77), p<0.05 for mother-loss <age 5	NCC	to 28	BD inpatients in medical databases	Non-BD matched controls identified through medical databases	Clinical	
		RR=1.93 (1.03–3.59), p<0.05 for mother-loss at age 5–10						
		RR=1.63 (1.09–2.45), p<0.05 for mother-loss at age 10–15						

Risk factors	Study	BD risk	Design	Follow up (y)	Cases (n)	Controls (n)	Assessment	Notes
		RR=2.42 (1.20–4.86), p<0.05 for father-loss before age 5						
Childhood adversities	Gilman 2012[79]	OR=1.27 (1.13–1.42 p<0.05) for physical abuse	C	3	Not reported	Not reported	AUDADIS-IV	Subjects with lifetime MDD
		OR=1.05 (1.00–1.11 p<0.05) for sexual abuse			Not reported	Not reported		
Past-year stressors	Gilman 2012[79]	OR=1.79 (1.19-2.68 p<0.05): social support group problems	C	3	Exposed (3879)	Not exposed (2,335)	AUDADIS-IV	Subjects with lifetime MDD
		OR=1.45 (1.03–2.06 p<0.05): economic problems			Exposed (1885)	Not exposed (4,329)		

Abbreviations: AHR: adjusted hazard ratio; AOR=adjusted Odds Ratio; AUDADIS = Alcohol Use Disorder and Associated Disability Interview Schedule; BD= bipolar disorder; C=community; CIDI = Composite International Diagnostic Interview; CS=cohort study; HR = hazard ratio; IRR = incident rate ratio; MDD = major depressive disorder; NCC=nested case-control; NOS = not otherwise specified; OR = odds ratio; RR = risk ratio; SUD = substance use disorder.

Table 4. Summary of studies assessing symptomatic predictors or prodromes of mania.

Reports	N	Population	Assessments	Pre-mania features
Uncontrolled without structured assessments				
Hirschfield et al. 2003[89]	600	Adults with BD	Self-report questionnaire	DSM-IV mania, depressive symptoms, sleep disturbances
Berk et al. 2007[90]	218	Adults with BD-I or schizoaffective disorder	Questionnaire	Symptoms of mania and depression; mood swings
Axelson et al. 2011[44]	152	Children & adolescents with BD-I	KSADS, LIFE, MRS	Subthreshold manic symptoms, family mood history
Uncontrolled with structured assessments				
Ozgurdal et al. 2009[91]	20	Adults with BD-I	Semi-structured eval. for mood swings	Mood swings, temperaments
Correll et al. 2007[13], 2014[93]	52	Children & adolescents with first episode mania ± psychosis	Bipolar Prodrome Symptom Scale (BPSS), retrospective	Manic symptoms, depressive symptoms, anxiety, psychotic experiences
Conus et al. 2010[92]	22	Youth with first episode mania + psychosis	Initial Mania Prodrome Questionnaire	Manic & depressive symptoms, mood swings
Controlled				
Rucklidge et al. 2008[94]	25	Adolescents with BD & healthy controls	KSADS-PL applied retrospectively	Elevated, depressed or irritable mood >6 hrs/day, for >2 days

Luckenbaugh et al. 2009[95]	27	Juveniles with BD & healthy controls	KSADS interviews of parents & children	Elevated mood, sleep disturbances
Papachristou et al. 2013[96]	56	Adolescents with BD-I in a prospective community study	Child Behavior Checklist-	DSM-IV mania symptoms in a "Mania Scale"
Bechdolf et al. 2010[97]	35*	Juveniles meeting BD-at-risk criteria & followed 1 year	Clinical assessment of at-risk criteria	BD-at risk criteria, subthreshold mania, depression with cyclothymic features (11.4% developed BD)
Meta-analysis of prodromal symptoms				
Van Meter et al. 2016[3]	1084	Varied participants aged 10.6–43.9 yrs	Varied structured & unstructured assessments	Excess energy, talkativeness, racing thoughts, decreased need for sleep, elated or irritable mood identified in a majority before initial mania

Abbreviations: BD, Bipolar Disorder; KSADS, Schedule for Assessment of Schizophrenia and Affective Disorders for School age Children; LIFE, Longitudinal Interval Follow-up Evaluation; MRS, Mania Rating Scale; DSM, APA Diagnostic and Statistical Manual; among 35 participants, 4 (11.4%) developed BD.

