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Psychopathology of young children aged 4 to 7 of parents with bipolar or major depressive disorder

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Abstract

Objective: Abundant literature has focused on the influence of parental mood disorders on mental health in offspring. However, most studies have shown the familial transmission of these disorders only from school-age onwards and, to our knowledge, only two high-risk studies have reported on psychopathology in very young children. However, these studies used parental reports of child psychopathology. Our first objective was to define the validity of an assessment approach used directly with very young children named the Dominic interview by examining the concordance of diagnoses according to the Dominic and to the Kiddie Schedule for Affective Disorders and Schizophrenia – Epidemiologic version (K-SADS-E) administered at age 7. The second objective of the present study was to determine whether psychopathology in 4 year olds, assessed using the Dominic, and 7 year olds, assessed using both approaches, was associated with parental mental health.

Methods: A total of 64 offspring aged 4 years of 54 probands (n=15 children of bipolar probands, n=14 of depressed probands, n=35 controls) were directly interviewed using the Dominic; and 131 offspring aged 7 years of 94 probands (n=41 children of bipolar probands, n=40 of depressed probands, n=50 controls) were directly assessed using the K-SADS from which a part also responded to the Dominic at age 7. Offspring data at 4 years included children between the ages of 3.0 and 5.0 years [mean age: 4.5 years] and at 7 years, the sample for the K-SADS-E included children between the ages of 6.3 and 9.0 years [mean age: 7.8 years]. Each child was interviewed by an interviewer who was blind to the disease status of the parent.

Results: There was a moderate to good concordance of diagnoses according to the Dominic and to the K-SADS-E administrated at the age of 7 years. Prevalence rates of psychiatric disorders in offspring of parents with mood disorders at age 4 did not differ from those of controls. At age 7, offspring of depressed probands conferred a significantly higher risk of having separation anxiety disorder compared to those of controls, even when parental comorbid disorders were covaried.

Conclusion: The study extends previous findings by focusing on very young children. Findings suggested that parental depression confers a risk of separation anxiety disorder for 7 year-old children, which might represent an early developmental marker of emotional dysfunction. Aside from separation anxiety, psychopathology was not yet increased among these very young children compared to children of controls which might be explained by the fact of interviewing children directly instead of their parents and by the European origin of the sample.

Key words: high-risk study; psychopathology; child; preschool; Dominic questionnaire, K-SADS-E.

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1. Introduction

Mood disorders can be divided, according to the DSM-5 (APA, 2013), into two broad categories: depressive disorders and bipolar and related disorders. Bipolar disorders were formerly known as manic depressive illness. Bipolar disorder is a pathological disturbance in mood that ranges from mania or hypomania to depression sometimes accompanied by trouble in thinking patterns, which may include psychotic symptoms such as hallucinations, and behavior disturbances. In the DSM-5, there are four basic types of bipolar disorders (BPD), which include bipolar-I and bipolar-II disorders, cyclothymic disorder and other specified and related bipolar disorders. The diagnosis of bipolar-I disorder requires that a person has one or more episodes of mania with or without episodes of depression at other times that lead to a significant change in functioning. Bipolar-II disorder entails episodes of hypomania and necessarily depression. The requirement of an episode of mania or hypomania at some time during the course of illness distinguishes bipolar disorders from the more common forms of mood disorders in the population, i.e. depressive disorders. The two major criteria for a major depressive episode (MDE) are depressed mood and a loss of interest or pleasure; however 5 out of 9 depressive symptoms in all are required to be present with at least one of the former two symptoms. Depressive disorders are determined by one or more episodes of depression without ever experiencing episodes of pathologically raised mania or hypomania.

According to the National Comorbidity Survey – Replication (Kessler et al., 2005), the prevalence of major depressive disorders (MDD) is approximately 17% with doubled rates in women compared to men. Numbers differ across populations and may be higher in some, such as in the Lausanne PsyCoLaus study population where MDD was found to be as high as around 43% (Glaus et al., 2013). Studies also show that depressive disorders are a huge “burden” on society and are ranked fifth among the causes of morbidity (WHO report, 2000). In the age group of 15-44 years, it is the second leading cause of disability (WHO report, 2000). Already considerable nowadays as shown by these estimates, we can speculate that the number of comorbidities attributable to depression is going to increase in the future. Regarding bipolar-I and bipolar-II disorders, the prevalence range has been estimated at around 4% with similar rates in males and females (Kessler et al., 2005). However, these disorders often go undetected, with over a third of patients reporting at least ten years between the onset of symptoms and receiving an accurate diagnosis (Lish et al., 1994).

Adolescence corresponds to the beginning of the peak risk period for the onset of mood disorders (Kessler et al., 2007).

Based on available data, the prevalence of MDD or dysthymia in adolescents is estimated at around 12% (Merikangas et al., 2010). If adolescent girls are more often affected than adolescent boys, with a sex ratio of 2/1 (Merikangas et al., 2010), this sex difference is not present among children aged 6 to 11, at which ages depression is reported to be equally common in boys and girls (Kessler et al., 2012). Lifetime self-reported MDD prevalence was situated at around 1% under age 12 (Glowinski et al., 2003). According to the prospective study of Weissman et al. (2016), prepubertal onset of MDD is uncommon and the period of highest risk for first onset is between ages 15 and 25. Bipolar disorders in adolescence have been estimated at about 3% (Merikangas et al., 2010) but the diagnosis of BPD remains controversial in childhood due to the absence of a unified description of the disorder in children. Indeed, current nosology still uses adult criteria for making diagnoses of BPD in children.

