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Original Article

The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents

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Objective: A major aim of this longitudinal high-risk study is to identify reliable early indicators of emerging bipolar disorder (BD) among offspring from well-characterized parents.

Methods: High-risk offspring were recruited from families in which one parent had BD diagnosed on the basis of the Schedule for Affective Disorders and Schizophrenia – Lifetime version (SADS-L) interviews and DSM-IV diagnostic criteria and the other parent was well. Bipolar parents were further subdivided on the basis of response or non-response to long-term lithium. A comparison group of offspring was recruited from well parents diagnosed on the basis of either SADS-L interviews or the family history method. All consenting offspring from high-risk and control families were assessed longitudinally with the Schedule for Affective Disorders and Schizophrenia for School-aged Children – Present and Lifetime version (KSADS-PL) interviews and DSM-IV diagnoses were made on a blind consensus review. The offspring were reassessed on average annually, as well as at any time symptoms developed.

Results: Antecedent conditions to BD in both high-risk groups included sleep and anxiety disorders, while attention-deficit hyperactivity disorder and pre-psychotic conditions were antecedents among the offspring of lithium non-responders only. Among those offspring developing BD, the index mood episode was almost always depressive.

Conclusions: Despite a specific genetic risk, BD began with non-specific psychopathology and/or depressive disorders in a majority of offspring. Therefore, diagnosis based only on cross-sectional assessment of symptoms appears to be insufficient for the accurate early detection of emerging BD. Other parameters such as family history and associated antecedents should be taken into account.

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Mood disorders are recognized as a major health care problem accounting for a high proportion of completed suicides and of the substantial illness burden worldwide (1, 2). Despite reports that an estimated 20–30% of bipolar cases onset prior to age 20 (3, 4), there is little reliable information to inform us as to the early manifestations of bipolar disorder (BD). In fact, there is considerable controversy regarding what constitutes early-onset BD (5–9). Heterogeneity of BDs may be a major contributing factor to varying outcomes and to difficulties in replicating clinical, biological and treatment findings (10–12). So far studies of heterogeneous samples of at-risk and early-onset bipolar youth have reported high rates of chronic non-remitting illness and treatment refractoriness (13–17). However, studies of adult patients have

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demonstrated different outcomes in identifiable sub-groups (18–22).

Accurate diagnosis early in the course of illness is important as it is the first step in intervening to reduce the associated risk of suicide (23–25), to prevent persistent cognitive changes (26–30) and to reduce the negative impact on school performance, self-esteem and relationships (31, 32), all known to be associated with repeated mood episodes. High-risk studies provide an opportunity to prospectively describe the evolution of psychopathology and to identify reliable antecedent symptoms and syndromes. Children of bipolar parents are a recognized high-risk group, given the familial nature of the disorder (33–35). To date, there have been a number of cross-sectional studies detailing lifetime rates of psychiatric disorders among the children of bipolar parents [for review see (36–38)]. These studies have consistently reported elevated rates of a broad spectrum of psychopathology. However, whether the non-specificity of disorders represents true antecedents or reflects the heterogeneity of parent samples is difficult to interpret (Table 1).

To date, there are three studies of the offspring of well-characterized bipolar families extending over at least five years of longitudinal observation (39–45). In all studies, depressive symptoms and syndromes and other varied psychopathology preceded hypomanic/manic episodes. In a Dutch study, sub-threshold depressive symptoms predicted subsequent BD (46). In an Amish study, prodromal symptoms included anxiety and somatic complaints, distractibility and role impairment in school, excitability, hyperalertness and mood lability (44). As these children developed, other antecedents were noted, including: excessive talking, high energy, problems with thinking and concentration and problems with sleep.

In our ongoing prospective longitudinal study of the offspring of bipolar parents, we have attempted to identify more homogeneous subgroups, on the basis of response to lithium in the family, in order to increase the probability of identifying differences in the clinical course between subgroups (39, 40). In order to differentiate between true antecedents in the evolution of a mood disorder, from psychopathology reflecting the general population level, we have limited enrollment to families in which only one parent met DSM-IV criteria for bipolar I disorder and the 'other' biological parent (non-proband) had no lifetime history of any major psychiatric illness. We added a control group of offspring from well parents in order to identify psychopathology occurring at elevated rates in high-risk groups.

