NEW RESEARCH

Beyond the Window of Risk? The Dutch Bipolar Offspring Study: 22-Year Follow-up

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Objective: Adolescent offspring of parents with bipolar disorder (BD) are at high risk to develop BD and other psychopathology, yet how this risk continues into middle adulthood remains unknown. This study aimed to determine the window of risk for BD and other psychopathology in offspring of parents with BD followed from adolescence into adulthood.

Method: This study reported on the 22-year follow-up assessment of the Dutch Bipolar Offspring Study, a fixed cohort study of 140 participants established in 1997. Offspring (n = 100; mean [SD] age = 38.28 [2.74] years) of parents with bipolar I disorder or bipolar II disorder were assessed at baseline and 1-, 5-, 12-, and 22-year follow-up.

Results: No new BD onsets occurred since the 12-year follow-up (lifetime prevalence = 11%-13%; bipolar I disorder = 4%; bipolar II disorder = 7%). Lifetime prevalence of any mood disorder was 65%; for major depressive disorder, prevalence was 36%; and for recurrent mood episodes, prevalence was 37%. Prevalence of major depressive disorder more than doubled in the past decade. Point prevalence of any psychopathology peaked between 20 and 25 years (38%-46%), subsiding to 29% to 35% per year after age 30. Overall, 71% of offspring contacted mental health services since the last assessment.

Conclusion: The risk for homotypic transmission of BD in offspring of parents with BD is highest during adolescence. The heterotypic risk for mood disorder onset and recurrences continues over the life course. Severe mood disorders are often preceded by milder psychopathology, emphasizing the need for early identification and interventions. This study allows for better understanding of the onset and course of mood disorders and specific windows of risk in a familial high-risk population.

Key words: bipolar disorder; bipolar offspring; COPMI; familial risk; mood disorders

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Bipolar disorder (BD) is a mood disorder characterized by episodes of depression and (hypo) mania that affects 1% to 4% of the population.[1,2] Early identification of BD is one of the biggest challenges, as a delay in correct diagnosis and treatment is associated with poor prognosis, increased burden of illness, and increased mortality.[3-5] One of the most robust predictors of developing BD is having a parent with BD.[6,7] Heritability of BD is supported in a Swedish register study showing that the relative risk for first-degree relatives (eg, offspring, parents) is between 5.8 and 7.9.[6] For second-degree relatives (eg, siblings, grandparents), the relative risk for BD is between 2.2 and 3.3. Indeed, prospective BD offspring studies with a follow-up into young adulthood show a high risk for BD (10%-13%), a high risk for any mood disorders (48%-63%), and psychopathology in general (70%-75%).[8-11] More specifically, these offspring studies illustrate the developmental trajectories of BD, including higher levels of anxiety, behavior, and sleep problems during childhood and begin with a (mild) depressive episode during early adolescence, often accompanied by subclinical manic symptoms, followed by hypomania or mania in the following years.[8-10,12]

Thus far, none of these longitudinal studies of offspring of parents with BD have followed offspring into middle adulthood. It is unknown how onset and course of mood disorders in offspring of parents with BD proceed. In general, evidence regarding age of BD onset suggests a trimodal distribution of subgroups: early-onset (approximately 17 years; 45% of BD patients), mid-onset (approximately 26 years; 35%) and late-onset (approximately 42 years; 20%).[13,14] As 20% of individuals with BD develop the disorder after age 40, transitions are still expected to occur in adulthood. Moreover, severity of psychopathology in terms of functioning and health care usage in adult offspring of parents with BD has not been investigated.[15] This is of particular interest because it is still unclear what psychopathology at an early age means for the daily life of adults,

especially for offspring at familial high risk. Addressing these gaps is crucial as a better understanding of mood disorders in the familial high-risk population could help determine whether adult offspring are beyond the window of risk and lead to improved strategies for risk detection and intervention at different life stages.

