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Title: **The Lausanne-Geneva cohort study of offspring of parents with mood disorders: methodology, findings, current sample characteristics and perspectives**

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Abstract

Purpose: Studies focusing on the offspring of affected parents utilize the well-established familial aggregation of mood disorders as a powerful tool for the identification of risk factors, early clinical manifestations and prodromes of mood disorders in these offspring. The major goals of the Lausanne-Geneva mood cohort study are to: 1) assess the familial aggregation of bipolar and unipolar mood disorders; 2) prospectively identify risk factors for mood disorders as well as their early signs and prodromes; 3) identify their endophenotypes including cognitive features, alterations in brain structure, HPA-axis dysregulation and abnormalities of the circadian rhythm of activity.

Methods: Probands with bipolar disorders, major depressive disorder and controls with at least one child aged from 4 to 17.9 years at study intake, their offspring as well as their spouses are invited to take part in follow-up assessments at predetermined ages of the offspring. Direct semi-structured diagnostic interviews have been used for allparticipants. Probands, spouses and adult offspring also undergo neurocognitive testing, anthropomorphic measures and biochemical exams, structural Magnetic Resonance Imaging as well as objective assessments of physical activity using accelerometers in combination with ecological momentary assessments.

Results: Currently, our study has up to seven follow-up assessments extending over a period of 20 years. There are 214 probands and 389 offspring with one direct interview before age 18 as well as a second assessment over follow-up. Data on 236 co-parents are also available from whom 55% have been directly interviewed. First publications support the specificity of the familial aggregation of BPD and the strong influence of an early onset of the parental BPD, which amplifies the risk of developing this disorder in offspring.

Conclusions: Information from clinical, biological, cognitive and behavioral measures, based on contemporary knowledge, should further enhance our understanding of mood disorder psychopathology, its consequences and underlying mechanisms.

Key words: familial aggregation; prospective study; offspring of bipolar and depressed parents; risk factors; endophenotypes.

1. Introduction

Studies focusing on the offspring of affected parents, frequently referred to as the high-risk study design [1], utilize the well-established familial aggregation of mood disorders [2-4] as a powerful tool for the identification of risk factors, early clinical manifestations and prodromes of mood disorders in these offspring [5]. Given the elevated risk of offspring of affected parents to also develop the parental disorder, studying these offspring maximizes the potential case yield by reducing the sample size of offspring needed to observe a given number of incident cases [6]. It also minimizes the heterogeneity that is likely to characterize unrelated clinical or community samples of youth given that etiologic factors for a specific disorder are assumed to be more homotypic within families than in the general population [6].

1.1. Parental psychopathology and the risk of disorders in offspring

The large body of research on the offspring of parents with mood disorders was traditionally based on one cross-sectional assessment. In the meantime, data are also available from several studies that followed the offspring of parents with mood disorders. This research has shown that these offspring are not only at an increased risk of mood disorders, but also of anxiety, behavioral and substance use disorders compared to offspring of controls (meta-analysis: [7]). Similarly, the results of several studies suggested a lack of specificity regarding the transmission of the two major subtypes of mood disorders as the offspring of parents with major depressive disorder (MDD) were at risk of MDD but not of bipolar disorder (BPD), whereas those of bipolar parents were at an increased risk of both BPD and MDD (meta-analysis: [7]). However, drawing definitive conclusions has been somewhat impeded by methodological differences across studies. First, the specificity of the familial transmission of the subtypes of mood disorders by including independent groups of offspring of parents with either BPD or MDD has seldom been tested within the same study [8, 9]. Second, there are other methodological limitations including: small sample sizes, lack of comparable control groups, lack

of incorporating parental comorbid psychiatric disorders, failure to account for the co-parent's psychopathology, or differences in methods for assessing disorders in youth. Furthermore, only a few studies to date have controlled for the potential effect of co-parental disorders on the risk of disorders in offspring [9-11].

1.2. Risk factors, early signs and prodromes of mood disorders

As adolescence corresponds to the beginning of the peak risk period for the onset of mood disorders [12], there has been a critical need to prospectively investigate offspring of parents with mood disorders as they cross through this period. Accordingly, studies that prospectively follow up offspring of affected parents from childhood into adulthood are a promising tool to identify risk factors for the onset as well as early signs and prodromes of mood disorders [13]. This information is crucial for prevention purposes given that offspring of depressed parents followed over 30 years were at a high-risk for developing somatic conditions or even dying in their middle years [14]. Nevertheless, only a few studies of offspring of parents with mood disorders with sufficient sample sizes for analyses and direct assessments of parents and offspring have conducted follow-up investigations to date. Yet already, this small body of prospective research has cast new insight into the trajectories of mood disorders.

Prospective research on offspring of parents or grandparents with MDD studied over more than 20 years [15] or of parents with MDD with or without panic disorder observed over 5 years [16] has shown that anxiety disorders, and separation anxiety disorder in particular, were the earliest signs of psychopathology in these offspring. One longitudinal study of offspring of depressed parents showed that affective bias or negative thinking styles were more present among adolescents with current or future episodes of depression than among adolescents that did not develop the disorder [17]. In addition, irritability and fear or anxiety were significant clinical antecedents of a new episode of MDD during adolescence in these high-risk offspring [18].

