Children of bipolar parents
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Chapter 4: The impact of birth weight and genetic liability on psychopathology in children of bipolar parents

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Abstract

Objective: To test different models for ways in which birth weight and familial loading influence the risk for psychopathology in bipolar offspring. Methods: DSM-IV diagnoses of 140 bipolar offspring (aged 12-21) were assessed with the K-SADS-PL. Parents were interviewed using the FH-RDC to determine familial loading (FL) of mood and substance use disorders. Parents reported the birth weight of their offspring. Age-and sex- adjusted hazard ratios were calculated. Results: Low birth weight was associated with mood and non-mood disorders in bipolar offspring (HR = 0.6, Confidence Interval (CI) = 0.4-0.8), even after controlling for familial loading of unipolar disorder, bipolar disorder or substance use disorder. There were no significant interactions between birth weight and familial loading of unipolar disorder, familial loading of bipolar disorder and familial loading of substance use disorder. Conclusions: Birth weight is associated with mood as well as non-mood disorders. This association is independent from the association of familial loading of mood and substance use disorder with mood- and non-mood disorders in bipolar offspring. Keywords: Bipolar disorder, birth weight, familial loading, bipolar offspring, substance use disorder

Introduction

Offspring of parents with bipolar disorder have an increased risk for psychopathology, especially mood disorders (DelBello and Geller, 2001; Lapalme et al., 1997). The reported risk for lifetime mood disorders is approximately 4 times higher for children of bipolar parents than for children of parents with no mental or no major mental disorder (Lapalme et al., 1997). Rates of mood disorders in child and adolescent offspring of bipolar parents range from 5 to 67% compared with rates in offspring of healthy volunteers of 0-38% (Delbello and Geller, 2001). We found a lifetime prevalence of mood disorder of 27% among a sample of 140 children, aged 12-21 years, of bipolar parents (Wals et al., 2001). To advance our understanding of the etiology, prevention, and treatment of mood disorders it is important to know which factors contribute to their development. The etiology of mood disorders is probably multifactorial; both genetic and environmental factors play a role in the development of mood disorders (Goodwin and Jamison, 1990; Harrington, 1993).

In a previous study, a positive family history of unipolar and substance use disorder was associated with a higher risk of mood disorders in the offspring of bipolar parents, hereafter referred to as bipolar offspring (Wals et al., 2003). The familial loading scores we used in this study largely concerned relatives that were distant from the proband, making it reasonable to assume that the familial loadings of mood disorder or substance use disorder reflect mostly genetic influences rather than direct environmental influences.

Among environmental factors increasing the risk for developing mood disorders low birth weight can be viewed as a marker of prenatal environmental
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influences. The relevance of prenatal factors that may influence birth weight has been stressed by Barker (1998) 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.

A number of studies have assessed the associations between obstetric complications (including birth weight) and unipolar as well as bipolar disorder (e.g. Botting et al., 1997; Browne et al., 2000; Buka and Fan, 1999; Guth et al., 1993; Hultman et al., 1999; Kinney et al., 1993; Kinney et al., 1998; Lewis and Murray, 1987; Sigurdsson et al., 1999; Stober et al., 1997; Thompson et al., 2001; Verdoux and Bourgeois, 1993; Waters et al., 1982), but the results of these studies on the association between birth weight and unipolar and bipolar disorder are not unequivocal. A possible reason for this is that previous studies did not take account of possible effects of familial loading reflecting genetic liability. Genetic liability reflected by familial loading might influence both birth weight and psychopathology, or the association between birth weight and psychopathology might be enhanced or reduced by genetic liability. This is important because the association between low birth weight and psychopathology may represent a true causal influence, but it could also represent the effect of a third genetic or environmental variable influencing both characteristics (van Os et al., 2001; Wichers et al., 2002).

