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Prediction of change in level of problem behavior among children of bipolar parents

Wals M, Reichart CG, Hillegers MHJ, Nolen WA, Van Os J, Ormel J, Verhulst FC. Prediction of change in level of problem behavior among children of bipolar parents. Acta Psychiatr Scand 2006; 113: 23–30. © 2005 Blackwell Munksgaard.

Objective: To determine the effects of familial loading, birth weight, and family problems on change in parent-reported problems across a 14-month period among children of bipolar parents.

Method: Emotional and behavioral problems in a sample of 140 offspring of bipolar parents and familial loading in first- and second-degree relatives were assessed at two measurements. Parents reported the birth weight of their offspring and completed a questionnaire on family problems. Multiple linear regression analyses were performed to assess associations of the three predictors with change in problem scores at follow-up.

Results: Familial loading of unipolar disorder was a unique predictor for an increase in problem scores from the first to the second measurement with β -coefficients ranging from 0.17 to 0.25. Birth weight and family problems were not associated with change in problem scores across the two measurements.

Conclusion: Familial loading of unipolar disorder predicted an increase in behavioral and emotional problems across the 14-month follow-up.

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Key words: bipolar disorder; offspring; familial loading; birth weight; family problems

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Significant outcomes

- Increased familial loading of unipolar disorder increases the risk for developing emotional and behavioral problems among children of bipolar parents during a 14-month follow-up interval.
- If there is high familial loading of unipolar disorder in families with bipolar parents and the offspring show first signs of behavioral or emotional disturbance, it is important to inform both the parents and the offspring of treatment possibilities.
- Family problems do not predict change in psychopathology across a 14-month follow-up in children of bipolar parents.

Limitations

- The sample is not population based. Only patients with children who were willing to participate were included.
- As the Family History-Research Diagnostic Criteria is relatively insensitive for the diagnosis of mood disorders when compared with the family study method, we may have missed diagnoses.
- Family problems were only assessed using parent reports. It is possible that parents with offspring who developed problems under- or over-reported the level of family problems. It therefore would have been interesting to assess family problems with child reports and observations of family interactions.

Introduction

Children of bipolar parents are at increased risk to develop mood disorders. A number of studies have stressed the importance of genetic factors in the etiology of unipolar and bipolar mood disorders (1). We found familial loading of unipolar mood disorder in first- and second-degree relatives of the children of bipolar parents to be positively associated with increased risk for meeting DSM-IV criteria for lifetime mood disorders (both unipolar and bipolar) in these offspring (2, 3).

Genetic factors alone are not a sufficient explanation for the etiology of depression, environmental factors seem to play a role as well (4, 5). Among environmental factors increasing the risk for developing mood disorders low birth weight can be viewed as a marker of prenatal environmental influences. The relevance of prenatal factors that may influence birth weight has been stressed by Barker (6) who studied the relationship between prenatal influences, especially fetal malnutrition resulting in low birth weight, and increased risk for adult physical diseases including cardiovascular diseases and diabetes. Birth weight has been reported to increase the risk for various types of psychopathology in childhood and adulthood (e.g. 7–12), although the exact mechanisms by which these associations work are not known yet. Other studies reported on the association between birth weight and cognitive functioning (e.g. 13). In accordance with these findings, we found in our sample of children of bipolar parents that birth weight was associated with an increased risk of DSM-IV mood as well as non-mood disorders. This association was independent of the association between genetic liability as measured by familial loading of unipolar, bipolar and substance use disorder and psychopathology (3).

Another environmental contributor to the risk of increasing behavioral and emotional problems in offspring of unipolar or bipolar parents seems to be poor family functioning. For instance, Billings and Moos (14) found variations in family stressors and resources to be strongly related to the probability of disturbance among 133 children of depressed parents when compared with 135 children of non-depressed parents. Chang et al. (15) found families with a bipolar parent to report significant differences in their family environment compared with population mean values. Families with a bipolar parent differed from the average family in having less cohesion and organization, and more conflict. However, Family Environment Scale scores did not differ significantly for 6- to 18-year-old children with or without an Axis I

disorder in these families. A drawback of these studies is that because of their cross-sectional nature it is not possible to determine the temporal relationship between family problems and child/adolescent psychopathology. Therefore, longitudinal research is needed.