Here, we present the results of the 22-year follow-up of the Dutch Bipolar Offspring Study (DBOS). The DBOS is a prospective fixed-cohort study that was established in 1997.[16] Offspring were followed from a mean age of 16 up to 38 years of age at baseline and 1, 5, 12, and 22 years of follow-up. At the last assessment, the 12-year follow-up (mean age of 28 years), we found that 13% of offspring had developed BD, with 88% of BD cases starting with a (mild) depressive episode.[10] More than half of the participants had developed a mood disorder, of whom many experienced comorbidity (67%) and recurrent mood episodes (31%). In the current fifth wave–outcome study, spanning more than 2 decades of follow-up, we aimed to provide an overview of the development of psychopathology across the life course and global functioning of adult offspring of parents with BD. We examined new onsets and course of BD after young adulthood; the onset, prevalence, and hierarchical course of mood disorders and psychopathology in general; and global functioning, sociodemographic, and family characteristics in this adult population at high familial risk for BD.

METHOD

Population and procedure

The DBOS is a prospective fixed cohort study in offspring of parents with BD. The DBOS was established in 1997 and contains 5 waves of assessment: baseline[16] and 1-,[17] 5-,[18] 12-,[10] and 22-year follow-up. The study design and recruitment procedure have been described in detail elsewhere.[16] In brief, 140 offspring of 86 parents with bipolar I disorder (BD-I) or bipolar II disorder (BD-II) between 12 and 21 years old were recruited between 1997 and 1999 through the Dutch Association for Manic Depressives and Relatives (Plusminus) and 9 outpatient clinics from adult mental health services. All parents with BD were treated in outpatient clinics at the time of recruitment. Parental BD-I and BD-II meeting *DSM-IV* criteria were affirmed by face-to-face interviews using the International Diagnostic Checklist[19] and verified by the clinical diagnosis of the treating psychiatrist.[16] The biological co-parent was assessed on lifetime *DSM-IV* disorders using the Family History Research Diagnostic Criteria method.[20] Over the years, retention rates were high: 132 offspring (94%) at the 1-year follow-up, 129 offspring (92%) at the 5-year follow-up, and 108 offspring (77%) at the 12-year follow-up. The 22-year follow-up assessments were performed between July 2020 and August 2021. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants were approved by the Medical Ethics Committee of the Erasmus Medical Centre in Rotterdam, the Netherlands. Written informed consents were obtained.

Instruments

Lifetime *DSM-IV* Axis I disorders are based on 5 semi-structured psychiatric interviews that were administered over the past 22 years. Each assessment evaluated past (lifetime) and current (last month) psychopathology. In instances in which mood disorders were in remission at the time of assessment (eg, no significant symptoms within the prior month), we reported no current psychopathology.[10] For all *DSM-IV* Axis I disorders, age of onset, duration, and number of episodes (for recurrent disorders) were obtained since the last follow-up. At baseline and 1-year follow-up, the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL)[21] was used to assess *DSM-IV* Axis I disorders during face-to-face interviews with both offspring and their parents. When offspring reached 18 years of age, the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I)[22] replaced the K-SADS-PL. Despite the introduction of the *DSM-5* containing changes in structure, content, and criteria, we chose consistency over recency. All interviews were completed by trained postgraduate students, postdoctoral level psychologists, or individuals with an equivalent background. Final *DSM-IV* Axis I disorders were reviewed at consensus meetings attended by a board-certified psychologist and psychiatrist (EM, MH).

At baseline, socioeconomic status (SES) was scored by parental occupational level on a 9-point scale (1 = lowest, 9 = highest).[16] In the case of 2 working parents, the highest score was used. At the 22-year follow-up, we calculated household income of offspring based on the Dutch average for adults between 35 and 45 years old[23] as a proxy for SES. We used the Global Assessment of Functioning (GAF) scale for an indication of global functioning for the best and worst week in the past year with a higher score indicating better functioning (range 0 to 100). Information on family composition was collected as well.

Statistical Analyses

We calculated median and interquartile range (IQR) of age of onset, number of mood episodes, and the GAF scale. We

tested dropout differences in baseline characteristics and biological sex differences in prevalence of lifetime psychopathology with a Pearson χ^2 test without Yates correction for dichotomous variables and with a t test for continuous variables. We used R version 4.1.1 for the analyses with $\alpha = .05$.

RESULTS

At the 22-year follow-up, 100 offspring with a mean (SD) age of 38.28 (2.74) years participated (retention rate of 71%; 93% since the 12-year follow-up). Demographic characteristics of offspring at the 22-year follow-up are presented in Table 1. The participants from the 22-year follow-up did not differ significantly from dropouts on any of the baseline characteristics (Table S1, available online).

