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Familial transmission of parental mood disorders: unipolar and bipolar disorders in offspring

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Abstract

Objectives—Offspring of depressed parents are at increased risk for psychiatric disorders. Although bipolar disorder (BD) and major depressive disorder (MDD) are both found in the same families, it is not clear whether transmission to offspring of BD or MDD tends to occur from parents with the same mood disorder subtype. The primary hypothesis was that offspring of parents with BD would be at increased risk for BD and other comorbid disorders common to BD such as anxiety and substance use relative to offspring of parents with MDD. Offspring of parents with BD versus those with MDD were also hypothesized to be at greater risk for externalizing disorders, i.e., conduct disorder, attention-deficit hyperactivity disorder, or antisocial personality disorder.

Methods—Parents (n = 320) with mood disorders and their offspring (n = 679) were studied. Adult offspring were administered the Structured Clinical Interview for DSM-IV Axis I Disorders to establish the presence of psychopathology. Offspring aged 10 to 18-years-old were assessed with the School Aged Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version, and parents of children under age 10 completed the Child Behavioral Checklist. Data were examined using Cox Proportional Hazard regression.

Results—There was no difference in hazard of mood disorders in the offspring of parents with BD as compared to offspring of parents with MDD. However, a number of other parent and offspring characteristics increased risk for mood, anxiety, externalizing, and substance use disorders in offspring, including self-reported childhood abuse in parent or offspring, offspring impulsive aggression, and age of onset of parental mood disorder.

Conclusions—Mood disorders are highly familial independent of whether the parent's condition is unipolar or bipolar, and considerable overlap in the familial basis of MDD and BD was found. Although parental characteristics had limited influence on risk of offspring psychopathology, reported childhood adversity, be it in the parent or child, is a harbinger of negative outcomes. These risk factors extend previous findings, and are consistent with diathesis-stress conceptualizations.

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Keywords

bipolar disorder; familial transmission; major depressive disorder

High risk or *top-down* studies of psychopathology among offspring of individuals with bipolar disorder (BD) are a relatively recent addition to the literature on the familial aggregation of mood disorder. Four reviews (1-4) in the last 15 years have found that offspring of parents with BD are more likely to have an Axis I diagnoses, major depressive disorder (MDD), BD, attention deficit disorders, and externalizing behavior disorders compared to offspring of healthy controls. Findings from a controlled study by Nurnberger et al. (5) conducted subsequent to these reviews also show excess risk of mood disorder, and specifically BD, among offspring of parents with BD. Offspring with BD were not, however, at increased risk of a primary externalizing or anxiety disorder compared to offspring of community-member probands (5).

High-risk studies that compare offspring of probands with BD with offspring of probands with MDD are scarce. A computer assisted literature search from 1966 to 2012 uncovered nine studies based on six different samples (6-14). Findings from these studies vary, with some reporting that offspring of MDD mothers/parents have more psychopathology than offspring of BD mothers/parents (6, 7, 9, 10). Others report that offspring of parents with BD have greater morbid risk (12, 14) or similar risk (8, 11, 13). Nonetheless, estimated rates of psychopathology range from 5% to 67% for offspring of parents with BD (1) and 15% to 80% for offspring of parents with MDD (15).

The largest study comparing psychopathology in offspring of MDD versus BD probands revealed higher rates of transmission of mood disorder from parents with BD to their offspring (12), and familial studies that include a broader range of first- and second-degree relatives find relatives of BD probands are at greater risk for mood disorder and specifically BD than relatives of unipolar probands [see (16) for a review, (17)]. Therefore, we hypothesized that parents with BD will transmit mood disorders to their offspring more often that parents with MDD (*Hypothesis 1*), and parents with BD will be more likely to have offspring with BD than parents with MDD (*Hypothesis 2*). We also hypothesized that parents with BD would more often transmit externalizing behavior disorders [conduct disorder, attention-deficit hyperactivity disorder (ADHD), antisocial personality disorder] (*Hypothesis 3*) and anxiety and substance use disorders to offspring than parents with MDD (*Hypothesis 4*). Finally, we hypothesized that parents BD or MDD with earlier age of onset would be more likely to transmit mood disorders than those with later onset (*Hypothesis 5*).