It is thus likely that offspring of bipolar parents are at increased risk of showing psychopathology through both genetic and environmental influences. The next question is whether or not vulnerability or risk factors, such as familial loading, birth weight and family functioning, can also be held responsible for *changes* in the level of psychopathology across time. Increases in the level of emotional and behavioral problems, even when occurring at a subclinical level, may signal increasing vulnerabilities in offspring who may eventually develop more serious psychopathology, including bipolar and other mood disorders. It is therefore important to identify early risk factors in order to prevent children of bipolar parents to develop a more chronic and severe course of psychopathology. In order to capture changes in the level of problems in this high-risk sample, we have chosen to study this sample at relatively short time intervals (14 months). Few studies have focused on the course of psychopathology in children of bipolar parents (e.g. 16–18). In a 3-year follow-up, Hammen et al. (17) found a chronic or intermittent course of both mood and non-mood disorders in 18 children of bipolar mothers, 22 children of unipolar mothers and 14 children of medically ill mothers after initial evaluation. Radke-Yarrow et al. (18) followed 22 children of bipolar parents (as well as offspring of unipolar and normal control parents) for up to 3 years. They found significantly more children of affectively ill, than well, mothers to show depressive and disruptive problems by middle and late childhood and that their problems increased over time. None of the above-mentioned studies have focused on factors influencing change in psychopathology over time.

In the present study, we expected our sample of children of bipolar parents, aged 12–21 years at initial assessment, to be in a developmental period with elevated risk for showing the first signs of psychopathology given their genetic vulnerability, and environmental risks.

Aims of the study

We aimed to study factors that are associated with possible changes in the level of problem behavior in these offspring of bipolar parents. Based on the previous findings that were discussed above, the most obvious candidate determinants of change

were familial loading of unipolar disorder and birth weight. In addition, we chose the amount of family problems reported at initial assessment as environmental factor that, in addition to familial loading and birth weight, may influence the risk for developing psychopathology.

Material and methods

Sample

The sample consisted initially of 140 children aged 12–21 years of a parent with bipolar disorder. Children with a severe physical disease or handicap or with an IQ below 70 were excluded. A family was excluded if one or more family members aged 12–21 years refused to participate.

All subjects were enrolled into the study between November 1997 and March 1998. Sixty-four bipolar I and 22 bipolar II patients and their offspring (72 boys and 68 girls) participated in the study. Fifty-two of 86 proband parents were mothers (60%). The mean age of the bipolar parents was 45.4 years. The mean age of the participating offspring at time 1 was 16.1 years ($SD = 2.7$; range 12–21). Fourteen months ($SD = 1.7$ months; range 11–19) after the first measurement (time 1), 132 subjects, aged 13–23 years, were reassessed.

The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study. After a complete description of the study was given to all participating parents, their spouses and their offspring, written informed consent of all participants was obtained.

For a more detailed description of the recruitment and demographic characteristics of the sample we refer to Wals et al. (19).

Instruments

Assessment of bipolar disorder in the parents. DSM-IV bipolar I or II diagnoses were confirmed by administering the mood disorders section of the International Diagnostic Check List (IDCL) (20) in the interview with the bipolar parent. We compared the IDCL-based diagnoses with the DSM-IV diagnoses made by the treating psychiatrist and did not find any discrepancies. The spouses of the bipolar parents did not have bipolar disorder but some of them were diagnosed with unipolar disorder [see the Family History-Research Diagnostic Criteria (FH-RDC) below]. Based on the information that we gathered with the IDCL and the FH-RDC we concluded that none of the affected parents was depressed or manic at the moment of completing the questionnaires and of administering the inter-

views. Of course, it is still possible that a parent was starting to become depressed at time of the assessment, or displayed some residual symptoms, but none of the parents was having a full-blown depression or mania at time of the assessment.