The association between birth weight and mood disorder does not seem to be specific since birth weight is also associated with other disorders, such as ADHD (Botting et al., 1997; Gjone and Novik, 1995; McCormick et al., 1990; Szatmari et al., 1990), schizophrenia (Cannon et al., 1997; Jones et al., 1998; Lewis and Murray, 1987; Rifkin et al., 1994), autism, mental retardation, learning and eating disorders (Eaton et al., 2001), depressive symptomatology (Frost et al., 1999; Hoy et al., 1992), and with behavioral problems (Horwood et al., 1998; Sommerfelt et al., 1996; Van Os et al., 2001; Wichers et al., 2002).

Thus, birth weight has been reported as a risk factor for unipolar and bipolar mood as well as non-mood disorders, but the results of previous studies are contradictory. Therefore the association between birth weight and psychopathology remains unclear. A possible interaction between birth weight and familial loading might explain the diverse findings on the relationship between birth weight and psychopathology in different samples. The association between birth weight and genetic liability and the risk to develop psychopathology has rarely been studied (van Os et al., 2001; Wichers et al., 2002).

This study tested whether birth weight predicts mood or non-mood disorders in bipolar offspring independent from, in addition to, or in interaction with familial loading of mood or substance use disorders. We compared the following three models: 1) familial loading and birth weight are each independently associated with psychopathology in bipolar offspring (independent association model); 2) the association of familial loading with psychopathology is mediated by birth weight (mediation-model); and 3) birth weight modifies the association of familial loading with psychopathology, or vice versa (interaction-model). Since socioeconomic status (SES) could be an environmental factor influencing both birth weight and psychopathology we corrected the analyses for SES.
Chapter 4

Methods

Population and Procedure
All subjects were enrolled into the study between November 1997-March 1999. The sample consisted of 86 bipolar parents (64 bipolar I and 22 bipolar II), their spouses and 140 offspring aged 12-21 years of a parent with bipolar disorder. Adolescents 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 to 21 years refused to participate. All bipolar parents were outpatients at the moment of recruitment.

The mean age of the participating offspring was 16.1 years (SD = 2.7; range 12-21). Fifty-two out of 86 proband parents were mothers (60%). The mean age of the bipolar parents was 45.4 years. 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. Achenbach et al. (1987) computed correlations between parental occupational level for a general population sample scored on Hollingshead SES versus the Dutch scoring system for SES that is comparable to the scores we used for the present study. The authors reported a Pearson correlation of 0.92 (p < 0.01) between the two sets of scores. The mean SES of the parents in our sample of 4.9 (SD = 2.1) did not differ significantly from the mean of 4.5 (SD = 2.1) from a Dutch general population sample (Netherlands Central Bureau of Statistics, 1993) (t = 1.941, p = .06). 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. (2001).

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; Hiller et al., 1993) 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.

Assessment of DSM-IV disorders in bipolar offspring
The K-SADS-present and lifetime version (K-SADS-PL; Kaufman et al., 1997) was used to derive DSM-IV diagnoses in the adolescent bipolar offspring. The K-SADS-PL is an interviewer-oriented diagnostic interview designed to assess current and past DSM-IV symptoms resulting in diagnoses in children and adolescents, by interviewing the parent(s) and child separately. If parents and child disagreed on the presence of a symptom, greater weight was typically given
to parents’ reports of observable behavior and children’s reports of subjective experiences (Kaufman et al., 1997). The K-SADS-PL was conducted by three of the authors (M.W., M.H.J.H., and C.G.R.) and by five intensively trained interviewers with graduate degrees in psychology. Different interviewers interviewed parents and offspring of the same family. In addition to the K-SADS–derived diagnoses (for mood, anxiety, attention deficit, conduct, substance abuse, eating, posttraumatic stress, adjustment, and tic disorders; enuresis/encopresis), we also screened for DSM-IV pervasive developmental disorders. All diagnoses were made without knowledge of subjects’ obstetrical histories.

Diagnoses in the offspring (the probands) were grouped into two categories: 1) any lifetime mood disorder (unipolar disorder, bipolar disorder, and other mood disorder) and 2) any lifetime non-mood disorder.