Methods

Sample

The sample consisted of 320 proband parents with mood disorders and their 679 offspring who were aged 10 years or older. Probands were either outpatients (47%) or recruited from inpatient units in New York and Pittsburgh (53%), and 49% had made at least one suicide attempt. Four previous communications reported on 299 offspring of 136 probands (18), 285 offspring of 141 probands (19), 365 offspring of 203 probands (20), and 507 offspring of 271 probands (21). Written informed consent/assent as approved by Institutional Review Boards at both institutions was obtained from all participating subjects.

All probands had a lifetime history of mood disorder and were categorized as having BD if they met DSM-IV-TR (22) criteria for bipolar I disorder (BD-I) or bipolar II disorder (BD-II) or if they were diagnosed with unipolar disorder but had a first-degree relative diagnosed

with BD-I, as is done in genetic studies of mood disorders [e.g., (23)]. All other probands were categorized as having MDD. Using this classification scheme: 234 probands had MDD and 86 had BD (BD-I: 42, BDI-II: 28, unipolar disorder with a first degree family member with BD: 16).

BD probands had a total of 177 offspring (mean age: 19.5 ± 10.0; 46% female). Parents with MDD had 502 offspring (mean age: 19.0 ± 8.6; 49% female). On average, there were 1.8 siblings aged 10 years or older per family. At the time of assessment, 35 offspring had BD and 125 had MDD.

Assessment

All subjects over age 18 years were assessed for the presence of lifetime and current DSM-IV psychiatric disorders using the Structured Clinical Interview for DSM-IV (SCID) (24). Offspring between the ages of 10 and 18 years were assessed for Axis I disorders using the School Aged Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL) (25). History of suicidal behavior was assessed using the Columbia University Suicide History Form (26) in all offspring. Offspring under the age of 10 were not included in this analysis.

Diagnostic procedure

All interviewers were at least Master's level clinicians or psychiatric nurses who received extensive training in the administration of semi-structured interviews. Interviewers of probands were blind to the diagnoses of the offspring and interviewers of offspring were blind to the diagnoses of the probands. Best-estimate diagnoses were made by consensus, and all available data sources were used in diagnostic consensus conferences. All diagnoses, including MDD, BD-I, and BD-II in the offspring, were defined according to DSM-IV criteria. Within and cross-site reliabilities on the SCID-I and SCID–II, K-SADS-PL, and suicide history were high [intraclass correlation coefficient (ICC) = 0.82–0.98, ICC = 0.86–0.95]; reliability analyses for BD in offspring: kappa = 0.88 (z = 4.65, p = 0.0000).

Data analysis

Demographic and clinical characteristics of probands with BD and MDD were compared using *t*-tests and chi-square statistics as appropriate. Mixed effects models were used to compare demographic and clinical characteristics of offspring of BD versus MDD probands. Because many of the offspring were not through the age of risk, we compared the two offspring groups with Cox Proportional Hazards (CPH) regression, rather than generating prevalences of disorders in offspring which would likely underestimate risk. Thus, CPH regression compared hazard for offspring of BD versus MDD probands of: (i) mood disorder, (ii) BD, (iii) externalizing disorders (conduct disorder, ADHD, and antisocial personality disorder), and (iv) anxiety disorders and/or substance use disorders. To test the proportional hazards assumption, we used the method of Therneau and Grambsch (27). We also examined whether parents with BD and parents with MDD parents with earlier age of onset were more likely to transmit mood disorders than those with later onset. Frailty analyses were conducted using family (i.e., proband) as a random effect to capture the correlation among family members. Because we (28) have reported that proband sexual abuse, offspring sexual abuse and offspring impulsive aggression have an effect on transmission of mood disorders, analyses were conducted controlling for these covariates as well as sex of proband and offspring.

Results

BD and MDD probands did not differ in terms of age, sex, race, income, educational level, marital status, or number of children (Table 1). The same was true for the offspring of BD and MDD probands (Table 2).

BD and MDD probands also did not differ on number of lifetime depressive episodes, history of childhood sexual or physical abuse, history of suicide attempt, or age of onset of disorder (Table 1). Regarding comorbidity among probands that could increase risk of psychopathology among offspring, BD and MDD probands were just as likely to have an externalizing disorder (7.0% versus 9.0%, $\chi^2(1) = 0.12$, $p = 0.73$) or an anxiety or substance use disorder (59.3% versus 59.4%, $\chi^2(1) = 0.01$, $p = 0.91$). Offspring of MDD probands were more likely to report a history of childhood physical abuse and trended to more frequently report a history of childhood sexual abuse than offspring of BD probands (Table 2).

