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Research report

The specificity of the familial aggregation of early-onset bipolar disorder: A controlled 10-year follow-up study of offspring of parents with mood disorders

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ABSTRACT

Background: Two major sources of heterogeneity of mood disorders that have been demonstrated in clinical, family and genetic studies are the mood disorder subtype (i.e. bipolar (BPD) and major depressive disorder (MDD)) and age of onset of mood episodes. Using a prospective high-risk study design, our aims were to test the specificity of the parent-child transmission of BPD and MDD and to establish the risk of psychopathology in offspring in function of the age of onset of the parental disorder.

Methods: Clinical information was collected on 208 probands ($n=81$ with BPD, $n=64$ with MDD, $n=63$ medical controls) as well as their 202 spouses and 372 children aged 6–17 years at study entry. Parents and children were directly interviewed every 3 years (mean duration of follow-up = 10.6 years). Parental age of onset was dichotomized at age 21.

Results: Offspring of parents with early onset BPD entailed a higher risk of BPD HR = 7.9(1.8–34.6) and substance use disorders HR = 5.0(1.1–21.9) than those with later onset and controls. Depressive disorders were not significantly increased in offspring regardless of parental mood disorder subtype or age of onset.

Limitations: Limited sample size, age of onset in probands was obtained retrospectively, age of onset in co-parents was not adequately documented, and a quarter of the children had no direct interview.

Conclusions: Our results provide support for the independence of familial aggregation of BPD from MDD and the heterogeneity of BPD based on patterns of onset. Future studies should further investigate correlates of early versus later onset BPD.

1. Introduction

The lack of successful identification of genetic markers underlying mood disorders has led to increasing scrutiny of sources of heterogeneity of the mood disorder spectrum (Kennedy et al., 2015; Major Depressive Disorder Working Group of the Psychiatric et al., 2013). Two of the major sources of heterogeneity of bipolar disorder are the subtypes of mood disorders, particularly bipolar disorder (BPD) and and major depressive disorder (MDD), and the age of onset of mood disorders (Etain et al., 2012; Geoffroy et al., 2013). Our recent evidence for the independence of familial transmission of BPD and MDD as well as their major components manic and major depressive episodes (Merikangas et al., 2014; Vandeleur et al., 2014) suggests that these mood disorder subtypes may represent distinct underlying continua rather than increasingly severe manifestations of a common underlying diathesis (Hickie, 2014). Studies of offspring of parents with BPD or MDD have confirmed elevated risks of BPD (Axelson et al., 2015; Birmaher et al., 2009; Duffy et al., 2010; Henin et al., 2005; Nurnberger et al., 2011) and of MDD (Hirshfeld-Becker et al., 2012) among offspring, but the independence of the familial aggregation of the two mood disorder subtypes could not be appropriately tested given the absence of controlled studies that simultaneously included parents with BPD and MDD.

There have also been numerous studies of subtypes within BPD (Phillips and Kupfer, 2013) and MDD (Lamers et al., 2013), but to date, the only consistent subtype that has been demonstrated in family studies of adults and high risk studies of offspring is early age of onset of mood disorders. Family studies have documented

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elevated rates of mood disorders among adult relatives (Bellivier et al., 2003; Grigoroiu-Serbanescu et al., 2001, 2014; Schurhoff et al., 2000; Somanath et al., 2002), siblings (Lin et al., 2006), and offspring (Oquendo et al., 2013) of probands with BPD with an early onset as compared to those with a later onset. Two studies however in adult relatives (Schulze et al., 2006) and high-risk offspring (Goldstein et al., 2010) did not find the risk of BPD to be determined by parental onset, reinforcing a lack of conclusiveness regarding the pertinence of this subtype of BPD. Regarding MDD, one study observed higher rates of MDD among the relatives of adult MDD probands with an age at onset before age 20 compared to those of probands with a later onset or controls (Weissman et al., 1984), whereas another study that followed probands from childhood to adulthood found the rates of MDD to be independent of the age of onset of the proband's MDD (Harrington et al., 1997). Recent large scale collaborative genetic studies of MDD have also shown that there is increased single nucleotide polymorphism (SNP)-based heritability of early onset MDD (Ferentinos et al., 2015).

To date, no controlled prospective study that included probands with both BPD and MDD has examined the incidence of mood disorder subtypes and other psychopathology in offspring by the age at onset of parental disorders. This design minimizes recall bias regarding the age of onset and permits evaluation of the sequence of onset of mood disorder subtypes and that of other types of psychopathology. Accordingly, using the high-risk design, the aims of the present study were to:

1. test the specificity of the parent-child transmission of BPD and MDD and establish the cumulative risk of non-mood psychopathology in offspring;
2. establish the risk of mood and non-mood psychopathology in offspring as a function of parental mood disorder age of onset. Age of onset was stratified at age 21 based on prior evidence (Etain et al., 2012; Geoffroy et al., 2013; Grigoroiu-Serbanescu et al., 2014) for age 20–21 as an early age of onset cut-off.