Assessment of DSM-IV diagnoses in children of bipolar parents. The schedule for affective disorders and schizophrenia for school-age children—present and lifetime version (K-SADS-PL, 21) Kaufman et al., 1997), a semi-structured interviewer-oriented diagnostic interview designed to assess current (2 months) and past DSM-IV symptomatology, was used to derive DSM-IV diagnoses in children of bipolar parents. The interviews were performed by three of the investigators (M.W., M.H., C.R.) and five interviewers with graduate degrees in psychology. All interviewers were intensively trained, and most interviews were discussed with a child/adolescent psychiatrist (C.R.), in order to guarantee consistency between the interviews.

At T2, 43 (33%) of the participating offspring ($n = 132$) were diagnosed with a lifetime mood disorder (22). Sixty-seven (51%) never had any lifetime diagnosis ($n = 67$, 32 females, 35 males, mean age = 17.0 years). Of the total sample 13 (10%, eight females, five males, mean age = 15.9 years) had developed a first onset mood disorder ($n = 8$) or a recurrence of a mood disorder ($n = 5$) during the 14-month follow-up. One of the offspring developed bipolar disorder during follow-up and four already had developed a bipolar disorder at first measurement. For a more detailed description of the prevalence of psychopathology in our sample we refer to our previous publications (19, 22).

Assessment of familial loading. Lifetime prevalence of psychopathology in the parents ($n = 177$) and their non-offspring first-degree relatives ($n = 932$) was assessed with the FH-RDC (23) interview which was administered to both parents. We only applied sections of the FH-RDC yielding the following diagnoses: unipolar disorder, bipolar disorder, and substance use disorder. A previously described method of calculating a familial loading score was used, considering family history as an attribute of the individual cases themselves, which might be related to their psychopathological outcome (24). This index of familial loading for the children of bipolar parents is based on the number and age of the affected first-degree relatives, excluding the siblings of the participating children of bipolar parents. Every relative examined with the FH-RDC contributed to the index depending on whether the person was affected and on the age

at which the person was affected. The FH-RDC was administered by two of the authors (M.W., M.H.), and by five intensively trained interviewers with graduate degrees in psychology. As described by Todd et al. (25), the completeness of FH-RDC information was rated by the interviewers on a five-point scale (1 = very good, 2 = good, 3 = fair, 4 = poor, 5 = essentially no information). A score of 1 was defined as a diagnosis of bipolar disorder, unipolar disorder or substance use disorder made by a clinician or if the family member fulfilled the criteria of the disorder of, e.g. bipolar disorder and was known to be treated with a mood stabilizer. A score of 2 was used when the exact diagnosis was not known but when symptoms were present which indicated the presence of a unipolar depression, a bipolar depression or a substance use disorder based on content, duration, and treatment in a treatment setting. Only individuals with scores of 1 or 2 were included. We therefore applied a relatively high threshold for family members to be diagnosed as mood disordered. A panel consisting of the five interviewers and three of the authors (M.W., C.R., M.H.) reached consensus on the disorders that raised rating problems. We decided to limit the analyses for this paper to the familial loading score for unipolar disorder because the variance of familial loading of bipolar disorder ranged from individuals with high familial loading to individuals with extremely high familial loading (the variance was always positive) thereby making differentiation between subjects more difficult. For a more detailed description of the familial loading score we refer to Wals et al. (2, 3).