Transmission of mood disorders

Whether the proband had BD or MDD did not determine risk for mood disorder, BD, or the other conditions of interest in offspring (Tables 3-6). Parents with BD were not more likely to transmit mood disorder in general, or BD in particular, compared to parents with MDD. Mood disorder and BD risk in offspring was also not associated with proband sex or proband self-reported sexual abuse. Reported sexual abuse and impulsive aggression among offspring increased the risk of both mood disorder and BD among offspring. Female offspring were at greater risk for mood disorder and trended ($p = 0.08$) to be at greater risk for BD than offspring of probands with MDD. For all outcomes, tests of the proportional hazards assumption indicated the risk for psychopathology due to proband mood disorder subtype or another covariate did not vary over time.

Risk for externalizing disorders

Parents with BD were no more likely to have offspring with externalizing disorders (conduct disorder, ADHD, or antisocial personality disorder) than parents with MDD. However, male offspring of probands with either BD or MDD were more likely than females to manifest these disorders. A history of sexual abuse in the proband and offspring impulsive aggression also increased risk of externalizing disorders in both male and female offspring.

Risk for anxiety or substance use disorders

Offspring of BD probands were not at greater risk than offspring of MDD probands for anxiety or substance use disorders. Sexual abuse of either the parent or the offspring increased risk, as did impulsive aggression in offspring. Neither proband nor offspring sex had an effect on risk.

Age of onset of proband mood disorder

In terms of age of onset, for every 10 years of earlier onset of mood disorder in the parent there was about a 29% increase in hazard of transmission of a mood disorder (Table 7). Offspring who reported sexual abuse or who showed more impulsive aggression were also at greater risk for mood disorder, as were females.

Discussion

We sought to elucidate differences in risk for psychopathology among offspring of probands with BD and MDD. Contrary to our hypotheses, there was no difference in hazard of offspring mood disorder or offspring BD based on proband mood disorder type. We also did

not find differences in rates of externalizing disorders, anxiety disorders, or substance use disorders in offspring of parents with BD versus parents with MDD. Our findings align with those of prior studies (8, 11, 13) that have found rates of psychopathology among offspring of probands with MDD and BD are similar. Radke-Yarrow et al. (8), for example, found children of MDD and BD probands were more, and comparably, symptomatic compared to children of healthy control parents, though onset of clinically significant externalizing, anxiety and depressive symptoms was later in offspring of BD compared to MDD probands. Findings from some *bottom-up* studies of psychopathology among relatives of adolescent BD and MDD probands also align with our findings, showing few differences in psychopathology among family members specific to type of proband mood illness. Kutcher and Marton (29), for example, found 20% of first-degree relatives of adolescents with MDD and BD had MDD, and more than 20% of the mood-disordered proband relatives had some other psychiatric illness, rates which were higher than those observed among first-degree relatives of normal controls. We based our hypotheses that psychopathology, including BD, would be more prevalent among offspring of probands with BD than MDD on findings showing BD and other disorders are more prevalent among relatives of BD than MDD probands (12, 16, 17). For example, Gershon et al. (12) in a study comparing adult offspring of MDD and BD probands and Smoller and Finn (16), in a review of familial studies, found relatives of probands with BD were at higher risk for mood disorder and specifically BD than relatives of MDD probands. Aukes et al. (17), in a large community sample, found the relative risk of BD among siblings of BD probands was three times the relative risk of BD among siblings of MDD probands. It may be that differences in the age of offspring in our and other studies explain differences in the observed relative rates of BD and MDD transmission. Future studies including adolescent and adult offspring are needed to confirm our findings.

Of note, findings from high risk studies specific to BD probands, which controlled for potential confounding factors (e.g., differences in SES and family structure that may explain higher rates of psychopathology among offspring of BD versus controls), show offspring of BD probands are at much greater risk for MDD, BD, and ADHD than controls. Birmaher et al. (30), for example, found offspring of parents with BD were at 18-, 15-, and 4-times greater risk of mood disorder, BD, and ADHD, respectively, than offspring of community controls. Similar studies specific to MDD probands show a three-fold greater lifetime risk of mood disorder among offspring of MDD probands, even when offspring have aged past the period of highest risk of onset of mood disorder (31). Thus, although offspring of probands with mood disorders are more likely to have psychopathology than offspring of healthy or community controls, the specific subtype of mood disorder may not be as relevant.