Table 5. Overview of prospective bipolar offspring studies

Reports	Cohort characteristics				Parent Characteristics					Offspring Characteristics				
	Follow-up (years)	Follow-up	Drop-out (%)	Cohort Type	*n*	BD parent	BD mother (%)	Recruitment	Country	*N*	Mean age (range)	Interview	Offspring diagnoses Vs. Controls (C)	Early course of BD
Duffy et al. 1998[19]; 2014[11]	≤16	Annually (mean follow-ups: 6.3)	5	Dynamic	113	41% BD-I 43% BD-II 4% +psychosis 10% I° relatives of BD probands	52	outpatient specialty clinics; lithium responders & nonresponders	Canada	229	22.6 (7–25)	K-SADS-PL; SADS-L	32% MDD (3% C) 30% SUD (16% C) 23% Anxiety (12% C) 22% BD-I, -II, -NOS, SCZ (0 % C) 20% Adjustment (41% C) 11%,Neurodev (6% C), 9% Minor mood (1.5% C) 2.5% DBD	85% index episode depressive Mean onset 16 ± 4 yrs Latency 5 yrs to hypo/mania Median hypomania/mania age 18 yrs 0% pre-pubertal hypo/mania antecedent anxiety predicted 2.5 fold risk mood disorder

Reports	Cohort characteristics				Parent Characteristics					Offspring Characteristics				
Wals et al. 2001[20];Mesman et al. 2013[21]	12	Baseline, 1, 5,12 yrs (4.0)	23	Fixed	86	74% BD-I 26% BD-II	60	82%: patient associations; 28%: outpatient clinic	Netherlands	140108	28 (22–33)	K-SADS-PL; SCID	28% minor mood 25% anxiety 23% SUD 17% MDD 13% BD-I, -II, Cyclo, psychotic 7% DBD 5% ADHD	88% index episode depressive Mean onset 15 ± 4.6 yrs Latency 5 yrs to hypo/mania Median onset hypomania 17 yrs Median onset mania 20 yrs 0 pre-pubertal hypo/manic onset
Egeland et al. 2003[100], 2012[58]	16	Annually (16)	0	Dynamic & Fixed	15	100% BD-I	43	Genetic linkage research; Amish community	USA	115	75% <14	CARE interview	39% risk rating (16% C) Episodes of Internalizing symptoms (childhood), shifted to externalizing (adolescence) 9% BD	Median onset 15 yrs hypo/mania 0 pre-pubertal hypo/mania onset All preceded anxiety/dep 0 evidence of SMD in childhood (0 disruptive, ADHD, irritability)

Reports	Cohort characteristics				Parent Characteristics					Offspring Characteristics				
Birmaher et al. 2009[22] Axelson et al. 2015[23]	7	Mean 2.5 yrs	9	Fixed	236	72% BD-I 28% BD-II	81	53%: advertisement, 31%: adult BD studies; 16%: outpatient clinics	USA	357	18.1 (6–18)	K-SADS-PL; SCID	Anxiety 30%–40% (18%–22% C) ODD/CD 35% (19% C), DBD 27% (15% C), MDD 19% (14% C) SUD 19% (10% C) BD-NOS 11% (1.2% C) Dep NOS 10% (7% C) BD 8.4% (0.8%C),	Mean onset 13 yrs hypo/mania Mean onset MDD 14 yrs 33% index hypo/mania ≤10yrs 53% onset hypo/mania ≤12 yrs
Nurnberger et al. 2011[24]	2–3	Baseline, 1, 2-yrs (3)	——	Fixed	32	BAD (NS) SCZBD	——	Oupatient research studies	USA	53	19.6 (15–25)	K-SADS (65% telephone)	18% SUD (9%C) 16% MDD (4% C) 11% DBD (8%C) 8.5% BD-I, -II, -NOS (0% C) 8% ADHD (5%C)	Youngest [hypo]mania 10 yrs Median onset MDD 12 yrs Median onset Mania 12.5 yrs Median onset Hypomania 16 yrs

Reports	Cohort characteristics				Parent Characteristics					Offspring Characteristics				
Vandeleur et al. 2012[25] Preisig et al. 2016[26]	10.6	Every 3 yrs (3–4)	—	Dynamic	81	66% BDI 15% BD II 19% BD+psychosis	58	Inpatient & outpatient facilities	Switzerland	145	21.1 (16–28)	K-SADS-E	**43.5% ANX (38.4% C)** **36.6% MDD (37.5% C)** **27.6% SUD (18.8% C)** **17.2 % BPS (4.5% C)** **16.6% ADHD (13.4% C)** **14.5% ODD (13.4% C)** **12.4% BD I/II (3.6% C)**	No information on early course of BD; Offspring of early-onset-BD parents had higher risk of BD (HR= 7.9 [1.8–34.6]) & of substance abuse (HR=5.0 [1.1–21.9] vs. later-onset or controls.