Among the offspring of parents with BPD, antecedents to mood disorders were found to include sleep and anxiety disorders [19], while the index mood episode was almost always depressive [19, 20]. One 16-year prospective study of initially well children of the Amish population [21] has described an array of early emotional (e.g. sensitivity, crying, worrying) and somatic (e.g. decreased sleep) symptoms to be potential prodromes to BPD onset, although the sample of offspring who developed BPD was still small. Childhood anxiety disorders also increased the risk of subsequent mood disorders in offspring of bipolar parents compared to controls [22]. Risk factors for manic, mixed or hypomanic episodes were found to be subthreshold hypomanic episodes among adolescent offspring of parents with BPD followed over a period of almost 7 years [11]. Other strong predictors of new-onset bipolar spectrum disorders among youths at risk for BPD were pre-existing anxiety/depression, affective lability and manic symptoms [23]. Furthermore, cross-sectional and prospective studies of adults have suggested that environmental risk factors such as physical or sexual abuse and stressful life events are involved in the development of mood disorders [24], although these risk factors have rarely been studied in the offspring of parents with mood disorders. So far, only high perceived neglect from the mother [25] and early life stress [26] have prospectively been shown to be risk factors for the development of mood episodes among the offspring of bipolar parents and more research is clearly needed here. Table 1 provides an overview of the latest publications of the prospective studies of offspring of parents with mood disorders with information on rates of disorders in offspring to date.

INSERT TABLE 1 HERE [9, 11, 14, 20-22, 27-29]

Regarding this emerging domain of interest, several recent lines of research have focused on defining prodromes and risk factors that typically develop during the phase of illness that precedes the syndromal onset of BPD that will allow for early intervention and reduction in morbidity and mortality [30]. Furthermore, similar to descriptions of the potential prodromes of

psychotic disorders which already began at the time of Kraepelin, staging models of adult BPD, although still not well characterized, have progressively been developed over the last decades to define illness stages [31-33]. Regarding MDD, a similar body of research has also been emerging [34]. For example, recent evidence in a prospective community sample of young adults points to subsyndromal depression in particular to be a clinical predictor of the onset of MDD [35]. Moreover, recent advances in the field suggest that numerous biological markers play a role in the development of the major psychiatric disorders [36]. Mapping biomarkers and other risk indicators to reliable clinical stages of mood disorders starting in childhood will allow for the early detection of illness and tailored interventions [32, 37, 38] as well as progress in the understanding of illness predisposition and progression [38]. In particular, studies of the offspring of parents with mood disorders have a great potential to describe biomarkers of mood disorders, which are still currently understudied [37].

1.3. Endophenotypes of mood disorders

Mood disorders, according to contemporary diagnostic definitions, vary largely across patients with the same diagnosis in terms of symptoms manifestations, course and treatment response [39, 40]. In order to increase diagnostic homogeneity, Gottesman and Gould have suggested studying endophenotypes in psychiatry *i.e.* measureable components of the disorder, which may represent intermediate forms of expression of underlying genes, rather than the disorder as a whole [41]. According to the endophenotype concept, these disorder components need to be state-independent and transmissible within families and studies of the offspring of affected parents are a suitable design to identify the endophenotypes of mood disorders. One postulated endophenotype of mood disorders encompasses cognitive performance [42-44]. However, only a few studies on neurocognitive deficits among the offspring of bipolar participants have been published to date and the results are mixed so far, showing deficits in the ventral prefrontal cortex [45] and executive or memory functions [46, 47] but not in early

information processing functions [48] compared to controls. To our knowledge, only one study among unaffected offspring of parents with MDD has been conducted to date and showed no neurocognitive deficits among these offspring compared to offspring of healthy controls [46]. Other postulated endophenotypes include physiological and biological underpinnings of mood disorders such as the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [13, 49, 50], by measures of the cortisol level which is implicated in stress management, structural neuroanatomical abnormalities assessed using Magnetic Resonance Imaging (MRI) [51-57] or of the circadian activity pattern, which can now be objectively assessed using accelerometers [58]. Through the parallel use of Ecological Momentary Assessments (EMA) relying on cell phones or micro-computers, correlates of activity, including the subjective levels of energy and mood [59-61] as well as food intake or the quality of sleep [62, 63], can simultaneously be registered avoiding recall bias of retrospective assessments by questionnaires. Although the establishment of activity patterns is of high interest regarding the development of mood disorders, to our knowledge there is only one study of the offspring of parents with mood disorders to date to have reported data on EMA [64]. This study found no differences in subjective ratings of positive affect collected on 12 occasions over the course of four days, between youth at high and low risk for MDD. In any case, pediatric populations are still largely understudied using techniques assessing circadian states and activity [65].

1.4. Specific aims of the Lausanne-Geneva high-risk mood cohort study

The major goals of this study are to:

1) assess the specificity of the familial aggregation of bipolar and unipolar mood disorders (i.e. determine whether the risk of BPD is only increased among the offspring of parents with BPD and the risk of unipolar mood disorders only among the offspring of parents with MDD);

2) prospectively identify risk factors for the onset of mood disorders as well as their early signs and prodromes;

3) identify their endophenotypes including cognitive features, alterations in brain structure, HPA-axis dysregulation and abnormalities of the circadian rhythm of activity.