The question of the transmission or influence of parental mental disorders on mental health in offspring has considerably grown these past decades due to the development of interest in epidemiology and genetic epidemiology. Since then, abundant literature has focused on the links between parental psychopathology and psychopathology in their children. Overall, many studies basically showed that individuals with a family history of psychiatric disorders are substantially more at risk for the development of various psychiatric psychopathologies including behavioral, anxiety, conduct and mood disorders. More particularly, family studies on bipolar and depressive disorders have shown that offspring of parents with one of these two psychopathologies are at an increased risk for developing a wide range of psychiatric disorders (Wilde et al. 2014). Two recent family studies of adults have also demonstrated higher rates (up to twelve times higher) of bipolar-I disorder in relatives of subjects suffering from this same disorder, whereas the risk of MDD was doubled among relatives of patients with MDD (Merikangas et al., 2014; Vandeleur et al., 2014). In a meta-analysis of 33 studies, Rasic et al. (2014) compared the prevalence rates of mental disorders among children of parents with mood disorders and schizophrenia to those of children of parents with no mental disorder. Results indicated that in comparison with children of parents with no mental disorders, children of parents with bipolar disorder are 2.4 times more likely to develop a severe mental disorder, 4 times more likely to develop BPD and twice as likely to develop MDD. Likewise, children of parents with MDD were more than twice as likely to develop a severe mental disorder or MDD than children of controls. In 2000, Chang et al. suggested that a parental history of early-onset BPD and/or childhood attention deficit and hyperactivity disorders (ADHD) may increase the risk for their offspring to develop BPD. More recent results from our own study have shown that offspring of parents with early onset BPD entailed a higher risk of BPD (HR = 7.9) than those with later onset and controls (Preisig et al., 2016). Our study also showed that substance use disorders (SUD) were increased (HR= 5.0) among the offspring of parents with early onset BPD

compared to controls, whereas depressive disorders were not significantly increased in offspring regardless of parental mood disorder subtype or age of onset (Preisig et al., 2016).

High-risk studies meeting specific criteria such as enrolling at least 40 subjects per group and having a child younger than 18 years have shown interesting results. Annex 1 provides a summary of the ten cross-sectional and prospective controlled studies that have focused on the offspring of parents with MDD or BPD.

First, Orvaschel et al. (1988) and Grigoroiu-Serbanescu et al. (1991) showed that rates of ADHD were elevated among offspring of parents with MDD.

Regarding offspring of parents with BPD, they were shown to be at a higher risk in childhood and adolescence of MDD, anxiety disorders and ADHD (Grigoroiu-Serbanescu et al., 1989) and also at a higher risk of BPD, anxiety and SUD (Nurnberger et al., 2011).

In another study of 288 children, 117 of parents with BPD versus 171 controls, Henin et al. (2005) considered the risk of developing psychopathology between the ages of 8 and 18 years. Analyses based on the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) indicated that high-risk children had significantly higher rates of mood disorders, anxiety disorders, disruptive behavior disorder (DBD) and ADHD.

Radke-Yarrow et al. (1992) compared psychopathology in offspring of parents with both BPD and MDD. The authors observed on the one hand, that offspring of MDD probands had higher rates of any psychopathology throughout childhood (from 5 to 11 years) and on the other hand, that offspring of MDD and BPD probands are at higher risk for developing MDD and DBD. For DBD, the risk appears to be highest after the preschool years (from 8 to 11 years).

The prospective studies also show interesting results which go in the same direction (Annex 1).

Concerning MDD, Weissman et al. (2016) published an article on the offspring of depressed parents assessed 30 years later, which is an extension of the baseline study. Among the 220 children from the initial sample, 147 were still present at the time of the fourth interview (thirty years later). Consistent with the 1987 baseline results, the authors showed that the risk of developing MDD was higher in the high-risk children than in children of controls. Moreover, at baseline, the offspring were at a higher risk of developing SUD, whereas thirty years later they were at a significantly higher risk of developing anxiety disorders than offspring of controls.

Biederman et al. (2001) and Hirschfeld-Becker et al. (2008, 2012) reported elevated rates of BPD, MDD, DBD or ADHD in offspring of parents with MDD compared to offspring of controls.

Regarding offspring of parents with BPD, Birmaher et al. (2009) and Axelson et al. (2015) have published similar results to those of Duffy et al. (2007, 2010, 2014). The authors reported the offspring of BPD probands to manifest higher rates of mood disorders, anxiety disorders, DBD, ADHD and SUD compared to controls.

In our own study which assessed offspring psychopathology in families of probands with both types of mood disorders, Vandeleur et al. (2012) demonstrated that offspring of BPD and MDD probands had an increased risk of depressive and anxiety disorders compared to those of controls. As already mentioned, four years later using the follow-up data, Preisig et al. (2016), showed elevated rates of BPD among offspring of BPD probands with an early onset only. In addition, the results showed an increased risk of separation anxiety disorder among offspring of MDD parents.

