



Risk factors for mood disorders among offspring of parents with bipolar disorder: Findings from a discordant-sibling study

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ARTICLE INFO

Key words:

High-risk study

Siblings

Temperament

Premorbid psychopathology

Family functioning

ABSTRACT

The purpose of this naturalistic, prospective study was to identify risk factors for mood disorders in offspring of parents with bipolar disorder (BPD) using the discordant-sibling design by comparing premorbid psychopathology or symptoms, temperament, personality traits and coping style as well as the perception of family-related characteristics among affected and unaffected siblings within the same family. This approach controls for confounding by unmeasured genetic and environmental factors shared within families. Our sample comprised 24 families of a parent with BPD with at least one child that developed BPD or major depressive disorder ($n = 31$), and at least one child who did not. Offspring were followed for a mean duration of 16.2 (s.d. 4.6) years. Information was collected from the offspring themselves. Generalized linear mixed models only revealed differences in three dimensions of the Dimension of Temperament Survey-Revised (DOTS-R) version: Offspring with mood disorders scored higher on "Approach-withdrawal", "Rhythmicity for daily habits", and "Task orientation" than their unaffected siblings. The higher scores, and not lower scores as expected, on these temperament dimensions observed in offspring that subsequently developed mood disorders may reflect increased vulnerability, but they could also mirror premorbid mood swings or strategies to cope with them.

1. Introduction

There is substantial evidence for the importance of studying risk factors early in development, particularly in children and adolescents at risk for mental illness through exposure to the parental disorder (Duffy, 2018; Duffy et al., 2023; Luthar, 2006; Thorup et al., 2015) known as "high-risk offspring" within the realm of family studies.

A recent systematic review has given a broad overview of social, familial and psychological risk factors for mental health according to sibling studies in neurocognitive disorders (Wolff et al., 2022). Among them, low socioeconomic status (SES), symptom severity and anxiety of the affected individual were found to be risk factors for mental health issues in unaffected siblings (Wolff et al., 2022). However, high

methodological heterogeneity has been observed across sibling studies (Wolff et al., 2022).

One potent tool to study risk factors within families is the discordant-sibling design whereby full siblings, who are discordant either in exposure or outcome, are compared (Li et al., 2014; Schlomer and Ellis, 2016). Compared to other sampling strategies, this design allows researchers to better control for confounding by unmeasured or even unknown family-level risk factors shared by the siblings including genetic and environmental factors such as culture, SES or religion (Li et al., 2014; Schlomer and Ellis, 2016; Sjölander et al., 2022). Hence, individual differences can be assessed by reducing extraneous variability to a minimum (Li et al., 2014; Sjölander et al., 2022).

One area of particular interest is children of parents with bipolar

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¹ MP, KJP and CLV provided supervision for this paper.

disorder (BPD), a group at high risk for developing mood disorders themselves (Rasic et al., 2014; Uher et al., 2023). Although several studies on the offspring of parents with BPD have assessed familial and individual risk factors in these children (Maciejewski et al., 2018; Petti et al., 2004; Stapp et al., 2020), none of them has applied a discordant-sibling design. Within the realm of individual psychological profiles, one of the most studied in the field of BPD are childhood temperament and personality (Maciejewski et al., 2018). Using a high-risk design of offspring with and without mood disorders, the Dutch study of BPD showed that passive coping style and harm-avoidance temperament (Kemner et al., 2015) were in fact risk factors for the manifestation of the onset or recurrence of mood disorders in these vulnerable offspring. Another high-risk study of BPD, studying both affected and unaffected offspring together, found that offspring of parents with BPD presented lower positive mood, lower task-orientation and lower flexibility than control offspring (Díaz-Caneja et al., 2018). It must however also be stated that there is a dearth of studies that have assessed temperament, personality or even coping strategies among offspring of parents with BPD using a truly prospective design.

Two high-risk studies of BPD in particular used a prospective design to assess precursors of psychopathology in offspring (Hafeman et al., 2016; Rudaz et al., 2021). Indeed, using the Child Behavior Checklist (CBCL) amongst other dimensional measures rated by parents with BPD regarding their offspring as well as similar scales directly used with the offspring, the BIOS study found that both parental and offspring reports of anxiety and depression symptoms as well as child-reported affective lability were the strongest predictors of BPD in offspring (Hafeman et al., 2016). Using our own study data, Rudaz et al. (Rudaz et al., 2021) found offspring reports of Major Depressive Episodes (MDE), conduct disorder and drug misuse, based on the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-E) interview (Orvaschel et al., 1982), to significantly predict the first onset of mania/hypomania in offspring of parents with BPD. In a systematic review of 21 high-risk cohorts of affected and unaffected offspring of parents with BPD, Raouana et al. (Raouana et al., 2018) described a clinical trajectory from anxiety disorders in childhood, to minor and subsequently major depression in early and later adolescence, to (hypo)manic episodes in early adulthood. Moreover, recurrent substance use disorders (SUD) manifesting during late adolescence and early adulthood were identified as additional risk factors for BPD (Raouana et al., 2018). Additional studies may shed light on individual precursors to mood disorders which can be teased apart from family factors or other influences shared among siblings.

Among the familial factors, offspring of parents with BPD have reported higher perceived maternal neglect (Doucette et al., 2016). Two other high-risk studies have shown that offspring already affected by mood disorders themselves reported more perceived emotional maltreatment than unaffected offspring (Koenders et al., 2020) and a higher perceived level of family control (Ferreira et al., 2013). Moreover, parental-reported stricter parental discipline (Petti et al., 2004), higher-conflict, lower parental rearing (Maciejewski et al., 2018), and lower cohesion (Stapp et al., 2020) have been indicated as factors that may promote the development of mood disorders among offspring of parents with BPD. Whereas parental reports were often preferred to those of the offspring, the former may be biased by the parents' own psychopathology (Stapp et al., 2020). Similarly, retrospective assessments of the family environment by already affected offspring may also be biased by the offspring's own psychopathology. Using an external rater of the family environment, Thorup et al. found that having a female caregiver who is not the only caregiver with good social functioning favored a healthy family environment for offspring of parents with schizophrenia or BPD, whereas severe life events experienced between the ages of 4 and 7 had a negative impact on this home environment (Thorup et al., 2022).

To sum it up, there is still a lack of research that specifically focuses

on factors that predict the risk of developing BPD or major depressive disorder (MDD) using reports from the offspring themselves in a truly prospective design and using a discordant sibling pair approach. Finally, there is a need of additional studies using standardized, validated measures resulting in a clear operationalization of risk factors for offspring development (Wolff et al., 2022). Considering all the previously mentioned caveats and using validated measures of potential risk factors for mood disorders prior to the onset of the first major mood episode in offspring, the aim of the present study was to identify factors reported by the offspring themselves, comparing measures between offspring who developed mood disorders with their siblings who did not, within the same family of a parent with BPD. The studied factors included premorbid non-mood disorders and symptoms, personality and temperament dimensions, coping strategies as well as the child's individual perception of characteristics related to the family. Our hypothesis was that in families of a parent with BPD, affected siblings have specific individual characteristics, which are not shared within the family promoting risk for mood disorders, that the unaffected siblings do not have.