At least one lifetime DSM-IV diagnosis was assigned to 61 (44%) out of 140 adolescents. 38 adolescents (27%) were assigned at least one mood disorder diagnosis of which 22 adolescents were also assigned a non-mood disorder. We decided to include these 22 in the mood disorder group and not in the non-mood disorders group. Twenty-three adolescents (16%) were assigned at least one non-mood disorder without comorbid mood disorder. These were included in the non-mood disorder group. Thus, the mood disorder group includes 38 unique individuals and the non-mood disorder group includes 23 unique individuals. There were no significant differences between the two samples in the distribution of gender and age.

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 Family History-Research Diagnostic Criteria (FH-RDC; Andreasen et al., 1977) interview and administered to both parents. The following diagnoses: unipolar disorder, bipolar disorder, and substance use disorder among first and second degree relatives were described predominantly in the literature to be associated with bipolar disorder (Goodwin and Jamison, 1990). Therefore, we decided to apply only sections of the FH-RDC yielding these disorders.

Although all children had at least one bipolar parent, the parents with bipolar disorder as well as the parent without bipolar disorder will differ in their level of background familial loading for mood and non-mood disorders, and therefore will have different probabilities to transfer vulnerability for these disorders to their offspring. Family history (FH) can be used as a dichotomous indicator of familial loading, but the use of a dichotomous FH+ and FH- variable does not take into account, for example, that two bipolar patients in a family of 10 with mean age 23 years is not the same as 2 bipolar cases in a family of 3 with mean age 60 years. Using a method developed previously for this purpose (Verdoux et al., 1996), we defined several variables reflecting the continuously distributed level of familial loading for mood and non-mood disorders transmitted from the parents to the child, taking into account i) the number of adult first-degree relatives of the parents and ii) their ages.
An appendix in which the familial loading score is described in more detail is available via the ArticlePlus feature on the Journal’s Web site at www.jaacap.com.

Assessment of birth weight
Parents gave us the birth weight of their offspring that was recorded in birth records that they obtained just after birth.

Statistical analysis
Tests for associations between birth weight (in units of 500 g) and familial loading, on the one hand, and psychiatric disorder in the probands, on the other were performed using Cox proportional hazard regression analysis. This analysis provides a convenient way of controlling for time in the analysis of cohort studies, in this case the cohort of children of bipolar parents who were assessed over varying periods of time (i.e. the period from birth to age at interview). Associations were expressed as the hazard ratio (HR). The HR is the exponentiated regression coefficient of the Cox proportional hazard regression procedure (STATA version 7.0), and is equivalent to the relative risk of the specified psychiatric disorder in the children of bipolar parents with varying degrees of familial loading or birth weight, but the independent/predictor variable is continuous rather than categorical. Because observations were clustered within families (47 families contributed more than one child), compromising statistical independence of the observations, standard errors were adjusted for clustering on family using the “cluster” and “robust standard error” options in the STATA regression procedure. First, models of mood and non-mood disorder in the adolescents were examined with the birth weight variable or a familial loading variable as the independent variable. Second, to correct for the possible confounding influence of gender of the offspring, the same models were assessed with adjustment for gender. Because of substantial co-morbidity between mood and non-mood disorders in adolescence (Verhulst et al., 1997) offspring with mood disorders (including those with comorbid non-mood disorders) were compared with offspring without any DSM-IV disorder and likewise, offspring with non-mood disorders (without comorbid mood disorders) as described above were compared with offspring without any DSM-IV disorder. To determine whether any association with birth weight was independent of the familial loading variables analyses were performed with all variables entered together.
Results

Table 1 shows the associations between birth weight and mood and non-mood disorders and between familial loading of mood and substance use disorders and mood and non-mood disorders in bipolar offspring. As described above, all analyses were adjusted for gender of the bipolar offspring.