Family Problems Questionnaire. The Family Problems Questionnaire (26) aims to assess family problems as perceived by the parents. All offspring lived with their parents at time 1. The questionnaire contains 130 items that can be scored 0 = not applicable, 1 = a little or sometimes applicable, and 3 = clearly or often applicable. Items can be scored on the following scales: 1. Support and communication; 2. Education; 3. Hostility; 4. Openness; 5. Execution of tasks; 6. Involvement; 7. Security; 8. Partner relationship; and 9. Problems with children. In addition to these scales a screen score and a total score can be derived. This instrument enables us to get a description of the experience of parents of strengths and weaknesses of family functioning. Good reliability (α s ranging from 0.72 to 0.97) of the Family Problems Questionnaire was found and all scales, except the Partner relationship and Involvement scale discriminated well between a referred and non-referred sample selected by Koot (26) from a

general population cohort of 488 families. The non-referred sample consisted of families of 368 children who did not use mental health services during the 12 months preceding completion of the questionnaire whereas the referred group consisted of families with 156 children who were referred for mental health service (26). On 125 of the 130 items of the questionnaire the referred group scored significantly higher than the non-referred group. The five items that did not discriminate between the two groups were excluded from the total score. Our sample of offspring of bipolar parents received significantly higher scores on the family problems questionnaire than offspring in the general population from the original non-referred sample by Koot (26). The total score on the Family Problems Questionnaire by mothers was 50.9 in our sample vs. 28.6 in the general population ($t = 8.0$, $P < 0.01$), and for fathers 45.7 in our sample vs. 27.8 in the general population ($t = 6.0$, $P < 0.01$).

For the purpose of this study both mothers and fathers were requested to complete the questionnaire. Total scores of mothers and fathers were averaged. The questionnaire was completed at both time 1 and time 2. However, as we were interested in whether family problems preceded changes in levels of psychopathology, we decided to use only the family problems scores of time 1.

Assessment of problem behavior in children of bipolar parents. Both affected and non-affected mothers completed the Child Behavior Checklist for ages 4–18 (CBCL; 27, 28). The CBCL is a questionnaire containing 120 problem items that can be scored 0 if the behavior is not true of the child, 1 if the behavior is sometimes or somewhat true, and 2 if the behavior is very true or often true. The problem items can be scored on eight syndrome scales and two broad-band groupings of syndromes: Internalizing (consisting of the Withdrawn, Somatic Complaints, and Anxious/Depressed scales) and Externalizing (consisting of the Delinquent Behavior and Aggressive Behavior scales). The sum of the 120 individual item scores is the total problems score. The good reliability and validity of the CBCL have been replicated for the Dutch translation (29). The Young Adult Behavior Checklist (YABCL; 30) is an upward extension of the CBCL for ages 18 years and older, and contains problem items that are completed by parents. The YABCL can be scored on syndrome scales similar to those of the CBCL, except for the Social Problems scale, which is replaced by the Intrusive Behavior scale. The syndrome scales can be scored on two broad-band groupings of syndromes: Internalizing (consisting of the Anxious/Depressed and Withdrawn

scales) and Externalizing (consisting of the Intrusive Behavior, Delinquent Behavior, and Aggressive Behavior scales). For the present study we computed a total problems score, and Internalizing and Externalizing scores from the items that were common to the CBCL and YABCL.

Socioeconomic status

Socioeconomic status (SES) was scored on a 9-point scale of parental occupational level with 1 = lowest and 9 = highest. If both parents worked, the highest score was used.

Statistical analysis

In order to assess the stability of problem behavior between time 1 and time 2, Pearson correlations were calculated. To evaluate the magnitude of stability coefficients Cohen's criteria were used (31). Paired sample *t*-tests were used to calculate differences in the mean values of problem behavior at time 1 and time 2.

Stepwise multiple linear regression analysis was used to identify which set of variables were the strongest predictors of increase in problem behavior at follow-up, while controlling for possible confounding effects from other predictors, yielding regression coefficients (β) as a measure of effect size. To determine their independent effects, familial loading, family problems and birth weight were entered stepwise into the regression equation. We added each model's RSQ, and for each step RSQ change as measures of effect size. In order to assess the effect of the predictors on problem behavior at time 2 over and above the effect of time 1 problem behavior, we entered time 1 (total problems, Internalizing, and Externalizing) problem scores as independent variables. For each of the three CBCL/YABCL problem scales we did a separate analysis. All analyses were adjusted for age of the offspring at time 2, gender and SES. These confounders were chosen *a priori*.