2. Methods

2.1. Sample

The sample stems from a prospective high-risk study of mood disorders, which has been described in detail (Vandeleur et al., 2017). Briefly, probands (index parents) 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 probands with mood disorders were: (1) a lifetime diagnosis of bipolar-I, bipolar-II, schizoaffective BPD or else MDD, and (2) having at least one biological child, aged 6.0 to 17.9 years at study intake, who participated in the study. Parents and offspring were invited to take part in follow-up assessments every three years at predetermined ages of the offspring (7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37 and 40 years). Among the 343 families of probands with a bipolar-I, bipolar-II, schizoaffective BPD, we selected out the 24 families with 1) at least one child that developed a bipolar or MDD over the whole follow-up period (i.e. lifetime diagnosis) with available interview data ($n = 31$), and 2) at least one full sibling with interview data that did not develop a BPD or a MDD over the whole follow-up period (i.e. lifetime diagnosis) and had at least one assessment after the age of onset of the mood disorder of the affected sibling. Hence, the variables were selected from the most complete assessment before the onset of a mood episode in affected offspring, and those of the siblings were age-matched to those of the affected offspring. This resulted in a sample of 24 families for the analyses involving pre-morbid psychopathology. Among them there was one family with three affected and one unaffected sibling, one family with two affected and three unaffected siblings, four families with two affected and one unaffected sibling and 18 families with one affected and one unaffected sibling. Given incomplete data of the self-reports, analyses based on these data needed to be restricted to the 15 families with 1) at least one child that developed a bipolar or MDD over the follow-up period with available self-ratings prior to the first mood episode ($n = 18$), and 2) at least one full sibling that did not develop a BPD or a MDD over the follow-up period with a self-report within the same age range as that of the affected child. Within these 15 families, three had two affected and one unaffected sibling, two had one affected and three unaffected siblings, one had one affected and two unaffected siblings and nine families had one affected and one unaffected sibling.

This research project was approved by the local institutional review board (Faculty of Medicine of the University of Lausanne - Protocol number 151/03). All parents and adult offspring gave written informed consent for their own participation prior to the assessments. Parents gave written consent for the participation of their offspring younger than 18 years.

2.2. Measures

2.2.1. Diagnostic interviews

Information on parents and adult offspring was obtained using the French version (Preisig et al., 1999) of 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 K-SADS-E (Orvaschel et al., 1982). The DIGS was completed using the anxiety disorder sections of the French version (Leboyer et al., 1991) of the Schedule for Affective Disorders and Schizophrenia – Lifetime and Anxiety disorder version (SADS-LA) (Endicott and Spitzer, 1978). In addition to the interviews, information on children and parents was systematically collected from all participants from the age of 15 years using the Family History-Research Diagnostic Criteria (FH-RDC) (Andreassen et al., 1977). The reliability of the French translation of the DIGS (Berney et al., 2002; Preisig et al., 1999), the reliability of the K-SADS-E (Chambers et al., 1985; Orvaschel et al., 1982; Vandeleur et al., 2012), and the validity of the French version of the FH-RDC (Rothen et al., 2009; Vandeleur et al., 2015) were extensively tested. Interviewers were required to be master-level psychologists and were trained over a one- to two-month period. They were blind to the disease status of the other family members. Each interview was reviewed by a senior research psychologist.

Diagnoses were made over lifetime using a best-estimate procedure (Leckman et al., 1982), using a combination of information from direct interviews, family history report(s), and medical records where available. Mood disorders or episodes were diagnosed according to the DSM-5 and non-mood disorders were diagnosed according to the DSM-IV. Using the DIGS of the parents, the SES of the family was determined by the professional category and the level of education of each spouse of the household according to the Hollingshead Index (Hollingshead, 1975).

2.2.2. Self-report questionnaires

The assessment of offspring also included a series of self-rating questionnaires. The offspring completed the questionnaires themselves before reaching the age of 18 years. More detailed information on the validity and reliability of each of these questionnaires is available in the “Supplemental Materials” section annexed to this paper.

2.2.2.1. Parental bonding instrument. The Parental Bonding Instrument (PBI) is a questionnaire with 25 items, measuring parental qualities during childhood and adolescent development (Parker et al., 1979). It was designed to assess the perception of maternal or paternal attitudes during the first 16 years of life. The French version of the PBI revealed three factors in a sample of parents of school-aged children in Lausanne (Mohr et al., 1999): the first factor “care”, and the partitioning of the “protection” factor into two separate factors. The care factor is defined by care and involvement of the parent (Parker et al., 1979). The original second factor “protection” is subdivided into “denial of autonomy” (a negative pole), with parents obstructing the autonomy of their children, and “encouragement of freedom” (a positive pole), with parents encouraging the child to progressively take distance from their secure base in order to achieve social competence (Mohr et al., 1999). The three-factor solution of the French version was confirmed in a large sample of 13 to 14 year-old school-children in the Lausanne area (Tercier et al., 2011).

2.2.2.2. Family adaptability and cohesion evaluation scales version III. Family functioning was assessed using the French version (Vandeleur et al., 1999) of the Family Adaptability and Cohesion Evaluation Scales version III (FACES III) (Olson et al., 1985), a 30-item format instrument measuring the dimensions of “cohesion” (family boundaries, emotional bonding, time spent together) and “adaptability” (discipline, roles, leadership). Only the cohesion scale was analyzed for the present paper.

2.2.2.3. Family attitude scale. The original English version of the Family Attitude Scale (FAS) is a 30-item questionnaire assessing a respondent’s attitudes and behaviors towards another family member (Kavanagh et al., 1997). The original scale showed a one-factor solution and the total score has a potential range of 0–120, with higher scores reflecting more negative attitudes or behaviors towards a family member. The French translation of the FAS was developed in Lausanne, to use with both adults (Vandeleur et al., 2013) and youngsters (see Supplemental Materials).

2.2.2.4. Child self-report of childhood inhibition. Behavioral inhibition in children was measured using the Child version of the Self-Report of Childhood Inhibition (CSRCI) (Reznick et al., 1992). Our research group established a French translation of the CSRCI and the two dimensions “general fears” and “fears at school” were validated using confirmatory factor analysis (Tercier et al., 2011).

2.2.2.5. Dimensions of temperament survey – revised version. The original Dimensions of Temperament Survey (DOTS) (Lerner et al., 1982), a temperament scale of 34 dichotomous items developed for children and adults, was extensively tested in 1386 subjects of three age groups, but considering its psychometric problems, Windle and Lerner (Windle and Lerner, 1986) developed an improved instrument, the DOTS-R. This scale contains 54 items to elicit 9 temperament dimensions: “activity level – general”, “activity level – sleep”, “approach – withdrawal”, “flexibility – rigidity”, “mood”, “rhythmicity – sleep”, “rhythmicity – eating”, “rhythmicity – daily habits”, “task orientation”, which were obtained by exploratory factor analysis. Our research group established a French translation of the DOTS-R (see Supplemental Materials).

2.2.2.6. Adapted version of the child behavior check-list. The presence of psychiatric symptomatology was assessed using an adapted version of the widely-used Child Behavior Check-List (CBCL) (Achenbach and Edelbrock, 1983), which assesses emotional and behavioral problems over the past 6 months in 4 to 16 year-old children, as observed by their parents. The psychometric properties of this scale, which groups 8 syndromes into the major dimensions of “internalizing” and “externalizing” disorders, were established by its originators (Achenbach and Edelbrock, 1983). We used the French translation of the parent version of the CBCL (Fombonne, 1989) which we adapted for use with children. Similar to the parent version, this translated version contains 112 items which the children rated themselves. Only the overall dimensions of “internalizing” (“withdrawn/depressed”, “somatic/complaints”, “anxious/depressed”) and “externalizing” (“rule-breaking behavior” and “aggressive behavior”) disorders were used in this study (Ivanova et al., 2019).

