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Baseline dimensional psychopathology and future mood disorder onset: findings from the Dutch Bipolar Offspring Study

Mesman E, Nolen WA, Keijsers L, Hillegers MHJ. Baseline dimensional psychopathology and future mood disorder onset: findings from the Dutch Bipolar Offspring Study.

Objective: To identify the early signs of mood disorder development, specifically bipolar disorder (BD), in a population at familial risk for BD.
Method: The sample included 107 Dutch adolescent bipolar offspring (age 12–21) followed into adulthood (age 22–32). Lifetime DSM-IV axis I diagnoses were examined at baseline, 1-, 5-, and 12- year follow-up. Symptoms were assessed at baseline on a 3-point Likert scale at baseline with the K-SADS-PL and were analyzed using symptom and sum scores. As observed in previous studies, BD typically starts with other mood disorders. Therefore, the sample was stratified in offspring with a mood diagnosis (n = 29) and without (n = 78) at baseline.
Results: Subthreshold manic experiences proved the strongest predictor of BD conversion (n = 10; HR2.16, CI95% 1.23–3.78). At symptom level, elated mood, decreased need of sleep, racing thoughts, suicidal ideation, and middle insomnia were significantly associated with BD conversion. Depressive symptoms proved the strongest predictor for first mood episode onset (n = 28; HR1.27, CI95% 1.02–1.58).
Conclusion: This study extends our knowledge of prodromal manifestations of BD in a high-risk population. Although preliminary, findings of this study provide potential targets for early identification and underscore the importance of detailed assessment of manic symptomatology in bipolar offspring.

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Key words: bipolar disorder; family studies; risk factors

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Significant outcomes

- Subthreshold manic experiences are the strongest predictor for conversion to BD in bipolar offspring with a history of mood disorders (i.e. major depressive disorder, dysthymia, depression NOS and cyclothymia).
- Subthreshold depressive symptomatology was an important antecedent for first mood episode onset (i.e. major depressive disorder, dysthymia, depression NOS and cyclothymia).
- Findings of this study further contribute to the construction of a clinical risk profile for those at familial risk for BD, and provide potential targets for the development of early recognition and intervention programs.

Limitations

- Although a relatively high (13%) transition rate to BD, absolute numbers are small, leading to inherent power issues in statistical analyses.
- The measures of dimensional psychopathology used in this study are limited and no information about the onset and duration were available.
- Bipolar offspring represent a specific high-risk population. Hence, generalizability to other populations is limited.

Introduction

Early identification of BD remains challenging. The diagnostic delay of BD is approximately 5-10 years from the index episode onwards (1, 2). In retrospect, most patients report the first discernible signs and symptoms years before the onset of the first mood episode, such as depressed mood, irritability, subthreshold manic symptoms, mood swings, irritability, aggressiveness, sleep disturbances, hyperactivity, psychotic symptoms, impaired attention, anxiety, and energy changes (for reviews see, 3–7). Reasons for the diagnostic delay of BD are the atypical course of disease, delayed help-seeking, and misdiagnosis by clinicians. The diagnostic delay and the concomitant treatment delay may result in serious consequences including suicidality and increased psychosocial burden (1, 2, 8). This, together with the progressive nature of BD (9), stresses the importance of a better understanding of the early trajectories of the illness. Ultimately, this may lead to earlier detection of those at risk and development of targeted early interventions programmes.

As a positive family history for BD is one of the strongest predictors for BD (e.g., 10, 11), prospective studies among children of patients with BD (bipolar offspring) are of specific interest to improve our understanding of the early trajectories. In the past decades, numerous studies have shown that bipolar offspring are at increased risk for BD, mood disorders in general, and other non-mood disorders (12–14). Prospective bipolar offspring studies have shown that BD typically presents with a (mild) depressive episode (67%–88%), often years before the onset of the first (hypo)manic episode (15–17). Duffy et al. (17, 18) noted in their cohort study (15+ years) that the early course of BD typically started with anxiety and sleeping disorders during childhood, followed by minor mood disorders, major depressive episodes, and (hypo)mania years later. Furthermore, 48% of the bipolar offspring met criteria of BD not otherwise specified (BD-NOS) prior BD onset, suggesting a role for subthreshold manic symptoms as well. Correspondingly, two more recent studies performed by the team of the Pittsburgh Bipolar Offspring Study showed that subthreshold manic or hypomanic symptoms are an important diagnostic risk factor for subsequent onset of a manic, mixed or hypomanic episode onset (16, 19). Also, major depressive episodes and disruptive disorders were found to be associated with BD conversion (19, 20).

