

Summary

Bipolar disorder is a psychiatric condition characterized by severe mood swings. An individual with bipolar disorder alternates between episodes of depression and episodes of (hypo) mania (elevated mood, including euphoria, irritability or both). Episodes of mania and depression can vary from a few weeks to several months and are usually severe enough to affect daily functioning at home or at work. Bipolar disorder can be a lifelong condition for which no curative treatment is available. However, adequate treatment reduces the number and severity of episodes and thereby reduces the level of handicap in the majority of patients. Bipolar disorder is often diagnosed many years after the illness has started. Consequently, adequate treatments are postponed or inadequate treatments are given. It is therefore important to detect early signs of bipolar disorder as well as risk factors for the development of the disorder.

By the end of 1997 the KBO-project (Dutch for "Children of Bipolar Parents") was launched. The major aim of the KBO-project was to study the early development of bipolar disorder and factors influencing this development. Children of bipolar parents are at increased risk of developing psychopathology, including bipolar disorder, compared to children from the general population. The lifetime risk for bipolar disorder in relatives of a bipolar proband was found to be 5-10% for first-degree relatives compared with 0.5-1.5% for unrelated individuals (Craddock and Jones, 1999).

This thesis concerns children of bipolar parents for two main reasons. First, children of bipolar parents are at genetic risk for developing psychopathology, including mood disorders (Alda, 1997; Gershon et al., 1987; McGuffin and Katz, 1989). Second, children of bipolar parents are subject to (mostly negative) environmental stressors associated with parental psychopathology. These multiple risks may be responsible for the emergence of multiple types of psychopathology that subsequently are subject to developmental change. In addition, disorders other than a mood disorder can be precursors of bipolar disorder. For instance, an oppositional defiant disorder in childhood can be followed by the development of a unipolar disorder in adolescence which subsequently evolves via a (hypo)manic episode into a bipolar disorder in adulthood. Little is known about the effects of environmental influences on the functioning of children of bipolar parents. Therefore, the global aim of this thesis is twofold; on the one hand we wished to determine the lifetime and current prevalence of psychopathology including mood disorders among offspring of bipolar parents and on the other hand we sought to test the effects of factors influencing the presence and onset of psychopathology, including mood disorders, among offspring of bipolar parents. To achieve these aims we studied a sample of 140 children of 86 bipolar parents aged 12 to 21 years. This thesis is based on two measurements with an interval of 14 months.

In chapter 1, the following research questions were presented:

1. What is the prevalence of psychopathology including mood disorders among offspring of bipolar parents? (chapter 2)
2. Are familial loading of mood and familial loading of substance use disorder associated with lifetime mood disorders in bipolar offspring? (chapter 3)
3. Does birth weight predict mood and non-mood disorders in bipolar offspring independent from, in addition to, or in interaction with familial loading of mood or substance use disorders? (chapter 4)
4. Are familial loading of mood and substance use disorder, birth weight, and family problems predictive of changes in the level of parent reported emotional and behavioral problems across a 14-month interval? (chapter 5)
5. Is there an association between life events and the onset of mood disorders across a 14-month interval? (chapter 6)

In chapter 2, the prevalence of psychopathology in children of bipolar parents aged 12 to 21 years was determined. The findings showed that, contrary to expectation based on previous research data, the prevalence of psychopathology in our sample was not highly elevated as compared to a general population sample. The mothers scored their daughters higher than the norm group of non-referred children in the general population on 8 of 11 CBCL scales and their sons on 4 of the 11 CBCL scales. Mothers reported elevated problem scores for girls aged 11-18 years on 8 of the 11 CBCL scales and on 4 of the 11 CBCL scales for boys. Adolescents scored themselves significantly lower on 4 YSR scales and 4 scales of the YASR. Only girls aged ≥ 19 years reported more attention problems than girls of the same age in the normative sample did. Teachers did not report more problems in children of bipolar parents than in children from the normative sample. The 2-month prevalence of all disorders (both mood and non-mood disorders) was 29%, while the 6-month prevalence in a general population sample was 35.5%. In our study, the recalculated 6-month prevalence was 30%.