2.2.2.7. State and trait anxiety inventory for children. The State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) is a validated instrument for the evaluation of both current (state) and lifetime (trait) anxiety in adults. The trait dimension was also measured in children using the STAI for Children (STAIC) which was also originally established by Spielberger (Spielberger, 1993) and further tested in a sample of children in France (Vila et al., 1999).

2.2.2.8. Euronet: problem resolution strategies. The Euronet questionnaire developed by Grob et al. (Grob et al., 1993) covers 3 domains: 1) daily constraints, 2) problem resolution strategies, and 3) well-being of adolescents. Only the second part of the instrument (problem resolution strategies) which contains 17 items (4-level Likert scale) on possible reactions in problematic situations was used. This factor can be split into 2 subscales: Active problem resolution strategy (8 items) and Emotional problem resolution strategy (5 items). In a large sample of adults from the Lausanne population, the French version of the scale revealed a 3-factor solution including the dimensions of Emotion-focused coping,

Help-seeking and Problem-focused coping (Perrin et al., 2014).

2.2.2.9. Eysenck personality questionnaire - Junior. The Eysenck Personality Questionnaire (EPQ) for adults (Eysenck and Eysenck, 1975) is a 90-item self-report personality inventory that assesses four dimensions: Extraversion, Neuroticism, Psychoticism, and social desirability (the Lie scale) (Eysenck et al., 1980). The Junior version of the EPQ (EPQ -Jr) was also developed by Eysenck and Eysenck (Eysenck and Eysenck, 1975) to elicit the same four personality dimensions as the adult version. Our group translated this questionnaire and tested its validity in a sample of 12-year old school-children in the Lausanne area (Rothen et al., 2008). We did not use the Lie scale for our analysis.

2.3. Data analysis

Demographic characteristics were first established in probands and then compared between affected and unaffected siblings using chi-square or ANOVA tests, as appropriate. Offspring dyads were compared on a series of non-mood disorders that had occurred before the onset of any potential mood episode, including anxiety disorders (separation anxiety disorder, specific and social phobias), behavioral disorders (conduct disorder, attention-deficit and hyperactivity disorder, and oppositional defiant disorder) as well as SUD (alcohol and drug abuse or dependence). Between-group analyses for each of these categorical variables were performed using generalized linear mixed models (Liang and Zeger, 1986), adjusted for sex and age of offspring as well as intra-familial correlations (two offspring or more per family). The offspring were further compared on the scores of self-report questionnaires using similarly adjusted models. These scores were taken from the assessment that preceded the onset of the first mood episode in affected offspring. For the comparison siblings, the assessment that corresponded the closest in age to that of the affected offspring was selected. Offspring with missing scores were eliminated from the respective analyses. For the description of potential risk factors tested in these models, we adopted a significance level of $p < 0.05$. All analyses were conducted using the Statistical Analysis System, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Description of the sample

Among the probands from the 24 selected families that included at least one affected and one unaffected offspring, 54.2 % were women. The mean (s.d) age of the probands at study intake was 40.0 (5.5) years, and their mean score on the Hollingshead index was 3.3 (1.1), indicating middle-class SES. The offspring were followed for a mean duration of 16.2 (4.6) years. Table 1 shows the characteristics of the affected and unaffected siblings. Among the 31 offspring that developed a major mood disorder during the follow-up period, 26 (83.9 %) developed MDD, 2 (6.4 %) bipolar I and 3 (9.7 %) bipolar II disorder. The 31 offspring that developed a major mood disorder during the follow-up and the 33 that did not, did not differ by sex or age at the first assessment. However, they differed significantly by age at the last assessment, affected offspring had a higher mean age than their unaffected sib-pairs. The mean age of onset of the first manic/hypomanic episode was 20.6 (s.d: 6.0) years and of the first major depressive episode was 15.0 (s.d: 6.6) years. The median number of mood episodes among affected offspring was 2.0 over the follow-up (Table 1).

3.2. Premorbid non-mood disorders

The offspring that developed a major mood disorder did not differ from those that did not during the follow-up regarding the frequency of non-mood disorders that occurred prior to the onset of the first mood

Table 1
Characteristics of offspring.

	Affected (n = 31)	Unaffected (n = 33)	Statistic	p-value
Female sex,%	64.5	51.5	$\chi^2_1=1.1$	n.s.
Age at first assessment, years, mean (s.d.)	10.2 (4.8)	8.3 (4.3)	$F_1=2.9$	n.s.
Age at last assessment, years, mean (s.d.)	27.2 (7.1)	23.7 (6.6)	$F_1=4.4$	0.041
BP-I,%	6.4	-	-	-
BP-II,%	9.7	-	-	-
Age of onset of first manic/hypomanic episode, years, mean (s.d.)	20.6 (6.0)	-	-	-
MDD,%	83.9	-	-	-
Age of onset of first major depressive episode, years, mean (s.d.) ¹	15.0 (6.6)	-	-	-
Number of mood episodes over the follow-up, median (IQR)	2.0 (1.0;5.0)	-	-	-

Key: n.s. = non significant ($p > 0.05$); s.d. = standard deviation; IQR = inter-quartile range. Significant differences are shown in bold. BPD-I = bipolar I disorder, BPD-II = bipolar II disorder; MDD = major depressive disorder.

¹ Among offspring with BPD-I, BPD-II and MDD with at least one major depressive episode.

episode in affected offspring (Table 2).

3.3. Scores according to the self-report measures as potential risk factors for the development of mood disorders

Table 3 provides the mean scores and the standard deviations (S.D.) for each dimension of the self-report measures by offspring mood disorder status. Given that self-report data prior to the first major mood

Table 2

Premorbid psychopathology among offspring-sibling pairs in the 24 families of bipolar spectrum probands. In the final version of the tables, please take care to align the columns correctly.

	Offspring		OR (95CI) ¹	p-value
	with mania/hypomania/depressive episode (n = 31) N (%)	with no mood episode (n = 39) N (%)		
Anxiety disorders	18 (58.1)	21 (53.9)	0.92 (0.37;2.33)	0.866
Separation anxiety disorder	10 (32.3)	15 (38.5)	0.61 (0.23,1.64)	0.327
Specific phobia	7 (22.6)	5 (12.8)	1.49 (0.39,5.61)	0.558
Social phobia	11 (35.5)	13 (33.3)	1.25 (0.43,3.63)	0.676
Behavioral disorders	6 (19.4)	3 (7.7)	3.27 (0.46,23.32)	0.236
Conduct disorder	2 (6.5)	0 (0.0)	-	-
Oppositional defiant disorder	3 (9.7)	1 (2.6)	5.02 (0.36,69.94)	0.230
Attention-deficit hyperactivity disorder	5 (16.1)	2 (5.1)	4.17 (0.48,36.00)	0.194
Substance use disorders²	2 (6.5)	1 (2.6)	2.83 (0.14,57.17)	0.497
Alcohol	1 (3.2)	1 (2.6)	0.98 (0.04,21.84)	0.988
Drug	1 (3.2)	0 (0.0)	-	-

Key: OR: odd's ratio; 95CI: 95 % confidence interval. ¹ Models adjusted for sex and age of offspring, as well as intra-familial correlations (varying number of offspring across families). ² abuse or dependence.