2. Methods

2.1. Participants

The participants of the Lausanne-Geneva prospective cohort study originally stem from the Lausanne-Geneva family study of mood disorders. Inclusion criteria for psychiatric probands were: 1) a lifetime diagnosis of bipolar-I, bipolar-II, schizoaffective bipolar disorder or major depressive disorder (MDD), 2) age between 18 and 65 years, 3) ability to speak French or English sufficiently well to complete a semi-structured diagnostic interview, and 4) having a first-degree relative (parent, sibling or child) who agreed to participate in the study. Spouses were also included to assess the effect of the co-parent's disorder(s) on the development of offspring. These probands were consecutively recruited from the inpatient and outpatient facilities of the psychiatric departments of Lausanne and Geneva between 1996 and 2004. An additional sample of inpatients and outpatients was recruited from the orthopedic departments of the Lausanne and Geneva hospitals during the same time period to serve as a control group. Inclusion criteria were the same as for the mood disorder probands with the exception of the lack of a lifetime history of a major mood or psychotic disorder. The choice of recruiting medical controls rather than participants from the general population was motivated by the goal to create a comparison group that was selected from the same clinical settings. The specific choice of recruiting in orthopedic rather than other medical facilities was due to the fact that orthopedic problems are less likely to be induced by psychiatric illnesses than other medical problems and that a large proportion of orthopedic patients are in the age range of the psychiatric patients.

Probands and spouses with at least one child aged from 4 to 17.9 years at study intake were invited to take part in the present study. All probands, their offspring and spouses have been and are still followed up every three years at the pre-determined ages of the children: 7, 10, 13, 16, 19, 22, 25, 28, 31 and 34 years. A flow chart of the recruitment of the probands of the present study is provided in Figure 1.

INSERT FIGURE 1 HERE

2.2. Assessments

Details regarding the assessment of parents and offspring are provided in Table 2 and Figure 2.

2.2.1. Diagnostic procedures

Diagnostic assignment is based on a best-estimate diagnostic procedure that takes into account all available information: diagnostic interviews, family history reports on each individual and medical records [66]. All lifetime diagnoses are assigned according to the DSM-IV, whereas mood disorders diagnoses can also be assigned according to DSM-5 criteria. If a family member does not participate at a follow-up assessment, his/her diagnoses are assigned according to family history reports as long as at least one family member participates at this follow-up [67-69].

Diagnostic information on parents at baseline was obtained using the semi-structured Diagnostic Interview for Genetic Studies (DIGS) [70], which elicits the symptoms of psychiatric disorders together with the timing of their onset and offset. The DIGS was developed by the National Institute of Mental Health to evaluate schizophrenia and mood disorders (NIMH Molecular Genetics Initiative 1992). The French translation of the DIGS [71] revealed excellent inter-rater reliability for major mood and psychotic disorders [72] as well as substance use

disorders [73], whereas the 6-week test-retest reliability was slightly lower [72, 73]. Indeed, the kappa estimate for test-retest reliability of bipolar-I and bipolar-II disorders was 0.63, whereas that of MDD – dysthymia was 0.62 [72]. The test-retest kappa for alcohol use disorders was 0.72, whereas those of illicit drug use disorders ranged from 0.65 to 1.00 [69]. The DIGS was completed with a section on generalized anxiety disorder (GAD) using the questions from the Schedule for Affective Disorders and Schizophrenia - Lifetime and Anxiety disorder version (SADS-LA [74]). Similarly, the brief phobia chapter of the DIGS was replaced by the corresponding more extensive chapters from the SADS-LA. The French translation of the SADS-LA revealed satisfactory test-retest reliability for anxiety disorders [75]. In our own reliability study we found excellent or perfect inter-rater reliability for all specific anxiety disorders, whereas the 6-week test-retest reliability was fair or good [67]. These Yule's Y coefficients were 0.58 for panic disorder, 0.55 for agoraphobia, 0.44 for social phobia, 0.77 for specific phobia and 0.64 for obsessive compulsive disorders [67].

Offspring from 7 to 17 years at baseline were directly interviewed using a French translation of the Schedule for Affective Disorders and Schizophrenia for School-aged Children – Epidemiologic version (K-SADS-E) [76]. The reliability of the K-SADS-E [76-79] has been extensively tested and has also been tested for the French version [77]. Children aged from 4 to 7 years at baseline responded to a paper version of the Dominic interview, which portrays pictures of a child named Dominic experiencing a range of psychiatric symptoms with whom the child can identify [80]. Children at age 7 children underwent both the Dominic interview and the K-SADS-E.

In order to guarantee comparability of information, follow-up exams are based on similar assessment instruments to the baseline investigation. Parents respond to a shortened interim DIGS at follow-up evaluations, which is based upon selected chapters of the DIGS (omitting 'childhood' and 'personality' chapters), to obtain information on symptoms and episodes during

the interval since the previous assessment. In offspring, at the follow-up at age 19 (or later if the follow-up at age 19 does not take place), the complete version of the DIGS is used to collect diagnostic information. At the subsequent follow-up evaluations from age 22 onwards, the shortened interim DIGS is used. Given the difficulties children and adolescents have to date psychopathological manifestations, a life-time K-SADS-E assessment of symptoms at each follow-up exam is used until the age of 17 years.

At baseline and follow-up evaluations, diagnostic information on parents and children is systematically elicited from all participants who are at least 15 years old using the Family History-Research Diagnostic Criteria (FH-RDC) [81]. The validity of the French version of the FH-RDC was extensively tested by our group in samples of adults [67-69] and children [82].