Aims of the Study

To date, most prospective offspring studies have focused on categorical psychopathology in the search for early trajectories of BD in bipolar offspring. A dimensional approach based upon symptomatology, although, may be an essential step for early recognition and/or preventative interventions. To our knowledge, only two studies have investigated the early symptomatic signs in bipolar offspring. The first study by Egeland et al. (21) focused on specific symptomatology and showed in the 16-year follow-up of the Amish Bipolar Offspring Study that offspring who converted to BD were best identified by anxiety, sad mood, low energy, decreased sleep, fearfulness, and role impairment at a young age (7–12 years). The second study by Hafeman et al. (19) investigated several measures of dimensional psychopathology (e.g., K-SADS-PL and CBCL) and found that especially early anxiety/depression symptomatology and affective lability were associated with future BD onset, subsyndromal mania symptomatology was found to be a significant predictor only close to BD onset. In the current study, we also investigated early dimensional symptomatology in bipolar offspring using data from the baseline assessment from the Dutch Bipolar Offspring Study. Dimensional psychopathology was examined at specific symptom level and scale level using the K-SADS-PL. The primary aim of this study was to identify early symptomatic signs of BD in those at the highest risk for BD, namely those with a history of mood disorders (15–17). The second aim was to explore the early symptomatic signs of first mood episode development.

Material and methods

Sample

The data used originated from The Dutch Bipolar Offspring Study, a fixed cohort study established in 1997. A detailed description of the study design and recruitment procedure has been described elsewhere (22). In short, 140 offspring (age 12–21) from 86 families with one bipolar parent (74% bipolar I; 26% bipolar II) were recruited in the years 1997–1999. Families were only included if all offspring in the age range 12–21 agreed to participate. Offspring with a severe physical illness or an IQ below 70 were excluded. Participants were recruited through the Dutch association for patients with bipolar disorder and relatives

(VMDB; 62 families, 102 children) and through out-patient clinics in nine psychiatric hospitals (24 families; 38 children). The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht. Written informed consent was obtained from both offspring and their parents after a complete description of the study. Bipolar offspring were assessed at baseline, one-, five-, and 12-years of follow-up (15, 22–24). In total, 108 (retention rate 77%) offspring were followed for the full 12-years until the mean age of 28 years old. The 32 offspring who dropped out from the study did not differ significantly on demographic or clinical characteristics at baseline from offspring who continued study participation (see supplemental material online Table S1).

Assessment

Psychopathology. At all four assessments, bipolar offspring were psychiatrically evaluated. At baseline and one-year follow-up, DSM-IV diagnoses in offspring were assessed by means of a direct semi-structured interview with both the child and parent(s): the Schedule of Affective Disorders and Schizophrenia Present and Lifetime Version for Children (K-SADS-PL) (25). The K-SADS-PL is a diagnostic interview designed to assess current (past 2 months) and past DSM-IV axis I diagnoses in children and adolescents by interviewing the parent(s) and child separately. Because of age increase in the offspring, the K-SADS-PL was replaced by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (26) after the second assessment. Lifetime DSM-IV diagnoses are based on all psychiatric interviews that took place during the study. For all the diagnoses the age at onset was established. Because of the broad determined criteria of bipolar disorder not otherwise specified (BD-NOS) in 1997 (27), BD-NOS was not assessed during this study. All psychiatric interviews were administered by intensively trained interviewers with graduate degrees in psychology or medicine, and results were evaluated in consensus meetings with board certified psychiatrists for child and adolescent as well as adult psychiatry. A detailed overview of the psychopathology of the 12-year follow-up is published elsewhere (15).

Symptomatology. The symptoms were evaluated using the K-SADS-PL interview of the baseline assessment. The K-SADS-PL surveys symptoms for current (present in the past two months) and most severe past episodes. The interview provides specific probes and scoring criteria to assess each symptom (25). Both child and parent(s) reports were rated on a three-point Likert scale: (i) symptom not present; (ii) symptom at subthreshold level; and (iii) symptom at threshold level. For each symptom, a detailed description of the different levels is provided in the K-SADS-PL. To determine whether a symptom meets the threshold or subthreshold level, severity, frequency, and duration of the symptom and level of impairment are to be examined by the assessor. Subsequently, parent and child ratings are merged into a current or past summary score per item according to the K-SADS-PL manual (25). In case of disagreement between the child and parent about the presence of a symptom, greater weight was given to parents' reports of observed behaviour and child's reports of subjective experiences. The K-SADS-PL interview includes a screen interview which surveys the primary symptoms of the DSM-IV axis-I diagnoses and five supplemental sections (affective disorders, psychotic disorders, anxiety disorders, behavioural disorders and substance abuse, and other disorders) with a complete assessment of the secondary symptoms of the different DSM-IV axis I diagnoses. In case of threshold primary symptoms presence, supplemental sections are to be explored. Apart from the depression section, the supplemental sections were only collected in bipolar offspring who met the threshold criteria. As a result, it is likely that subsyndromal symptomatology that was present in the supplement was missed. Unfortunately, age of onset of symptomatology was not assessed. The K-SADS-PL screen documents a total of 78 symptoms.