Though our findings do not support an increased risk of psychopathology among offspring of BD, as opposed to MDD probands, our findings extend evidence of the deleterious effects of childhood sexual abuse on offspring mental health and add additional evidence supporting an association between impulsive aggression and psychopathology. We found that childhood sexual abuse and impulsive aggression were associated with elevated risk of offspring anxiety or substance use disorder, MDD, and BD and that impulsive aggression was also associated with externalizing disorders (i.e., conduct disorder, ADHD, antisocial personality disorder) among offspring. Findings from a large scale epidemiological study are similar and show childhood sexual abuse increases the risk of anxiety disorder, mood disorder, including BD, and substance use disorder (32). Our findings also extend those of Brent et al. (28), which identified these variables as risk factors for the transmission of MDD in this same sample. Hirshfeld-Becker et al. (33) similarly showed behavioral disinhibition, a precursor to aggression and mood disorder (34, 35), was elevated among child offspring of parents with BD compared to parents with no BD. Clearly, these factors are important, and

perhaps equally or even more important than proband psychopathology, for transmission of mood disorders.

Similarly, Grano et al. (36) found impulsivity predicted first episode of depression among adults followed for two years. The relationship remained significant even after other known risk factors, such as female sex and lack of social support, were controlled. Trait impulsivity is also prominent in BD (37, 38). Specifically, although impulsivity is higher during mood episodes, even between mood episodes, adults with BD score in the 85th percentile on trait impulsivity measures (39) suggesting impulsivity is not solely dependent on mood state. Swann et al. (40), however, found certain aspects of impulsivity were specific to depressive or manic mood state among adults with BD, with motor impulsivity, i.e., impulsive action, linked to mania and non-planning impulsiveness, i.e., present orientation (41), being associated with depression.

Trait aggression is also robustly associated with BD (42, 43), with some finding aggression predicts early onset BD and/or more severe course of illness (44). The observed relationship between impulsive aggression, i.e., a propensity towards unpremeditated and spontaneous aggression, and mood disorder is further supported by biological data showing common neurobiological factors, e.g., disrupted dopaminergic (45) or serotonergic function (46), to impulsive aggression and affective symptoms.

Perhaps not surprisingly, male offspring, along with those high in impulsive aggression, were at increased risk for externalizing disorders. Female offspring were at increased risk of mood disorders. These sex differences are consistent with large-scale epidemiological study showing associations between male sex and externalizing disorders and female sex and internalizing disorders (47).

Interestingly, *proband* history of childhood sexual abuse was a risk factor for externalizing, anxiety, and substance use disorders among offspring. This finding is consistent with findings from previous investigations using subsamples of the current sample showing parental sexual abuse is associated with offspring psychopathology (20, 21, 28).

Finally, we found that early age of onset of mood disorder in the proband increased the hazard of mood disorder in offspring. A similar association of age of onset to familial transmission has been found in twin pairs (48). Further, Birmaher et al. (30) found age of onset of proband psychopathology predicted the age of onset in offspring. Early age of mood disorder onset is considered a proxy for genetic loading, high liability to illness, and subsequent elevated risk for familial transmission (48, 49). Thus, age of onset is a well-established and powerful predictor of many negative outcomes in probands and their family members. Taken together with the lack of differential risk based on proband diagnosis, these results suggest that mood disorders are likely closely related and result from interactions between genetic loading or risk and early adverse events.

There were limitations to this investigation. First, the majority of probands in our sample were in treatment, which may have resulted in selection bias (3). Probands were grouped according to their primary diagnosis, but subcategories of BD were not considered. We did not consider the psychiatric status of the non-proband parent, though it has been shown to be associated with offspring psychopathology in some studies (30) but not others (50). We did not consider bipolar disorder not otherwise specified (BD-NOS) separately as an outcome in offspring, though Birmaher et al. (51) has shown a significant minority of children and young adolescents with BD-NOS will develop BD-I or BD-II over the course of two years. Problems with self-reported and retrospective data (e.g., over-endorsement biases) might have been in effect (52). We did, however, use clinical interviews to assess psychopathology