Table 1: Impact of birth weight and familial loading (FL) on psychopathology in bipolar offspring

<table>
<thead>
<tr>
<th></th>
<th>Any mood disorder</th>
<th></th>
<th>Any non-mood disorder</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (CI) (^b)</td>
<td>(p)</td>
<td>HR (CI) (^b)</td>
<td>(p)</td>
</tr>
<tr>
<td>Birth weight</td>
<td>0.6 (0.4-0.8)</td>
<td>0.001</td>
<td>0.6 (0.4-0.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>FL unipolar disorder</td>
<td>1.5 (1.2-2.0)</td>
<td>0.002</td>
<td>1.3 (0.9-1.8)</td>
<td>NS</td>
</tr>
<tr>
<td>FL bipolar disorder</td>
<td>0.8 (0.5-1.1)</td>
<td>NS</td>
<td>0.8 (0.6-1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>FL substance use disorder</td>
<td>1.8 (1.3-2.4)</td>
<td>0.000</td>
<td>1.9 (1.0-3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight, adjusted for FL unipolar disorder</td>
<td>0.6 (0.4-0.8)</td>
<td>0.001</td>
<td>0.5 (0.4-0.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>Birth weight, adjusted for FL bipolar disorder</td>
<td>0.6 (0.4-0.8)</td>
<td>0.001</td>
<td>0.6 (0.4-0.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Birth weight, adjusted for FL substance use disorder</td>
<td>0.5 (0.4-0.8)</td>
<td>0.001</td>
<td>0.6 (0.5-0.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Birth weight, adjusted for SES</td>
<td>0.6 (0.4-0.8)</td>
<td>0.001</td>
<td>0.6 (0.4-0.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>BW, adjusted for:</td>
<td>0.5 (0.4-0.8)</td>
<td>0.001</td>
<td>0.6 (0.4-0.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>- SES</td>
<td></td>
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<td></td>
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<tr>
<td>- FL unipolar disorder</td>
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<tr>
<td>- FL bipolar disorder</td>
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<td></td>
</tr>
<tr>
<td>- FL substance use disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight x FL unipolar disorder</td>
<td>1.1 (0.8-1.5)</td>
<td>NS</td>
<td>1.1 (0.9-1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight x FL bipolar disorder</td>
<td>0.8 (0.7-1.0)</td>
<td>NS</td>
<td>0.9 (0.6-1.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight x FL substance use disorder</td>
<td>1.1 (0.4-2.9)</td>
<td>NS</td>
<td>1.6 (0.3-8.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight x SES</td>
<td>1.0 (0.9-1.2)</td>
<td>NS</td>
<td>1.0 (0.9-1.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: HR = Hazard Ratio; CI = 95% Confidence Interval; SES = socioeconom status; NS = not significant

\(^a\) Corrected for gender of the proband

\(^b\) HR = 1 indicates no association between variable and diagnosis in proband. HR > 1 indicates positive association; a higher score on the predictor variable predicts the disorder in the proband. HR < 1 indicates negative association; a lower score on the predictor variable predicts the disorder in the proband.
Chapter 4

**Associations between birth weight and mood and non-mood disorders**

Birth weight was significantly associated with mood disorders and with non-mood disorders (HR = 0.6, CI = 0.4-0.8 for both, see table 1); lower birth weight is associated with an increased risk for mood and non-mood disorders.

**Associations between familial loading and mood and non-mood disorders**

Familial loading of bipolar disorder was not significantly associated with mood disorder in the adolescents (HR = 0.8, CI = 0.5-1.1), but familial loading of unipolar disorders was (HR = 1.5, CI = 1.2-2.0). Thus, only higher familial loading with unipolar disorder is significantly associated with mood disorders in bipolar offspring.

Familial loading of substance use disorder was significantly associated with mood disorders in bipolar offspring (HR = 1.8, CI = 1.3-2.4); higher familial loading with substance use disorder is associated with an increased risk for mood disorders.

None of the associations between the three familial loading indices and the presence of non-mood disorders in the offspring was significant.