This high-risk study has been ongoing since 1995. In a smaller subset of families, we had reported on lifetime psychopathology and clinical course among offspring who developed mood disorders (39, 40). Briefly, key findings included the observation that both high-risk groups manifest varied psychopathology that in some cases evolves into a mood disorder. Further, relative to the offspring of lithium responders, the offspring of lithium non-responders had higher rates of attention-deficit hyperactivity disorder (ADHD), often comorbid with learning disabilities and pre-psychotic presentations including Cluster A traits. The current report represents an update in a larger number of identically recruited families and focuses specifically on the evolution of BD. Based on these earlier findings, we hypothesized that: (i) high-risk offspring would develop a broad spectrum of psychiatric disorders and mood disorders in particular; (ii) in a substantial proportion of high-risk offspring, mood disorders

Table 1. Parent characteristics in published high-risk studies

Study	Proband parent diagnosis	Setting	Sex	Psychiatric status of other parent
Gershon et al. 1985 (87)	BD I	Unspecified		41.4% of offspring had one bipolar parent and one parent with an unspecified diagnosis
Klein et al. 1985 (88)	BD I	Inpatients	M, F	25% other parents affected
Laroche et al. 1989 (89)	Unspecified	In and outpatients	M, F	An unspecified number 'showed strong psychopathic trends'
Grigoroiu-Serbanescu et al. 1989 (90)	BD I	Inpatients	M, F	72% unaffected, 17% alcohol abuse, 4% mood, 6% other
Hammen et al. 1990 (91)	BD I, II	In and outpatients	Only F	Unspecified
Todd et al. 1996 (92)	BD I, II & MDD	Outpatients	M, F	One parent MDD (out of 12)
Chang et al. 2000 (93)	BD I, II	Outpatients	Largely F	Unilineal and bilineal families
Henin et al. 2005 (94)	BD I, II	Outpatients	M, F	Unspecified

BD I = bipolar disorder I; BD II = bipolar disorder II; M = male; F = female; MDD = major depressive disorder.

would be preceded by non-specific psychopathology; (iii) offspring of lithium non-responders would manifest higher rates of ADHD, learning disabilities and Cluster A traits compared to offspring of lithium responders; and (iv) in those manifesting BD, the index mood episode would most often be depressive in polarity.

Methods

Families

All high-risk parents were recruited from families participating in ongoing molecular genetic studies (47, 48) and selected from affective disorder outpatient clinics at the Hamilton Psychiatric Hospital, Hamilton, ON, the Royal Ottawa Hospital, Ottawa, ON and the Queen Elizabeth II Hospital, Halifax, NS. All bipolar parents were interviewed in a blind fashion by pairs of experienced research clinicians using the Schedule for Affective Disorders and Schizophrenia – Lifetime version (SADS-L) interview format. Final DSM-IV diagnoses were decided using all available clinical materials in a blind consensus fashion by an independent panel of senior clinical researchers. Non-proband parents were screened for lifetime psychiatric disorder using face-to-face SADS-L interviews (83%) or based on family history from the proband and at least one other family member (17%) in accordance with the Family History Research Diagnostic Criteria (FH-RDC) method (49). In all included families, the other biological parent had no lifetime history of a major affective disorder, schizophrenia, schizoaffective disorder, substance use disorder or personality disorder.

In this paper we also report on a comparison group of families identified through two local schools in Ottawa following the methods of Goodyer et al. (50). Briefly, the families were informed about the study through a school mail-out. Interested families completed a screening questionnaire inquiring about psychopathology in the parents and about family composition. Those indicating no lifetime occurrence of a major psychiatric or chronic medical disorder in either parent were invited to an interview. At least one parent from each control family was interviewed in accordance with the SADS-L format by a research psychiatrist and confirmed not to have met DSM-IV lifetime criteria for a major psychiatric disorder (major affective, psychotic, schizoaffective and substance use or personality disorder) or chronic medical illness (e.g., cancer, spinal cord injury, multiple sclerosis). In cases in which the other parent was unavailable for interview, psychiatric history was taken from the attending parent (usually the mother) in accordance with FH-RDC (49).