Results

Stability and change of problems across the 14-month follow-up interval

Table 1 shows the CBCL/YABCL mean total problems, Internalizing and Externalizing scores at time 1 and time 2 and the Pearson correlations between time 1 and time 2 scores. Differences between time 1 and time 2 scores were computed by paired sample *t*-tests. Mean total problems, Internalizing and Externalizing scores were some-

Table 1. Mean values, standard deviations and Pearson correlations of CBCL/YABCL. Total problems, internalizing and externalizing scores between time 1 (T1) and time 2 (T2)

	T1		T2		<i>t</i> value	<i>P</i> value*	<i>r</i> †	<i>P</i> value
	Mean	SD	Mean	SD				
Total problem score	20.91	17.3	18.74	16.4	1.87	n.s.	0.70	<0.01
Internalizing	8.39	8.7	7.26	7.5	1.97	n.s.	0.69	<0.01
Externalizing	6.50	5.9	6.23	6.3	0.64	n.s.	0.71	<0.01

CBCL, Child Behavior Checklist; YABCL, Young Adult Behavior Checklist.

*Mean difference between CBCL scores at T1 and T2.

†Pearson correlations time 1 vs. time 2.

what lower at time 2 than at time 1. However, none of the differences were significant. Pearson correlations between time 1 and time 2 scores were significant and could be regarded as large ($r \geq 0.5$) according to Cohen's criteria.

Prediction of change in problem scores: multivariate analyses

Table 2 shows the results of the multiple linear regression analysis. As can be seen from this table, familial loading of unipolar disorders significantly predicted an increase in total problems, Internalizing, and Externalizing problems ($\beta = 0.24$,

Table 2. Multiple linear regression analyses (stepwise forward), of familial loading, birth weight, and family problems at time 1 predicting change in CBCL/YABCL total problems, internalizing and externalizing behavior at 14-month follow-up, adjusted for gender, socioeconomic status (SES) and age at time 2

		Dependent variable CBCL/YABCL time 2		
Predictor variables†		Total problems	Internalizing	Externalizing
Model 1				
Corresponding time 1 problem scores	β	0.67**	0.67**	0.73**
Gender	β	n.s.	n.s.	n.s.
Age	β	n.s.	n.s.	n.s.
SES	β	n.s.	n.s.	n.s.
RSQ‡	%	46	46	53
Model 2				
Corresponding time 1 problem scores	β	0.67**	0.67**	0.73**
FL unipolar depression	β	0.24**	0.25**	0.17*
Birth weight	β	Exc.	Exc.	Exc.
Family problems	β	Exc.	Exc.	Exc.
Gender	β	n.s.	n.s.	n.s.
Age	β	n.s.	n.s.	n.s.
SES	β	n.s.	n.s.	n.s.
RSQ‡	%	52	53	55
RSQ change§	%	5.3	6.2	2.8

†All variables were adjusted for time 1 total problems, internalizing and externalizing scores and for gender, age and SES.

‡RSQ, total percentage of explained variance by the model.

§RSQ change = percentage of *additional* explained variance by familial loading.

* $P < 0.05$; ** $P < 0.01$; n.s., not significant (although factor included in overall significant model); Exc., factor, not significant, excluded from the model.

$P < 0.01$, $\beta = 0.25$, $P < 0.01$, $\beta = 0.17$, $P < 0.05$, respectively). There were no significant associations between family problems and change in problem behavior and between birth weight and change in problem behavior between time 1 and time 2. We re-analyzed the data with the total family problems for mothers and fathers separately and did not find any significant differences in results. The percentage of explained variance for model 1, including corresponding time 1 problem scores, gender, age and SES, varied from 46% to 53%. Familial loading additionally explained 2.8% to 6.2% of the variance.