If a subject was treated in a psychiatric setting in Switzerland, information from medical records is gathered at each assessment on his/her treatment history in order to acquire supplemental data on symptoms, impairment, duration, and timing of illness.

2.2.2. Additional phenotypic data collection

Additional information was collected through interviews on headache and life events at baseline and follow-up exams. The presence of a lifetime diagnosis of migraine headache was verified in participants from 10 years of age using the semi-structured Diagnostic Interview for Headache Syndromes (DIHS). The DIHS was developed through an inter-site collaboration centered at the Genetic Epidemiology Research Unit of Yale University School of Medicine for an observational study of chronic daily headache. The DIHS begins with an open-ended section whereby the subject describes each type of headache experienced including the degree of associated impairment. This segment is followed by a set of questions regarding symptoms, frequency/duration and treatment. Regarding life events, we have employed the lifetime version of the Junior High Life Experiences Survey [83], which gathers information on 35 types of life-events in children and adolescents. In adults, the short interview of F. Amiel-Lebigre has been

employed [84] to elicit information on 53 types of life-events (including time of occurrence, duration and impact of the event). Additional information on parents and children was collected at baseline and follow-up exams using self-report questionnaires. These questionnaires (Table 2) mainly focused on personality and temperament, family functioning, parental bonding, coping and expressed emotion.

INSERT TABLE 2 HERE [85-109]

2.2.3. Somatic and biological data

Since 2007, parents and adult offspring have been invited to undergo a somatic exam at each follow-up which focuses on cardio-vascular risk factors. This somatic check-up includes: 1) basic anthropometric data including weight and height as well as waist and hip circumference; 2) measurements of pulse rate and blood pressure (triplicate readings); 3) blood analyses including lipid profile (cholesterol and triglycerides), fasting plasma glucose and inflammatory markers (hs-CRP, cytokines). In addition, the diurnal salivary cortisol profile is determined through salivary samples provided four times during the same day. Finally, biological materials including blood samples for genotyping analyses and recently fibroblasts (minor skin biopsies) have been collected. In addition, our participants are just starting to undertake a Magnetic Resonance Spectroscopy exam.

Since March 2015, we have also assessed circadian activity patterns in participants from age 12 onwards using accelerometer in combination with an ecological momentary assessment (EMA) in the form of an electronic diary loaded onto a cell-phone. Participants respond to the electronic diary four times a day for a one-week period, to record information on daily life activities, emotions, stress, sleep and food intake.

2.2.4. Neurocognitive and MRI assessments

Since 2010, all adult participants aged 18 years or older have also been invited to undergo a neuropsychological assessment and structural MRI. The neuropsychological testing relies on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) [110, 111], which was recently proposed to assess cognition in BPD [112]. The MCCB assesses seven neurocognitive domains: 1) speed of processing; 2) verbal learning; 3) non-verbal working memory; 4) verbal working memory; 5) reasoning/problem solving; 6) visual learning; and 7) attention/vigilance. In addition, we have applied the Victoria Stroop Test [113], which is considered to be an effective measure of executive functioning and selective attention, and the Visual masking test [114], which assesses acuity and visual deficits.

INSERT FIGURE 2 HERE

2.2.5. Data collection, data management and quality control

All interviewers are required to be masters-level psychologists and have been trained over a one to two-month period. Individualized training includes ratings of tapes and supervised co-ratings. In order to provide ongoing supervision throughout the study, each interview and diagnostic assignment has been reviewed by an experienced senior psychologist. Interviewers are blind to the disease status of the other family members.

This research project was approved by the local institutional review board. All participants gave written informed consent for their participation prior to the assessments and parents provided informed consent for the participation of their children younger than 18 years.

Phenotypic data have been entered into a secured, internet-based database. The database was designed to confirm the validity of identification codes, establish the completeness of the information keyed in and to perform basic data checks. All discrepancies have been recorded in a case report form kept in a locked room. All modifications of the data have been recorded,

including the identity of the investigator who made each modification, the date, and the old and new values.

3. Results

3.1. Current sample characteristics

Table 3 provides the characteristics of the sample as ofJanuary 2017. The proband sample includes 54 patients with lifetime bipolar-I, 10 with bipolar-II, 17 with schizoaffective bipolar disorder, 68 with major depressive disorder as well as 65 controls. The offspring sample includes 389 children with at least one direct interview before age 18 and one additional assessment (second interview or family history report on them). About half of the sample (49.4%) is male. The majority of families included one (n=82) or two (n=96) children; 36 families have included three or more children. As of July 2016, participants had up to seven follow-up assessments extending over a period of 20 years. The mean age of offspring at the first assessment was 9.9 years (s.d.=4.4 years) and 21.7 years (s.d.=6.0 years) at the last assessment. The average number of assessments of the offspring is 4.5 (s.d.=1.3). The current mean duration of follow-up for all participants is 11.9 (s.d.: 3.6) years. Data are also available on 236 co-parents from whom 55% have been directly interviewed. Participation rates at each follow-up are at around 75% and attrition is approximately a third across the 7 follow-ups.

INSERT TABLE 3 HERE

3.2. Power estimates

The power for the analysis of associations between dichotomous variables (potential risk factors) and the cumulative incidence of BPD or MDD in the offspring sample is provided in Table 4 according to the formula for dichotomous variables [115] and assuming a two-tailed p-

value of 0.05. Given the low prevalence of 2% of BPD in the general population [116], an association between a potential risk factor to which 25% of the sample were exposed and BPD could only be detected with a probability of more than 70% if this factor entails at least a four times elevated relative risk. In contrast, the association between the same risk factor and MDD documented to have a prevalence rate of approximately 17% [117], could be detected with a probability of more than 90% if this risk factor confers a 2 times increased risk.