2. Methods

2.1. Sample

The sample stemmed from a large family study of mood disorders conducted in the French-speaking part of Switzerland (Vandeleur et al., 2014). Probands with BPD and MDD were consecutively recruited from the inpatient and outpatient facilities of the psychiatric departments of Lausanne and Geneva between 1996 and 2004. Inclusion criteria for mood disorder probands were: (1) lifetime bipolar-I ($n=53$), bipolar-II ($n=10$), schizoaffective bipolar disorder ($n=18$), or MDD ($n=64$), (2) age between 18 and 65 years, (3) ability to speak sufficient French or English to complete the diagnostic interview, and (4) availability of diagnostic data on one or more offspring (aged 6.0–17.9 years at study intake) from a minimum of two assessments with at least one direct interview. Comparison probands ($n=63$) were recruited from the orthopedic departments of Lausanne and Geneva. Inclusion criteria for the comparison probands were: (1) the absence of a lifetime mood or psychotic disorder, (2) age between 18 and 65 years, (3) ability to speak sufficient French or English to complete the diagnostic interview, and (4) the same inclusion criterion for offspring as that of the mood disorder cases. The choice of recruiting medical controls rather than subjects from the general population was motivated by our goal to create a comparison group that was selected from the same clinical settings as the probands with affective disorders. The specific choice of recruiting in orthopedic rather than other medical facilities was motivated by the fact that orthopedic problems are less likely to be induced by a psychiatric problem than other medical problems (e.g. cardiovascular or metabolic problems) and that a relatively large proportion of orthopedic patients are in the same age range as psychiatric patients (18–65 years).

An effort was made to interview all co-parents of biological offspring. Data on 202 co-parents were available of whom 60% had been directly interviewed. Parents and offspring were invited to take part in follow-up assessments at predetermined ages of the offspring (7, 10, 13, 16, 19, 22, 25, 28, 31 and 34 years). The average number of assessments of the 372 offspring was 4.2 (s.d.=1.3; range: 2–7) with a mean duration of 10.6 years follow-up (s.d.: 3.6). Three quarters of the assessments included direct interviews. The mean offspring age at the first assessment was 10.0 years (s.d.=4.3 years) and 20.6 years (s.d.=5.6 years) at the last assessment.

2.2. Procedures

Diagnostic methods for this study were also described in previous publications (Vandeleur et al., 2012). Information on parents and adult offspring was obtained using the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) and offspring younger than 18 years were directly interviewed using a French translation of the modified version of the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-E) (Orvaschel et al., 1982). In addition to direct interviews, information on children and parents was systematically elicited from all participants who were at least 15 years old using the Family History-Research Diagnostic Criteria (FH-RDC) (Andreasen et al., 1977). The validity and French translation of the DIGS (Berney et al., 2002; Leboyer et al., 1995; Preisig et al., 1999), the reliability of the K-SADS-E (Chambers et al., 1985; Gammon et al., 1983; Orvaschel et al., 1982; Vandeleur et al., 2012), and the validity of the FH-RDC (Rothen et al., 2009; Rougemont-Buecking et al., 2008; Vandeleur et al., 2008; Vandeleur et al., 2015) have been extensively tested. Interviewers were required to be masters-level psychologists and were trained over a two-month period. They were blind to the disease status of the other family members. Each interview was reviewed by a senior psychologist.

Diagnoses were made over lifetime using a best-estimate procedure (Leckman et al., 1982), which relied on the combination of information from direct interviews, family history report(s), and medical records. Diagnostic algorithms for “Other Specified Bipolar and Related Disorders” (OSBARD) and “Other Specified Depressive Disorders” (OSDD) were defined according to the DSM-5 to assign subthreshold diagnoses. Non-mood disorders were defined according to the DSM-IV. The SES of the families was based on income and education level of both spouses of the household (Hollingshead, 1975). The severity of probands' disorders over lifetime was assessed using the DSM-IV Global Assessment of Functioning (GAF) scale, which provides an assessment of the probands' level of psychological, social and occupational functioning.

This research project was approved by the local institutional review board. All participants gave written informed consent for their own participation prior to the assessments. In addition, parents gave written consent for the participation of their offspring younger than 18 years.

2.3. Data analysis

Between-group analyses were performed using the chi-square, *t*-tests or ANOVA and using multilevel models for non independent data in offspring. Hazard ratios were computed using serially adjusted shared gamma frailty models for survival data

(Rondeau et al., 2012) to assess the impact of the probands' disorder on incidence of offspring disorders. The offspring of probands with mood disorders were compared to the offspring of controls. These models account for the lack of independence of the observations (varying number of offspring across families). Model 1 was adjusted for sex, age, and the number of information points in offspring as well as the probands' age and the SES. Model 2 was further adjusted for probands' comorbid anxiety disorders (generalized anxiety disorder, panic disorder, social phobia, agoraphobia), SUD (alcohol and drug abuse or dependence) and behavioral disorders that mainly occurred during childhood (conduct, oppositional defiant disorder, and attention-deficit hyperactivity disorder). Model 3 was further controlled for the effects of the co-parents' disorder(s). One hundred multiple imputations were performed using the MissForest procedure based on random forests (Stekhoven and Buhlmann, 2012) to adjust for missing data in co-parents (24 diagnoses of SUD, mood and anxiety disorders and 111 diagnoses of behavioral disorders). In an additional model, we adjusted for disorder severity according to the GAF score. Moreover, in order to verify that our results were not biased by the inclusion of 35 offspring of 18 probands with schizoaffective bipolar disorder rather than BPD, we also ran the models excluding the offspring of probands with schizoaffective disorder.