Whenever there were problems amongst children of bipolar parents these were problems in the affective spectrum. The number of affective problems as reported by mothers among their daughters and the number of mood disorders among both girls and boys was increased as compared to a general population sample. The 2-month prevalence of mood disorders was 14% while the 6-month prevalence in the general population was 7.2%. The prevalence of lifetime mood disorders in our sample was 27%.

A possible explanation for the overall lower prevalence of psychopathology in our study as compared to the majority of previously published studies is that our sample may be overrepresented by parents who are less impaired than the samples of previous studies. There are a number of reasons indicating that this might be true. Firstly, two third of the offspring in our sample was recruited via the Dutch Bipolar patient association. Most other studies did not recruit their patients via patient associations, but via outpatient or inpatient clinics. Possibly, patients recruited via patient associations are relatively well functioning. Secondly, the divorce rate in our sample (24%) is lower compared to other studies. For instance, the New Zealand study reported that only 20% of patients were married

prior to their hospitalization compared to 55% in the general population (McPherson et al., 1992). Thirdly, whereas other studies showed that psychosocial outcome in bipolar patients is considerably impaired (see McQueen et al., 2000 for a review on psychosocial outcome in bipolar disorder over the last 25 years), the occupational level of the parents in our sample did not differ from that of the general population. This indicates that even though the families included a bipolar parent the socioeconomic status based on occupational level of the parents is not significantly different from that of families without a bipolar parent. Fourthly, although other studies did not provide information on IQ in bipolar offspring, it was remarkable that the mean IQ of the offspring of our sample was significantly higher than in the general population (113, SD = 16 versus 100, SD = 15 respectively). In our sample, a relatively high IQ could protect the offspring from developing psychopathology. Unfortunately, in most studies the IQ of the offspring and the SES of the parents is not reported. Therefore, we are not able to conclude whether differences in occupational level and/or IQ between the various studies are responsible for differences in prevalences. Finally, it is also possible that the American samples were overrepresented with patients who were more impaired. For example, cross-cultural differences may have arisen because of differences in accessibility to mental health care.

Another possible explanation for the difference in prevalence between our own and other studies could be that the children in our sample were on average younger than those in other studies. However, as shown in chapter 2, the ages in the KBO-cohort are not lower than the ages used in other studies.

A third possibility is that the risk for Dutch bipolar offspring is similar to the risk as reported in US studies but that this risk is expressed at a later age in our sample than in the US samples. Recent results of the third measurement, 5 years after the first measurement, of our sample point in this direction (Hillegers et al., submitted). However, it should be stressed that at the third measurement a different assessment procedure than in the first two measurements was used hampering the comparability over time.

In chapter 3, we determined whether familial loading of unipolar, bipolar and substance use disorder is associated with DSM-IV mood disorders in adolescents at risk for bipolar disorder. An important finding was that a positive family history of unipolar disorder was a strong and independent predictor of the development of mood disorders in the offspring of bipolar parents. Another important finding was that familial loading of substance use disorder also was a strong and independent predictor of the development of mood disorders in the offspring of bipolar parents. It is possible that the family members with substance use disorder were actually having a masked mood disorder or they could still develop a mood disorder in the future. Another possibility is that substance use disorder and mood disorder share a common risk factor, which results in the clustering of the two traits across generations. However, since there was no correlation between the two genetic vulnerabilities this explanation seems unlikely.

Because the results remained unchanged when we excluded the first-degree relatives from our familial loading index, we concluded that the familial risk of disorders that are present in adolescence in our sample seems to be predominantly genetic in origin. Familial loading of unipolar disorder and substance use disorder increased the risk of mood disorder in offspring in a specific way because we did not find an increased risk for non-mood disorder in relation to familial loading of mood disorders.

Since the adolescents who did not have a mood disorder at time of the interview might develop a mood disorder as they grow older, it is possible that the association between familial loading and mood disorders will disappear in the future. The conservative interpretation of our findings is therefore that familial loading influences the age at which a mood disorder first manifests itself, higher familial loading being associated with earlier expression. Since the associations remained significant when we excluded the bipolar offspring from the analyses we concluded that familial loading of unipolar disorder and substance abuse are not only related to bipolar disorder but to unipolar disorders in children of bipolar parents as well.