Table 3
Self-rated assessments among offspring in the 15 families of bipolar spectrum probands.

	Offspring		β (95CI) ¹	p-value
	with mania/hypomania/depressive episode (n = 18) mean (SD)	with no mood episode (n = 20) mean (SD)		
PBI				
Mother care	28.4 (5.8)	27.6 (6.9)	0.44 (-2.54,3.42)	0.771
Mother encouragement of freedom	14.0 (3.0)	13.0 (2.7)	0.63 (-0.28,1.54)	0.177
Mother denial of autonomy	4.2 (3.5)	4.5 (3.4)	-0.28 (-2.34,1.78)	0.789
Father care	26.4 (7.8)	25.3 (6.6)	0.61 (-3.24,4.47)	0.756
Father encouragement of freedom	12.3 (3.8)	12.9 (2.4)	-0.62 (-2.31,1.08)	0.476
Father denial of autonomy	3.6 (2.5)	4.1 (2.6)	-0.78 (-2.38,0.83)	0.343
FACES III				
Perceived: cohesion	32.3 (7.3)	32.9 (7.6)	-0.54 (-3.79,2.72)	0.747
Perceived: adaptability	22.8 (6.4)	25.3 (7.7)	-2.11 (-5.12,0.90)	0.169
FAS-30*				
Mother: total score	20.7 (18.0)	22.2 (16.4)	-0.79 (-8.90,7.33)	0.849
Father: total score	25.2 (23.4)	25.3 (21.5)	1.49 (-11.50,14.47)	0.822
CSRCI				
Behavioral inhibition: school	22.9 (4.4)	22.6 (4.1)	1.01 (-1.20,3.23)	0.370
Behavioral inhibition: fears	16.1 (3.4)	15.6 (1.8)	0.30 (-1.02,1.62)	0.655
Behavioral inhibition: total score	50.3 (6.4)	49.6 (4.5)	1.09 (-1.72,3.89)	0.447
DOTS-R*				
Activity level (general)	13.5 (4.5)	15.1 (5.4)	-1.78 (-5.69,2.12)	0.371
Activity level (sleep)	9.2 (3.3)	9.7 (2.2)	-0.44 (-2.44,1.56)	0.669
Approach-withdrawal	20.7 (2.1)	19.0 (2.7)	1.43 (0.16,2.70)	0.028
Flexibility-Rigidity	16.3 (2.6)	16.3 (1.9)	0.09 (-1.88,2.06)	0.929
Mood	25.1 (2.5)	24.2 (4.2)	0.87 (-1.06,2.79)	0.377
Rhythmicity (sleep)	14.5 (2.8)	13.5 (3.5)	0.94 (-0.55,2.44)	0.216
Rhythmicity (eating)	13.4 (3.5)	14.1 (3.2)	-1.71 (-4.16,0.75)	0.174
Rhythmicity (habits)	10.7 (2.4)	9.0 (2.5)	2.29 (0.55,4.04)	0.010
Task orientation	22.6 (4.2)	19.3 (2.6)	3.40 (1.11,5.69)	0.004
CBCL				
Internalizing	7.0 (3.8)	6.6 (3.0)	0.21 (-2.38,2.79)	0.876
Externalizing	7.1 (5.9)	8.0 (3.9)	-0.94 (-3.86,1.98)	0.527
Total	21.1 (10.8)	23.0 (7.9)	-1.69 (-7.39,4.01)	0.561
STAI				
Total score	27.9 (5.3)	26.1 (4.1)	1.73 (-0.95,4.42)	0.206
EURONET*				
Emotion-focused	7.2 (4.0)	6.7 (3.5)	0.62 (-1.49,2.74)	0.564

Table 3 (continued)

	Offspring		β (95CI) ¹	p-value
	with mania/hypomania/depressive episode (n = 18) mean (SD)	with no mood episode (n = 20) mean (SD)		
Problem-focused	6.9 (2.2)	6.2 (1.5)	0.22 (-0.77,1.20)	0.667
Help-seeking	3.7 (2.4)	4.1 (2.6)	-0.41 (-1.78,0.96)	0.556
EPQ-J*				
Psychoticism	2.1 (2.9)	1.7 (1.4)	-0.04 (-1.74,1.65)	0.959
Extraversion	16.6 (3.3)	16.2 (4.0)	0.03 (-1.45,1.50)	0.972
Neuroticism	4.8 (3.3)	4.9 (3.0)	-0.86 (-3.69,1.97)	0.551

Key: *N = 13 offspring with a depressive episode, no manic/hypomanic episode, N = 15 offspring without a mood episode. SD: standard deviation; 95CI: 95 % confidence interval; ¹ Models adjusted for sex and age of offspring, as well as intra-familial correlations. Significant differences are shown in bold.

PBI: Parental bonding instrument; FACES III: Family adaptability and cohesion evaluation scales III; FAS-30: Family attitude scale; CSRCI: Child self-report childhood inhibition; DOTS-R: Dimensions of temperament survey revised; CBCL: Child behavior checklist; STAI: state-trait anxiety inventory; EPQ-J: Eysenck personality questionnaire - junior version.

episode were not available for all offspring, analyses involving these measures were restricted to 15 families with 18 affected and 20 unaffected offspring (or 13 affected and 15 unaffected offspring for the FAS-30, DOTS-R, Euronet and EPQ-J scales). Offspring that subsequently developed major mood disorders did not differ from those that did not on most of the self-rating dimensions, but scored higher on the DOTS-R temperament dimensions: “approach-withdrawal”, “rhythmicity for daily habits” and “task orientation” (Table 3).

4. Discussion

The present paper is the first to prospectively identify risk factors for mood disorders in families of patients with BPD using the discordant sib-pair approach, which controls for genetic and environmental factors shared by siblings. Overall, except for three out of nine temperament dimensions, offspring who had developed a mood disorder did not differ from their unaffected siblings in any of the assessed risk factors including premorbid psychopathology or symptoms, personality features, coping style and perceived family-related characteristics. The observed differences were restricted to the three temperament dimensions “rhythmicity of habits” (regularity in performing daily habits), “task-orientation” (high persistence and low distractibility) and “approach to novelty” (tendency to approach new objects and persons). The higher and not lower scores on these temperament dimensions observed in offspring that subsequently developed mood disorders could reflect increased vulnerability to mood disorders, but they could also be the indirect consequences of premorbid mood swings or else strategies to cope with them. One hypothesis is that offspring that subsequently developed MDD were more regularly habit-formed and task-oriented than their unaffected siblings, possibly reflecting an attitude of minor distractibility and a certain lack of flexibility, or perhaps even persistent repetitive thoughts (Kaplan et al., 2018) that could predispose these offspring to adopt a pattern of negative affect and cognitions and represent a precursor for the development of major depression. Regarding the higher approach - withdrawal in affected offspring compared to their unaffected siblings, this finding might be explained by the fact that these offspring try to protect themselves from depressive affect by seeking excitement and searching for new stimuli, which

corresponds to Cloninger's hypothesis underlying personal dynamics in people with high novelty-seeking (Zappitelli et al., 2013). The exact mechanisms potentially underlying the development of depression in these offspring would need to be further studied.