Lithium response in bipolar parents

The majority of bipolar parents (85%) met research criteria for a clear response or non-response to lithium monotherapy as described in previous reports (47). Briefly, all probands had to have a highly recurrent illness course prior to lithium. Lithium responders had to have no recurrences of illness during a minimum observation period of three years on adequate lithium monotherapy (plasma levels >0.7 mmol/L). Lithium non-responders had to have at least two additional recurrences while on adequate lithium treatment (as documented by a therapeutic plasma level at the time of relapse). In 15% of cases the bipolar parent was a first-degree relative of a lithium responder or non-responder (as defined above), but had not been treated in accordance with research protocol. We were able to subtype these bipolar parents based on their family history of treatment response and their clinical profile (51, 52).

Offspring assessment

All consenting families with offspring aged 8–25 years were included in the study. An effort was made to recruit as many offspring from consenting families as possible, independent of their clinical state. Offspring with mental retardation, severe learning disabilities or any other major problem prohibiting completion of the study were excluded (see Results section). The offspring completed a Schedule for Affective Disorders and Schizoprenia for School-aged Children – Present and Lifetime version (K-SADS-PL)/SADS-L format interview at baseline conducted by the principal investigator, a child psychiatrist blind to family affiliation and parental lithium response. Either one or both parents were interviewed separately about each child. DSM-IV diagnoses were made in a blind fashion on the basis of all relevant clinical material by a panel of senior research psychiatrists (RM, PG, MA). There was one case of disagreement regarding diagnosis, which was resolved when one of us (MA) independently re-interviewed the offspring and the findings were reviewed again on a blind consensus basis. After the first baseline assessment, all consenting/assenting offspring were re-interviewed on average annually following the K-SADS-PL/SADS-L format. In this study, all cases meeting DSM-IV criteria for bipolar disorder not otherwise specified (BD NOS) did so on the basis of manic symptoms meeting threshold criteria but not the minimal duration criteria.

In follow-up interviews, emphasis was placed on the interval between the first and subsequent assessments. In most cases, at least one parent was re-interviewed about each child. In all cases, decisions about diagnosis and change in diagnostic status were made blindly by a consensus team including at least two psychiatrists specializing in mood disorders and one child and adolescent specialist, using relevant clinical material.

Written informed consent was obtained from all participating families and this research protocol was approved by the local Research Ethics Boards.

Results

Sample description

At the time of this report, there were comparable numbers across study groups of enrolled families and offspring (Tables 2 and 3). In the families under study, the biological parents were largely living together and most mothers and fathers had completed at least some university or college-level courses. Education status of the parents was similar across study groups, except that a higher proportion of control mothers had participated in and/or completed graduate-level university studies. The high-risk subgroups tended to be recruited in mid-adolescence and were older than the control subgroup. The control group will be followed prospectively until age 30, as will the high-risk groups; therefore age differences and associated probability of illness risks will be increasingly comparable. The mean length of follow-up for the high-risk subgroups was similar (Table 3). Over the entire length of the study period (up to nine years for some offspring), we have lost to follow-up three offspring representing less than 2% of the entire population. We excluded two offspring: one owing to inability to follow the protocol and one due to severe developmental delay. So far, we have eight completers in the study defined as being followed prospectively until age 30.

Lifetime psychopathology

A two-way contingency table analysis was conducted to evaluate whether specific categories of lifetime psychopathology were more common among the offspring of lithium responders, non-responders or the comparison group (Table 4). Due to the small numbers of cases we used the maximum likelihood chi-square. Follow-up pairwise comparisons were conducted for the diagnostic categories that yielded a significant result. These pairwise comparisons demonstrated that rates of BD, depressive disorders, anxiety disorders, substance use disorders and sleep disorders were

Table 2. Family descriptive features

	LiR (n = 36)	LiNR (n = 27)	Comparison (n = 41)	Statistic	p-value
Intact families at recruitment (%)	80.6	59.3	82.9	$\chi^2(2) = 5.6$	p = 0.060
Sex ratio of affected parents (M/F)	19/17	12/15	n/a	$\chi^2(1) = 0.4$	p = 0.513
Father's education (%)				$\chi^2(6) = 12.4$	p = 0.054
Up to/completed high school	13.3	0.0	5.3		
Some college/university	3.3	14.3	0.0		
Completed college/university	46.7	38.1	34.2		
Some/completed graduate school	36.7	47.6	60.5		
Mother's education (%)				$\chi^2(6) = 16.3$	p = 0.012
Up to/completed high school	20.0	21.7	5.1		
Some college/university	6.7	13.0	0.0		
Completed college/university	63.3	56.5	59.0		
Some/completed graduate school	10.0	8.7	35.9		

LiR = lithium responders; LiNR = lithium non-responders; M = male; F = female.