**Adjustment for familial loading**

The associations between birth weight and mood disorders and non-mood disorders remained significant after controlling for the effect of familial loading of unipolar disorder (HR = 0.6, CI = 0.4-0.8 and 0.5, CI = 0.4-0.8, respectively) or for the effect of familial loading of bipolar disorder (HR = 0.6, CI = 0.4-0.8 for both).

The association between birth weight and mood and non-mood disorders remained significant after adjustment for familial loading of substance use disorder (HR = 0.5, CI = 0.4-0.8 and HR = 0.6, CI = 0.5-0.9, respectively).

**Birth weight, adjusted for SES**

The associations between birth weight and mood disorders and non-mood disorders remained significant after controlling for the effect of SES (HR = 0.6, CI = 0.4-0.8 for both).

**Birth weight, adjusted for familial loading and SES**

The association between birth weight and mood and non-mood disorders remained significant after adjustment for all three familial loading scores and SES of the parents (HR = 0.5, CI = 0.4-0.8 and HR = 0.6, CI = 0.4-0.9, respectively).

**Interactions with familial loading**

There were no significant interactions between birth weight and familial loading of unipolar disorder on mood as well as non-mood disorders (HR = 1.1, CI = 0.8-1.5 and HR = 1.1, CI = 0.9-1.4, respectively) and between birth weight and familial
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loading of bipolar disorder on mood as well as non-mood disorders (HR = 0.8, CI = 0.7-1.0 and HR = 0.9, CI = 0.6-1.3, respectively).

There were no significant interactions between birth weight and familial loading of substance use disorder on mood and non-mood disorders (HR = 1.1, CI = 0.4-2.9 and HR = 1.6, CI = 0.3-8.7, respectively).

**Interaction with SES**
There was no significant interaction between birth weight and SES on mood as well as non-mood disorders (HR = 1.0, CI = 0.9-1.2 and HR = 1.0, CI = 0.9-1.1, respectively).

**Discussion**

In the present study, we compared three models of the association of birth weight and familial loading with the risk for lifetime mood and non-mood disorders in the adolescent offspring of parents with bipolar disorder.

The main conclusion to be drawn from our findings is that birth weight and familial loading of unipolar and substance use disorder are each associated with mood disorders among bipolar offspring. Birth weight is also associated with non-mood disorders, but familial loading of unipolar and substance use disorder is only associated with mood disorders. Of course, it is still possible that the bipolar offspring in this sample will eventually develop mood disorders and will cross over from the non-mood or no disorder group to the mood disorder group.

An interesting finding was that only familial loading of unipolar disorder was associated with mood disorder in offspring, but not familial loading of bipolar disorder. An explanation of this finding is that every participating adolescent in our sample had a bipolar parent resulted in a ceiling effect; 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), whereas the variance of familial loading of unipolar and substance use disorder ranged from no loading to extremely high familial loading.

The risks associated with lower birth weight and a positive familial loading are independent, since adjustment for familial loading did not reduce the risk associated with birth weight. It is therefore unlikely that the association of familial loading of unipolar, bipolar or substance use disorder with mood and non-mood disorders was mediated by the association of birth weight with mood and non-mood disorders in bipolar offspring (mediation-model).

The associations between birth weight and mood or non-mood disorders were independent from SES, since the associations remained significant after adjustment for SES.

Gene-environment interaction in the context of birth weight indicates that the effect of genetic factors on psychopathological outcome is not the same in individuals who differ in their birth weight (interaction-model). Our findings indicated that birth weight did not modify the association of familial loading of (unipolar and bipolar) mood disorders and of familial loading with substance use.
disorders with mood or non-mood disorders in bipolar offspring. We therefore did not find support for the interaction-model.