There are several explanations for these findings. First, genetic vulnerability for bipolar disorder could be phenotypically expressed as bipolar, unipolar disorder and substance use disorder (pleiotropy). However, the fact that the three familial loading indices were not correlated, suggested that mood disorder and substance use disorder are not phenotypical variants of the same underlying vulnerability.

A second possible explanation for the findings is that unipolar, bipolar and substance use disorder do not overlap genetically, but influence the expression of each other via epistase or gene-gene interaction. If this were true, given a certain amount of risk of bipolar disorder an additional familial loading of unipolar and/or substance use disorder would result in a higher probability of expression of or at least an earlier expression of mood disorders. For instance, the fact that familial loading of substance use disorder increased the risk of mood disorders and not of substance use disorder itself suggests that familial loading of substance use disorder potentiated the risk for mood disorders. However, a comparison sample is needed to verify if the effects of familial loading of unipolar disorder and substance use disorder is the same or even smaller than in a comparison group of children of parents without psychiatric disorders.

A third explanation for our findings is that unipolar, bipolar and substance use disorder do not overlap genetically, but influence the expression of each other true gene-environment interaction. It is possible that the environmental influence of growing up with a bipolar parent results in mood disorders when there is also additional familial loading of unipolar or substance use disorder in among second degree relatives. However, if this were true, we would have expected more heterotopy in the transmission of disorders. In other words: if having a bipolar parent is a non-specific environmental factor than it may be expected that children with increased familial loading of substance use disorder would show more conduct disorders and substance use disorders. However, this is not the case.

The most plausible explanation for the association between familial loading of unipolar and substance use disorder and lifetime mood disorders in bipolar offspring is gene-gene interaction, but further research in which a comparison sample of children of parents without psychiatric disorder is included is needed.

In chapter 4, different models for ways at which birth weight and familial loading influence the risk for psychopathology among children of bipolar parents were studied. Low birth weight was associated with mood and non-mood disorders, even when adjusted for familial loading of unipolar, bipolar and substance use disorder. Familial loading and birth weight were each independently associated with psychopathology among children of bipolar parents (the independent association model). Because the association between familial loading and psychopathology remained after adjustment for birth weight it may be concluded that the association between familial loading and psychopathology was not mediated by birth weight (mediation-model). Finally, birth weight did not modify the association between familial loading and psychopathology or vice versa (interaction-model).

Although our findings indicate that there is a link between birth weight and various aspects of human functioning involving the brain, the exact mechanisms by which these associations work are far from clear. Birth weight is determined by various genetic and non-genetic factors. Understanding the role of birth weight or of the mediating role of birth weight in the mechanisms responsible for the development of psychopathology may give us clues for preventive interventions in the future.

In chapter 5, we determined the influence of familial loading of unipolar disorder, birth weight and family problems on the course of psychopathology in children of bipolar parents. In order to accurately determine changes the level of psychopathology we have chosen for a relatively short follow-up of 14-month. Scores of the parents were obtained with the Child Behavior Checklist (CBCL) and the Young Adult Behavior Checklist (YABCL). Familial loading of unipolar disorder appeared to be associated with an increase in level of behavioral and emotional problems during the 14-month follow-up. We concluded that genetic factors not only have an influence on the development of lifetime mood disorders, but also on the increase of behavioral and emotional problems during a relatively short period.

An explanation for the finding that familial loading of unipolar disorder not only predicted an increase of Internalizing scores but also of Externalizing scores on the CBCL/YABCL could be that externalizing behaviors precede the development of mood disorder in bipolar offspring. Further longitudinal research in order to test this hypothesis is advised. In the study that is described in chapter 6 (see hereafter), familial loading of unipolar disorder was not associated with onset or recurrence of mood disorders during the follow-up of 14 months. Thus, familial loading of unipolar disorder only predicted increases in emotional and behavioral problems across a wide scoring range, including subclinical changes.

Possibly, the number of first or recurrent mood episodes during the 14-months follow-up was too small to detect statistically significant associations.

Birth weight and family problems did not predict change in psychopathology across a 14-month follow-up in children of bipolar parents. In chapter 4, birth weight was however, associated with the onset of mood and non-mood disorders. Birth weight does appear to exert its influence on a lifetime basis. For now, we can conclude that birth weight and family problems do not predict changes in level of problem behavior during a 14-month interval.