To sum up, these high-risk studies of offspring with parents with BPD or MDD have confirmed elevated risks of both BPD (Axelson et al., 2015; Birmaher et al., 2009; Duffy et al., 2014; Henin et al., 2005; Hirshfeld-Becker et al., 2008; Nurnberger et al., 2011; Preisig et al., 2016) and of MDD (Biederman et al., 2001; Duffy et al., 2014; Grigoroiu-Serbanescu et al., 1989; Henin et al., 2005; Hishfeld-Becker et al., 2008; Radke-Yarrow et al., 1992; Vandeleur et al., 2012; Weissman et al., 2006; 2016) among offspring. They also demonstrated the elevation of other conditions, including anxiety disorders, DBD, ADHD and SUD among high-risk offspring.

However, most of these studies have shown the familial transmission of these disorders only from school age onwards (about eight years of age) and, to our knowledge, only two studies have reported data on psychopathology in very young children. In the current literature, there are only two high-risk controlled studies about young children.

First, Hirshfeld-Becker et al. (2006) suggested that psychopathology, mostly assessed using the K-SADS-E, was already evident in early childhood (mean age = 6.8 years: mean age offspring BPD = 7.1., s.d. = 2.6; mean age offspring psychiatric comparisons = 6.7., s.d. = 2.6; mean age offspring non psychiatric controls = 6.8., s.d. = 1.9). Even if the small size of the sample may have led to unreliable estimates, the authors showed that offspring of bipolar parents had significantly higher rates of DBD and of ADHD, anxiety disorders (including any anxiety disorder, separation anxiety disorder and overanxious disorders), and of BPD than offspring from comparison groups. In addition, offspring of bipolar parents had increased rates of bipolar-I disorder, compared to

offspring of controls. Despite the young age of most of the children, these offspring, even in the early elementary school years, already displayed significant psychopathology.
The high rate of ADHD identified in offspring of bipolar parents is consistent with previous controlled studies documenting elevated rates of ADHD (Axelson et al., 2015; Birmaher et al.,2009; Duffy et al., 2007; Grigoroiu-Serbanescu et al., 1989; Henin et al., 2005) in older offspring of bipolar probands compared to those of controls.

Second, the study of Birmaher et al. (2010) focused on the development of psychiatric problems in preschool children aged 2-5 years of parents with bipolar disorder. In order to assess the impact of parental disease on child psychopathology, the authors evaluated 121 children of bipolar probands using parental reports gathered by the K-SADS. They were particularly interested in mood disorders in order to detect potentials warning signs of bipolarity among these offspring. Results indicated that the offspring of BPD probands, particularly those older than 4 years, were twice as likely to develop two or more psychiatric disorders compared to the offspring of the comparison parents. They were also eight times more likely to develop ADHD. Moreover, children of BPD parents, especially those with ADHD and oppositional defiant disorder, showed more symptoms of mania and depression than comparison children. However, these symptoms were not yet sufficiently pronounced to make a diagnosis of a mood disorder (except for 3 of the 121 children assessed).

Nowadays, it is widely accepted that the assessment of child psychopathology is not an easy task. In the past, parents were considered as the best informants regarding the health of their children because of the child's "cognitive immaturity". Parents were, therefore, the only persons included in the assessment of children. When this point of view changed and when children were finally considered as reliable and valid informants in the diagnosis of mental disorders (Grills and Ollendick, 2002; Rothen et al., 2009), it was necessary to design specific instruments suitable for their age. However, most interviews created then were still extensions of adult versions. Grills and Ollendick (2002) reported information on instruments that adapted questions to a level of understanding for children. One of the most frequent interviews used is the K-SADS (Chambers et al., 1985). Despite this advancement, the psychometric properties of this sort of questionnaire for children between six and ten years are disputable. According to Valla et al. (1994), the test-retest reliability in young children is low. Indeed, the reduction of positive responses between the first and the second evaluation is relatively important. These results could be explained by the length of the interview, the vocabulary used, the low attentional abilities of the child or by the fact that the examples chosen are not always appropriate for children. Therefore, it seemed necessary to create questionnaires taking these difficulties into account. Valla et al. (1994) created the Dominic, a structured pictorial questionnaire that assesses DSM-III-R based diagnoses in 6 to 11 year old

children by means of drawings of a child named “Dominic” in various situations to which the interviewed child can identify. In this way, children from six years are considered as full informants.

In summary, if the familial aggregation of mood disorders is currently well established, only two studies (Hirschfeld-Bekcker et al., 2005; Birmaher et al., 2010) on children of parents with BPD examined child psychopathology at age 4. As already said, mood disorders are one of the most debilitating psychiatric disorders with high rates of disability and comorbidities. Because of these severe consequences, there is a need for identification of the early manifestations of mood disorders. However, to identify prodromal symptoms in a group below the age of risk for the onset of mood disorders, it is necessary to study very young children. At this age, the assessment with traditional diagnostic instruments is not yet possible. Therefore, existing studies were essentially based either on interviews with parents without directly interviewing these young children or on retrospective data collected from children already older at the time of the interview. According to Birmaher et al. (2010), these young children could already present psychopathology, such as ADHD or subthreshold manic and depressive symptoms.

During the past twenty years, instruments such as the Dominic have been developed to directly investigate children at this young age. This instrument, administered by psychologists and based on pictures, was designed to make diagnoses according to the DSM-III-R.