**Implications**

To our knowledge, this is the first study in high-risk offspring that shows that the association of birth weight with mood and non-mood disorders is independent from genetic liability, as measured with familial loading of unipolar and bipolar mood disorders and substance use disorders among first and second-degree relatives of bipolar offspring. However, as birth weight itself is subject to both genetic and environmental influences, any explanation for the apparent association between birth weight and psychopathology in bipolar offspring should consider genetic and environmental mechanisms including the possibility that the observed relationship between lower birth weight and DSM-IV diagnosis is due to a shared environmental or genetic variable that influences both characteristics (Wichers et al., 2002). In the present study we found an association between birth weight and psychopathology in children of bipolar parents; the lower the birth weight the greater the probability of psychopathology. Other studies reported on the association between birth weight and cognitive functioning (e.g. Eaton et al., 2001). Although these 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 possibly give us clues for preventive interventions in the future. At this moment we cannot go beyond the mere acknowledgement that birth weight plays a role in the risk of psychopathology. Further investigations are warranted to examine to what degree birth weight influences mental health outcomes directly and how these influences might be modified to reduce the risk.

**Limitations**

The prospective nature of the design does not ensure that birth weight is causal since it may be mediating or reflecting a more basic or antecedent causal event or characteristic, i.e. confounding variables such as a genetic predisposition, lifestyle, perhaps associated with social class.

The FH-RDC is an indirect assessment of the family history and may therefore have led to a relatively over- or underestimation of the number of diagnoses in the family. Furthermore, as the FH-RDC is relatively insensitive for the diagnosis of unipolar mood disorders when compared to the family study method (Andreasen et al., 1977), we may have missed diagnoses. However, we feel that the most severe disorders are likely to be identified using the FH-RDC and that the scores would be proportional whether additional information were available through family study or not.

The calculation of the lifetime risk for bipolar offspring to develop mood or substance use disorders by use of the FH-RDC is an approximation.
Appendix

To calculate the familial loading index, each child is regarded as either a potential "familial" or a "sporadic" case. This designation is just a conceptual starting point, not some real characteristic. In the case of bipolar disorder, it is assumed that the lifetime risk of this disorder in a first-degree relative is 10% for "familial" probands, whereas for unipolar disorder and substance use disorder this risk was estimated at 20%. As the lifetime risk for "sporadic" bipolar probands is not precisely known, we rather arbitrarily assumed that this lifetime risk is 0.5%, i.e. half of the lifetime risk for "familial" plus "sporadic" bipolar illness, which is approximately 1%. In addition, we assumed that the age at risk extended from 10 to 50 years, and that in this age range risk increases linearly with age from zero at 10 years to the lifetime risk at 50 years. The probability that a relative of age X is affected with bipolar disorder if the proband is "familial" is therefore (0.1)(X-10)/(50-10) and the probability that such a relative is unaffected is 1 minus this. Similarly, the probability that a relative of age X is affected if the proband is "sporadic" is (0.005)(X-10)/(50-10). The likelihood ratio for whether the proband is familial or sporadic, given that a relative of age X is affected is therefore [(0.1)(X-10)/(50-10)]/[(0.005)(X-10)/(50-10)]=20, and a similar ratio can be defined for an unaffected relative, although this ratio will be dependent on age. Such a likelihood ratio was calculated for every relative of a proband, and an overall likelihood ratio for whether the proband is "familial" or "sporadic" was obtained by multiplying these individual likelihood ratios. Because this overall likelihood ratio is likely to be highly skewed, we took its common logarithm and defined it as the familial loading score. A familial loading score of 0 indicates that there is equal support for the proband to be "familial" or "sporadic", a positive score indicates that there is greater support for the proband to be "familial", while a negative score indicates that there is greater support for the proband to be "sporadic". A similar procedure was followed for unipolar disorder and substance use disorder. The lifetime risks for unipolar disorder and substance use disorder for sporadic probands are also unknown and were assumed at 5%, i.e. half of the lifetime risk for “familial” plus “sporadic” illness of approximately 10%. Only 2 relatives showed a substance use disorder, therefore the familial loading score for substance use disorder comprised mostly relatives with alcohol use disorder.

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