Age of onset in parents was based on the age of the first full mood episode described (mania, hypomania or major depressive episode (MDE)). In the case of missing data or ambiguity ages of onset were based on the medical records where available. The ROC curve contrast estimation coefficient was used to validate the thresholds for the ability of probands' age of onset to discriminate mood status in offspring. Measures of sensitivity, specificity and total accuracy were used as an indication of the optimal threshold (Fawcett, 2006). Using the thresholds that subdivided the probands into early versus later onset subtypes, cumulative risk estimates and hazard ratios were then established for offspring disorder outcomes using the same methodology as for the previous analyses. Early onset was defined as age 20–21 and younger and late onset was defined as age 22 and older. Analyses were conducted using the Statistical Analysis System, version 9.3 (SAS Institute, Inc., Cary, NC, USA), and the statistical analyses environment R (R Core Team. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/).

We performed a power analysis (Hsieh and Lavori, 2000) using the powerSurvEpi package (R package version 0.0.9. http://CRAN.R-project.org/package=powerSurvEpi). The power of the model was calculated for each disorder in offspring in function of the proband's disorder status. Regardless of the parental diagnostic status, the power to detect a difference between the offspring of affected parents and controls was >0.7 for HRs of at least 2.0 for any mood disorder, depressive spectrum disorders, MDD, anxiety disorders and separation anxiety disorder. For all other disorders, the power was only sufficient to detect associations with a HR of at least 3.0, whereas for bipolar disorders, only very strong associations could be detected.

3. Results

Table 1 reveals the characteristics of probands and offspring as a function of the proband's diagnosis. About half the sample was male. Probands with mood disorders and controls differed with respect to marital status and lifetime history of anxiety disorders and substance use disorders (SUD) ($p<0.001$). Families of probands with MDD had the lowest socio-economic status (SES) (<0.01) and their offspring had the lowest age at the last follow-up and the lowest number of assessments. In addition, the spouses of probands with BPD (25.0%) or MDD (33.3%) reported SUD more frequently than those of controls (8.1%; $\chi^2_2=11.8$, $p<0.01$).

Table 2 provides the cumulative incidence of offspring disorders as well as the results of the shared gamma frailty models. Four hazard ratios were significant until adjusted for probands' comorbid and spouses' disorders. The hazard ratios for: (1) offspring BPD, either any BPD (including subthreshold BPD) or bipolar-I and bipolar-II disorders combined of BPD probands were both 5.4(1.3,21.6) unadjusted and 2.8(0.6,12.9) adjusted; (2) risk of separation anxiety disorder (SAD) in the offspring of BPD probands were 1.9(1.1,3.3) unadjusted and 1.7(0.9,3.0) adjusted; (3) ADHD in the offspring of MDD probands were 2.1(1.1,4.2) unadjusted and 1.9(0.8,4.4) adjusted; (4) SUD in offspring of MDD probands were 2.9(1.1,7.9) unadjusted and 2.4(0.8,7.8) adjusted. The unadjusted association for SAD in offspring of MDD probands 2.9(1.6,5.1)

Table 1
Sample characteristics.

Probands ($n=208$)	**Probands with BPD ($n=81$)**	**Probands with MDD ($n=64$)**	**Control probands ($n=63$)**	**Statistic**	***p* value**	**Pairwise**
Female, %	58.0	56.3	44.4	$\chi^2_2=2.9$	n.s.	–
Age at baseline, mean (s.d.)	40 (6.7)	41 (7.6)	41 (6.8)	$F_2=0.3$	n.s.	–
Married, %	61.7	57.8	77.8	$\chi^2_2=6.4$	<0.05	AB
Number of offspring included, mean (s.d.)	1.8 (0.9)	1.8 (0.8)	1.8 (0.8)	$F_2=0.0$	n.s.	–
Proband comorbidity						
Anxiety disorder,[a] %	29.6	45.3	6.4	$\chi^2_2=24.6$	<0.001	AB
Substance use disorder,[b] %	39.5	48.4	12.7	$\chi^2_2=19.7$	<0.001	AB
Any behavioral disorder,[c] %	19.8	21.9	7.9	$\chi^2_2=5.2$	n.s.	–
SES of the family, mean (s.d.)	3.2 (1.0)	2.8 (1.0)	3.4 (1.0)	$F_2=6.3$	<0.01	BC
Offspring ($n=372$)	**Offspring of BPD ($n=145$)**	**Offspring of MDD ($n=115$)**	**Offspring of CTRLS ($n=112$)**			
Female, %	51.0	51.3	45.5	$Z_2=0.8$	n.s.	–
Age at first assessment, mean (s.d.)	10.4 (4.3)	10.1 (3.8)	9.3 (4.8)	$F_2=0.5$	n.s.	–
Age at last assessment, mean (s.d.)	21.1 (5.6)	19.5 (5.2)	21.0 (5.9)	$F_2=3.1$	<0.05	BC
Number of assessments, mean (s.d.)	4.3 (1.3)	3.8 (1.1)	4.6 (1.3)	$F_2=7.4$	<0.001	ABC
Number of interviews, mean (s.d.)	3.3 (1.5)	2.9 (1.2)	3.3 (1.4)	$F_2=1.8$	n.s.	–

Key: BPD=bipolar disorder; MDD=major depressive disorder; CTRLS=controls.

[a] includes generalized anxiety disorder, social phobia, panic disorder and/or agoraphobia.

[b] includes alcohol and drug abuse or dependence.