The first main objective of the present study is to define the validity of the Dominic at 7 years by establishing the concordance of diagnoses according to the Dominic and to the K-SADS administrated at the age of 7 years. A second objective is to determine whether psychopathology in these young children is associated with parental mental health.

We first expected to see satisfactory agreement (Yule > 0.4) between the two instruments at age 7 and a potential association between parental mental health and the development of child psychopathology at ages 4 and 7. This research is still exploratory, because it investigates psychopathology in very young children, which has seldom been done before.

If the Dominic appears valid, it would open new perspectives for the assessment of psychopathology at a very young age. Clinically, the establishment of an association between parental mental health and psychopathology in these young children will indicate, at what age these high risk children deserve early clinical attention. Hence, this would then provide us with an essential tool to evaluate these children as early as possible because without intervention, childhood psychopathology settles more sustainably and has a worse prognosis (Treuer et al.,

2010). A fast identification of these diagnoses is important for the prevention of complications such as difficulties in social relationships, poor school performance (Se et al., 2000), risk of suicide (Rouillon et al., 2008) and the development of SUD (Wilens et al., 2016; Rouillon et al., 2008). From a public health perspective, it would enable the development and delivery of early intervention programs in order to prevent the further development of psychiatric disorders.

2. Methods

2.1 Procedures

Diagnostic information on parents was obtained using the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). The French translation of the DIGS (Leboyer et al., 1995) revealed high kappa coefficients for inter-rater reliability and only slightly lower coefficients for test–retest reliability for major Axis-I diagnoses including mood (Preisig et al., 1999) and substance use disorders (SUD) (Berney et al., 2002).

Children at age 7 were interviewed directly using the French translation of the modified version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Epidemiologic version (K-SADS-E) (Orvaschel et al., 1982). Diagnoses were made using DSM-IV criteria. The K-SADS-E has been found to be a reliable and valid instrument for obtaining lifetime diagnoses in prepubertal children (Orvaschel et al., 1982) and adolescents (Chamber et al., 1985; Gammon et al., 1983). Inter-rater reliability analyses of the French translation in a clinically referred sample revealed high kappa coefficients for major psychiatric diagnoses, ranging from 0.84 for depression and 0.86 for separation anxiety disorder to 1.0 for social phobia and psychosis (Vandeleur et al., 2012).

Offspring aged 4 and 7 years were directly interviewed using a child interview approach: the Dominic questionnaire. This structured pictorial questionnaire assesses DSM-III-R based diagnoses in 6 to 11 year old children by means of drawings of a child named “Dominic” in various situations to which the interviewed child can identify. An example of an item assessing simple phobia is “are you afraid of insects, like Dominic” (showing a picture of Dominic panicking with a spider on his/her arm) or assessing separation anxiety disorder is “do you refuse to go to school, like Dominic, because you don’t want to leave your parents”. The psychometric properties of the Dominic were confirmed in extensive validation studies in North America (Valla et al., 1994, 1997,

2000). This pictorial approach provided acceptable test-retest reliability and according to the authors of these studies the instrument makes standardized assessment possible for children as young as 6 years of age. Alphas measuring internal consistency ranged from 0.62 to 0.88 according to diagnoses (Valla et al., 1997). Intraclass correlation coefficients between test and retest reliability ranged from 0.59 to 0.74 for the total sample (Valla et al., 1997). For children aged 6, intraclass correlation coefficients ranged from 0.44 for conduct disorder to 0.83 for depression. For children aged 7, the lowest value was for conduct disorder (0.72) and the highest for separation anxiety (0.85), whereas at 8 years, separation anxiety got the lowest coefficient (0.64) and attention deficit and hyperactivity disorders the highest (0.87) (Bergeron et al., 1997; Valla et al., 2000). Good criterion validity against clinical judgment was evidenced by the kappas found between Dominic-based diagnoses and DSM-III-R diagnoses (Valla et al., 1997). In our study, we attempted to assess psychopathology using the Dominic questionnaire in children from as early as age 4.

Moreover, information on children and parents was systematically collected from all participants who were at least 15 years old using the Family History-Research Diagnostic Criteria (FH-RDC) (Andreasen et al., 1977). This also allowed to access information on non-interviewed co-parents and offspring. The validity of the French version of the FH-RDC has previously been tested through the assessment of agreement between diagnoses relying on direct interviews and family history reports for a series of diagnoses in adults (Rougemont-Buecking et al., 2008; Vandeleur et al., 2008; Vandeleur et al., 2015) and children (Rothen et al., 2009).

Interviews were conducted by Master degree level psychologists or psychiatrists, under the supervision of senior psychologists. Interviewers were intensively trained over a one- to two-month period that included supervision of videotaped interviews by clinically experienced senior psychologists. Each member of a given family was interviewed by a different interviewer who was blind to the disease status of the other family members.

Diagnoses were made over lifetime according to a best-estimate procedure (Leckman et at., 1982), which relied on the combination of information from direct interviews, family history report(s), and medical records.

This study was approved by the local institutional review board. All participants signed written informed consent for their own participation prior to the assessments. In addition, parents gave written consent for the participation of their offspring.