In chapter 6 the association between severe stressful life events (SLEs) and the development of first or recurrent episodes of mood disorder episodes (MDEs) during a 14-month follow-up was determined. SLEs were measured with the Bedford College Life Event and Difficulties Schedule (LEDS) (Brown and Harris, 1978, 1989) which Monck and Dobbs (1985) adapted for use with adolescents (the K-LEDS). Both SLEs and mood disorder episodes were dated carefully and only SLEs that occurred within the 6 months prior to onset, or a control period for those without a diagnosis, were used for analyses. Dependent SLEs were associated with a first or recurrent MDE. This association remained after adjustment for SES and familial loading. However, the association disappeared entirely after adjustment for affective problems at first measurement. Baseline affective problems appeared to increase the risk for both SLEs and mood disorders.

Since the association between early symptoms and onset/recurrence of MDE did not change after adjustment for SLEs we concluded that SLEs did not mediate the association between early affective symptoms and MDE onset/recurrence. Further research with assessments of the offspring over a longer follow-up interval and thereby probably a higher number of new onsets and/or recurrences of mood disorders is necessary in order to determine whether the association between SLEs and onset/recurrence of a mood episode still disappears after adjustment for baseline affective problems.

In chapter 7, the most important findings and conclusions of the current study were summarized and research and clinical implications of our findings are given. The chapter ends with the most important research implications and clinical implications of our findings.

The strength of this study was the relatively large sample of offspring ($n = 140$), the longitudinal character, the low attrition rate at follow-up of 14 months, the use of multiple informants, the fact that we studied the effects of familial loading on the onset of mood disorders and of both genetic and environmental factors independent from each other and in interaction with each other.

The most important shortcomings of this study are the representativeness of the sample and the lack of normative data for psychiatric interviews, thereby hampering the interpretation of prevalence data. Even if we would study representative samples of children of bipolar parents this would not result in findings that are generalizable to all individuals who develop bipolar disorder, since there are individuals who develop bipolar disorder without having parents

who develop a bipolar disorder. Therefore, this study underlines the need of longitudinal research in which a large cohort of children from the general population is followed in order to identify new cases with bipolar disorder.

It remains difficult to determine the exact magnitude of the risk for children of bipolar parents to develop psychopathology because there is a lack of studies that generated prevalence data based on information from multiple informants, using both rating scales and interviews in representative samples of children from bipolar parents, with population norms available for these assessment instruments. Future studies should not only compare children of patients with bipolar disorder with children of healthy parents but also with children of parents with other psychiatric disorders. Only then will it be possible to determine the extent to which psychopathology in bipolar offspring is due to specific factors related to having parents with a bipolar disorder or to having parents with a psychiatric disorder in general. In addition, this study underlines the importance of carefully describing the sample procedure, including recruitment, sample selection, sample composition, e.g. SES, IQ, and educational level of both parents and offspring. Only then will it be possible to compare and interpret findings from different studies.

For clinicians it is important to know that children of bipolar parents have an increased risk of developing internalizing problems, especially when there is additional familial loading of unipolar disorders and substance use disorders. It is therefore advised to obtain an overview of the occurrence of mood disorders and substance use disorders among first- and second-degree relatives of children of bipolar parents. If children of bipolar parents do not fulfill the criteria of bipolar or unipolar disorder this does not mean that they are not at increased risk of developing mood disorders, especially those who show more affective problems compared to the general population. Clinicians working with bipolar patients should be alerted by internalizing problems in offspring of bipolar parents. Once these are present, full diagnostic assessment should be done in order to start adequate treatment as soon as the first episode emerges.

The studies described in this thesis concern the first and, 14 months later, the second measurement of the KBO (Children of Bipolar Parents)-project. These studies have contributed to a better understanding of the development of psychopathology, especially mood disorders, among these children, as well as factors increasing the risk for the development of these mood disorders. The third measurement of our sample, 5 years after the first measurement, will help us to answer further and other research questions on the prevalence of psychopathology and on factors influencing the development of mood disorders, including bipolar disorders. Such longitudinal research among representative samples of bipolar offspring is very important for those who are prone to develop bipolar and other mood disorders.