INSERT TABLE 4 HERE

3.3. Findings

Genetic data of the probands have already contributed to a series of publications of consortia focusing on BPD or MDD. Regarding findings on the offspring a publication using only baseline data corroborated results of previous studies showing rates of both mood and anxiety disorders to be elevated among the offspring of probands with BPD and MDD as compared to offspring of controls [77]. Our data also showed that recurrent MDD was more frequent among offspring of BPD probands than among those of controls. Another paper focusing on mood disorders and personality traits found intra-individual associations between Neuroticism and mood disorders in currently affected as well as remitted probands and offspring [118]. However, there was no association between mood disorders in parents and personality traits in their children, and conversely, parental personality traits were not associated with the risk of depression in offspring, suggesting that the occurrence of abnormal personality traits in participants with MDD is likely to be a consequence of previous depressive episodes.

The first publication relying on follow-up data showed that diagnostic information provided by offspring younger than 18 years on themselves was a better predictor of their diagnoses in adulthood than the information provided by the parents on these children [82]. A second

publication using the follow-up data provided further evidence for the specificity of the parent-child transmission of BPD and MDD and highlighted the importance of the age of onset of the parental BPD for the risk of BPD in their offspring [9]. Indeed, only offspring of probands with a BPD that started before the age of 21 years were at an elevated risk of developing BPD.

4. Conclusions

The controlled Lausanne-Geneva high-risk mood cohort study presented herein relies on contemporary methodological features including the recruitment of an appropriate clinical control group and the use of a best-estimate procedure, which also takes into account information from semi-structured interviews of parents and children conducted by interviewers who are blind regarding the diagnostic status of the other members within a given family. Furthermore, compared to the limited number of other prospective studies on offspring of parents with either BPD or MDD a particular aspect of the Lausanne-Geneva High-Risk study is the recruitment of offspring of both probands with BPD and MDD. This allows us to prospectively test the specificity of risk factors for the two types of mood disorders and to compare their course and outcome characteristics. Moreover, owing to a particular effort to collect information from co-parents, diagnostic information is available from nearly all co-parents enabling us to simultaneously determine the effect of the disorder of each parent on the trajectory of the offspring. In addition, the lowering of the threshold for entering the depression section of the diagnostic interview has made it possible to assign diagnoses of minor mood disorders since the baseline assessment as suggested by Angst et al. [119, 120] and introduced by the DSM-5.

With a mean follow-up duration of 12 years our study is among the longer ongoing follow-up studies of offspring of parents with mood disorders to date. Our efforts to stay in contact with families after the baseline evaluation through information bulletins, regular thank-you letters, as well as name and address information on multiple family members have enabled us to locate

most of the potential follow-up participants, to maintain participation rates at each follow-up at around 75% and minimize attrition to approximately a third across up to seven follow-ups.

The Lausanne-Geneva High-Risk study incorporates a broad phenotypic assessment that also includes MRI, inflammatory markers, the daily cortisol profile as well as objective measures of circadian activity besides diagnostic and cognitive measures. This comprehensive assessment takes into account the latest developments in the field and will allow us to address biological hypotheses emerging from basic neuroscience.

4.1. Limitations

Limitations of our study are related to the design and result from the recruitment of treated parents, the sample size and the evolution of the assessments across the follow-up. Indeed, a limitation of studying the offspring of affected parents is that the findings stem from a particular type of family, i.e. families with an affected parent, and therefore it remains uncertain to which degree they are applicable to disorders in offspring of unaffected parents. Moreover, as we recruited treated parents, they were likely to have a more severe mood disorder with more frequently comorbid disorders than probands recruited from the community, which was likely to also affect the morbid risk of their offspring. The sample size of our study is comparable to those of the other similar prospective studies of the offspring of parents with mood disorders with the exception of the BIOS study [10], the Cardiff study [28] and the ARIADNE study [29], which are much larger. However, with 389 offspring the statistical power is still low for detecting associations with BPD. Only strong risk factors entailing an increased risk of at least 4 for BPD can be detected. The sample size is also too small to separately analyze families of probands with bipolar-I, bipolar-II and schizoaffective bipolar disorders. The inclusion of these three subtypes of BPD may introduce heterogeneity. Finally, given the evolution of our assessment battery in the light of more generous funding and the progress of the field since the onset of the study in 1996, several measures were improved and a series of biological assessments could

be added during the follow-up and therefore only a part of the measures are available from baseline on.

4.2. Perspectives

The mean age of the offspring samples is currently around 21 years. The further follow-up of these samples will allow us to establish the trajectories of these children from childhood to adulthood and to prospectively test the age-specific determinants of the onset and the course of mood disorders. We have established the familial aggregation pattern of early onset BPD [9] and we will still be able to test whether there is an aggregation pattern of later onset BPD as the offspring grow older. Our prospective design with data from childhood to adulthood should also be suitable for the identification of prodromes and early signs of unipolar and bipolar mood disorders. Indeed, the inclusion of very young offspring from as early as 4 years of age will still provide valuable information for the understanding of the development of mood disorders. In addition, the inclusion of a comprehensive array of phenotypic measures will enable us to test a series of potential cognitive, biological and neuro-anatomical endophenotypes of mood disorders.