2.2. Sample

The sample in this study is based on a large controlled family study of adults with unipolar or bipolar mood disorders. Probands with bipolar and major depressive disorders had been recruited from the inpatient and outpatient facilities of the psychiatric departments in the French-speaking part of Switzerland, that are Lausanne and Geneva. Mood disorder probands were included if they met the following inclusion criteria: (i) lifetime DSM–IV bipolar I disorder (BPD-I), bipolar II disorder (BPD-II), schizoaffective bipolar disorder, or major depressive disorder (MDD) and (ii) allowance to enroll at least one child under the age of 18 years.

Comparison parents were recruited from orthopedic departments of Lausanne and Geneva in the same inpatient and outpatient clinical settings. Inclusion criteria for the comparison probands were: (i) the absence of a lifetime DSM–IV mood or psychotic disorder and (ii) the same criterion for inclusion of offspring as that in the mood disorder cases. Recruiting medical controls rather than subjects from the general population was based on the intention to create a comparison group that was selected from the same clinical settings as the subjects with mood disorders. Furthermore, recruiting specifically in orthopedic rather than other medical facilities was a choice motivated by the fact that orthopedic problems are less likely to be induced by a psychiatric problem than other medical problems and that most of orthopedic patients are about in the same age range as psychiatric patients (18-65 years).

A positive family history of mood disorders was not an exclusion criterion for either comparison or MDD/BPD probands. A total of 28 BPD (29.8 %), 31 MDD (33.0 %), and 35 orthopedic patients (37.2 %) who had at least one of their children aged 7 years were selected from the study sample for the present analyses of children aged 7 years. Furthermore, a total of 15 BPD (27.8 %), 14 MDD (25.9 %), and 25 orthopedic patients (46.3 %) who had at least one child aged 4 years were selected from the study sample for the present analyses of children aged 4 years.

Among the 28 probands with BPD of children aged 7 years, 21 met the criteria for BPD-I, 2 for BPD-II, and 5 for schizoaffective BPD; and among the 31 MDD probands of children aged 7 years, 14 had had a single episode and 17 had a history of recurrent episodes. Among the 15 probands with BPD of children aged 4 years, 12 met the criteria for BPD-I, 1 for BPD-II, and 2 or schizoaffective BPD; and among the 14 MDD probands of children aged 4, 6 had had a single episode and 8 had a history of recurrent episodes.

The offspring data at 4 years (n = 64) included all of the children of the probands between the ages of 3.0 and 5.0 years [mean age: 4.5 years, standard deviation (SD) = 0.53 years; 46.9% girls]. At 7 years (n = 131), the sample included all of the children of the probands between the ages of 6.3 and 9.0 years [mean age: 7.8 years, standard deviation (SD) = 0.70 years; 50.4% girls]. Offspring were stratified into three mutually exclusive groups: offspring of parents with BDP, offspring of parents with MDD and offspring of comparison probands. Most families of children aged 7 years included one (n = 60) or two (n = 31) children, whereas 3 families included three children. The proportions found among families of children aged 4 years were as follows: one (n = 44) or two (n = 10) children. Offspring who presented mental retardation, autistic disorder, or any organic disorder were excluded from the study.

2.3. Statistical analyses

In order to assess agreement between the Dominic and K-SADS instruments at age 7, we used the data from the 7 year olds of the present high-risk study and added extra data from offspring aged 7 from our population-based PsyCoLaus study who had also replied to the Dominic in order to have a larger sample. The Y statistic provided a more conservative measure of agreement as either low prevalence estimates were expected for disorders in our children (less than 10%) (Spitznagel and Helzer, 1985) or the samples were very small. According to the propositions of Fleiss (1981) for the kappa statistic, Y was interpreted as follows: values of less than 0.40 were considered as poor agreement, values between 0.40 and 0.75 as fair to good agreement and values of 0.76 and above as excellent agreement. As direct diagnostic K-SADS-E interviews cannot be considered to be a true “gold standard” (Heun and Muller, 1998), the sensitivity and specificity estimates were computed for descriptive purposes, as these measures provide some evidence regarding the nature of the discrepancy between the two assessment methods. In addition, the positive predictive values (PPV) and negative predictive values (NPV) were established which basically measure the proportion of true positives and true negatives, respectively.

The frequencies of offspring disorders at ages 4 and 7 were calculated in function of the proband’s mood disorder status. In four-year old children, the frequencies were first compared between mood disorder subgroups and controls using z-tests because of the small sample size. In four and seven-

year old children, odd's ratios were computed for each disorder outcome in children by parental mood diagnostic status whenever possible using generalized linear mixed models adjusted for within family correlations (sometimes more than one child per family). In four-year old children, models were only adjusted for offspring sex, whereas in seven-year old children, there were adjusted for offspring sex, proband sex and age, socio-economic level (Hollingshead scale) (Hollingshead et al., 1975) of each family (model 1) as well as for proband comorbidities in addition to the adjustments of the previous model (model 2). All analyses were conducted using the Statistical Analysis System, version 9.3 (SAS Institute, Inc., Cary, NC, USA).

3. Results

The sample characteristics of probands and offspring aged 4 and 7 years are presented in Tables 1 and 2, respectively. There was a higher proportion of females among BPD probands of four-year old offspring compared to control probands. Parents with mood disorders of seven-year old children were also more likely to be female compared to controls whereas the families of MDD probands had a lower mean socio-economic status (SES) than those of control probands. None of the other parental socio-demographic characteristics or comorbid disorders differed in function of proband mood disorder status in either sample. Furthermore, there was no statistically significant difference in age or sex among offspring stratified by parental diagnosis in either sample.