Table 3. Characteristics of offspring

	LiR (n = 67)	LiNR (n = 60)	Comparison (n = 61)	Statistic	p-value
Sex ratio (M/F)	27/40	22/38	26/35	$\chi^2(2) = 0.5$	p = 0.797
Mean age at first assessment (years)	16.75 ± 5.65	16.07 ± 5.06	14.44 ± 2.72	$F(2,185) = 4.0$	p = 0.019
Range (years)	8–25	8–25	9–25		
Mean age at last assessment (years)	21.01 ± 7.03	19.72 ± 5.65	n/a	$t(125) = 1.1$	p = 0.257
Range (years)	8–30	9–30			
Mean duration in study (years)	4.13 ± 3.21	3.65 ± 3.18	n/a	$t(125) = 1.1$	p = 0.283
Range (years)	0–9	0–9			

LiR = lithium responders; LiNR = lithium non-responders; M = male; F = female.

Table 4. Lifetime diagnoses

Diagnosis	Comparison (n = 61)	Offspring of LiR (n = 67)	Offspring of LiNR (n = 60)	Maximum likelihood chi-square	Follow-up pairwise comparisons		
					LiR versus comparison	LiNR versus comparison	LiR versus LiNR
Bipolar disorder	0	14	12	$\chi^2(2) = 22.4$ p = 0.000	[a]	[a]	
Schizoaffective disorder, bipolar type	0	0	1	$\chi^2(2) = 2.3$ p = 0.317			
Depressive disorder	1	13	17	$\chi^2(2) = 20.7$ p = 0.000	[a]	[a]	
Anxiety disorder	3	13	19	$\chi^2(2) = 15.9$ p = 0.000	[a]	[a]	
Eating disorder	1	0	1	$\chi^2(2) = 1.8$ p = 0.412			
Adjustment disorder	4	8	9	$\chi^2(2) = 2.4$ p = 0.307			
Substance use disorder	0	7	13	$\chi^2(2) = 19.8$ p = 0.000	[a]	[a]	
Sleep disorder	0	14	10	$\chi^2(2) = 20.8$ p = 0.000	[a]	[a]	
Conduct disorder	0	0	1	$\chi^2(2) = 2.3$ p = 0.317			
Somatoform disorder	0	0	1	$\chi^2(2) = 2.3$ p = 0.317			
Cluster A traits disorder	0	1	5	$\chi^2(2) = 10.4$ p = 0.006		[a]	[b]
Psychosis NOS	0	0	1	$\chi^2(2) = 2.3$ p = 0.317			
ADHD and/or learning disability	1	3	10	$\chi^2(2) = 10.9$ p = 0.004		[a]	[b]
Unaffected	52	23	18	$\chi^2(2) = 50.1$ p = 0.000	[a]	[a]	

[a]Significant at the 0.01 level; [b]significant at the 0.05 level.
LiR = lithium responders; LiNR = lithium non-responders; Psychosis NOS = not otherwise specified; ADHD = attention-deficit hyperactivity disorder.

similar between the two high-risk groups and occurred at significantly higher rates than in the comparison group. Further, cognitive problems including ADHD and/or learning disabilities and Cluster A traits occurred more frequently among the lithium non-responder offspring than among comparison or lithium responder offspring.

Antecedent disorders to mood disorders

In order to capture the stability or change in diagnoses over time, we followed the method of Hillegers et al. (42) and Reichart et al. (46). Specifically, in Fig. 1 we describe the change of DSM-IV diagnoses from first to last study assessment. A major finding was that offspring who had no lifetime history of psychopathology in childhood and adolescence up until enrollment (on average in their mid-adolescence) remained well. In terms of antecedent conditions to bipolar disorder, so far, 3 out of 9 subjects (33%) with a diagnosis of depression have met criteria for BD. Further, the rate of depressive disorders as a lifetime diagnosis has increased significantly. Non-mood antecedents to a subsequent mood disorder in this cohort included sleep and anxiety disorders. Of the 40 offspring with one or both of these conditions, 12 have evolved into BD and 12 into a depressive disorder. In contrast, among those with comorbid mood and substance use disorders, the latter appears to be a later complication of the pre-existing mood disorder in 10 of the 15 cases.