Adulthood: Prevalence of Lifetime Psychopathology

The prevalence of lifetime and current *DSM-IV* Axis I disorders for 12- and 22-year follow-up assessments is presented in Table 2. Since the 12-year follow-up (mean age 28 years), no new onsets of BD were observed. Prevalence of any mood disorder increased by 9% (up to 65%) since the 12-year follow-up, and prevalence of major depressive disorder (MDD) more than doubled (from 17% to 36%). After 22 years of follow-up, 80% of the cohort met criteria for at least one lifetime *DSM-IV* Axis I disorder. The effects of sex, becoming a parent, and COVID-19 on psychopathology can be found in Supplement 1 (available online).

Age of Onset and Psychopathology Over the Life Course

Figure 1A shows the age of onset for BD, any mood disorder, MDD, and any lifetime *DSM-IV* Axis I disorder. The median (IQR) age of onset was 15.19 (IQR = 11.87-16.90) years for BD, 18.23 (IQR = 13.80-24.45) years for the first mood episode, 26.77 (IQR = 20.93-33.51) years for MDD, and 15.25 (IQR = 6.79-20.33) years for any disorder.

The point prevalence (ie, prevalence at a particular age) during the life course is depicted in Figure 1B. A peak in point prevalence can be observed between ages 20 and 25, ranging from 38% to 46%. After age 30, point prevalence ranges from 29% to 35%. This indicates that most disorders are present during young adulthood, but a significant number of disorders are still present during later adulthood. Point prevalence across the life course split per psychiatric disorder can be found in Figure S1 (available online).

Course and Comorbidity of Mood Disorders

Looking at the course of mood disorders, all offspring with BD (11%) participating at the 22-year follow-up experienced recurrent mood episodes, with a mean (SD) 2.27 (2.10) hypomanic/manic episodes and 4.09 3.33) depressive episodes. None of the offspring with BD experienced an episode during the month before the assessment—hence the absence of current BD (Table 2). Since the 12-year follow-up, 1 participant transitioned from BD-II to BD-I, and 1 participant with cyclothymia transitioned to BD-II. Taking the full study period into account, 17 (12%) participants were diagnosed with a bipolar spectrum disorder. The lifetime prevalence of BD at the 22-year follow-up is lower (11%) than at the 12-year follow-up (13%), as 3 offspring with BD dropped out of the study. Overall, 37 of 65 offspring with mood disorders experienced recurrent mood episodes (57%, mean [SD] =3.72 [5.73]). Among offspring with MDD, 14 of 36 offspring (39%) experienced recurrent major depressive episodes (mean [SD] =2.59 [2.02]). Comorbidity among offspring with any mood disorder was high (75%), including anxiety (46%), substance use (23%), and other (42%, including attention-deficit/hyperactivity disorder [3%] and disruptive behavior disorders [5%]).

To gain a better insight into the hierarchical developmental course of mood disorders, we depicted the transition of psychopathology over the 22 years in Figure 2. Among offspring with BD, 88% experienced a depressive episode at the start of their illness. The onset of the first manic or hypomanic episode was mean (SD) 5.3 (4.10) years after the onset of the depressive episode.[10] Of 36 offspring with MDD, 26 experienced at least 1 episode of psychopathology before onset (72%); 11 experienced one or more minor mood episodes before MDD (31%), 4 had a prior anxiety disorder (11%), and 4 had a prior substance use disorder (11%). The mean (SD) time between a first minor mood episode and MDD was 12.96 (7.35) years. MDD was the first mood episode in 25 of 36 offspring (69%).