Table 1: Sample characteristics of probands (n = 54) and offspring aged 4 years (n = 64) according to proband diagnosis

	Probands with BPD (n = 15)	**Probands with MDD (n = 14)**	**Comparison Probands (n = 25)**	**Statistic**	**p-value**	**Pairwise comparison**
Demographic						
Female, %	80.0	64.3	36.0	$X_2^2 = 7.9$	0.019	A
Age at baseline, mean (SD)	34.5 (5.4)	37.8 (6.0)	37.3 (5.5)	$F_2 = 1.5$	n.s	-
Married, %	73.3	71.4	80.0	$X_2^2 = 0.4$	n.s	-
SES, mean (SD)	3.1 (1.1)	2.9(1.4)	3.5 (1.1)	$F_2 = 1.4$	n.s	-
Non-mood disorders						
Any anxiety disorder, %	40.0	35.7	16.0	$X_2^2 = 3.3$	n.s	-
Substance abuse/dependence, %	26.7	21.4	28.0	$X_2^2 = 0.2$	n.s	-
Behavioral disorder, %	20.0	28.6	20.0	$X_2^2 = 0.4$	n.s	-

	Offspring of BPD (n = 17)	Offspring of MDD (n = 15)	Offspring of controls (n = 32)			
Demographic						
Female, %	64.7	20.0	50.0	$X_2^2 = 0.3$	n.s	-
Age, mean (SD)	4.5 (0.5)	4.5 (0.6)	4.6 (0.5)	$F_2 = 0.2$	n.s	-

BPD = bipolar disorder; MDD = major depressive disorder; CTRL = controls; ns = not significant; SD = standard deviation; SES = socio-economic status. A = BPD versus CTRL; B = MDD versus CTRL; C = BPD versus MDD.

Table 2: Sample characteristics of probands (n = 94) and offspring aged 7 years (n = 131) according to proband diagnosis

	Probands with BPD (n = 28)	Probands with MDD (n = 31)	Comparison Probands (n = 35)	Statistic	p-value	Pairwise comparison
Demographic						
Female, %	64.3	61.3	34.3	$X_2^2 = 7.2$	0.028	AB
Age at baseline, mean (SD)	35.4 (4.6)	38.0 (5.3)	37.8 (5.6)	$F_2 = 2.3$	n.s	-
Married, %	67.9	64.5	80.0	$X_2^2 = 2.2$	n.s	-
SES, mean (SD)	3.2 (0.9)	2.8 (1.3)	3.7 (1.0)	$F_2 = 5.4$	0.006	B
Non-mood disorders						
Any anxiety disorder, %	21.4	41.9	17.1	$X_2^2 = 5.7$	n.s	-
Substance abuse/dependence, %	42.9	45.2	37.1	$X_2^2 = 0.5$	n.s	-
Behavioral disorder, %	25.0	25.8	20.0	$X_2^2 = 0.4$	n.s	-
	Offspring of BPD (n = 41)	**Offspring of MDD (n = 40)**	**Offspring of controls (n = 50)**			
Demographic						
Female, %	46.3	57.5	48.0	$X_2^2 = 0.0$	n.s	-
Age, mean (SD)	7.5 (0.7)	7.9 (0.7)	7.9 (0.7)	$F_2 = 2.9$	n.s	-

BPD = bipolar disorder; MDD = major depressive disorder; CTRL = controls; ns = not significant; SD = standard deviation; SES = socio-economic status. A = BPD versus CTRL; B = MDD versus CTRL; C = BPD versus MDD.

Table 3 indicates the level of agreement between the Dominic and K-SADS instruments at age 7 for disorders using both the DSM-III-R and DSM-IV definitions. The measure of agreement is provided by the Y statistic. All values (Yule's Y) were between 0.45 and 0.65, which corresponds to a moderate to good level of agreement. Sensitivity estimates were low for MDD and ADHD, whereas specificity estimates were high for all disorders. Likewise the PPV were lower for several

disorders indicating that these disorders were not always detected by the Dominic instrument. Although the sensitivity estimate was 100% for conduct disorders, the PPV was low indicating that there were few true positives among the cases detected by the Dominic. The NPV were high for all disorders, although slightly lower for separation anxiety disorders indicating some cases of false negatives according to the Dominic interview for this diagnosis (Table 3). As very similar estimates were found for disorders using the DSM-III-R and DSM-IV definitions (see Annex for a comparison of DSM-III-R and DSM-IV criteria for all disorders), further analyses were computed using the more recent DSM-IV definitions only.

Table 4 presents prevalence rates of psychiatric disorders across the three groups of offspring aged 4 according to the Dominic. Offspring aged 4 of BPD or MDD probands did not significantly differ from offspring aged 4 of controls. Some of the models could not be computed due to the absence of the target disorder among offspring or due to the very small sample size.

Table 5 presents the prevalence rates of psychiatric disorders among offspring aged 7 by instrument and by parental diagnostic status. Table 5 also provides the adjusted odds ratios (ORs), which included an increasing number of variables.

Analyses of the K-SADS using Model 1, that adjusted for child sex and proband sex and age, and socio-economic status, revealed an association between MDD in the proband and any psychiatric disorders in the offspring (OR = 2.21, CI: 1.04-4.70) as well as between MDD in the proband and separation anxiety disorder in offspring (OR = 4.40, CI:1.43-13.55).