Figure 1: title: Flow chart of the recruitment of probands and their family members from study intake to current follow-up (January 2017)

Figure 2: title: Overview of measures administered in the adult and offspring samples

Figure 2 legend

Key: DIGS = Diagnostic Interview for Genetic Studies; K-SADS-E = Schedule for the assessment of Affective Disorders and Schizophrenia in School-aged Children – Epidemiological Version; MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia; CDR = Clinical Dementia Rating; MRI = Magnetic Resonance Imaging; MRS = Magnetic Resonance Spectroscopy

* For participants older than 65 years who have already responded to the MATRICS.

Ethics

The study protocols at the baseline and follow-up assessments were approved by the review board of the University Hospital of Lausanne and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave written informed consent for their participation prior to the assessments and parents provided informed consent for the participation of their children younger than 18 years.

Conflict of interest

The authors declare that they have no competing interests.

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Table 1: Prospective high-risk studies of bipolar and major depressive disorders

Study	Parents						Offspring					Duration of follow-up in years (mean)
	Parents with mood disorders			Comparison parents		Parents	High-risk		Low-risk		Offspring	
	N	Diagnosis	Source	N	Source	Assessment	N	Mean age range	N	Mean age range	Assessment	
Studies on BPD												
Egeland (2012)[21]	15	BP-I	Amish population	12	Amish population	Consensus diagnosis	115	5-13	106	5-13	CARE	16
Mesman (2013)[20]	86 (Intake)	BP-I, BP-II	Bipolar association, Outpatients	-	-	International diagnostic checklist and clinical diagnoses	140 (Intake) 108 (FU)	16.5 12-21	-	-	K-SADS-PL, SCID	12
Duffy (2014)[22]	113	BP-I lithium and non-lithium responders	Out-patients	55	Parents of school-children	SADS-L	229	16.4 7-25	86	14.7 7-25	K-SADS-PL, SADS-L	16 (6)
Axelson (2015)[11]	236	BP-I, BP-II	Advertisement, BP studies, Outpatients	141	Matched controls from the community	SCID	391	11.9 6-18	248	11.8 6-18	K-SADS-PL	(7)

Studies on MDD												
Hirshfeld-Becker (2012)[27]	85 with Panic, 131 with MDD	Panic MDD Both	Clinical referrals, Advertisements	?	Advertisements	SCID	26 48 137	5-25	80	5-25	K-SADS-E, SCID	10
Mars (2012)[28]	337 (Intake) 288 (FU)	Recurrent MDD	Recruited through primary care and advertisements	-	-	SCAN	275	12.4 9-17 (Intake)	-	-	CAPA	(16 months)
Weissman (2016)[14]	?	MDD	Outpatient specialty settings	?	Epidemiological sample from same community	SADS-L	103	19.7 (Intake) 47.9 (FU)	44	18.5 (Intake) 46.3 (FU)	K-SADS-E, SADS-L	30 (28)
Havinga (2017)[29]	366	MDD, dysthymia and / or anxiety disorder	Specialty psychiatric services	-	-	CIDI	523	28.5 23-37 (FU)	-	-	CIDI	(23)
Study on both BPD and MDD												
Preisig (2016)[9] (Present	81	BP-I, BP-II, SAM	Inpatients, Outpatients	63	Orthopedic patients	DIGS	145	10.4 7-17 (Intake)	112	9.3 7-17 (Intake)	K-SADS-E, DIGS	18 (11)

study)								21.1 (FU)		21.0 (FU)		
	64	MDD					115	10.1 7-17 (Intake) 19.5 (FU)				

Key: BPD = bipolar disorders; MDD = major depressive disorder; BP-I = bipolar-I disorder; BP-II = bipolar-II disorder; SAM = Schizoaffective disorder with mania; CARE = Children and Adolescent Research Evaluation; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-aged Children – Present and Lifetime Version; SCID = Structured Clinical Interview for DSM-IV Axis-I Disorders; SADS - L = Schedule for Affective Disorders and Schizophrenia - Lifetime Version; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; CAPA = Child and Adolescent Psychiatric Assessment; K-SADS-E = Schedule for Affective Disorders and Schizophrenia for School-aged Children - Epidemiologic Version; CIDI = Composite International Diagnostic Interview; DIGS = Diagnostic Interview for Genetic Studies; Intake = at study intake; FU = at study follow-up.

Table 2: Interviews and self-rating scales completed during the Lausanne-Geneva high-risk cohort study