Adulthood: Functional Outcomes and Health Care Use

At the last assessment, mean (SD) GAF score for best week in the year before assessment was 84.92 (11.19). Hence, the offspring group as a whole experienced no or minimal symptoms of psychopathology and good functioning in all areas during the best week of the past year. Mild to severe impairment (score <70) was experienced by 10 participants (10%) during their best week in the past year. All offspring with a score <70 had experienced a mood disorder within the past 10 years and showed high rates of experiencing recurrent mood episodes (100%), comorbidity (70%), or an episode at the time of the current assessment (80%). During the worst week in the past year, offspring had a mean (SD) GAF score of 69.95 (13.79). This indicates that the

TABLE 1 Demographics of Dutch Bipolar Offspring Study at 22-Year Follow-up

	n	(%)
High-risk offspring	100	(100.00)
Males	46	(46.00)
Females	54	(54.00)
	Mean	(SD)
Age at T1, y	16.10	(2.70)
Age at T5, y	38.28	(2.74)
	n	(%)
Ethnicity		
Black	1	(1.00)
More than one race	10	(10.00)
White	89	(89.00)
Family composition		
Parent with BD	69	(—)
Bipolar mothers	39	(56.50)
Bipolar fathers	30	(43.50)
BD-I	52	(75.40)
BD-II	17	(24.60)
	Mean	(SD)
Age at first depression episode, y	26.79	(10.98)
Age at first mania episode, y	31.31	(8.69)
	n	(%)
Non-bipolar proband	69	(—)
BD	—	(—)
Unipolar mood disorder	17	(24.60)
Psychosis	1	(1.40)
Substance use disorders	3	(4.30)
No diagnosis	44	(63.80)
Baseline characteristics		
	Mean	(SD)
SES baseline	4.90	(2.09)
	n	(%)
Divorced parents at baseline	23	(23.00)
Any psychopathology baseline	43	(43.00)
	Mean	(SD)
Total IQ at baseline	114.57	(15.53)
Functioning		
GAF, best week past year	84.92	(11.19)
	n	(%)
Relationship status		
Married	45	(45.00)
Cohabitation	41	(41.00)
In a relationship	5	(5.00)
No relationship	9	(9.00)
Work		
Full-time (≥36 h/wk)	49	(49.00)
Part-time	43	(43.00)
Sick leave	2	(2.00)
Disabled	1	(1.00)
Unemployed not by choice	2	(2.00)
Unemployed by choice	2	(2.00)
Annual income, €		
<38,400	26	(26.00)
38,401-60,000	37	(37.00)
>60,001	37	(37.00)
Children		
Offspring with children	76	(76.00)
1 child	23	(23.00)
2 children	35	(35.00)
3 children	18	(18.00)
Offspring without children	24	(24.00)
Total number of children	147	(—)
	Mean	(SD)
Age, y	6.80	3.90

Note: *BD = bipolar disorder; BD-I = bipolar I disorder; BD-II = bipolar II disorder; GAF = Global Assessment of Functioning; SES = socioeconomic status; T1 = baseline; T5 = 22-year follow-up.*

offspring group as a whole experienced mild impairments during their worst week in the past year.

In terms of mental health services, 71% of participants had contacted mental health services since the 12-year follow-up, and 26% were using psychopharmacotherapy. Among participants with a lifetime mood disorder (n = 65), 86% contacted mental health services, and 38% received pharmacological treatment (mood stabilizer: n = 6; antidepressants: n = 14) (Table S2, available online). Among participants with lifetime BD (n = 11), 73% received pharmacological treatment since the last assessment (mood stabilizer: n = 5; antidepressants: n = 3).

Looking at current family composition, 91% of offspring were in a relationship at the time of the interview, and 76% had children. Almost half of the cohort (49%) had a full-time job, and 43% had a part-time job. In 86% of participants, household income was above Dutch average for adults between 35 and 45 years old.[23] None of the participants had an income below social minimum.

DISCUSSION

This is the first longitudinal study to our knowledge to present the developmental course of offspring of parents with BD from adolescence into middle adulthood, using a fixed cohort design. With this study, we aimed to determine the onset, prevalence, and hierarchical course of BD in a familial high-risk population; study the onset, risk, and