Model 2 that further included proband comorbid disorders showed the association with any psychiatric disorders to no longer reach statistical significance, whereas the association with separation anxiety disorder was attenuated but remained significant (OR = 4.10, CI: 1.26-13.32).

Regarding the Dominic results at age 7, there was no association between parental mood disorders and offspring disorders. Again, some models could not be computed due to the absence of the target disorder in some groups or due to the very small sample size.

Table 3: Agreement for mental disorders according to the Dominic and K-SADS (gold standard) assessments at age 7 (n= 120)

DSM-III-R	DOM+ KSADS+	DOM+ KSADS-	DOM- KSADS+	DOM- KSADS-	Yule's Y	95 CI	Sensitivity	Specificity	PPV	NPV
Separation anxiety disorder	21	10	15	74	0.53	(0.36,0.70)	58.3	88.1	67.7	83.1
Oppositional defiant disorder	6	6	6	99	0.60	(0.38,0.83)	50.0	94.3	50.0	94.3
Conduct disorder	1	4	0	112	0.45	(-0.50,1.00)	100.0	96.6	20.0	100.0
Major depressive disorder	2	2	5	111	0.65	(0.34,0.96)	28.6	98.2	50.0	95.7
ADHD	4	4	7	103	0.59	(0.33,0.85)	36.4	96.3	50.0	93.6
DSM-IV										
Separation anxiety disorder	20	9	15	76	0.54	(0.37,0.71)	57.1	89.4	69.0	83.5
Oppositional defiant disorder	5	9	6	97	0.50	(0.24,0.76)	45.5	91.5	35.7	94.2
Conduct disorder	1	4	0	112	0.45	(-0.50,1.00)	100.0	96.6	20.0	100.0
Major depressive disorder	2	2	5	111	0.65	(0.34,0.96)	28.6	98.2	50.0	95.7
ADHD	3	2	9	104	0.61	(0.31,0.91)	25.0	98.1	60.0	92.0

DOM : Dominic questionnaire; K-SADS : Kiddie-SADS-Epidemiological version

95 CI : 95% Confidence Interval ; PPV : Positive Predictive Value ; NPV : Negative Predictive Value

DOM+KSADS+ : positive on both assessments

DOM+KSADS- : positive on Dominic assessment only

DOM-KSADS+ : positive on KSADS assessment only

DOM-KSADS- : negative on both assessments

Level of agreement indicated by Yule's Y ≤0.4 poor, 0.41-0.75 moderate to good, ≥0.75 excellent.

Table 4: Child disorder at age 4 according to the Dominic (DSM-IV), in function of proband status

Children n = 64 Child Disorder	Proband status								
	BPD n = 17				MDD n = 15				CTR n = 32
	%	Z	p-value	OR[a] (95 CI)	%	Z	p-value	OR[a] (95 CI)	%
Any disorder	47.1	1.3	n.s.	2.24 (0.67;7.47)	40.0	0.8	n.s.	1.68 (0.43;6.65)	28.1
Separation Anxiety	29.4	0.3	n.s.	1.23 (0.32;4.73)	6.7	-1.4	n.s.	0.20 (0.02;1.72)	25.0
Oppositional Disorder	5.9	-0.1	n.s.	0.92 (0.09;9.44)	13.3	0.8	n.s.	2.21 (0.18;27.54)	6.3
Simple Phobia	23.5	1.4	n.s.	3.19 (0.66;15.51)	13.3	0.4	n.s.	1.33 (0.20;9.00)	9.4
Conduct Disorder	5.9	-[b]	-[b]	-[b]	0	-[b]	-[b]	-[b]	3.1
Depression	0	-[b]	-[b]	-[b]	0	-[b]	-[b]	-[b]	0
ADHD	0	-[b]	-[b]	-[b]	13.3	-[b]	-[b]	-[b]	0

Z = z-test; BPD = bipolar disorder; MDD = major depressive disorder; CTR = controls; OR = odd's ratio; 95 CI = 95% confidence interval; [a] adjusted for offspring sex; [b]models could not be calculated.

* p<.05; ** p<.01; *** p<.001.