[c] includes disruptive behavioral disorders and attention-deficit hyperactivity disorder; SES=socio-economic status. Pairwise comparisons: A: BPD vs. CTRL; B: MDD vs. CTRL; C: BPD vs. MDD.

Table 2
Rates (%) and risk (HR, 95CI) of lifetime psychiatric disorders in offspring ($N=372$) by proband mood disorder.

	Proband disorder								**Other**[a]
	BPD				**MDD**				
Offspring *N*	145				115				112
		Model 1	Model 2	Model 3		Model 1	Model 2	Model 3	
Offspring disorder	%	HR 95CI	HR 95CI	HR 95CI	%	HR 95CI	HR 95CI	HR 95CI	%
Any mood disorder	62.8	1.0 (0.7,1.6)	0.9 (0.6,1.4)	0.9 (0.6,1.5)	67.8	1.4 (0.9,2.3)	1.2 (0.7,2.0)	1.2 (0.7,2.2)	60.7
Any BPD	17.2	**5.4*** **(1.3,21.6)**	3.4 (0.7,16.2)	2.8 (0.6,12.7)	7.0	1.7 (0.3,8.6)	0.7 (0.1,4.9)	0.7 (0.1,4.7)	4.5
BPD	12.4	**5.4*** **(1.3,21.6)**	3.4 (0.7,15.8)	2.8 (0.6,12.9)	4.4	1.7 (0.3,8.6)	0.7 (0.1,4.9)	0.7 (0.1,4.7)	3.6
OSBARD[b]	4.8	– –	– –	– –	2.6	– –	– –	– –	0.9
Depressive spectrum	45.5	0.7 (0.5,1.1)	0.7 (0.4,1.1)	0.7 (0.4,1.1)	60.9	1.2 (0.8,2.0)	1.2 (0.7,2.0)	1.3 (0.7,2.2)	56.3
MDD	36.6	1.0 (0.6,1.6)	0.8 (0.5,1.4)	0.9 (0.5,1.5)	46.1	1.5 (0.9,2.6)	1.2 (0.7,2.3)	1.3 (0.7,2.5)	37.5
Dysthymia	1.4	– –	– –	– –	1.7	– –	– –	– –	2.7
OSDD[b]	7.6	0.5 (0.2,1.2)	0.6 (0.2,1.4)	0.6 (0.2,1.6)	13.0	1.0 (0.4,2.2)	1.2 (0.5,3.2)	1.3 (0.4,3.7)	16.1
Anxiety disorders[c]	43.5	1.4 (0.8,2.2)	1.2 (0.7,2.0)	1.2 (0.7,2.0)	41.7	1.3 (0.8,2.2)	1.0 (0.6,1.8)	1.0 (0.5,1.9)	38.4
Separation anxiety	40.7	**1.9*** **(1.1,3.3)**	1.7 (0.9,2.9)	1.7 (0.9,3.0)	53.9	**2.9***** **(1.6,5.1)**	**2.3*** **(1.2,4.3)**	**2.4*** **(1.2,4.6)**	26.8
Any behavioral disorder	31.0	1.4 (0.8,2.4)	1.3 (0.7,2.3)	1.3 (0.7,2.4)	37.4	1.8 (1.0,3.2)	1.7 (0.9,3.2)	1.7 (0.9,3.4)	25.9
Conduct	11.7	1.1 (0.5,2.5)	1.1 (0.5,2.6)	1.1 (0.5,2.6)	11.3	1.1 (0.4,2.7)	1.2 (0.4,3.1)	1.2 (0.4,3.4)	11.6
ODD	14.5	1.3 (0.6,2.8)	1.3 (0.6,3.0)	1.2 (0.5,3.0)	17.4	1.6 (0.7,3.7)	1.6 (0.6,4.0)	1.7 (0.6,5.0)	13.4
ADHD	16.6	1.5 (0.8,2.8)	1.4 (0.7,2.7)	1.4 (0.6,2.9)	22.6	**2.1*** **(1.1,4.2)**	1.9 (0.9,4.1)	1.9 (0.8,4.4)	13.4
Any substance disorder	27.6	2.4 (1.0,5.7)	2.2 (0.9,5.6)	2.1 (0.8,5.6)	28.7	**2.9*** **(1.1,7.9)**	2.5 (0.8,7.7)	2.4 (0.8,7.8)	18.8
Alcohol abuse/dependence	15.9	1.9 (0.7,5.3)	2.0 (0.7,5.9)	2.7 (0.7,10.5)	15.7	2.6 (0.8,8.1)	2.8 (0.8,9.8)	3.9 (0.8,17.7)	10.7
Drug abuse/dependence	18.6	2.3 (0.8,6.7)	1.6 (0.6,4.4)	1.3 (0.4,3.8)	20.0	2.6 (0.8,8.3)	1.4 (0.4,4.8)	1.2 (0.3,4.8)	13.4