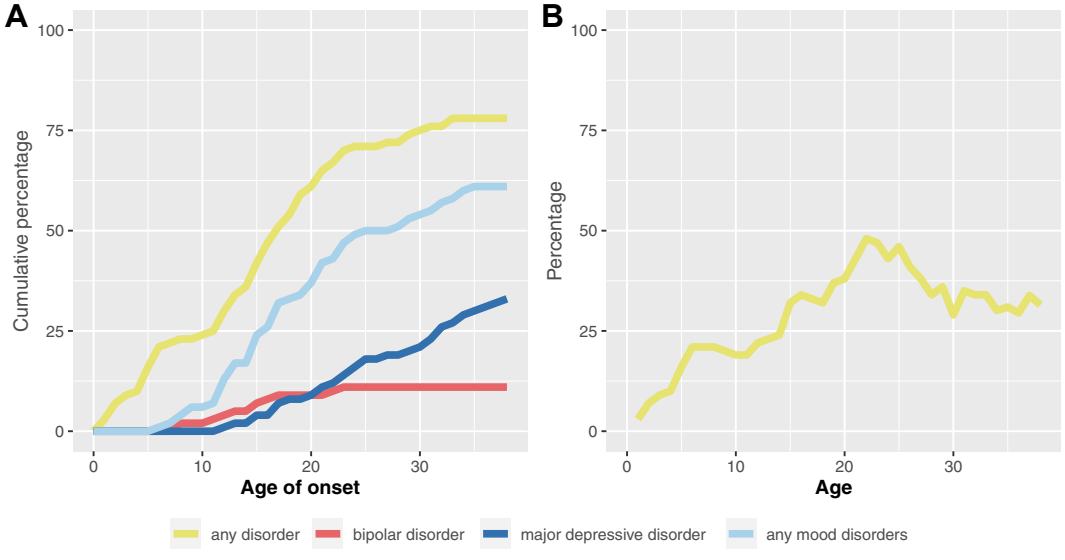
TABLE 2 Prevalence of Offspring of Parents With Bipolar Disorder With Lifetime and Current *DSM-IV* Axis I Disorders at 12-Year (n=108) and 22-Year (n=100) Follow-up (FU)

	Lifetime				Current			
	12-y FU		22-y FU		12-y FU		22-y FU	
	n	(%)	n	(%)	n	(%)	n	(%)
Any mood disorder	58	(54)	65	(65)	15	(14)	18	(18)
Major depressive disorder	18	(17)	36	(36)	6	(6)	3	(3)
Dysthymic disorder	9	(8)	8	(8)	2	(2)	—	(—)
Depressive disorder NOS	22	(20)	24	(24)	0	(0)	3	(3)
Bipolar spectrum disorders	14	(13)	11	(11)	8	(7)	0	(0)
BD-I	3	(3)	4	(4)	0	(0)	0	(0)
BD-II	9	(8)	7	(7)	6	(6)	0	(0)
Schizoaffective disorder	1	(1)	—	(—)	1	(1)	—	(—)
Cyclothymia	1	(1)	—	(—)	1	(1)	—	(—)
Adjustment disorder—mood	4	(4)	4	(4)	0	(0)	1	(1)
Non-affective psychosis	—	(—)	—	(—)	—	(—)	—	(—)
Anxiety disorders	27	(25)	35	(35)	9	(8)	12	(12)
Disruptive behavioral disorders	8	(7)	5	(5)	2	(2)	—	(—)
Attention-deficit disorder	5	(5)	3	(3)	3	(3)	—	(—)
Substance abuse disorder	25	(23)	24	(24)	8	(7)	6	(6)
Other disorders[a]	25	(23)	28	(28)	5	(5)	4	(4)
Any disorder	78	(72)	80	(80)	33	(31)	32	(32)

Note: Lifetime psychopathology has been defined as a DSM-IV Axis I disorder that has occurred anytime during a participant's life. Lower lifetime BD prevalence at the 22-year follow-up is explained by dropouts. Current psychopathology is defined as psychopathology present during the month preceding the assessment. For a mood disorder to count, the participant should have had at least one mood episode related to the disorder during the specified time period. BD-I = bipolar I disorder; BD-II = bipolar II disorder; NOS = not otherwise specified.