Data preparation

Sample selection

From the initial sample, 107 offspring were selected for this study. Thirty offspring were lost during follow-up and were excluded as their diagnostic outcome was uncertain. Two offspring who dropped out of the study, had developed BD before dropping out and were therefore included. Offspring with a BD-I or II diagnosis at baseline were excluded for analyses (n = 4, of which 1 also was lost during follow-up), resulting in a total sample of 107 bipolar offspring.

Diagnostic outcome categories

As most offspring studies show that BD starts with other mood disorders, mostly years prior (hypo)mania onset (15–17), the sample was stratified in bipolar offspring with a history of mood

disorders (one or more) at the baseline assessment (AnyMD, $n = 29$) and without (NoMD, $n = 78$). The AnyMD category at baseline comprised of a lifetime diagnosis of major depressive disorder, dysthymia, depression not otherwise specified (minor depressive disorder, recurrent brief depressive disorder and adjustment disorder—mood) or cyclothymia (as BD outcome was yet uncertain). Based on the diagnostic outcome after the 12-year follow-up, offspring were divided into the following two categories: (i) conversion to bipolar disorder type I or II (MD→BD, $n = 10$) and (ii) no conversion to BD after 12-years follow-up (MD=, $n = 19$). Subjects of the MD= category may have been remitted during follow-up. Subsequently, the NoMD group was stratified to (i) conversion to any mood disorder (NewMD, $n = 28$) including major depressive disorder, dysthymia, depression not otherwise specified (minor depressive disorder, recurrent brief depressive disorder, and adjustment disorder—mood), and bipolar spectrum disorders (cyclothymia, BD type I or II) or (ii) no conversion to mood disorders (NoMD=, $n = 50$).

Symptomatology at adolescent age

Two different exploratory approaches were used to investigate the early signs of mood disorders. The first approach explored the association of specific symptoms with conversion to mood disorders. The second approach explored the total sum scores of symptoms.

Approach 1 'individual symptoms'. All 78 symptoms of the K-SADS-PL screen were explored individually. For each symptom, the highest rating for both past and present was recoded into an overall lifetime score. Subsequently, due to the relatively small group sizes, symptoms were dichotomized into absence (0) versus presence of subthreshold or threshold criteria (1). For an overview of all symptoms, see Table S1 online.

Approach 2 'sum scores'. For the second approach, we were interested in sum scores of all symptoms reported lifetime. A scale for *depression-, mania-, anxiety-*, *externalizing-*, *substance use-,* and *residual* symptoms was obtained by calculating the total sum of lifetime symptom ratings, including 21, 4, 23, 12, 6, and 12 items respectively. The original classification of K-SADS-PL was followed for the *depression-, anxiety-* (including primary symptoms of social phobia, post-traumatic stress disorders and obsessive compulsive disorder etc.), *externalizing-* (including ADHD, oppositional defiant-, and conduct disorder) and *substance use scale*. A *residual scale* was conducted for symptoms of enuresis/encopresis, eating disorders, and tic disorders. As psychotic symptoms were not very common these symptoms were also included in the *residual scale* to limit the number of symptom scale for the final analyses (see also supplemental material Table S2).

Statistical analyses

The statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA). Groups were compared on demographic characteristics using one-way ANOVA or Fisher exact tests as appropriate. Individual symptom ratings as identified with the K-SADS-PL were evaluated using Fisher exact tests. Next, to explore the association of symptoms between baseline and time to conversion K-SADS-PL sum scores were explored using multiple predictor cox regression analyses. For all analyses, the two-sided alpha level for statistical significance was set at 0.05. However, as we tested a total of 79 tests per hypotheses, we also evaluate these *P*-values against a Bonferroni corrected alpha (=0.05/79 = 0.0006) for multiple comparisons.

Results

The sample characteristics are shown in Table 1. Parental characteristics, age, and gender did not differ between diagnostic outcome categories.

Prodromal features of (hypo)mania onset

At baseline, 29 (27%) offspring had a history of a mood disorder (AnyMD: including major depressive disorder, $n = 5$; dysthymia, $n = 8$; depression NOS, $n = 17$ and cyclothymia, $n = 2$). During follow-up, 10 of these 29 (34%) offspring converted to BD (BD-I, $n = 1$, BD-II, $n = 9$). The median time to (hypo)mania onset after the baseline assessment was 2.7 years. A detailed presentation of the prevalence of symptoms in adolescent bipolar offspring is presented in supplemental table 2 online (Table S2). At the individual symptom level, five symptoms were significantly associated with BD conversion—although none of them were significant against a Bonferonni-corrected alpha of 0.0006. Offspring at risk reported relatively more frequent elated mood (60% vs 11%, $P = 0.009$), decreased need of sleep (50% vs 5%, $P = 0.011$), racing thoughts (40% vs 5%, $P = 0.036$), suicidal ideation (50% vs 11%, $P = 0.030$), and middle