Interactions

There were no significant interactions between family problems, birth weight, SES on the one hand and familial loading of unipolar disorder on the other on change of problem behavior between time 1 and time 2; these are not shown in the table.

Discussion

As far as we know, this is the first study examining predictors of changes in the level of problems in children of bipolar parents. Our findings indicate that the risk to offspring of bipolar parents to develop psychopathology is not transitory. Stability coefficients for total problems, Internalizing and Externalizing scores were large according to Cohen's (31) criteria, indicating that behavioral and emotional problems of children of bipolar parents aged 12–21 years at initial assessment were stable across this relatively short time interval. The mean problem scores did not change significantly across the 14-month follow-up indicating that there was no change in the overall level of problems in our sample.

The most salient finding of the present study was that familial loading of unipolar disorder in first- and second-degree relatives of children from bipolar parents was predictive of an increase in total, Internalizing and Externalizing CBCL/YABCL problem scores. Given the relatively short follow-up interval, it was striking to find familial loading to be associated with an increase in the level of problems. The percentage of explained variance for the model which included corresponding time 1 problem scores, gender, age and SES, varied from 46% to 53%. Familial loading explained 2.8% to 6.2% of the variance when added to this model, which is not large but also not negligible.

In our previous study, in which we used K-SADS interviews to derive DSM-IV mood disorders

in our sample, we found familial loading of unipolar disorder to be associated with mood disorders and not with non-mood disorders (2). In the present study familial loading of unipolar disorder predicted an increase of both Internalizing and Externalizing scores on the CBCL/YABCL. Externalizing behaviors have been found to precede the development of mood disorder in children of bipolar parents. For instance, Carlson and Weintraub (32) found a unique relationship between childhood behavioral and attention problems and the development of mood disorder in a sample of 134 children of bipolar parents aged 7–16 years. Externalizing behavior may be an as yet undifferentiated early stage of the development of bipolar disorder. This might explain the significant association we found between familial loading of unipolar disorder and increase in externalizing problem behavior. Of course, further research on this matter is necessary.

Another finding of the present study was that family problems and birth weight were not associated with an increase of problem behavior between the two measurements. The finding that family problems did not differentiate between offspring who showed an increase in problem behavior and those who did not does not mean that families in which one of the parents has a bipolar disorder do not experience more family problems. In line with Chang et al. (14), we did find families of children of bipolar parents to experience more family problems than general population mean values. However, in the study by Chang et al. (15) family problems did not differentiate children with or without psychopathology. Likewise, in the present study family problems did not predict change in behavioral and emotional problems among children from bipolar parents. Moreover, family problems did not moderate the impact of familial loading on increase of problem behavior.

The familial loading score that we calculated largely concerned effects in relatives that are distant from the proband. Therefore, it is assumed that familial loading reflects genetic influences, although some environmental influences cannot be totally ruled out.

In conclusion, the major finding of the present study is that familial loading of unipolar disorder predicted an increase in behavioral and emotional problems in children of bipolar parents across a 14-month follow-up interval. Birth weight and family problems did not predict change in psychopathology across a 14-month follow-up in children of bipolar parents. This does not preclude the possibility that other

important environmental factors could predict developmental change in psychopathology among children of bipolar parents.

Implications

All subjects in our sample were similar in that they shared the risk that one of their parents had a bipolar disorder. In addition to this risk, the familial occurrence of unipolar disorder was positively associated with change of emotional and behavioral problems in our sample. This finding can make clinicians and researchers aware of the fact that familial loading of unipolar disorder increases the risk of developing emotional and behavioral problems in children of bipolar parents. If there is high familial loading of unipolar disorder in families with bipolar parents, it is important to inform parents and offspring of treatment possibilities whenever the offspring show first signs of behavioral or emotional disturbance in order to prevent them from developing more problems.

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