*$p<.05$; **$p<.01$; ***$p<.001$.
HR (hazard ratios); 95CI (95% confidence intervals); BPD (bipolar disorder); OSBARD (Other Specified Bipolar and Related Disorders).
MDD (major depressive disorder); OSDD (Other Specified Depressive Disorders); ODD (oppositional defiant disorder).
ADHD (attention-deficit/hyperactivity disorder); substance abuse/dependence (DSM-IV criteria).
Model 1: adjusted for sex, age and number of information points in offspring, proband age, socio-economic status of the family and within-family correlations;
Model 2: Model 1+adjusted for proband comorbid disorders (substance abuse/dependence, anxiety disorders, behavioral disorders);
Model 3: Model 2+adju.ted for spouse mood disorders (bipolar and unipolar) and spouse comorbid disorders (substance abuse/dependence, anxiety and behavioral disorders).
Models could not be calculated to assess the risk of OSBARD and dysthymia in offspring due to the low proportion of affected offspring. [a] This category includes offspring of probands with either no disorder or with subthreshold BPD, hyperthymic personality, subthreshold depression, anxiety disorders, as well as alcohol or drug abuse.
[b] Includes information from interviews only.
[c] Includes generalized anxiety disorder, agoraphobia, panic disorder and social phobia.

remained significant in the models adjusted for probands' comorbid 2.3(1.2,4.3) and spouses' disorders 2.4(1.2,4.6).

Among the 81 bipolar probands and 64 MDD probands, 31 (38.3%) and 19(29.7%) respectively had a disorder that started before the age of 21 years. Mean age of bipolar probands with an early compared to late onset were 38.5 and 41.6, $F=4.2$, $p<0.05$, respectively. No significance was found between bipolar probands' onset age and history of comorbid disorders or SES. Their children, however, were younger at the first (9.1 vs. 11.1 years, $F=4.6$, $p<.05$) and last interview (18.4 vs. 22.6 years, $F=10.8$, $p<.01$) and had less assessments (3.8 vs. 4.5, $F=4.3$, $p<.05$) and interviews (2.8 vs. 3.6, $F=6.2$, $p<.05$). Early onset MDD probands were younger than those with a later onset (38.3 vs. 42.6 years, $F=4.5$, $p<.05$). No significance was found between MDD probands' onset age and history of comorbid disorders or SES. Their children did not differ regarding age at the first or last interview, or the number of assessments and interviews.

Table 3 provides the cumulative incidence of offspring disorders by age of onset as a function of probands' mood disorder subtype. Also presented are hazard ratios from the serially adjusted shared gamma frailty models. In all models, the offspring of early onset BPD probands displayed an elevated risk for any BPD and the combined bipolar-I, bipolar-II category [both model 3 HR 7.9(1.8,34.6)]. These associations remained significant when effect of the severity of probands' disorder, as represented by the GAF score, was considered (HR=7.4 (1.1,51.9)). No evidence was found for increased mood disorder risk in offspring with late onset BPD probands 0.9(0.6,1.4). In addition, there was no evidence of increased risk of offspring MDD with BPD probands regardless of adjustment of covariates. Although there was an increase in risk of offspring mood disorder with early MDD probands 1.9(1.0,3.5), the association

Table 3
Rates (%) and risk (HR, 95CI) of lifetime psychiatric disorders in offspring ($N=372$) by proband mood disorder subtype.