In this sample, ADHD was comorbid with Cluster A traits and psychosis NOS in 6 out of 7 cases; therefore we combined these disorders into one 'neurodevelopmental' category. In keeping with other reports, so far 4 out of 11 cases in this category have developed a mood disorder, all with premorbid ADHD (5, 53, 54). Neurodevelopmental antecedents are well described as precursors to psychotic disorders and in some cases to early-onset BD (55–59).

Bipolar disorder in the high-risk cohorts

At the time of this report, 26 high-risk offspring had met lifetime DSM-IV criteria for a bipolar

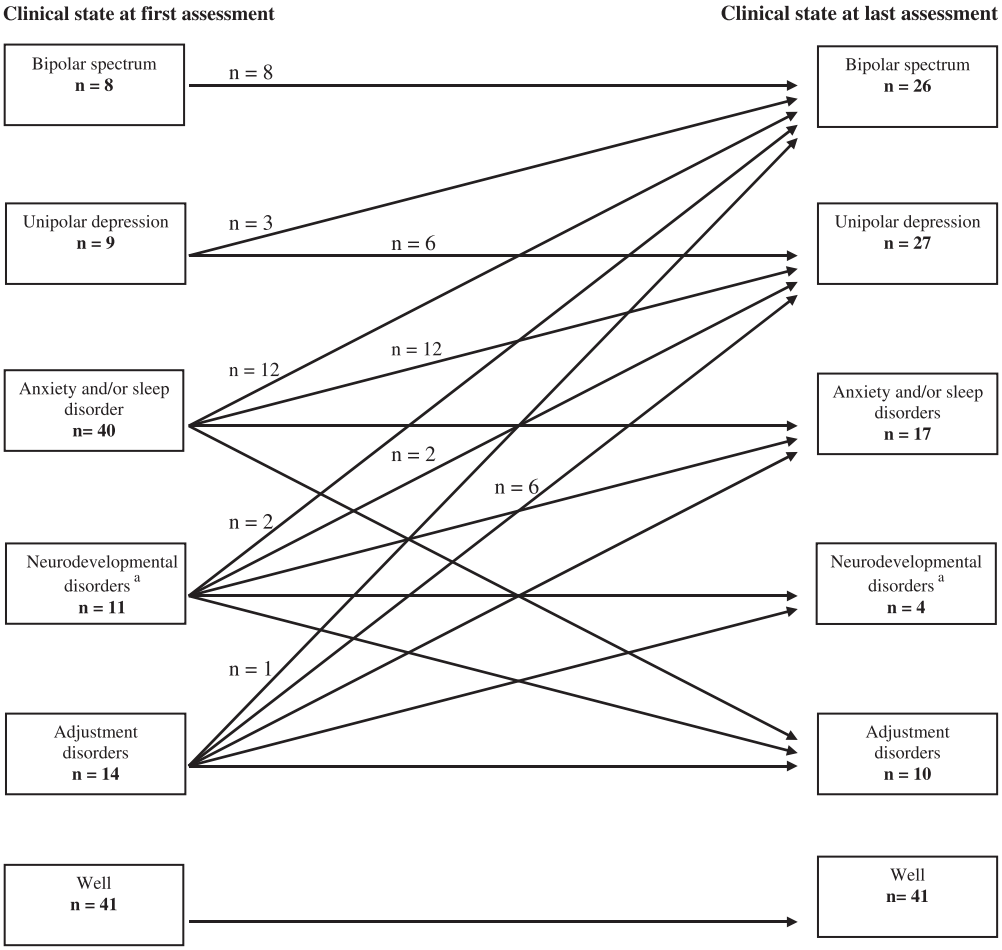

Fig. 1. Evolution of psychopathology in high-risk offspring. [a]Includes attention-deficit hyperactivity disorder, learning disability, Cluster A personality disorders and psychosis not otherwise specified.

spectrum disorder (Table 5). In the majority of cases in both high-risk groups, the index mood episode was depressive in nature (13/14 lithium responder offspring and 8/12 non-responder offspring). There was no significant difference between the high-risk groups with regard to the age of onset of the index mood episode ($t = 0.204$, $p = 0.840$) or the age of onset of the first hypo/manic episode ($t = 0.499$, $p = 0.622$). Specifically, the mean age of onset of the index mood episode was 15.8 (± 3.90) years among the lithium responder offspring and 15.5 (± 3.18) years for the lithium non-responder offspring. The mean age of onset of the first hypomanic/manic episode was 18.9 years (± 3.36) for lithium responder offspring and 17.6 years (± 4.52) for lithium non-responder offspring. Among those offspring ($n = 21$) who started their illness with an index episode of depression, there was a mean interval of 3.29 years (± 3.52) before the first hypomanic/manic episode, although this was highly variable (range 1–13 years).