The absence of differences between affected and unaffected offspring in the present study with respect to premorbid psychopathology or perceived family-related characteristics is partially inconsistent with existing research including a previous publication in our own data. Indeed, the lack of differences between the groups for either premorbid disorders or internalizing and externalizing scores on the CBCL contrasts with studies that have found anxiety to be an important early precursor of mood disorders in high-risk offspring (Duffy et al., 2019), in particular in the subgroup of offspring who later developed MDD (Rudaz et al., 2021). With regard to disruptive-behavioral disorders, our data again contrast with the study by Rudaz et al. that showed a significantly higher likelihood to develop conduct disorders and SUD among children who subsequently developed mania/hypomania. However, the results of the present study that compared offspring *within* families controlling thereby for shared familial factors cannot be easily compared with those of previous high-risk studies that compared offspring *across* families. Indeed, in the present analysis, the "control" offspring stemmed from the same family with an affected parent, whereas the cited previous studies compared all offspring of affected parents to all offspring of unaffected control parents. Hence, in the present study, the compared offspring recruited within the same family were more similar with respect to genetic and family-shared factors than offspring from two different families with two different parents in previous studies. Given that genetic and potentially shared family factors underly the development of the studied premorbid anxiety disorders, SUD and behavioral disruptive disorders (Jami et al., 2021), it is not surprising that siblings of the same family differed less with respect to these disorders than unrelated offspring from different families. This is also illustrated by the previously published discrepant findings from our own study (Rudaz et al., 2021), which did not rely on a discordant sib-pair approach and, in addition, was based on our entire cohort.

Aside from the Dutch study that showed passive coping styles and harm-avoidance temperament (Kemner et al., 2015) to be risk factors for the onset or recurrence of mood disorders, there is a dearth of studies that have assessed personality features or coping strategies as risk factors among offspring of parents with BPD using a prospective design. We did not assess a passive coping style or harm-avoidance attitudes in our study which makes findings difficult to compare to those of the Dutch study. However, our findings did not show affected and unaffected offspring to differ in the personality scores on psychoticism, extraversion or neuroticism or in emotion-focused, problem-focused or help-seeking coping strategies. Again, given the contribution of genetic and exposure to shared family environment also to personality traits and coping style (Jami et al., 2021), offspring from the same family are more likely to share these traits and coping styles than offspring from two different families.

With respect to the perception of family-related characteristics, previous high-risk research comparing children across families has yielded conflicting findings with some studies emphasizing the protective value for mental health of positive family functioning or emotional relationships (Maciejewski et al., 2018; Menculini et al., 2020), whereas other studies did not find inter-group differences (Stapp et al., 2020). Our results revealed that neither the PBI (mother/father care, encouragement of freedom, and denial of autonomy), nor the FAS-30 (expressed emotions in family relationships), nor the FACES III (perceived cohesion and adaptability), were associated with the subsequent development of mood disorders, suggesting that previously published positive findings could have been confounded by genetic or environmental factors shared by siblings, which could have shaped the child's perception of the assessed family-related characteristics. These findings do coincide with those of our recent prospective analysis (Moulin et al., 2022), which also used the PBI and the FACES III

questionnaires, in the whole sample of affected versus unaffected families, to not show any association of the perception of familial factors with offspring mood disorder outcomes. Taken together, the results of our two studies seem to suggest that the perception of familial factors do not play a key role in the development of mood disorders. Comparisons remain difficult as in our study, questionnaires were filled in by the offspring themselves before the onset of the mood disorder, whereas most previous research used questionnaires that had been filled in by already affected offspring or else by their parents (Stapp et al., 2020).

4.1. Limitations of the study

First, one important limitation is the small sample size involving low statistical power to detect group differences. However, despite the limited statistical power we could identify variables associated with the development of subsequent mood disorders in offspring. The power available in a sibling comparison design depends on the prevalence of both exposure and outcome, as well as on their association with each other, and is thus difficult to establish (Frisell, 2021). Second, we cannot exclude the attenuation of associations due to random measurement error of the within-pair estimates, which could be higher than the unpaired estimates of more traditional offspring studies (Frisell et al., 2012) and may have further diminished our ability to detect between-group differences. Third, the temperament dimensions approach – withdrawal and rhythmicity of daily habits entailed low reliability estimates (Cronbach alpha coefficients). However, the bias resulted from this potential measurement error was likely to be non-differential (conservative).

4.2. Conclusion and future outlook

We have identified three dimensions of temperament that distinguished offspring who have subsequently developed mood disorders from those who have not within families of a parent with BPD, suggesting that higher task-orientation, higher rhythmicity of habits and higher approach to novelty may in fact be precursors of the development of mood disorders. Through their ability to adjust for factors shared within families, sibling-pair studies are a useful method for identifying individual and non-shared familial risk factors in offspring. However, given that such studies generally suffer from low sample size data based on this approach, similar studies need to be combined worldwide.

CRedit authorship contribution statement

Francesca Di Giacomo: Conceptualization, Writing – original draft, Writing – review & editing. **Marie-Pierre F. Strippoli:** Validation, Formal analysis, Resources, Data curation, Writing – review & editing. **Enrique Castelao:** Data curation, Resources, Writing – review & editing. **Joëlle Rosselet Amoussou:** Resources, Writing – review & editing. **Mehdi Gholam:** Methodology, Data curation. **Setareh Ranjbar:** Methodology, Data curation. **Jennifer Glaus:** Investigation, Writing – review & editing. **Pierre Marquet:** Writing – review & editing. **Martin Preisig:** Conceptualization, Methodology, Validation, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Kerstin Jessica Plessen:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision. **Caroline L. Vandeleur:** Conceptualization, Methodology, Validation, Investigation, Writing – review & editing, Visualization, Supervision.

Declaration of Competing Interest

All authors have no conflicts of interest to disclose.

Role of funding sources

This research was and is supported by five grants from the Swiss

National Foundation (SNF: #3200-040677, #32003B-105969, #32003B-118326, #3200-049746 and #3200-061974), three grants for a National Centers of Competence in Research project “The Synaptic Bases of Mental Diseases” (#125759, #158776, and #51NF40 – 185897) financed by the Swiss National Foundation, one grant from the Swiss State Secretariat for Education, Research and Innovation (SERI #22.00170), one grant from the Foundation Campus Biotech Geneva, and one grant from GlaxoSmithKline Clinical Genetics. The funders had no involvement in any aspect of this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2023.115615](https://doi.org/10.1016/j.psychres.2023.115615).