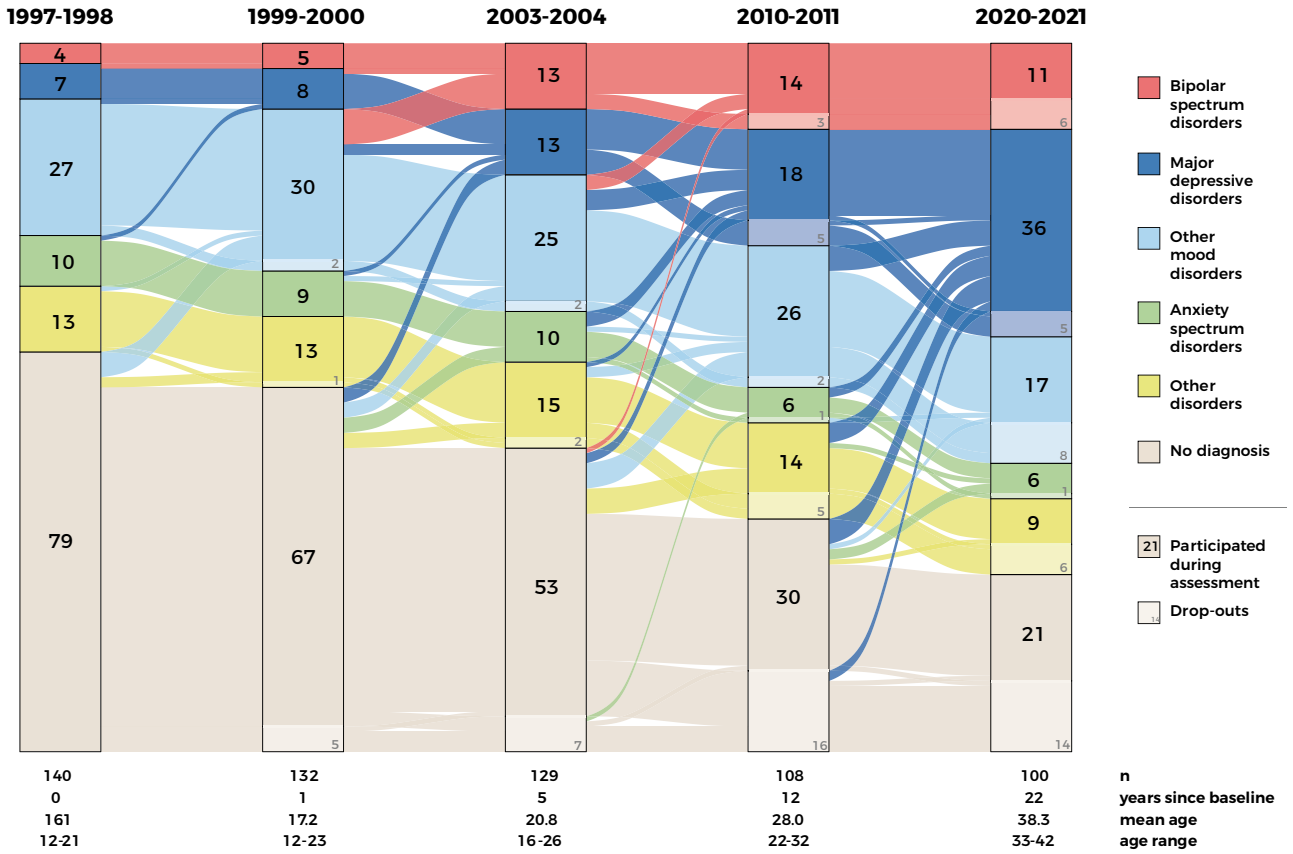
[a]*Consists of enuresis, encopresis, pervasive developmental disorder, tic disorders, body dysmorphic disorders, and eating disorders.*

FIGURE 1 Age of Onset and Prevalence of Psychiatric Disorders Over the Life Course



Note: (A) Cumulative rates of age of onset for psychiatric disorders. (B) Age-specific prevalence of any present DSM-IV Axis I disorder. As not all participants (n = 100) had reached age 38 at the time of the 22-year follow-up, the total number from age 34 and further decreased every year (age 34: n = 93; age 35: n = 84; age 36: n = 78; age 37: n=68; age 38: n=54). Point prevalence split per psychiatric disorder can be found in Figure S1 (available online). Note that color figures are available online.