insomnia (40% vs 5%, $P = 0.036$). Noteworthy, was the association between subthreshold manic symptomatology and BD-conversion. Furthermore, increased goal directed behaviour was reported more frequently in offspring converting to BD, although not significantly so (40% vs 16%, $P = 0.193$). Figure 1 illustrates the specific subthreshold manic symptomatology across all study groups and its relative specificity for transition to BD. Moreover, none of the offspring without a mood disorder (NoMD) at baseline but who did develop BD later on ($n = 3$) reported subthreshold manic symptoms prior to the onset of a mood diagnosis (data not shown), suggesting a more proximal role for mild manic symptomatology in the course the BD.

Cox regression analysis using all six K-SADS-PL sum scores as independent variables revealed that the mania scale was significantly associated with conversion to BD (HR 2.16, 95% CI: 1.23–3.78, $P = 0.007$ see Table 2a). None of the other symptom scales were significantly associated with BD conversion. In supplementary analyses, we explored whether findings would remain consistent when excluding offspring with cyclothymia at baseline ($n = 2$) and found similar results (mania scale HR 2.17; 95% CI 1.13–4.14, $P = 0.019$, Table S3 online). Neither age nor gender affected the findings (see Table S4a online). Within the externalizing scale, no evidence for a distinct effect for ADHD or disruptive behavioural symptomatology and conversion to BD was observed (data not shown). Overall, these results suggest an association between subclinical manic symptomatology and BD conversion.

Prodromal features of mood disorders

Of the 78 offspring without a mood diagnosis at baseline, 28 (36%) developed a mood disorder during follow-up (major depressive disorder, $n = 10$; depression NOS, $n = 16$, BD-II, $n = 2$ and cyclothymia, $n = 1$). The two offspring with a final diagnosis of BD debuted with depression NOS and dysthymia which was not yet present at baseline. The median time up till the mood disorder onset after baseline was 4.9 years. At symptom level, none of the symptoms were significant with a Bonferonni corrected alpha of 0.0006. However, when testing against an alpha of 0.05, four symptoms significantly differentiated offspring developing any mood disorder from those who remained resilient, namely: recurrent thoughts of death (32% vs 6%, $P = 0.006$), marked feeling of tension/unable to relax (43% vs 14%, $P = 0.006$), marked self-consciousness (36% vs 12%, $P = 0.019$), and compulsions (25% vs 6%, $P = 0.03$) (Table S2 online).

Despite a non-significant model fit of the cox-regression model ($P = 0.071$), depression symptoms were related to a more likely conversion to mood disorders (HR: 1.27, 95% CI 1.02–1.58, $P = 0.033$) (Table 2b). No significant associations were found between manic, anxiety, externalizing, substance use or residual symptoms and first mood

Table 1. General characteristics study population per diagnostic outcome category

		Diagnostic outcome categories					
		AnyMD, $n = 29$		NoMD, $n = 78$			
	All offspring	MD→BD	MD=	NewMD	NoMD=	Test	*P*
Offspring characteristics							
Offspring, *n* (% of total sample)	107 (100)	10	19	28	50		
Male, *n* (%)	57 (53)	5 (50)	10 (53)	12 (43)	30 (60)	FET	0.540
Age at baseline, mean (range)	16 (12–21)	16.2 (12–21)	16.6 (12–21)	15.9 (12–21)	15.8 (12–21)	$F = 0.365$	0.779
Age at 12-year follow-up	27.9 (22-32)	28.5 (24-32)	28.6 (24-32)	27.9 (22-32)	27.5 (22-32)	$F = 0.787$	0.504
Parental characteristics							
Bipolar mother, *n* (%)	62 (58)	6 (60)	8 (42)	17 (61)	31 (62)	FET	0.505
Bipolar I disorder, *n* (%)	78 (73)	8 (80)	12 (63)	18 (64)	40 (80)	FET	0.320
K-SADS-PL sum scores							
Depression sum score, 21 items, mean (SD)		34.1 (8.5)	30.3 (4.5)	23.3 (2.3)	22.1 (2.2)		
Mania sum score, 4 items, mean (SD)		6.0 (1.8)	4.4 (0.9)	4.1 (0.4)	4.1 (0.4)		
Anxiety sum score, 23 items, mean (SD)		31.8 (4.3)	30.3 (4.0)	27.7 (3.9)	25.9 (2.7)		
Externalizing sum score, 12 items, mean (SD)		15.8 (3.6)	14.7 (2.8)	13.6 (2.3)	13.5 (2.3)		
Substance sum score, 6 items, mean (SD)		7.9 (1.8)	8.0 (2.0)	7.6 (2.2)	7.6 (1.6)		
Residual sum score, 12 items, mean (SD)		15.2 (2.4)	13.4 (1.8)	12.9 (1.3)	12.6 (0.9)		

AnyMD: offspring with a mood disorder at baseline; MD→BD: offspring with a mood disorder converting to BD; MD=: offspring with a mood disorder diagnosis at baseline without a transition to BD; NoMD=: offspring without a mood disorder diagnosis at baseline, but possible other diagnoses; NewMD offspring developing a first mood episode after the baseline assessment.