in both probands and offspring, and we used different interviewers for parent and offspring, which is an improvement over the methods used in some previous studies (11, 53, 54). Additionally, although there is a high familial liability to mood disorder (55), the direction of transmission or the influence of third variables cannot be assumed given the cross-sectional design of the present investigation. Further, cross-sectional data collected when offspring were 19-years-old on average may preclude accurate understanding of psychopathology as offspring may not yet have passed through the age of highest risk for certain disorders, e.g., substance use disorder (56). Importantly, on average, offspring in our sample had passed through adolescence, the period when major depressive episodes often onset (57). Offspring, and even parents, classified as MDD in our study, however, may have been incorrectly subtyped, developing a manic or hypomanic episode subsequent to assessment. Twenty-five is the median age of onset for BD, and 10% of BD cases onset at age 50 years or older (58). In contrast to these concerns, Lewinsohn et al. (59) found support for the stability of mood disorder subtype across adolescence and young adulthood. In their study, very few depressed adolescents developed BD during young adulthood. In consideration of this limit to the data, we used CPH regression, which is an improvement over the statistical methods used in previous studies comparing offspring with BD and offspring with MDD that did not control for differences in length of offspring exposure to risk (6, 7, 9, 11, 13).

Despite these considerations, findings from this study should be confirmed by prospective follow-up, data we are currently collecting. Finally, we did not statistically correct for testing multiple outcomes. In exploratory studies, such as this one, this is acceptable (60).

Regardless of these limiting factors, these findings add to the growing literature on familial transmission of MDD and BD. If, in fact, transmission of psychopathology does not hinge on the specific type of mood disorder in the parent, the distinctiveness of these two diagnoses may be in question. Moreover, given that environmental aspects of an offspring's upbringing, such as childhood history of sexual abuse, increase risk, a model of vulnerability to mood disorder based on neurobiology and stressful life events is plausible. Indeed, DelBello and Geller (1) reviewed 17 studies of child and adolescent offspring of BD probands that met stringent review criteria, and recommended continued investigation of: phenotypic specification of pediatric BD, unaffected siblings who have genetic risk for BD, symptom onsets and offsets, and environmental factors. Beardslee et al. (61), in reviewing studies conducted from 1999–2011 of mood and anxiety disorder outcomes among offspring of mothers with MDD, concluded future studies should investigate psychobiological and environmental mechanisms underlying vulnerability to mood disorder among children of affectively ill mothers. It may also be fruitful to include healthy probands and those with non-affective disorder diagnoses to assess the influence of environmental factors and further rule out concomitants of other types of proband mental illness (62). As well, investigation of factors associated with long-term resilience in offspring of mood disorder probands is a compelling avenue for continued study, which may inform the development of optimal preventative therapies.

Conclusions

In summary, we found that mood disorders rates of transmission are similar among offspring of parents with MDD and BD. We also found that a number of risk factors inherent to offspring predict psychopathology among offspring, including impulsive aggression and history of childhood sexual abuse. Proband history of childhood sexual abuse also increased offspring risk of externalizing disorder, substance use disorder, and anxiety disorder. Earlier onset of mood disorder among probands also predicted higher mood disorder risk among

offspring. Continued study is needed to elucidate etiological factors, mechanisms of family transmission, and predictors of treatment response in this high risk and vulnerable group.

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Table 1

Demographic and clinical characteristics of bipolar disorder and major depressive disorder probands

	Bipolar disorder (n = 86)	Major depressive disorder (n=234)	Analysis		
			$t/\chi^2/W$	df	p-value
Demographics					
Age, mean ± SD, [median, range]	43.8 ± 11.0 [41.9, 24–73]	43.4 ± 10.3 [43.6, 24–80]	0.46	143	0.64
Sex, male, n (%)	12 (14.0)	44 (18.8)	0.72	1	0.40
Race, white, n (%)	54 (77.1)	157 (70.7)	0.80	1	0.37
Household income level (over $40,000/year), n (%)	33 (39.3)	80 (35.1)	0.30	1	0.58
Educational level, mean ± SD, [median, range][a]	5.0 ± 1.2 [5, 1–7]	4.9 ± 1.2 [5, 1–7]	0.55	134	0.58
Married, n (%)	36 (41.9)	112 (47.9)	0.69	1	0.41
No. of children, mean ± SD, [median, range]	2.7 ± 1.1 [3, 1–5]	2.5 ± 1.2 [2, 1–8]	W = 10664.5	NA	0.29
Clinical characteristics					
Age of onset, mean ± SD, [median, range]	24.1 ± 12.7 [21, 4–60]	25.8 ± 13.7 [24.5, 3–66]	1.0	158.8	0.31
No. of depressed episodes, mean ± SE, [median, range]	20.0 ± 4.0 [4[b], 0–99]	13.3 ± 1.9 [3[b], 1–99]	W = 7658.5	NA	0.10
Past suicide attempt, n (%)	46 (53.5)	112 (47.9)	0.59	1	0.44
History of sexual abuse, n (%)	36 (41.9)	100 (42.7)	0.005	1	0.94
History of physical abuse, n (%)	44 (51.2)	101 (43.5)	1.18	1	0.28