References

- Achenbach, T., Edelbrock, C., 1983. *Manual For the Child Behavior Checklist and the Revised Child Behavior Checklist profile*. University of Vermont, Burlington, VT.
- Andreasen, N.C., Endicott, J., Spitzer, R.L., Winokur, G., 1977. The family history method using diagnostic criteria. Reliability and validity. *Arch. Gen. Psychiatry* 34, 1229–1235. <https://doi.org/10.1001/archpsyc.1977.01770220111013>.
- Berney, A., Preisig, M., Matthey, M.L., Ferrero, F., Fenton, B.T., 2002. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of alcohol and drug diagnoses. *Drug Alcohol Depend.* 65, 149–158. [https://doi.org/10.1016/S0376-8716\(01\)00156-9](https://doi.org/10.1016/S0376-8716(01)00156-9).
- Chambers, W.J., Puig-Antich, J., Hirsch, M., Paez, P., Ambrosini, P.J., Tabrizi, M.A., Davies, M., 1985. The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. *Arch. Gen. Psychiatry* 42, 696–702. <https://doi.org/10.1001/archpsyc.1985.01790300064008>.
- Díaz-Caneja, C.M., Morón-Nozaleda, M.G., Vicente-Moreno, R.P., Rodríguez-Toscano, E., Pina-Camacho, L., de la Serna, E., Sugranyes, G., Baeza, I., Romero, S., Sánchez-Gistau, V., Castro-Fornieles, J., Moreno, C., Moreno, D., 2018. Temperament in child and adolescent offspring of patients with schizophrenia and bipolar disorder. *Eur. Child Adolesc. Psychiatry* 27, 1459–1471. <https://doi.org/10.1007/s00787-018-1135-y>.
- Doucette, S., Levy, A., Flowerdew, G., Horrocks, J., Grof, P., Ellenbogen, M., Duffy, A., 2016. Early parent-child relationships and risk of mood disorder in a Canadian sample of offspring of a parent with bipolar disorder: findings from a 16-year prospective cohort study. *Early Interv. Psychiatry* 10, 381–389. <https://doi.org/10.1111/eip.12195>.
- Duffy, A., 2018. Early intervention in bipolar disorders: where we are now and need to go next. *Bipolar. Disord.* <https://doi.org/10.1111/bdi.12599>.
- Duffy, A., Goodday, S., Keown-Stoneman, C., Grof, P., 2019. The emergent course of bipolar disorder: observations over two decades from the Canadian high-risk offspring cohort. *Am. J. Psychiatry* 176, 720–729. <https://doi.org/10.1176/appi.ajp.2018.18040461>.
- Duffy, A., Goodday, S.M., Christiansen, H., Patton, G., Thorup, A.A.E., Preisig, M., Vandeleur, C., Weissman, M., de Girolamo, G., 2023. The well-being of children at familial risk of severe mental illness: an overlooked yet crucial prevention and early intervention opportunity. *Nature Mental Health* 1, 534–541.
- Endicott, J., Spitzer, R.L., 1978. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch. Gen. Psychiatry* 35, 837–844. <https://doi.org/10.1001/archpsyc.1978.01770310043002>.
- Eysenck, H., Eysenck, S., Gauquelin, M., Gauquelin, F., Pascal, C., Pascal, D., 1980. La structure de la personnalité chez les Français confrontée à celle des Anglais, comparaison “cross-culturelle”. *Personnalité* 2, 7–29.
- Eysenck, H.J., Eysenck, S.B.G., 1975. *Manual of the Eysenck Personality Questionnaire*. Hodder and Stoughton, London.
- Ferreira G.S., Moreira C.R., Kleinman A., Nader E.C., Gomes B.C., Teixeira A.M., Rocca C. C., Nicoletti M., Soares J.C., Busatto G.F., Lafer B., Caetano S.C., Dysfunctional family environment in affected versus unaffected offspring of parents with bipolar disorder. *Aust. N. Z. J. Psychiatry* 2013; 47: 1051–1057. <https://doi.org/10.1177/0004867413506754>.
- Fombonne, E., 1989. The child Behaviour checklist and the rutter parental questionnaire: a comparison between two screening instruments. *Psychol. Med.* 19, 777–785. <https://doi.org/10.1017/s0033291700024387>.
- Frisell, T., Öberg, S., Kuja-Halkola, R., Sjölander, A., 2012. Sibling comparison designs: bias from non-shared confounders and measurement error. *Epidemiology* 23, 713–720. <https://doi.org/10.1097/EDE.0b013e31825fa230>.
- Frisell, T., 2021. Invited commentary: sibling-comparison designs, are they worth the effort? *Am. J. Epidemiol.* 190, 738–741. <https://doi.org/10.1093/aje/kwaa183>.
- Grob, A., Bodmer, N., Flammer, A., 1993. *Living Conditions in Europe: the Case of Switzerland*. University of Bern, Institute of Psychology, Bern.
- Hafeman, D.M., Merranko, J., Axelson, D., Goldstein, B.I., Goldstein, T., Monk, K., Hickey, M.B., Sakolsky, D., Diler, R., Iyengar, S., Brent, D., Kupfer, D., Birmaher, B., 2016. Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. *Am. J. Psychiatry* 173, 695–704. <https://doi.org/10.1176/appi.ajp.2015.15040414>.
- Hollingshead, A.B., 1975. *Four Factor Index of Social Status*. Yale University, New Haven, CT.
- Ivanova, M.Y., Achenbach, T.M., Rescorla, L.A., Guo, J., Althoff, R.R., Kan, K.J., Almqvist, F., Begovac, I., Broberg, A.G., Chahed, M., da Rocha, M.M., Dobrea, A., Döpfner, M., Erol, N., Fombonne, E., Fonseca, A.C., Forns, M., Frigerio, A., Grietens, H., Hewitt-Ramirez, N., Juárez, F., Kajokienė, L., Kanbayashi, Y., Kim, Y.A., Larsson, B., Leung, P., Liu, X., Maggolini, A., Minaei, A., Moreira, P.A.S., Oh, K.J., Petot, D., Pisa, C., Pomalima, R., Roussos, A., Rudan, V., Sawyer, M., Shahini, M., Ferreira de Mattos Silveiras, E., Simsek, Z., Steinhausen, H.C., Szivovica, L., Valverde, J., Viola, L., Weintraub, S., Metzke, C.W., Wolanczyk, T., Woo, B., Zhang, E.Y., Zilber, N., Zukauskienė, R., Verhulst, F.C., 2019. Testing syndromes of psychopathology in parent and youth ratings across societies. *J. Clin. Child Adolesc. Psychol.: Off. J. Soc. Clin. Child Adolesc. Psychol. Am. Psychol. Assoc. Divis.* 53, 596–609. <https://doi.org/10.1080/15374416.2017.1405352>, 48.