Kaplan–Meier analyses were completed to determine the distribution of the age of onset for a mood disorder and the age of onset for the first hypomanic/manic episode (Fig. 2A, B, respectively). These distributions were similar between the two high-risk groups. The specific morbidity rates should be interpreted with caution, as this was a selected non-epidemiological sample.

Discussion

The major finding from this ongoing prospective study of the offspring of well-characterized bipolar parents was that in a subset of high-risk youths, BD began with varied antecedent psychopathology, including sleep and anxiety disorders. These non-specific conditions manifest despite the specific familial risk for recurrent mood disorders (60). These observations are in keeping with those of other groups who have reported an association between childhood anxiety disorders and subsequent adolescent depression (61–63), likely on a

Table 5. Characteristics of offspring meeting lifetime DSM-IV criteria for bipolar disorder

Affected parent	Familial lithium response	Index mood episode	Age at onset of index mood episode	Age at onset of first (hypo) mania	Diagnosis
F	LiR	MD	16	18	BD II
M	LiR	Dep NOS	13	15	BD II
F	LiR	Dep NOS	15	21	BD I
F	LiR	Dep NOS	17	18	BD II
F	LiR	Dep NOS	16	16	BD II
M	LiR	Dep NOS	12	20	BD II
F	LiR	Mania	22	22	BD I
M	LiR	MD	16	17	BD II
F	LiR	MD	13	23	BD II
M	LiR	MD	10	17	BD II
F	LiR	MD	15	18	BD II
F	LiR	MD	14	15	BD NOS
F	LiR	MD	25	27	BD NOS
F	LiR	MD	17	18	BD NOS
M	LiNR	Hypomania	18	18	BD II
M	LiNR	MD	15	16	BD II
F	LiNR	MD	18	20	BD I
M	LiNR	MD	19	20	BD II
F	LiNR	Hypomania	12	12	BD II
M	LiNR	MD	13	16	BD NOS
F	LiNR	Cyclothymia	13	13	Cyclothymia
M	LiNR	MD	18	19	BD NOS
M	LiNR	Cyclothymia	12	12	BD NOS
F	LiNR	MD	21	21	BD NOS
M	LiNR	Dysthymia	15	28	BD NOS
M	LiNR	MD	12	16	SchiAff

M = mother; F = father; LiR = lithium responder; LiNR = lithium non-responder; Dep NOS = depression not otherwise specified; BD I = bipolar disorder I; BD II = bipolar disorder II; BD NOS = bipolar disorder not otherwise specified; MD = major depression; SchiAff = schizoaffective disorder.

genetic basis. There was also evidence of differential antecedents between high-risk subgroups. Specifically, only offspring of lithium non-responders had elevated rates of antecedent ADHD, learning disabilities and Cluster A traits. This agrees with reports of an association between ADHD and subsequent early-onset BD (5, 64, 65).

In this study, the index mood episode in those offspring developing BD was almost always depressive, regardless of high-risk group. Depressive episodes tended to recur and preceded the activated episodes by several years. This supports previous observations from family studies (66, 67) and clinical follow-up studies (68–71) suggesting that a significant proportion of adolescents initially meeting criteria for a depressive disorder later manifest BD. In this study, so far, the majority of offspring diagnosed with BD have milder forms, namely BD NOS or BD II. As the cohort continues to be followed to the planned completion at age 30, it will be interesting to observe the proportion of offspring evolving from depressive disorders and soft-spectrum BD into full-blown BD I.

Another very important observation from this study was that those adolescents who were completely well and asymptomatic in their childhood and early to mid-adolescent years have remained well over the observation period. While it is possible to develop BD at anytime over the lifespan, this finding may indicate a reduced probability if completely well through this developmental stage.