SD = standard deviation; SE = standard error; df = degrees of freedom.

[a]Education was rated as 7 = completed post-graduate training; 6 = completed college, received four-year academic degree; 5 = attended college, but did not receive four-year academic degree; 4 = completed high school, trade school, or other non-academic training requiring high school completion for admission; 3 = partial high school (10^{th} or 11^{th} grade); 2 = junior high school (7^{th}, 8^{th}, or 9^{th} grade); 1 = less than 7^{th} grade.

[b]Median quartile.

Table 2

Characteristics of offspring of bipolar disorder and major depressive disorder probands

	Bipolar disorder (n = 177)	Major depressive disorder (n = 502)	Analysis			
			$t/Z/\chi^2$	df	Den.df	p-value
Demographics						
Age, mean ± SD, [median, range]	19.5 ± 10, [15.6, 10–50.9]	19.0 ± 8.6 [16.6, 10–50.6]	0.75	1	293	0.45
Sex, male, n (%)	81 (54.3)	217 (50.1)	0.77	–	NA[d]	0.44
Race, white, n (%)	93 (75.0)	279 (70.1)	0.22	1	NA	0.82
Household income level (over $40,000/year), n (%)	33 (26.0)	81 (21.8)	0.37	1	NA	0.71
Educational level, mean ± SD, [median, range][a]	4.9 ± 1.2 [5, 1–7]	4.8 ± 1.2 [5, 2–7]	0.79	1	NA	0.43
Married, n (%)[b]	18 (30.5)	60 (33.5)	0.16	1	NA	0.87
Clinical characteristics						
History of sexual abuse, n (%)[c]	13 (10.7)	48 (12.6)	3.5	1	NA	0.06
History of physical abuse, n (%)[c]	13 (10.7)	63 (16.5)	6.9	1	NA	< 0.01

SD = standard deviation; df = degrees of freedom.

[a] Used proband data if offspring was under 18 years-of-age and offspring data if 18 or older. Education was rated as 7 = completed post-graduate training; 6 = completed college, received four-year academic degree; 5 = attended college, but did not receive four-year academic degree; 4 = completed high school, trade school, or other non-academic training requiring high school completion for admission; 3 = partial high school (10^{th} or 11^{th} grade); 2 = junior high school (7^{th}, 8^{th}, or 9^{th} grade); 1 = less than 7^{th} grade. (Mixed model did not converge; chi-squared test used.).

[b] Used only data of offspring 18 years-of-age and older.

[c] Likelihood ratio test based on mixed logistic regression adjusting for offspring sex.

[d] Mixed model software in *R* does *Z*-test instead of *F*-test. In that case df is infinity.

Table 3

Effect of parental bipolar disorder on transmission of mood disorder to offspring, adjusted for sex of proband, history of sexual abuse of proband, sex of offspring, impulsive aggression of offspring, and sexual abuse of offspring

Variable	Hazard ratio	95% CI	Chi square	df	p-value	Model
Bipolar proband	0.92	0.58–1.47	0.13	1	0.72	R^2 = 0.243
Sex of proband	0.96	0.57–1.61	0.03	1	0.86	
Sexual abuse of proband	1.36	0.88–2.09	1.89	1	0.17	LRT = 119
Sex of offspring	1.64	1.11–2.41	6.29	1	0.012	df = 31.6
Impulsive aggression of offspring	1.75	1.45–2.12	33.07	1	< 0.001	p ≤ 0.001
Sexual abuse of offspring	2.09	1.32–3.32	9.84	1	0.002	
Frailty	–	–	31.39	26.5	0.24	

CI = confidence interval; df = degrees of freedom; LRT = likelihood ratio test.