FIGURE 2 Hierarchical Flow of Psychopathology From Baseline to 22-Year Follow-up



Note: *Darker-colored blocks contain the total number for the respective psychopathology group. Lighter-colored blocks represent the number of dropouts that belonged to the respective psychopathology group at the respective assessment. Flow lines between the blocks indicate movement between psychopathology groups from time point T to time point T_{+1}. The figure is a hierarchical reflection of psychopathology development, and participants belong to only one psychopathology group at one time point. In case of comorbidity, the highest in hierarchy was represented in this figure. Note that color figures are available online.*

course of mood disorders; and examine functional outcomes in adulthood. Within this Dutch cohort, we did not observe new onsets of BD since the 12-year follow-up (mean age 28 years; 13%), but transitions appeared within the bipolar spectrum. In general, BD offspring are at high risk to develop any mood disorder (65%), mostly with comorbidity (75%). Recurrent mood episodes were also common (37%) with a mean of >3 episodes. Total lifetime prevalence of any *DSM-IV* Axis I disorder was 80%, with a point prevalence of 29% to 35% per year after age 30. While aging into middle adulthood, MDD became more prominent (36%). Since the 12-year follow-up, 71% of all offspring contacted mental health services. Despite the high risk for psychopathology, global functioning and sociodemographic characteristics (such as family composition and income) were generally unaffected. In sum, in the past 10 years, at a mean age of 38 years, the homotypic risk for BD did not further increase, but the heterotypic risk for (recurrent) mood disorders and other psychopathology is high.

Our primary objective was to investigate the risk and course of BD in offspring of parents with BD from adolescence onward. Despite 2 conversions within the bipolar spectrum, rates did not further increase in the past 10 years. Therefore, the risk estimate to develop BD in offspring of parents with BD remained 11% to 13%, most often starting before age 30.[8,9,11] Our findings suggest that when reaching middle adulthood without (hypo)mania, offspring of parents with BD are less likely themselves to develop BD after age 30. This is in line with the trimodal age-of-onset model for BD[13,14] and studies suggesting that early-onset BD might be more related to familial risk than late-onset BD.[24-29] On the other hand, late-onset BD (>30 years) is not uncommon with 20% of all BD onsets.[13] Notwithstanding, caution is warranted, as a meta-analysis on age at onset including 192 epidemiological studies showed that the median age at onset for BD was 33 years of age with a 75th percentile of 49 years.[30] Another meta-analysis showed that a quarter of the people with MDD

developed BD later in life, especially within the first 5 years after the initial depressive episode and particularly people with a family history of BD.[31] There is also literature suggesting that parental age of onset is associated with parental risk.[32,33] In the present study, most offspring have passed the parental BD age of onset. Taken together, awareness of potential BD onset remains of great importance in adulthood.[3-5]

The specific risk for BD-I within our study has increased from 3% to 4% in the past decade, but remains, as previously reported,[10] relatively low. This relatively low rate of BD-I compared with BD-II might explain the limited use of pharmacological treatment in offspring with lifetime BD. Other prospective bipolar offspring cohorts have reported prevalence of BD-I within the range of 4% to 8% (Pittsburgh Bipolar Offspring Study: 3.8%, mean age = 18.1 years[8]; Canadian High-Risk Offspring Cohort: 8.45%, mean age = 23.6 years[9]; Lausanne-Geneva High-Risk Study: 6.2%, mean age = 25.5 years[11]). Differences are likely explained by methodological differences such as cohort composition and recruitment strategies.[12,34] Moreover, as reported in the 12-year follow-up,[10] despite the evidence for shared genetic susceptibility between BD and schizophrenia, only one participant of our cohort developed a schizoaffective disorder. Together, these numbers indicate that the risk for BD-I specifically is significantly lower than the risk for mood disorders in general (48%-65%).[8,9,11] From an etiological perspective of BD, there is dispute on whether mania and depression are part of the same dimension or 2 separate, but commonly co-occurring states.[35-38] In terms of intergenerational transmission, this raises the question whether offspring inherit a specific risk for (hypo)mania or a more general vulnerability for mood disorders. A recent study on molecular genetics shows an independent effect of polygenetic risk scores in the association with the risk for BD in offspring.[39] Our study, however, supports a more general vulnerability for mood disorders, where offspring of parents with BD are predominantly at risk for depression, notwithstanding alongside a relatively high risk for (hypo)mania early in life.