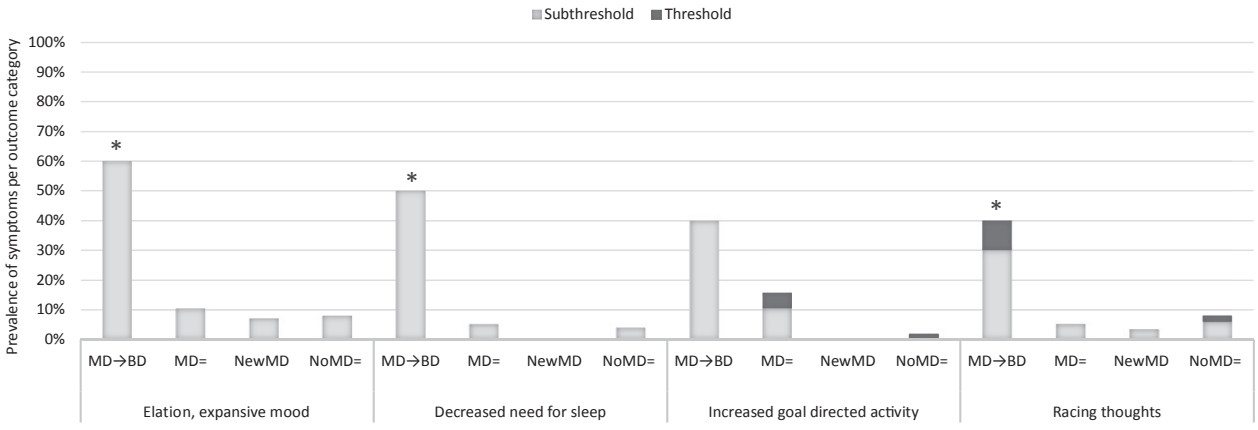

Fig. 1. Manic symptomatology in bipolar offspring at adolescent age. The four mania screen items from the K-SADS-PL per diagnostic outcome category. Subthreshold (in light gray) means a subthreshold rating as defined by the K-SADS-PL (2, see materials method section), threshold resembles a 3 as defined by the K-SADS-PL (dark gray).*$P < 0.05$ and reflects the comparison between the categories MD→BD versus MD=, see also Table S1 online.

Table 2. Cox regression analyses.

(a) Transition to BD

					95% CI	
MD → BD (n = 10)	B	SE	P	HR	Lower	Upper
Depression sum score	0.04	0.05	0.430	1.04	0.94	1.15
Mania sum score	**0.77**	**0.29**	**0.007**	**2.16**	**1.23**	**3.78**
Anxiety sum score	−0.07	0.11	0.511	0.93	0.76	1.15
Externalizing sum score	0.06	0.12	0.600	1.07	0.84	1.35
Substance use sum score	−0.34	0.23	0.146	0.71	0.45	1.13
Residual sum score	0.25	0.15	0.089	1.28	0.96	1.70

(b) Transition to a first mood episode

					95% CI	
NewMD (n = 28)	B	SE	P	HR	Lower	Upper
Depression sum score	**0.24**	**0.11**	**0.033**	**1.27**	**1.02**	**1.58**
Mania sum score	−0.44	0.56	0.434	0.64	0.21	1.95
Anxiety sum score	0.90	0.07	0.204	1.09	0.95	1.26
Externalizing sum score	0.03	0.10	0.738	1.03	0.86	1.24
Substance use sum score	0.14	0.12	0.226	1.15	0.92	1.45
Residual sum score	−0.31	0.25	0.204	0.73	0.45	1.19

Reference category MD = (n = 19), Model X^2 (6) = 21.325, P = 0.002. Reference category NoMD = (n = 49, One subject was excluded from analyses for statistical reasons), Model X^2 (6) = 11.602, P = 0.071. Significant values ($P < .05$) are presented in bold.

episode onset. The results were not affected by age or gender (see Table S4b online). Again, within the externalizing scale, no distinct effect for ADHD or disruptive behavioural symptoms was observed (data not shown).