Module	Instrument / Assessed domain	Offspring 4-6 years	Offspring 7-9 years		Offspring 10-17 years		Offspring ≥18 years		Parents	
		B	B	FU	B	FU	B§	FU	B	FU
Interviews	1. Diagnostic Interview for Genetic Studies (DIGS)[70] / DSM-IV and DSM-5 Axis-I diagnoses						X	X+	X	X+
	1. Kiddie-Schedule for Affective Disorders and Schizophrenia – Epidemiologic version (K-SADS-E) [74] / DSM-IV and DSM-5 Axis-I diagnoses		X	X	X	X				
	1. Dominic interview[80] / DSM-III-R Axis-I diagnoses	X								
	2. Family History-Research Diagnostic Criteria (FH-RDC)[81] / DSM-IV and DSM-5 Axis-I diagnoses in 1st degree relatives				X*	X*	X	X	X	X
	3. Diagnostic Interview for Headache Syndromes (DIHS) / Migraine with or without aura				X	X	X	X	X	X
	4. Short life-event interview of Amiel-Lebigre[84] / Life events						X	X		X
Self-rating scales	1. Junior High Life Experiences Survey[83] / Life events	X°	X°	X°		X				
	2. Childhood Trauma Questionnaire (CTQ)[85] / Traumatic events during childhood						X’			X’
	3. State-Trait Anxiety Inventory (STAI)[86,87] / Anxiety level						X	X	X	X
	3. State-Trait Anxiety Inventory for children (STAIC)[86,87] / Anxiety level		X	X	X	X				
	4. Retrospective Self-Report Childhood Inhibition (RSRCI)[88,89] / Childhood inhibition						X	X	X	X
	4. Child Self-Report Childhood Inhibition (CSRCI)[88,89] / Childhood inhibition		X	X	X	X				
	5. Dimensions of Temperament Survey (DOTS), DOTS Revised[90,91]/ Temperament				X	X	X	X	X	X
	6. Eysenck Personality Questionnaire (revised) (EPQ, EPQ-R)[92,93] / Personality dimensions						X	X	X	X
	6. Eysenck Personality Questionnaire - Junior version (EPQ-J)[92,94] / Personality dimensions					X				
	7. Parental Bonding Instrument (PBI) (mother, father)[95,96] / Perception of parenting style				X	X	X	X	X	X
	8. Child Behavior Checklist (CBCL)[97,98] / Behavior, psychopathology during childhood				X	X				
	9. Family Adaptability and Cohesion Evaluation Scales III (FACES III)[99,100] / Family adaptability and cohesion				X	X	X	X	X	X
	10. Family Attitude Scale (FAS)[101,102] / Emotional climate in family					X	X	X		X
	11 Daily Hassles Evaluation Scale[103] / Daily hassles					X				
	12. Dyadic Adjustment Scale (DAS)[104,105] / Marital adjustment						X	X	X	X
	13. Euronet Problem Resolution Strategy[106,107] / Coping dimensions					X	X	X		X
	14. Pubertal Development Scale[108] / Pubertal development					X				
	15. Cyclothymic/Hypersensitive Temperament Scale[109] / Affective temperament					X				

B: Baseline; FU: Follow-up

§ first adult interview (after the age of 18 years) during the follow-up

+ FU version of the DIGS

* from 15 years onwards

° completed by the child's parent

‘ CTQ filled out only once.