Abbreviations: ADHD, attention deficit hyperactivity disorder; ANX, anxiety, disorders; BD, bipolar disorder; BAD, DSM-III bipolar affective disorder; BPS, bipolar spectrum disorders, including BD-I, -II, -NOS (not otherwise specified), cyclothymia, and bipolar type schizoaffective disorder; BD-I, bipolar-I disorder; BD-II, bipolar II disorder; C, controls; Cyclo, cyclothymia; Dys, dysthymic disorder; DBD, disruptive behavioral disorder: including oppositional defiant disorder(ODD) & conduct disorders (CD); MDD, major depressive disorder; SzAff, schizophrenia/affective; SUD, substance use disorder;

F, fixed population recruited within a fixed enrollment period; mixed design was fixed, but new siblings or new families when parents with newly emerging BD could be added; Dynamic, recruiting new families, no fixed enrollment period;

Age, at baseline; 357/391 offspring (91.3%) were followed prospectively; those lost to follow-up were included for analysis.

Note that the overall risk of any BD-like illness among probands averaged 195/1039 (18.8% [16.4–21.3]), compared to only (1.26% [0.51–2.58] (14.9x-less) in controls.

[1]Baseline 140; at 12 year follow-up 108; [2]114 of 141 offspring had a parent as proband.

Abbreviations: ADHD = attention deficit-hyperactivity disorder; ANX = anxiety, disorders; BD = bipolar disorder; DBD = disruptive behavior disorder; MDD = major depressive disorder; ODD = oppositional-defiant disorder; SUD = substance use

Table 6. Affective temperaments in bipolar disorder types and versus healthy controls or major depressive disorder patients.

Temperament Type	Sex	BD vs Healthy Controls	BD vs MDD	Type I vs II BD	Clinical characteristics associated with temperament	Suicidal Risk (proportion of reports)
Cyclothymic	F = M	BD > HC SMD=2.20 [1.61–2.84]	BD > MDD SMD=0.54 [0.38–071]	BD-I = BD-II (p= 0.29)	More atypical features; younger onset; more recurrences/year; twice more likely BD vs MDD	Higher scores if suicidal (17/23)
Anxious	F > M	BD > HC SMD=1.38 [0.66–2.09]	BD = MDD (p= 0.54)	BD-I = BD-II (p= 0.72)	more depressive episodes with mixed features; more medical & psychiatric comorbidity	Higher scores if suicidal (11/22)
Irritable	F = M	BD > HC SMD=1.29 [0.86–1.72]	BD > MDD SMD=0.41 [0.22–0.60]	BD-I = BD-II (p= 0.84)	More psychosis with first-episodes; more mixed or psychotic features; more manic switch-risk	Higher scores if suicidal (6/23)
Depressive	F > M	BD > HC SMD=1.19 [0.55–1.82]	BD = MDD (p= 0.29)	BD-II > BD-I SMD = 0.25 [0.41–0.009]	More predominant depression; more depressive episodes; more depressive first episodes	Higher scores if suicidal (15/23)
Hyperthymic	F < M	BD < HC SMD=–0.44 [–0.74 to 0.15]	BD > MDD SMD=0.39 [0.18–0.60]	BD-I = BD-II (p= 0.12)	More predominant mania more manic episodes; more manic or psychotic episodes; greater manic switch; more recurrences/year	Lower scores if suicidal (9/11)

Abbreviations: F, female; M, male; BD, Bipolar Disorder; HC, Healthy Controls; MDD, Major Depressive Disorder; SMD (with 95% CI), standardized mean difference.

Data are based on TEMPS-A scores, from Rihmer et al 2010[119], Vázquez & Gonda 2013[120], Solmi et al 2016[127]. [*] Suicidal ideation or attempts as the proportion of reports noting higher or lower TEMPS-A score among suicidal subjects, from Vázquez et al. 2017[135].

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