Discussion

In a previous study (15), we found that 13% of 108 bipolar offspring developed a bipolar spectrum disorder. Approximately 90% of the offspring developing BD debuted with a mild depressive episode. The current study aimed at extending knowledge with regard to the early trajectories of mood disorders in adolescent bipolar offspring via a thorough study of early symptomatology. This study demonstrated that signs of mild manic symptomatology, suicidal ideation, and middle insomnia are associated with an increased risk for future BD onset in bipolar offspring with a history of mood disorders (i.e., major depressive disorder, dysthymia, depression NOS, and cyclothymia). Subthreshold depression and general anxiety symptoms were associated with a first mood episode onset.

The most clinically relevant finding of this study is the presence of mild manic symptomatology prior BD onset in bipolar offspring with a vulnerability for mood disorders. Although subclinical manic symptomatology has only recently gained attention in bipolar offspring studies, findings perfectly correspond with some recent studies, such as in the large Pittsburgh bipolar offspring study (n = 359) (16, 19). In these studies, it was shown that subclinical manic symptoms were a strong predictor for subsequent (hypo)mania onset, especially close to onset (16, 19). Despite the lack of information on the age of symptom onset in this study, findings do suggest a role for time duration between the first signs to onset. Findings also remained significant when excluding offspring with already a diagnosis of cyclothymia. Moreover, among the offspring without a mood disorder at baseline but developing BD during the study (n = 3) none reported subthreshold manic symptoms at the baseline assessment, indeed suggesting a more proximal role for subclinical manic symptomatology. Also, in the 15+ year follow-up of the

Canadian offspring study (12), 48% of the offspring developing BD had met criteria of BD not otherwise specified prior to (hypo)mania onset. The findings also correspond with the five-year follow-up of the course and outcome of bipolar youth (COBY) study in which 45% of the youth diagnosed with BD-NOS made the transition into BD-I or II within 58 weeks, especially those with a first or second degree family member (28). Together, these findings illustrate the importance of detailed evaluation of subclinical manic symptomatology in bipolar offspring with a vulnerability for mood disorders.

In terms of specific symptomatology associated with future BD, suicidal ideation and middle insomnia were also diagnostic risk factors. Looking at sleep disturbances, the finding of middle insomnia and decreased need for sleep are in line with ample evidence that sleep disturbances are associated with BD, also prior to onset (17, 21, 29–31). The association of suicidal ideation and BD onset has been studied before, but findings are inconsistent (32, 33). In adolescents with BD, prevalence of suicidal ideation has been estimated at 58% and suicide attempts at 20%–25%. Among psychiatric disorders, BD is associated with the highest rate of suicidal attempts and completed suicides (34). As suicidal ideation is a strong predictor for future suicidal behaviour, these findings underscore the need for early recognition of suicidality in bipolar offspring. Consequently, apart from subthreshold manic symptomatology, sleep disturbances, and suicidal ideation suggest possible prognostic value in terms of early identification and prevention programmes. However, these findings require replication and further study.

With regard to the prodromal signs of first mood disorder onset, the results illustrate that subthreshold depressive symptomatology was associated with conversion. At symptom level, recurrent thoughts of death, but also more general anxiety symptoms (including marked feeling of tension, marked self-consciousness, and compulsions) were associated with mood disorder onset. These findings are partially in line with the existing literature (5, 16–19, 35, 36). Unlike other studies (17, 19, 35), we found in our multivariable models no overall additional effect for anxiety symptoms above pre-existing depressive symptoms in predicting a first mood episode or conversion to bipolar disorder. As reported previously, also at a categorical level we reported relatively low number of childhood anxiety disorders in bipolar offspring at the first assessment as compared to the Pittsburgh offspring study for example (37), this difference was partially explained by differences in sample characteristics. Nonetheless, clinically, anxiety symptoms may precede or co-occur with early mood symptoms and may indicate vulnerability for mood disorders in offspring at risk. Future studies are necessary to further disentangle the relation between anxiety disorders and development of mood disorders and the risk for bipolar disorder development in bipolar offspring.