	Proband disorder															
	BPD subtypes								**MDD subtypes**							**Other**[a]
	Onset BPD < 21 yrs				**Onset BPD > 21 yrs**				**Onset MDD < 21 yrs**				**Onset MDD > 21yrs**			
Offspring *N*	52				93				36				79			112
		Model 1	Model 2	Model 3		Model 1	Model 2	Model 3		Model 1	Model 2	Model 3		Model 1	Model 2	Model 3	
Offspring disorder	%	HR 95CI	HR 95CI	HR 95CI	%	HR 95CI	HR 95CI	HR 95CI	%	HR 95CI	HR 95CI	HR 95CI	%	HR 95CI	HR 95CI	HR 95CI	%
Any mood disorder	65.4	1.3 (0.7,2.2)	1.1 (0.6,1.9)	1.1 (0.6,2.0)	61.3	0.9 (0.6,1.4)	0.8 (0.5,1.3)	0.8 (0.5,1.3)	80.6	**1.9*** **(1.0,3.5)**	1.5 (0.8,2.8)	1.6 (0.8,3.1)	62.0	1.2 (0.7,2.1)	1.0 (0.6,1.8)	1.1 (0.6,1.9)	60.7
Any BPD	26.9	**15.3*** **(3.3,70.2)**	**7.9*** **(1.6,39.1)**	**7.9**** **(1.8,34.6)**	11.8	2.3 (0.5,9.9)	1.8 (0.4,8.3)	1.4 (0.3,6.1)	8.3	4.5 (0.7,29.1)	2.3 (0.3,16.8)	1.3 (0.1,10.9)	6.3	1.0 (0.2,7.1)	0.6 (0.1,4.7)	0.8 (0.1,6.2)	4.5
BPD	21.2	**15.3*** **(3.3,70.2)**	**7.9*** **(1.6,39.1)**	**7.9**** **(1.8,34.6)**	7.5	2.3 (0.5,9.9)	1.8 (0.4,8.3)	1.4 (0.3,6.1)	8.3	4.5 (0.7,29.1)	2.3 (0.3,16.8)	1.3 (0.1,10.9)	2.5	1.0 (0.2,7.1)	0.6 (0.1,4.7)	0.8 (0.1,6.2)	3.6
OSBARD[b]	5.8	– –	– –	– –	4.3	– –	– –	– –	0.0	– –	– –	– –	3.8	– –	– –	– –	0.9
Depressive spectrum	38.5	0.6 (0.3,1.1)	0.6 (0.3,1.1)	0.6 (0.3,1.1)	49.5	0.8 (0.5,1.2)	0.7 (0.5,1.2)	0.8 (0.5,1.3)	72.2	1.5 (0.8,2.8)	1.4 (0.7,2.7)	1.6 (0.8,3.4)	55.7	1.1 (0.7,1.8)	1.0 (0.6,1.8)	1.1 (0.6,2.0)	56.3
MDD	28.9	0.8 (0.4,1.5)	0.6 (0.3,1.3)	0.6 (0.3,1.3)	40.9	1.1 (0.6,1.8)	0.9 (0.5,1.6)	1.0 (0.6,1.7)	55.6	1.9 (0.9,3.8)	1.5 (0.7,3.2)	1.7 (0.8,3.6)	41.8	1.3 (0.8,2.4)	1.0 (0.5,1.9)	1.1 (0.6,2.0)	37.5
Dysthymia	0.0	– –	– –	– –	2.2	– –	– –	– –	2.8	– –	– –	– –	1.3	– –	– –	– –	2.7
OSDD[b]	9.6	0.6 (0.2,1.9)	0.7 (0.2,2.3)	0.8 (0.2,2.6)	6.5	0.5 (0.2,1.3)	0.5 (0.2,1.5)	0.5 (0.2,1.6)	13.9	1.0 (0.3,3.2)	1.1 (0.3,4.0)	1.4 (0.3,5.7)	12.7	1.0 (0.4,2.7)	1.3 (0.5,3.7)	1.3 (0.4,4.0)	16.1
Anxiety disorders[c]	40.4	1.3 (0.7,2.5)	1.1 (0.5,2.2)	1.0 (0.5,2.1)	45.2	1.4 (0.8,2.4)	1.3 (0.7,2.2)	1.3 (0.7,2.3)	61.1	**2.6**** **(1.3,5.2)**	2.0 (0.9,4.4)	2.2 (0.9,5.0)	32.9	0.9 (0.5,1.6)	0.7 (0.4,1.4)	0.7 (0.3,1.4)	38.4
Separation anxiety	44.2	**2.1*** **(1.1,4.3)**	1.8 (0.9,3.7)	1.7 (0.8,3.6)	38.7	**1.8*** **(1.0,3.3)**	1.6 (0.9,3.0)	1.6 (0.9,3.1)	50.0	**2.3*** **(1.1,5.2)**	2.0 (0.9,4.7)	2.2 (0.9,5.4)	55.7	**3.1***** **(1.7,5.8)**	**2.4*** **(1.2,4.8)**	**2.4*** **(1.2,4.9)**	26.8
Any behavioral disorder	36.5	1.7 (0.9,3.3)	1.5 (0.8,3.1)	1.6 (0.8,3.3)	28.0	1.2 (0.7,2.2)	1.2 (0.6,2.1)	1.1 (0.6,2.1)	44.4	**2.4*** **(1.1,5.0)**	**2.3*** **(1.0,5.1)**	2.1 (0.9,5.0)	34.2	1.6 (0.8,2.9)	1.4 (0.7,2.8)	1.6 (0.8,3.1)	25.9
Conduct	17.3	2.0 (0.8,5.0)	2.4 (0.9,6.7)	**3.0*** **(1.0,8.6)**	8.6	0.7 (0.3,1.7)	0.8 (0.3,2.0)	0.7 (0.3,1.9)	11.1	1.2 (0.4,4.1)	1.9 (0.5,7.3)	1.2 (0.2,6.0)	11.4	1.0 (0.4,2.5)	1.1 (0.4,3.1)	1.5 (0.5,4.3)	11.6
ODD	17.3	1.5 (0.5,4.1)	1.5 (0.5,4.1)	1.7 (0.6,5.2)	12.9	1.2 (0.5,2.8)	1.2 (0.5,2.8)	1.0 (0.4,2.6)	22.2	2.0 (0.7,5.9)	2.1 (0.7,6.6)	1.8 (0.5,6.6)	15.2	1.4 (0.6,3.6)	1.4 (0.5,3.6)	1.7 (0.6,5.1)	13.4
ADHD	21.2	1.8 (0.8,4.1)	1.5 (0.7,3.7)	1.5 (0.6,3.6)	14.0	1.3 (0.6,2.7)	1.1 (0.5,2.5)	1.1 (0.5,2.4)	25.0	2.2 (0.9,5.4)	2.0 (0.8,5.2)	1.9 (0.7,5.1)	21.5	**2.1*** **(1.0,4.4)**	1.8 (0.8,4.1)	1.7 (0.7,4.0)	13.4
Any substance disorder	25.0	**4.4*** **(1.4,13.8)**	**3.9*** **(1.1,14.3)**	**5.0*** **(1.1,21.9)**	29.0	1.7 (0.7,4.1)	1.7 (0.6,4.5)	1.6 (0.6,4.5)	22.2	3.1 (0.8,12.1)	3.1 (0.7,14.2)	3.9 (0.7,23.9)	31.7	2.6 (1.0,7.2)	2.6 (0.8,8.6)	2.8 (0.7,10.8)	18.8
Alcohol abuse/dependence	15.4	4.9 (0.9,26.1)	5.2 (1.0,27.0)	**7.9*** **(1.4,45.0)**	16.1	1.3 (0.4,4.3)	1.4 (0.4,4.7)	1.8 (0.5,6.7)	11.1	3.2 (0.5,18.8)	3.3 (0.5,20.5)	5.1 (0.7,38.3)	17.7	2.9 (0.8,11.0)	3.4 (0.8,14.3)	4.4 (0.9,21.5)	10.7
Drug abuse/dependence	17.3	**4.4*** **(1.2,16.1)**	2.4 (0.6,9.5)	3.0 (0.6,15.1)	19.4	1.6 (0.5,4.8)	1.3 (0.5,3.7)	1.0 (0.3,3.0)	13.9	2.8 (0.5,15.1)	1.9 (0.4,9.7)	1.7 (0.2,12.7)	22.8	2.5 (0.8,8.3)	1.4 (0.4,4.9)	1.3 (0.3,6.0)	13.4