These key findings question the validity of a primarily symptom-based approach to diagnosis early in the course of illness. For example, in this high-risk sample, if one had relied only on symptoms for diagnosis, one would have missed identifying latent BD in 68% of those offspring. This failing to recognize future BD in symptomatic youth results in the delay of effective intervention and gives rise to the possibility of trials of ineffective treatment, including stimulants and antidepressants, that may actually worsen the course of illness (72–78). In fact, one can speculate that latent bipolarity may explain at least a proportion of youths experiencing a paradoxical worsening and/or suicidal ideation and/or behaviour while on antidepressant therapy (79, 80).

From this and other studies, a particularly helpful predictor of BD remains a positive family history, especially in first-degree relatives (81–83). If this approach is to be useful, the accuracy of the

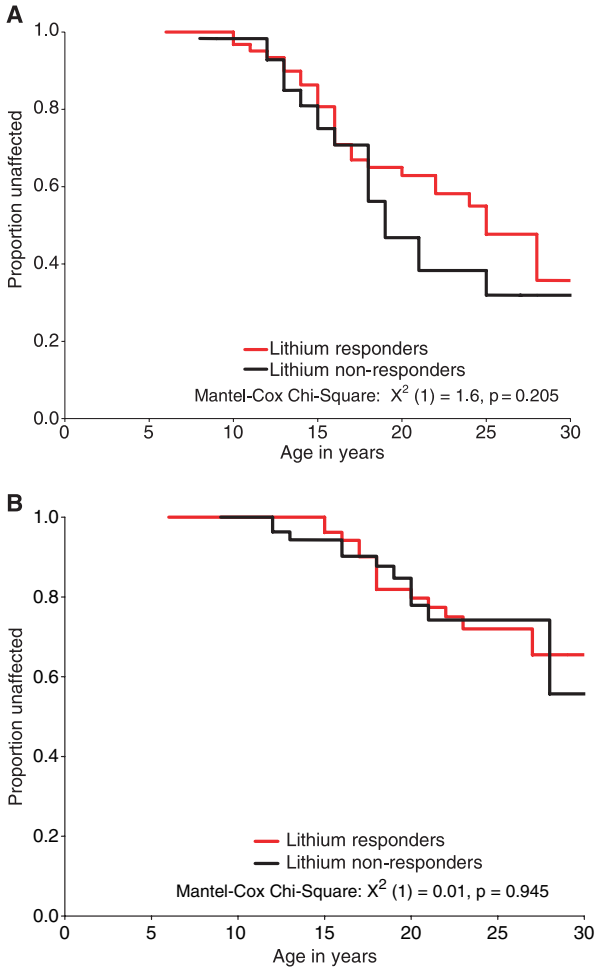

Fig. 2. Age of onset of (A) mood disorder; (B) first hypomanic/manic episode.

family history is paramount. Therefore, it is important to gain as much detail as possible on the affected family members (preferably in face-to-face interviews) in order to determine the specific nature of the disorder(s) (82). This is underscored by the fact that BD has become a popular diagnosis made in favour of other diagnoses such as schizophrenia (84, 85).

It was interesting to note that premorbid problems in cognition, including ADHD and/or learning disabilities, occurred mostly among the offspring of lithium non-responders. In addition, pre-psychotic conditions almost exclusively occurred in this subgroup including Cluster A traits and psychosis NOS. This suggests that heterogeneity is an important variable to consider in terms of differences in clinical course and may have relevance for possible differential treatment outcomes. Further, heterogeneity may explain the seemingly discrepant findings between different studies with regard to the association between ADHD and BD in youth. The finding of premorbid neurodevelopmental antecedents in a subgroup of bipolar youth has been reported previously (58) and overlaps to some degree with the literature on the early course of children who later manifest psychotic disorders (55–57, 59).

One limitation of the present study is the variable lengths of time offspring have been under observation and the variable age of recruitment. The comparison offspring are somewhat younger in age than the high-risk offspring, but as all children will be followed until age 30 this difference will be resolved. At this stage, there are not enough offspring evolving from a unipolar to a bipolar diagnosis to identify reliable characteristics differentiating converters from non-converters. This is also a complicated issue, given that the majority of unipolar relatives of bipolar probands are estimated to have a genetically related disorder (67) and that conversion to BD continues throughout the lifespan (86). Finally, this study was designed specifically to address the issue of identifying early reliable antecedents to BD. This study was not designed therefore to generalize to a non-selected heterogeneous cohort of at-risk children.

In this paper, we have focused on the evolution of psychopathology. In other publications we report on other aspects of this study, including psychosocial risk factors, treatment histories and differences in the clinical course.

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