Strengths and limitations

The key strengths of the present study are its long follow-up, high retention rate, and detailed clinical psychiatric evaluations including subthreshold symptomatology at baseline. Therefore, this study further extends the knowledge of the early prodrome of mood disorders in bipolar offspring. However, there are also major limitations: (i) The first limitation is the sample size. Although a relatively high (13%) transition rate to BD, absolute numbers are small, leading to inherent power issues in statistical analyses. After Bonferroni correction for the number of tests, none of the effects reported here were significant at an alpha level of 0.0006. Given the exploratory nature of the study in a unique longitudinal high-risk cohort, this study still provides an impetus for future research with bigger samples at potentially relevant prodromal symptoms; (ii) The K-SADS-PL obtains unique information on symptomatology; however, in this study it was only possible to use the baseline screen items, and apart from the depression scale, information on the supplemental interviews was left out. Also, no information about the onset and duration of the specific symptoms was available. Hence, the measure of dimensional psychopathology should be considered limited regarding the symptom spectrum as well longitudinal symptomatology information. Thus, only speculation about the sequential order of specific symptoms and time to transition can be made; (iii) Bipolar offspring represent a specific population; therefore results may not generalize to other populations; (iv) In the present study, most offspring developed BD-II. Therefore, future studies are needed to examine whether findings can be generalized to offspring developing BD-I. Nevertheless, retrospective and prospective patient studies have repeatedly shown evidence that subthreshold manic symptomatology is present prior to onset in both type I and II in-patient and in help seeking populations as well (7, 38–41). And finally (v), despite the prospective nature of the study, age of onset, symptomatology and diagnoses were assessed retrospectively at baseline and between assessments (at 1-, 5-, and 12 years' follow-up) and therefore remain susceptible to recall bias.

In conclusion, the present work adds to our understanding of the early trajectories of BD by a thorough, yet exploratory, study of the early symptomatic signs at the adolescent age. Results of this study stress the importance of detailed evaluation of subthreshold manic symptomatology in bipolar offspring with a vulnerability for mood disorders and—when confirmed in larger studies with more power—the results provide potential targets for the development of early recognition and preventative intervention programmes.

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Declaration of interest

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References

1. Altamura AC, Dell'Osso B, Berlin HA, Buoli M, Bassetti R, Mundo E. Duration of untreated illness and suicide in bipolar disorder: a naturalistic study. Eur Arch Psychiatr Clin Neurosci 2010;**260**:385–391.
2. Drancourt N, Etain B, Lajnef M, et al. Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment. Acta Psychiatr Scand 2013;**127**:136–144.
3. Correll CU, Hauser M, Auther AM, Cornblatt BA. Research in people with psychosis risk syndrome: a review of the current evidence and future directions. J Child Psychol Psychiatry 2010;**51**:390–431.
4. Malhi GS, Bargh DM, Coulston CM, Das P, Berk M. Predicting bipolar disorder on the basis of phenomenology: implications for prevention and early intervention. Bipolar Disord 2014;**16**:455–470.
5. Skjelstad DV, Malt UF, Holte A. Symptoms and signs of the initial prodrome of bipolar disorderA systematic review. J Affect Disord 2010;**126**:1–13.
6. Correll CU, Hauser M, Penzner JB et al. Type and duration of subsyndromal symptoms in youth with bipolar I disorder prior to their first manic episode. Bipolar Disord 2014;**16**:478–492.
7. Faedda GL, Marangoni C, Serra G et al. Precursors of bipolar disorders. J Clin Psychiatry 2015;**76**:614–624.
8. McCraw S, Parker G, Graham R, Synnott H, Mitchell PB. The duration of undiagnosed bipolar disorder: effect on outcomes and treatment response. J Affect Disord 2014;**168**:422–429.
9. Berk M, Kapczinski F, Andreazza AC et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 2011;**35**:804–817.
10. Craddock N, Sklar P. Bipolar disorder 1 – genetics of bipolar disorder. Lancet 2013;**381**:1654–1662.
11. Gottesman II, Laursen TM, Bertelsen A, Mortensen PB. Severe mental disorders in offspring with 2 psychiatrically ill parents. Arch Gen Psychiatry 2010;**67**:252–257.
12. Duffy A, Doucette S, Lewitzka U, Alda M, Hajek T, Grof P. Findings from bipolar offspring studies: methodology matters. Early Interv Psychiatry 2011;**5**:181–191.
13. DelBello MP, Soutullo CA, Hendricks W, Niemeier RT, McElroy SL, Strakowski SM. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. Bipolar Disord 2001;**3**:53–57.
14. Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. Can J Psychiatry 1997;**42**:623–631.
15. Mesman E, Nolen WA, Reichart CG, Wals M, Hillegers MHJ. The Dutch Bipolar Offspring Study: 12-year follow-up. Am J Psychiatry 2013;**170**:542–549.
16. Axelson D, Goldstein B, Goldstein T et al. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. Am J Psychiatry 2015;**172**:638–646. appiajp201414010035.
17. Duffy A, Horrocks J, Doucette S, Keown-Stoneman C, McCloskey S, Grof P. The developmental trajectory of bipolar disorder. Br J Psychiatry 2014;**204**:122–128.
18. Duffy A. The early natural history of bipolar disorder: what we have learned from longitudinal high-risk research. Can J Psychiatry 2010;**55**:477–485.
19. Hafeman DM, Merranko J, Axelson D et al. Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. Am J Psychiatry2016;**173**:695–704. appi.ajp.2015.1.
20. Goldstein BI, Shamseddeen W, Axelson DA et al. Clinical, demographic, and familial correlates of bipolar spectrum disorders among offspring of parents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2010;**49**:388–396.
21. Egeland JA, Endicott J, Hostetter AM, Allen CR, Pauls DL, Shaw JA. A 16-year prospective study of prodromal features prior to BPI onset in well Amish children. J Affect Disord 2012;**142**:186–192.
22. Wals M, Hillegers MH, Reichart CG, Ormel J, Nolen WA, Verhulst FC. Prevalence of psychopathology in children of a bipolar parent. J Am Acad Child Adolesc Psychiatry 2001;**40**:1094–1102.
23. Reichart CG, Wals M, Hillegers MHJ et al. Psychopathology in the adolescent offspring of bipolar parents. J Affect Disord 2004;**78**:67–71.
24. Hillegers MH, Reichart CG, Wals M, Verhulst FC, Ormel J, Nolen WA. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. Bipolar Disord 2005;**7**:344–350.
25. Kaufman J, Birmaher B, Brent D et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial Reliability and Validity Data. J Am Acad Child Adolesc Psychiatry 1996;**135**:153–162.
26. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV Axis I disorders –