- Jami, E.S., Hammerschlag, A.R., Bartels, M., Middeldorp, C.M., 2021. Parental characteristics and offspring mental health and related outcomes: a systematic review of genetically informative literature. *Transl. Psychiatry* 11, 197. <https://doi.org/10.1038/s41398-021-01300-2>.
- Kaplan, D.M., Palitsky, R., Carey, A.L., Crane, T.E., Havens, C.M., Medrano, M.R., Reznik, S.J., Sbarra, D.A., O'Connor, M.F., 2018. Maladaptive repetitive thought as a transdiagnostic phenomenon and treatment target: an integrative review. *J. Clin. Psychol.* 74, 1126–1136. <https://doi.org/10.1002/jclp.22585>.
- Kavanagh, D.J., O'Halloran, P., Manicavasagar, V., Clark, D., Piatkowska, O., Tennant, C., Rosen, A., 1997. The Family Attitude Scale: reliability and validity of a new scale for measuring the emotional climate of families. *Psychiatry Res.* 70, 185–195. [https://doi.org/10.1016/S0165-1781\(97\)00033-4](https://doi.org/10.1016/S0165-1781(97)00033-4).
- Kemner, S.M., Mesman, E., Nolen, W.A., Eijckemans, M.J., Hillegers, M.H., 2015. The role of life events and psychological factors in the onset of first and recurrent mood episodes in bipolar offspring: results from the Dutch Bipolar Offspring Study. *Psychol. Med.* 45, 2571–2581. <https://doi.org/10.1017/S0033291715000495>.
- Koenders, M.A., Mesman, E., Giltay, E.J., Elzinga, B.M., Hillegers, M.H.J., 2020. Traumatic experiences, family functioning, and mood disorder development in bipolar offspring. *Brit. J. Clin. Psychol.* 59, 277–289. <https://doi.org/10.1111/bjc.12246>.
- Leboyer, M., Maier, W., Teherani, M., Lichtermann, D., D'Amato, T., Franke, P., Lépine, J.P., Minges, J., McGuffin, P., 1991. The reliability of the SADS-LA in a family study setting. *Eur. Arch. Psychiatry Clin. Neurosci.* 241, 165–169. <https://doi.org/10.1007/bf02219716>.
- Leckman, J.F., Sholomskas, D., Thompson, W.D., Belanger, A., Weissman, M.M., 1982. Best estimate of lifetime psychiatric diagnosis: a methodological study. *Arch. Gen. Psychiatry* 39, 879–883. <https://doi.org/10.1001/archpsyc.1982.04290080001001>.
- Lerner, R.M., Palermo, M., Spiro, I.I.A., Nesselroade, J.R., 1982. Assessing the dimensions of temperamental individuality across the life span: the Dimensions of Temperament Survey (DOTS). *Child Dev.* 149–159.
- Li, Z., McKeague, I.W., Lumey, L.H., 2014. Optimal design strategies for sibling studies with binary exposures. *Int. J. Biostat.* 10, 185–196. <https://doi.org/10.1515/ijb-2014-0015>.
- Liang, K.-Y., Zeger, S.L., 1986. Longitudinal data analysis using generalized linear models. *Biometrika* 73, 13–22. <https://doi.org/10.1093/biomet/73.1.13>.
- Luthar, S.S., 2006. Resilience in development: a synthesis of research across five decades. Cicchetti, D., Cohen, D.J. (Eds.). *Developmental psychopathology: Risk, disorder, and Adaptation*. John Wiley & Sons, Inc., Hoboken, NJ, US, pp. 739–795. ^pp.
- Maciejewski, D., Hillegers, M., Penninx, B., 2018. Offspring of parents with mood disorders: time for more transgenerational research, screening and preventive intervention for this high-risk population. *Curr. Opin. Psychiatry* 31, 349–357. <https://doi.org/10.1097/ycp.0000000000000423>.
- Menculini, G., Balducci, P.M., Attademo, L., Bernardini, F., Moretti, P., Tortorella, A., 2020. Environmental risk factors for bipolar disorders and high-risk states in adolescence: a systematic review. *Medicina* 56. <https://doi.org/10.3390/medicina56120689>.
- Mohr, S., Preisig, M., Fenton, B.T., Ferrero, F., 1999. Validation of the French version of the parental bonding instrument in adults. *Pers. Individ. Dif.* 26, 1065–1074. [https://doi.org/10.1016/S0191-8869\(98\)00210-4](https://doi.org/10.1016/S0191-8869(98)00210-4).
- Moulin, F., Gholam, M., Strippoli, M.F., Castelao, E., Merikangas, K.R., Stapp, E.K., Marquet, P., Aubry, J.M., Plessen, K.J., Di Giacomo, P., Glaus, J., Pistis, G., Lavigne, B., Elowe, J., Ranjbar, S., Preisig, M., Vandeleur, C.L., 2022. Environmental factors in offspring of parents with mood disorders and their role in parent-child transmission: findings from a 14-year prospective high-risk study. *Int. J. Bipolar. Disord.* 10, 11. <https://doi.org/10.1186/s40345-022-00257-5>.
- Nurnberger Jr., J.I., Blehar, M.C., Kaufmann, C.A., York-Cooler, C., Simpson, S.G., Harkavy-Friedman, J., Severe, J.B., Malaspina, D., Reich, T., 1994. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH genetics initiative. *Arch. Gen. Psychiatry* 51. <https://doi.org/10.1001/archpsyc.1994.03950110009002>, 849–859; discussion 863–844.
- Olson, D.H., Portner, J., Lavee, Y., 1985. FACES III. *Family Social Science. University of Minnesota, St Paul*.
- Orvaschel, H., Puig-Antich, J., Chambers, W., Tabrizi, M.A., Johnson, R., 1982. Retrospective assessment of prepubertal major depression with the Kiddie-SADS-e. *J. Am. Acad. Child Psychiatry* 21, 392–397. [https://doi.org/10.1016/S0002-7138\(09\)60944-4](https://doi.org/10.1016/S0002-7138(09)60944-4).
- Parker, G., Tupling, H., Brown, L.B., 1979. A parental bonding instrument. *Brit. J. Med. Psychol.*
- Perrin, M., Vandeleur, C.L., Castelao, E., Rothen, S., Glaus, J., Vollenweider, P., Preisig, M., 2014. Determinants of the development of post-traumatic stress disorder, in the general population. *Soc. Psychiatry Psychiatr. Epidemiol.* 49, 447–457. <https://doi.org/10.1007/s00127-013-0762-3>.