Table 4

Effect of parental bipolar disorder on transmission of bipolar disorder to offspring, adjusted for sex of proband, history of sexual abuse of proband, sex of offspring, impulsive aggression of offspring, and sexual abuse of offspring

Variable	Hazard ratio	95% CI	Chi square	df	p-value	Model
Bipolar proband	1.53	0.51–4.61	0.57	1	0.45	R^2 = 0.081
Sex of proband	0.58	0.17–2.03	0.72	1	0.40	
Sexual abuse of proband	1.04	0.32–3.33	0.00	1	0.95	LRT = 36.3
Sex of offspring	2.86	0.89–9.16	3.12	1	0.08	df = 11.5
Impulsive aggression of offspring	2.02	1.17–3.49	6.30	1	0.01	p ≤ 0.001
Sexual abuse of offspring	6.03	2.08–17.45	10.97	1	0.001	
Frailty	–	–	6.23	5.88	0.38	

CI = confidence interval; df = degrees of freedom; LRT = likelihood ratio test.

Table 5

Effect of parental bipolar disorder on risk of externalizing behavior disorders (conduct disorder, ADHD, antisocial personality disorder) to offspring, adjusted for sex of proband, history of sexual abuse of proband, sex of offspring, impulsive aggression of offspring, and sexual abuse of offspring

Variable	Hazard ratio	95% CI	Chi square	df	p-value	Model
Bipolar proband	1.09	0.61–1.96	0.09	1	0.76	R^2 = 0.287
Sex of proband	1.77	0.75–4.18	1.67	1	0.20	
Sexual abuse of proband	1.70	1.01–2.85	3.98	1	0.05	LRT = 145
Sex of offspring	0.20	0.11–0.35	30.73	1	< 0.001	df = 39.5
Impulsive aggression of offspring	1.76	1.37–2.26	19.96	1	< 0.001	p ≤ 0.001
Sexual abuse of offspring	1.45	0.73–2.89	1.10	1	0.29	
Frailty	–	–	43.54	34.5	0.14	

ADHD = attention-deficit hyperactivity disorder; CI = confidence interval; df = degrees of freedom; LRT = likelihood ratio test.

Table 6

Effect of parental bipolar disorder on risk for anxiety or substance use disorders in offspring, adjusted for sex of proband, history of sexual abuse of proband, impulsive aggression of offspring, and sexual abuse of offspring[a]

Variable	Hazard ratio	95% CI	Chi square	df	p-value	Model
Bipolar proband	0.92	0.61–1.40	0.14	1	0.71	$R^2 = 0.30$
Sex of proband	1.36	0.82–2.23	1.42	1	0.23	
Sexual abuse of proband	1.48	1.01–2.17	3.96	1	0.05	LRT = 152
Impulsive aggression of offspring	1.60	1.36–1.89	31.08	1	< 0.001	df = 46.2
Sexual abuse of offspring	1.61	1.05–2.48	4.76	1	0.03	$p \leq 0.001$
Frailty	–	–	55.40	42.3	0.09	

CI = confidence interval; df = degrees of freedom; LRT = likelihood ratio test.

[a]The variable sex of offspring violated the proportional hazards assumption. Because bivariate analysis demonstrated offspring sex was not related to anxiety or substance use disorder risk [$\chi^2(1) = 0.2$, $p = 0.635$], this variable was dropped from the multivariate model. Results from the final, more parsimonious model are reported.

Table 7

Effect of proband's age of onset of mood disorder on transmission of mood disorders to offspring, adjusted for sex of proband, history of sexual abuse of proband, sex of offspring, impulsive aggression of offspring, and sexual abuse of offspring

Variable	Hazard ratio	95% CI	Chi square	df	p-value	Model
Proband's mood age of onset	0.98	0.96–0.99	11.37	1	0.001	R^2 = 0.217
Sex of proband	0.76	0.46–1.28	1.05	1	0.31	LRT = 101
Sexual abuse of proband	1.06	0.69–1.64	0.07	1	0.79	df = 22.5
Sex of offspring	1.55	1.05–2.28	4.87	1	0.03	
Impulsive aggression of offspring	1.69	1.40–2.05	28.80	1	< 0.001	p ≤ 0.001
Sexual abuse of offspring	1.79	1.11–2.88	5.69	1	0.02	
Frailty	–	–	19.20	17.1	0.33	

CI = confidence interval; df = degrees of freedom; LRT = likelihood ratio test.