*$p < .05$; **$p < .01$; ***$p < .001$. HR (hazard ratios); 95CI (95% confidence intervals).
BPD (bipolar disorder); OSBARD (Other Specified Bipolar and Related Disorders); MDD (major depressive disorder); OSDD (Other Specified Depressive Disorders).
ODD (oppositional defiant disorder); ADHD (attention-deficit/hyperactivity disorder); substance abuse/dependence (DSM-IV criteria).
Model 1: adjusted for sex, age and number of information points in offspring, proband age, socio-economic status of the family and within-family correlations.
Model 2: Model 1+adjusted for proband comorbid disorders (substance abuse/dependence, anxiety disorders, behavioral disorders).
Model 3: Model 2+adjusted for spouse mood disorders (bipolar and unipolar) and spouse comorbid disorders (substance abuse/dependence, anxiety disorders, behavioral disorders).
Models could not be calculated to assess the risk of OSBARD and dysthymia in offspring due to the low proportion of affected offspring. [a] This category includes offspring of probands with either no disorder or with subthreshold BPD, hyperthymic personality, subthreshold depression, anxiety disorders, as well as alcohol or drug abuse.
[b] Includes information from interviews only.
[c] Includes generalized anxiety disorder, agoraphobia, panic disorder and social phobia.

was no longer significant after controlling for probands comorbid disorders 1.5(0.8,2.8).

Regarding non-mood disorders, early onset proband BPD was significantly associated with the risk of offspring conduct disorder 3.0(1.0,8.6) and SUD 5.0(1.1,21.9), owing to the risk of alcohol abuse/dependence 7.9(1.4,45.0), after adjusting for probands' comorbid and spouses' disorders. The later onset bipolar subtype in probands was not associated with an increased risk of any offspring disorder, except for offspring SAD in the unadjusted model 1.8(1.0,3.3). The offspring of probands' with early MDD were found to be at an increased risk for anxiety disorders 2.6(1.3,5.2), SAD 2.3 (1.1,5.2) and behavioral disorders 2.4(1.1,5.0), but not after adjustments. The later onset MDD subtype in probands was associated with an increased risk of ADHD 2.1(1.0,4.4), but not after adjustments. Finally, the later onset MDD subtype in probands was associated with an increased risk of SAD in all models [model 3 HR 2.4(1.2,4.9)].

The exclusion of offspring of probands with bipolar schizoaffective disorders from analyses only marginally changed the results. The strong associations between early onset BPD in probands and any BPD (HR=9.0(1.9,43.0) $p<.01$), BPD (HR=9.0 (1.9,43.0) $p<.01$), any SUD (4.6(1.1,19.6) $p<.05$) and alcohol abuse/dependence (5.5(1.0,30.1) $p<.05$) in offspring remained significant. Only the association between early onset BPD in probands and conduct disorder in offspring no longer reached the level of statistical significance (2.4(0.8; 6.8)).

To test whether the chosen age of 21 years was an appropriate cut-off we conducted ROC analyses. This analysis revealed that age of onset of probands' BPD was a better predictor than chance for determining the risk of offspring mania/hypomania (Area Under Curve=0.72; 95% CI=0.60,0.84; $p=0.0004$). The optimal age of onset was 20–21 years according to the sensitivity, specificity and total accuracy estimates. Similarly, the ROC curve analysis testing showed that age of onset was a better predictor than chance for determining the risk of MDD in offspring (Area Under Curve=0.57; 95% CI=0.50,0.64; $p=0.0485$). However, in contrast to BPD no clear delineation for determining the optimal cut-off for the age of onset according to the sensitivity, specificity, and total accuracy estimates was observed.

4. Discussion

The present study provides the first evidence for an association between early age of onset of parental BPD or MDD and the incidence of mood and non-mood psychopathology in offspring during a follow-up period of more than 10 years. The most salient findings were: (1) the specificity of familial aggregation of BPD; and (2) the critical role of the age of onset of the parental disorder in the transmission of BPD. The highly specific transmission of BPD and the absence of evidence for shared familial risk between BPD and MDD confirms the results of our two recent family studies of adult relatives (Merikangas et al., 2014; Vandeleur et al., 2014), as well as those of twin studies of clinical samples (McGuffin et al., 2003). Likewise, studies of treatment, course, and comorbidity have distinguished these two subtypes in both children and adults (Cuellar et al., 2005), and recent neuroimaging studies have indicated distinct neural architecture and function of BPD and MDD (Diler et al., 2013; Lan et al., 2014; Liang et al., 2013; Redlich et al., 2014). Taken together, these results provide strong evidence for the diagnostic separation of unipolar and bipolar mood disorders.