Patient Edition.. New York: New York State Psychiatric Institute; 1996.
27. Goodwin F, Jamison KR. Manic-depressive illness: bipolar disorders and recurrent depression. New York: Oxford University Press 2012. https://doi.org/10.1111/j.1365-2745.2011.01925.x.
28. Axelson DA, Birmaher B, Strober MA et al. Course of subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. J Am Acad Child Adolesc Psychiatry 2011;**50**:1001–1016.
29. Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar disorder. J Affect Disord 2010;**121**:127–135.
30. Ritter PS, Marx C, Bauer M, Lepold K, Pfennig A. The role of disturbed sleep in the early recognition of bipolar disorder: a systematic review. Bipolar Disord 2011;**13**:227–237.
31. Ritter PS, Marx C, Lewtschenko N et al. The characteristics of sleep in patients with manifest bipolar disorder, subjects at high risk of developing the disease and healthy controls. J Neural Transm 2012;**119**:1173–1184.
32. Goldstein TR, Obreja M, Shamseddeen W et al. Risk for Suicidal Ideation Among the Offspring of Bipolar Parents: results From the Bipolar Offspring Study (BIOS). Arch Suicide Res 2011;**15**:207–222.
33. Uchida M, Serra G, Zayas L, Kenworthy T, Faraone SV, Biederman J. Can unipolar and bipolar pediatric major depression be differentiated from each other? A systematic review of cross-sectional studies examining differences in unipolar and bipolar depression. J Affect Disord 2015;**176**:1–7.
34. Hauser M, Galling B, Correll CU. Suicidal ideation and suicide attempts in children and adolescents with bipolar disorder: a systematic review of prevalence and incidence rates, correlates, and targeted interventions. Bipolar Disord 2013;**15**:507–523.
35. Nurnberger JI, McInnis M, Reich W et al. A high-risk study of bipolar disorder: childhood clinical phenotypes as precursors of major mood disorders. Arch Gen Psychiatry 2011;**68**:1012–1020.
36. Skjelstad DV, Malt UF, Holte A. Symptoms and behaviors prior to the first major affective episode of bipolar II disorder. An exploratory study. J Affect Disord 2011;**132**:333–343.
37. Mesman E, Birmaher BB, Goldstein BI et al. Categorical and dimensional psychopathology in Dutch and US offspring of parents with bipolar disorder: a preliminary cross-national comparison. J Affect Disord 2016;**205**:95–102.
38. Tijssen MJA, Van Os J, Wittchen HU et al. Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. Br J Psychiatry 2010;**196**:102–108.
39. Boschloo L, Spijker AT, Hoencamp E et al. Predictors of the onset of manic symptoms and a (Hypo)manic episode in patients with major depressive disorder. PLoS ONE 2014;**9**:e106871.
40. Youngstrom EA, Youngstrom JK, Freeman AJ, De Los Reyes A, Feeny NC, Findling RL. Informants are not all equal: predictors and correlates of clinician judgments about caregiver and youth credibility. J Child Adolesc Psychopharmacol 2011;**21**:407–415.
41. Bechdolf A, Ratheesh A, Cotton SM et al. The predictive validity of bipolar at-risk (prodromal) criteria in help-seeking adolescents and young adults: a prospective study. Bipolar Disord 2014;**16**:493–504.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Demographic and clinical characteristics at baseline of offspring participating at 12-years follow-up and offspring who dropped out from the study.

Table S2. Prevalence (%) of (sub-)threshold symptomatology in bipolar offspring at adolescent age.

Table S3. Cox regression analysis transition to BD excluding subjects with the diagnosis cyclothymia at adolescent age.

Table S4. Cox-regression analyses adjusted for age at baseline and gender.