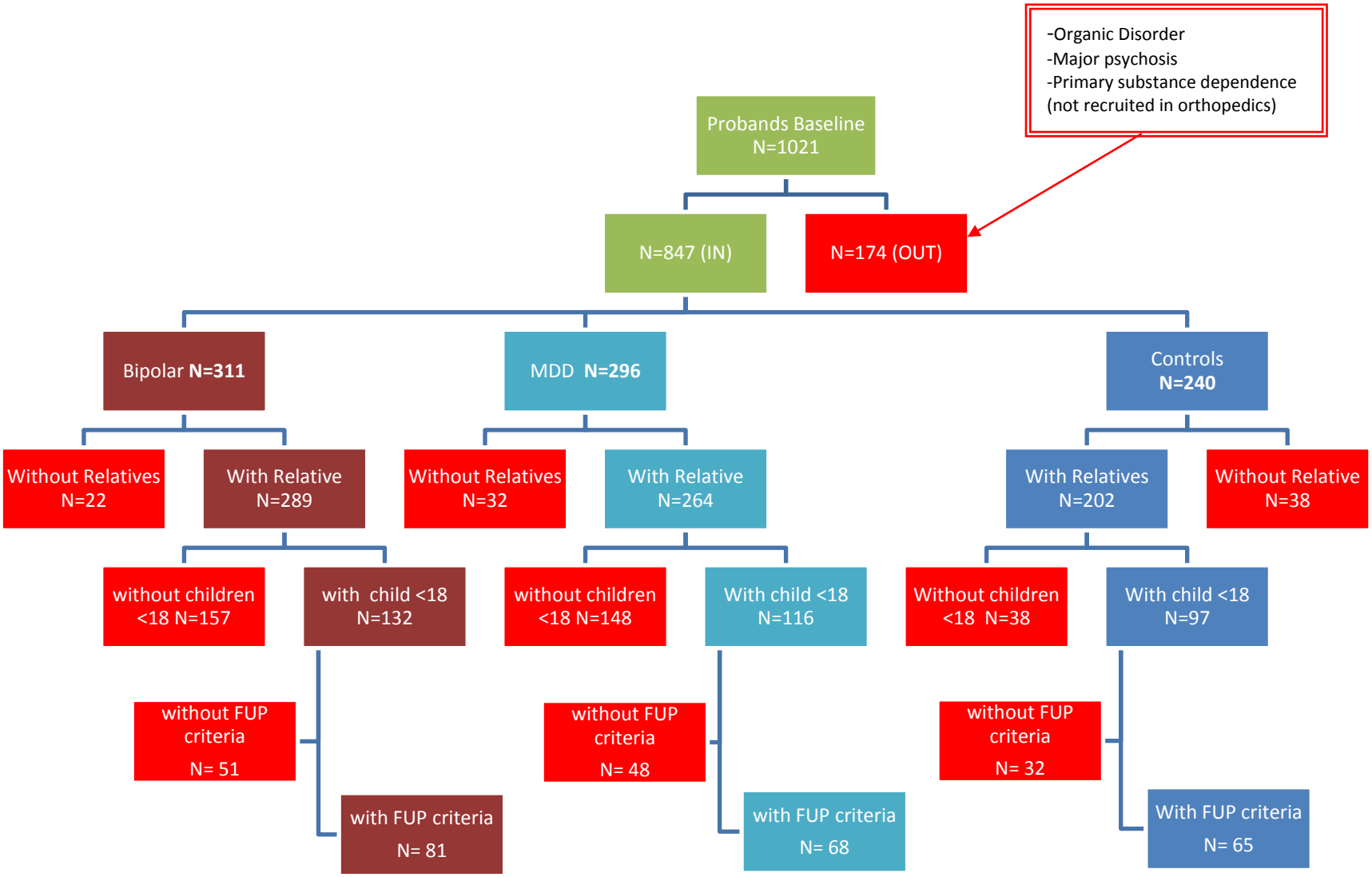
Table 3: Sample characteristics

Probands (n=214)	**Probands with BPD (n=81)**	**Probands with MDD (n=68)**	**Control probands (n=65)**	**Statistic**	**p value**
Female, % (n)	58.0 (47)	58.8 (40)	43.1 (28)	X_2^2=4.3	n.s.
Age at baseline, mean (s.d.)	40 (6.7)	41 (7.5)	41 (6.8)	F_2=0.3	n.s.
Married, %	63.0	58.8	78.5	X_2^2=6.4	<0.05
Number of offspring included, mean (s.d.)	1.8 (0.9)	1.8 (0.8)	1.8 (0.7)	F_2=0.1	n.s.
Proband comorbidity					
Anxiety disorder*, %	30.9	44.1	6.2	X_2^2=24.7	<0.001
Substance use disorder§, %	38.3	47.1	15.4	X_2^2=15.8	<0.001
Any behavioral disorder$^+$, %	18.5	20.6	9.2	X_2^2=3.6	n.s.
Lifetime GAF scores, mean (s.d.)	58.6 (12.7)	62.0 (10.9)	84.2 (8.3)	F_2=107.9	<0.001
Worst GAF scores, mean (s.d.)	27.0 (11.2)	34.9 (10.7)	73.0 (12.8)	F_2=305.9	<0.001
Current GAF scores, mean (s.d.)	52.8 (16.5)	54.4 (17.3)	84.1 (8.8)	F_2=93.1	<0.001
SES of the family, mean (s.d.)	3.2 (1.0)	2.8 (1.0)	3.4 (1.1)	F_2=5.1	<0.01
Offspring (n=389)	**Offspring of BPD (n=149)**	**Offspring of MDD (n=122)**	**Offspring of CTRLS (n=118)**		
Female, % (n)	52.4 (78)	52.5 (64)	46.6 (55)	Z_2=0.9	n.s.
Age at first assessment, mean (s.d.)	10.1 (4.5)	10.1 (3.8)	9.4 (4.8)	F_2=0.2	n.s.
Age at last assessment, mean (s.d.)	22.4 (6.3)	20.8 (5.4)	21.9 (6.1)	F_2=1.5	n.s.
Number of assessments, mean (s.d.)	4.6 (1.3)	4.0 (1.1)	4.8 (1.3)	F_2=7.4	<0.001
Number of interviews, mean (s.d.)	3.7 (1.6)	3.2 (1.4)	3.6 (1.6)	F_2=2.9	n.s.

Key: BPD=bipolar disorder; MDD=major depressive disorder; CTRLS=controls; *includes generalized anxiety disorder, social phobia, panic disorder and/or agoraphobia;
§ includes alcohol and drug abuse or dependence; + includes disruptive behavioral disorders and attention-deficit hyperactivity disorder; GAF scores = Global Assessment of Functioning scores; SES=socio-economic status. Pairwise comparisons: A: BPD vs. CTRL; B: MDD vs. CTRL; C: BPD vs. MDD.

Table 4: Power for analyses of the associations between a dichotomous risk factor as independent variable and the cumulative incidence of BPD or MDD as dependent variables in the sample of 389 offspring (%)

Outcome disorder (cumulative incidence assumed for the offspring without the specific risk factor)	Relative risk for the cumulative incidence of a mood disorder in offspring who were exposed to a specific risk factor as compared to those who were not	Proportion of the sample who were exposed to a dichotomous risk factor							
		5%	10%	15%	25%	50%	75%	90%	95%
Bipolar disorder (2%)[116]	2.0	16	19	21	23	21	11	4	2
	3.0	31	39	45	51	52	31	8	3
	4.0	45	57	64	73	78	56	16	4
	5.0	56	70	78	87	92	78	28	6
	6.0	65	80	87	94	97	92	45	10
	7.0	73	86	93	97	99	97	63	17
	8.0	79	91	96	99	100	99	78	26
	9.0	83	94	98	100	100	100	89	37
Major depressive disorder (17%)[117]	2.0	48	70	82	93	97	92	59	31
	2.5	76	93	98	100	100	100	92	63
	3.0	92	99	100	100	100	100	100	90
	3.5	99	100	100	100	100	100	100	99
	4.0	100	100	100	100	100	100	100	100



FUP (follow-up) criteria = children with a direct interview before age 18 and at least one additional follow-up assessment (second interview or family history report on them).