Similar to prior high risk studies of BPD, we found an elevated risk of SUD, particularly alcohol use disorders, among offspring of probands with BPD, but not MDD. The prospective data demonstrating an increased risk of alcohol dependence among community adults with BPD (Merikangas et al., 2008) highlight the potential benefit of prevention of alcohol dependence through intervention in youth with early manifestations of BPD. The other non-affective disorder associated with parental BPD was childhood SAD, replicating the findings of an earlier prospective community study of youth (Bruckl et al., 2007) which found a 7-fold increased risk of BPD among youth with earlier SAD. We also found a more than two-fold increased risk of early SAD in youth of parents with MDD, which again replicates the findings of the prospective community study, even if this association did not reach statistical significance in the latter study. Future studies of this association are necessary to examine the specificity and potential explanation for the specific links between SAD and mood disorders that emerged in our study.

Our findings of an increased incidence of mood disorders among parents with early onset BPD suggest that early onset BPD could also distinguish genetic and biologic factors that may be masked in current studies of the full range of ages of onset and subtypes of mood disorders. This is consistent with growing evidence that early age of onset distinguishes genetic forms of breast cancer (King et al., 2003), colorectal cancer (Tanskanen et al., 2015), multiple sclerosis (Giacalone et al., 2015) and numerous other diseases. Parallel to other diseases, later onset disorders are more likely to have different genetic and environmental exposures than the early onset forms of these conditions. The importance of age of onset as the primary index of a more heritable form of BPD (Visscher et al., 2001) was indicated by its persistence after we controlled for potential correlates of age of onset including severity of mood disorder and comorbidity, suggesting that age of onset may be the primary index of a more heritable subset of BPD. We could also show that our results were not affected by the inclusion of offspring of probands with bipolar schizoaffective disorder. Although our data are compatible with a distinct early onset bipolar subtype, the findings remain limited by the relatively young age of the cohort at last interview that precludes our ability to study the specificity of both early and late onset forms of mood disorders. In particular, offspring of probands with the later onset BPD subtype may still develop mania/hypomania further on in life, and provide evidence for the familial aggregation of later onset BPD possibly with its own specific mechanisms. Future follow-up will be critical to our completing the full portrait of age of onset of BPD and MDD across the life span.

In contrast to BPD, irrespective of the parental age of onset, there was no increase in MDD over the 10 years of follow-up. Although this finding apparently fails to confirm numerous earlier high risk studies of MDD cited above, our study is the largest to date that included parent proband groups of both BPD and MDD, a larger well-characterized group of co-parents, and a comparable medically ill control group that may have led to differences in the findings regarding specificity of parental-offspring MDD. As noted above, future increases in the incidence of MDD could distinguish offspring of proband parents with MDD from controls. Alternatively, the lack of difference in risk between offspring of depressive probands and those of controls might have been attributable to the relatively high incidence of depressive symptoms/disorders among the adolescent offspring of controls. Finally, the generally lower heritability of MDD relative to that of BPD (Merikangas et al., 2014) may also contribute to this negative finding.

There are several limitations that should be considered in interpreting our findings. First, although our study is the largest to date that included offspring of parent proband groups of both BPD and MDD, type II error cannot be ruled out because of the limited sample size. In particular, the power to detect an association for BPD was very limited given the rarity of the disorder in offspring. However, given the very strong association we have observed between parental early-onset BPD and the risk of BPD in offspring, the power of our analyses was still sufficient to detect this

association. Second, although we minimized offspring recall bias by prospectively assessing ages of onset, the age of onset in probands was obtained retrospectively. Third, despite our efforts to directly interview all offspring across all assessments, almost a quarter of the assessments were derived from family history reports, similar to other prospective studies of adolescents. Fourth, although offspring were assessed every three years, the information collected for the interval of time between evaluations was necessarily retrospective. Fifth, the ages of onset in co-parents could not be adequately tested based on information from the family history reports for those who were not interviewed.

Despite these limitations, we present the first high risk study that assesses simultaneously the specificity of familial transmission of both BPD and MDD and non-mood psychopathology and the effect of age of onset in offspring across more than a decade of follow-up. These findings have significant clinical and scientific implications. The offspring of parents with early onset BPD deserve particular clinical attention during adolescence when preventive efforts may reduce progression and consequences of this disorder. The confirmation of the independent familial transmission of BPD and MDD further emphasizes the need for diagnostic distinction between these subgroups in genetic studies, particularly in light of differences in the heritability of mania and depression. This is especially pertinent in molecular genetic studies that are currently comprised of heterogeneous samples of probands with the full spectrum of bipolar disorder. Our data also provide compelling evidence that the early onset BPD subtype is a promising phenotype for such studies. Up to now, molecular genetic studies on the early onset subtype of BPD have encountered methodological problems including limited statistical power, varying ages of onset, inclusion of subjects with bipolar-II disorder and varying criteria for selecting affected families, which have hindered the progress of this research (Kennedy et al., 2015). Future studies should therefore make efforts to standardize methodology and particularly use consistent definitions of early and later onset BPD (Kennedy et al., 2015). Finally, future prospective high risk research that follows offspring across adulthood is also warranted to further determine the relationship between the early and later onset BPD phenotypes.

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Conflict of interest

All authors declare no conflict of interest.

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