- Petti, T., Reich, W., Todd, R.D., Joshi, P., Galvin, M., Reich, T., Raymond DePaulo, J., Nurnberger, J., 2004. Psychosocial variables in children and teens of extended families identified through bipolar affective disorder probands. *Bipolar Disord.* 6, 106–114. <https://doi.org/10.1111/j.1399-5618.2004.00105.x>.
- Preisig, M., Fenton, B.T., Matthey, M.L., Berney, A., Ferrero, F., 1999. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of the French version. *Eur. Arch. Psychiatry Clin. Neurosci.* 249, 174–179. <https://doi.org/10.1007/s004060050084>.
- Raouna, A., Osam, C.S., MacBeth, A., 2018. Clinical staging model in offspring of parents with bipolar disorder: a systematic review. *Bipolar Disord.* 20, 313–333. <https://doi.org/10.1111/bdi.12604>.
- Rasic, D., Hajek, T., Alda, M., Uher, R., 2014. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. *Schizophr. Bull.* 40, 28–38. <https://doi.org/10.1093/schbul/sbt114>.
- Reznick, J.S., Hegeman, I.M., Kaufman, E.R., Woods, S.W., Jacobs, M., 1992. Retrospective and concurrent self-report of behavioral inhibition and their relation to adult mental health. *Dev. Psychopathol.* 4, 301–321. <https://doi.org/10.1017/S095457940000016X>.
- Rothen, S., Vandeleur, C.L., Lustenberger, Y., Jeanpretre, N., Ayer, E., Sisbane, F., Fornerod, D., Chouchena, O., Gamma, F., Halfon, O., Ferrero, F., Preisig, M., 2008. Validation of the French version of the EPQ-Junior. *Pers. Individ. Dif.* 44, 464–474. <https://doi.org/10.1016/j.paid.2007.09.011>.
- Rothen, S., Vandeleur, C.L., Lustenberger, Y., Jeanpretre, N., Ayer, E., Gamma, F., Halfon, O., Fornerod, D., Ferrero, F., Preisig, M., 2009. Parent-child agreement and prevalence estimates of diagnoses in childhood: direct interview versus family history method. *Int. J. Methods Psychiatr. Res.* 18, 96–109. <https://doi.org/10.1002/mpr.281>.
- Rudaz, D., Vandeleur, C.L., Gholam, M., Castelayo, E., Strippoli, M.F., Marquet, P., Aubry, J.M., Merikangas, K.R., Preisig, M., 2021. Psychopathological precursors of the onset of mood disorders in offspring of parents with and without mood disorders: results of a 13-year prospective cohort high-risk study. *J. Child. Psychol. Psychiatry* 62, 404–413. <https://doi.org/10.1111/jcpp.13307>.
- Schlomer, G.L., Ellis, B.J., 2016. Sibling studies. In: weekes-Shackelford, V., Shackelford, T.K., Weekes-Shackelford, V.A. (Eds.). *Encyclopedia of Evolutionary Psychological Science*. Springer International Publishing, Cham, pp. 1–3. p. pp.
- Sjölander, A., Öberg, S., Frisell, T., 2022. Generalizability and effect measure modification in sibling comparison studies. *Eur. J. Epidemiol.* 37, 461–476. <https://doi.org/10.1007/s10654-022-00844-x>.
- Spielberger, C.D., Rl, Gorsuch, Lushene, R.E., 1970. *STAI Manual: For the State-Trait Anxiety Inventory ("Self Evaluation Questionnaire")*. Consulting Psychologists Press, Palo Alto.
- Spielberger CD, Inventaire d'anxiété État-Trait. Les Éditions Du Centre de Psychologie Appliquée, Paris. 1993.
- Stapp, E.K., Mendelson, T., Merikangas, K.R., Wilcox, H.C., 2020. Parental bipolar disorder, family environment, and offspring psychiatric disorders: a systematic review. *J. Affect. Disord.* 268, 69–81. <https://doi.org/10.1016/j.jad.2020.03.005>.
- Tercier, D., Vandeleur, C., Jeanpretre, N., Rothen, S., Vidal, S., Halfon, O., Preisig, M., 2011. Parent-offspring similarity for childhood behavioral inhibition and associations between inhibition and parental care. *Fam. Sci.* 2, 230–239.
- Thorup, A.A., Jepsen, J.R., Ellersgaard, D.V., Burton, B.K., Christiani, C.J., Hemager, N., Skjaerbaek, M., Ranning, A., Spang, K.S., Gantriis, D.L., Greve, A.N., Zahle, K.K., Mors, O., Plessen, K.J., Nordentoft, M., 2015. The Danish High Risk and Resilience Study—VIA 7—a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders. *BMC Psychiatry* 15, 233. <https://doi.org/10.1186/s12888-015-0616-5>.
- Thorup, A.A.E., Gantriis, D.L., Greve, A.N., Henriksen, M.T., Zahle, K.K., Stadsgaard, H., Ellersgaard, D., Burton, B.K., Christiani, C.J., Spang, K., Hemager, N., Jepsen, J.R.M., Plessen, K.J., Nordentoft, M., Mors, O., Bliksted, V., 2022. Exploring protective and risk factors in the home environment in high-risk families - results from the Danish high risk and resilience study-VIA 7. *BMC Psychiatry* 22, 100. <https://doi.org/10.1186/s12888-022-03733-5>.
- Uher, R., Pavlova, B., Radua, J., Provenzani, U., Najafi, S., Fortea, L., Ortuno, M., Nazarova, A., Perroud, N., Palaniyappan, L., Domschke, K., Cortese, S., Arnold, P.D., Austin, J.C., Vanyukov, M.M., Weissman, M.M., Young, A.H., Hillegers, M.H.J., Danese, A., Nordentoft, M., Murray, R.M., Fusar-Poli, P., 2023. Transdiagnostic risk of mental disorders in offspring of affected parents: a meta-analysis of family high-risk and registry studies. *World Psychiatry* 22, 433–448. <https://doi.org/10.1002/wps.21147>.
- Vandeleur, C., Rothen, S., Gholam-Rezaee, M., Castelayo, E., Vidal, S., Favre, S., Ferrero, F., Halfon, O., Fumeaux, P., Merikangas, K.R., Aubry, J.M., Burstein, M., Preisig, M., 2012. Mental disorders in offspring of parents with bipolar and major depressive disorders. *Bipolar Disord.* 14, 641–653. <https://doi.org/10.1111/j.1399-5618.2012.01048.x>.
- Vandeleur, C.L., Preisig, M., Fenton, B.T., Ferrero, F., 1999. Construct validity and internal reliability of a French version of FACES III in adolescents and adults. *Swiss J. Psychol.* 58, 161–169. <https://doi.org/10.1024//1421-0185.58.3.161>.
- Vandeleur, C.L., Kavanagh, D.J., Favez, N., Castelayo, E., Preisig, M., 2013. French version of the family attitude scale: psychometric properties and relation of attitudes to the respondent's psychiatric status. *Psychiatry Res.* 210, 641–646. <https://doi.org/10.1016/j.psychres.2013.07.008>.
- Vandeleur, C.L., Rothen, S., Lustenberger, Y., Glaus, J., Castelayo, E., Preisig, M., 2015. Inter-informant agreement and prevalence estimates for mood syndromes: direct interview vs. family history method. *J. Affect. Disord.* 171, 120–127. <https://doi.org/10.1016/j.jad.2014.08.048>.
- Vandeleur, C.L., Strippoli, M.F., Castelayo, E., Gholam-Rezaee, M., Ferrero, F., Marquet, P., Aubry, J.M., Preisig, M., 2017. The Lausanne-Geneva cohort study of offspring of parents with mood disorders: methodology, findings, current sample characteristics, and perspectives. *Soc. Psychiatry Psychiatr. Epidemiol.* 52, 1041–1058. <https://doi.org/10.1007/s00127-017-1382-0>.
- Vila, G., Nolle-Cléménçon, C., de Blic, J., Falissard, B., Mouren-Simeoni, M.C., Scheinmann, P., 1999. Assessment of anxiety disorders in asthmatic children. *Psychosomatics* 40, 404–413. [https://doi.org/10.1016/s0033-3182\(99\)71205-3](https://doi.org/10.1016/s0033-3182(99)71205-3).
- Windle, M., Lerner, R.M., 1986. Reassessing the dimensions of temperamental individuality across the life span: the revised dimensions of temperament survey (DOTS-R). *J. Adolesc. Res.* 1, 213–229. <https://doi.org/10.1177/074355488612007>.
- Wolff, B., Magiati, I., Roberts, R., Pellicano, E., Glasson, E.J., 2022. Risk and resilience factors impacting the mental health and wellbeing of siblings of individuals with neurodevelopmental conditions: a mixed methods systematic review. *Clin. Psychol. Rev.* 98, 102217. <https://doi.org/10.1016/j.cpr.2022.102217>.
- Zappitelli, M.C., Bordin, I.A., Hatch, J.P., Caetano, S.C., Zunta-Soares, G., Olvera, R.L., Soares, J.C., 2013. Temperament and character traits in children and adolescents with major depressive disorder: a case-control study. *Compr. Psychiatry* 54, 346–353. <https://doi.org/10.1016/j.comppsy.2012.10.009>.