Where the absolute risk of MDD and mood disorders in offspring is higher than the absolute risk for BD, the relative risk for offspring to develop BD is more pronounced, as can be seen when comparing our cohort with a general population cohort. Compared with the NEMESIS-3 cohort, a Dutch general population study (age range 35-44 years, n = 1,003; NEMESIS-3),[40] despite some differences in methodologies, our cohort showed a 3 times higher chance to develop BD, 2.1 times higher chance to develop any mood disorder, and 1.4 times higher chance to develop MDD. We see a similar pattern regarding point prevalence through life, where the 12-month prevalence in a given year is highest in young adulthood and slightly decreases during adulthood. However, the point prevalence at any given time point is higher in our cohort than in the general population. Based on this comparison, offspring of parents with BD who reach middle adulthood are at increased risk for psychopathology, although a shift seems to have taken place from new onsets to recurrent and more severe episodes. MDD was more common during adulthood, with a rise from 17% to 36% in the past 10 years between the 12-year and 22-year follow-up. This is in line with other population-based studies on age at onset of MDD.[30] Overall, new MDD onsets were often preceded by minor psychopathology and increased use of mental health services since the last follow-up. This indicates that psychopathology became more pronounced during adulthood.

Despite high rates of psychopathology, our current study showed that global functioning and sociodemographic characteristics were only slightly impaired, but lower scores were common among offspring with recurrent mood episodes and comorbidity. The high functional outcomes for the cohort as a whole could potentially partly be explained by a possible recruitment bias and the high SES of the participating families. In a recent systematic review on bipolar offspring and functional outcomes, we found predominantly mixed results in terms of functional outcomes. We also found that both age and offspring psychopathology are associated with lower social functioning in offspring.[15] This review highlights the importance of incorporating a developmental perspective when it comes to psychopathology and functioning. Not only is it important to examine functional outcomes of offspring currently experiencing psychopathology, but also it is important to take current psychopathology into account when thinking of future functional outcomes. In the future, we hope to further disentangle functional outcomes of offspring and the connection between psychopathology during adolescence and young adulthood and the resulting impact on adult daily life functioning.

Regardless of the unique character of the DBOS, findings should be interpreted with the following limitations in mind. First, inevitably, after 22 years we have lost 29% of our original cohort, resulting in a considerably smaller sample size. Notwithstanding, our study can be considered hypothesis generating and stress the importance of future replication in other prospective studies. Second, the time between the fourth and fifth wave was 10 years, potentially leading to a recall bias. Over the past 10 years, we might have missed specific precursors or milder episodes; this may be especially true for offspring reporting MDD without a history of (mild) psychopathology in the past. Third, our sample might be biased in representativeness.

Our sample of offspring was recruited through outpatient clinics in psychiatric hospitals and the Dutch Patient Association for BD, suggesting a selection of better informed, functioning, and treatment-seeking parents with BD. Moreover, our sample has a relatively high SES and predominantly consists of individuals of White race and may therefore be less representative. Fourth, participation within this study may have led to a better informed population and may have served as a preventive intervention. Finally, our study does not include a longitudinally followed control group. Despite these limitations, the strengths of this study are the long follow-up period (22 years), high retention rate (71%), and the focus on the course of psychopathology and global functioning.

Taken together, this study demonstrates that offspring of bipolar parents from adolescence to middle adulthood have an increased risk of developing (bipolar) mood disorders and psychopathology in general. Compared with the general population, the risk for BD is relatively highest; however, mood disorders in general have the highest absolute risk. Moreover, this study suggests that homotypic risk for BD onset is highest in adolescence and young adulthood, but the heterotypic risk for (recurrent) mood disorders and other psychopathology continues over the life span. Importantly, this study suggests that offspring of parents with BD appear to be beyond the window of high risk for BD after age 30, but replication in larger offspring studies is needed. In the majority of participants with a major mood disorder, mild psychopathology was present years before, stressing the importance of early identification. This study allows for better understanding of the onset and course of mood disorders and specific windows of risk in a familial high-risk population and aids in the improvement of strategies for risk detection and intervention at different life stages.

CRediT authorship contribution statement

Fleur G.L. Helmink: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Esther Mesman:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Manon H.J. Hillegers:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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