Table 5: Child disorder at age 7 by instrument and proband status

	Dominic (DSM-IV)							K-SADS (DSM-IV)						
	Proband status													
	BPD n = 17			MDD n = 26			CTR n = 34	BPD n = 41			MDD n = 40			CTR n = 50
Child Disorder	%	OR[a] (95 CI)	OR[b] (95 CI)	%	OR[a] (95 CI)	OR[b] (95 CI)	%	%	OR[a] (95 CI)	OR[b] (95 CI)	%	OR[a] (95 CI)	OR[b] (95 CI)	%
Any disorder	41.2	1.30 (0.40;4.3)	2.74 (0.89;8.44)	19.2	0.35 (0.09;1.33)	0.47 (0.09;2.54)	38.2	48.8	1.79 (0.92;3.48)	1.71 (0.92;3.18)	52.5	2.21* (1.04;4.70)	2.04 (0.95;4.37)	38.0
Separation Anxiety	35.3	0.77 (0.22;2.66)	0.90 (0.25;3.31)	15.4	0.23 (0.05;1.11)	0.22 (0.04;1.11)	35.3	29.3	2.41 (0.87;6.66)	2.50 (0.88;7.15)	45.0	4.40** (1.43;13.55)	4.10* (1.26;13.32)	18.0
Oppositional Disorder	29.4	1.98 (0.41;9.54)	1.57 (0.30;8.08)	7.7	0.32 (0.05;1.92)	0.40 (0.04;3.97)	17.7	10.3	0.80 (0.20;3.10)	0.64 (0.19;2.10)	5.0	0.45 (0.09;2.29)	0.33 (0.06;1.82)	12.0
Simple Phobia	5.9	- [c]	- [c]	7.7	- [c]	- [c]	0	17.1	1.24 (0.39;3.96)	1.09 (0.33;3.54)	17.5	1.60 (0.47;5.44)	0.86 (0.24;3.00)	16.0
Conduct Disorder	11.8	- [c]	- [c]	0	- [c]	- [c]	2.9	2.6	- [c]	- [c]	0	- [c]	- [c]	0
Depression	17.7	- [c]	- [c]	0	- [c]	- [c]	0	9.8	1.41 (0.23;8.68)	0.60 (0.12;3.01)	2.5	0.54 (0.03;8.83)	0.29 (0.04;2.26)	6.0
ADHD	11.8	2.94 (0.54;15.84)	- [c]	3.9	0.27 (0.03;2.28)	- [c]	5.9	12.5	1.29 (0.33;5.02)	1.27 (0.33;4.85)	5.0	0.28 (0.04;2.05)	0.29 (0.06;1.47)	8.0

BPD = bipolar disorder; MDD = major depressive disorder; CTR = controls; OR = odd's ratio; 95 CI = 95% confidence interval; [a] model 1 adjusted for child age and sex and proband age, sex and socio-economic status; [b] model 2 adjusted for child age and sex and proband age, sex, socio-economic status and comorbid disorders; [c] models could not be calculated.

* p<.05; ** p<.01; *** p<.001.

4. Discussion

Our findings first revealed that the Dominic appears to be a valid instrument as there is a fair to good concordance of diagnoses according to the Dominic compared to those of the K-SADS administrated at the age of 7 years. However, the fact that the sensitivity estimates were low for all disorders, except for conduct disorder, suggests that some disorders were sometimes undetected by the Dominic interview. This could be due to the difficulty of detecting psychopathology in offspring using identification to pictures at such an early age. Indeed, the responses of the offspring were directly coded by the interviewer without discussing the disorders in any depth. In contrast, when the offspring were interviewed using the more comprehensive and semi-structured K-SADS, more disorders were detected at this age. However, it must be noted that the diagnoses according to the Dominic were computed according to the presence of a single symptom coded positively twice, and it is possible that certain children had the disorder but not the particular symptom that was presented in the picture. Therefore, certain diagnoses could have been missed because not all the symptoms of a disorder were presented in the Dominic interview. Only conduct disorder seemed to be somewhat over-diagnosed using the Dominic interview compared to the K-SADS, reflected by the low PPV. Nevertheless, the fair to good concordance between the two methods suggests that the Dominic interview is still relatively accurate in detecting disorders at age 7 taking the K-SADS interview as the “gold standard”.

The second objective of the present study was to determine a potential association between parental mental health and the development of child psychopathology in children as young as four- and seven years old. Regarding the risk of psychiatric disorders at age 4, the offspring of BPD or MDD probands in our sample did not significantly differ from offspring of controls. Later, at age 7, MDD in the proband was associated with a significantly higher risk of having any psychiatric disorder in the offspring, although this association no longer reached statistical significance in the fully adjusted model (model 2).However, compared with offspring of comparison parents, results demonstrated a significantly increased risk of separation anxiety in offspring of MDD probands even when the presence of parental comorbid disorders was introduced into the model. This suggests that parental MDD confers a risk for childhood separation anxiety disorder for other reasons than its association with comorbid anxiety in the affected MDD proband.

The elevated rate of separation anxiety disorder identified in seven-year old offspring of MDD probands is consistent with a prior controlled prospectivehigh-risk study documenting higher rates of anxiety disorders in older offspring of MDD parents compared to those of controls (Weissman et al., 2006; 2016).

Besides, our study also found that the families of MDD parents had a lower mean SES than those of control families. Another epidemiological study (Keenan et al., 1997) reported elevated rates of mood and anxiety disorders in children from low-income families from the community. However, as our analyses were adjusted for the level of SES in the family, the association between MDD in the parents and separation anxiety disorder in the children subsists over and above the effect of a lower SES. The mechanisms through which major depression in the parent leads to separation anxiety disorder in the child should still be further examined. One hypothesis is that depression in the parent could lead to neglectful parenting which might favor the development of attachment disorders (Cummings et al., 2013) and of separation anxiety disorder in particular in the seven year old child, but this hypothesis should be further tested in future studies.

Although most studies have mainly focused on children in late childhood and adolescence, the present study extends previous findings by focusing on very young children. As already mentioned, there are two studies that provided data on high-risk preschool children (Hirschfeld-Becker et al., 2005; Birmaher et al., 2010) and that supported that child psychopathology was already evident in early childhood. Despite the fact that our results suggested overall higher prevalence rates among offspring of BPD or MDD parents compared to those of controls, none of the results reached statistical significance at age 4. However, we must acknowledge that the small sample size could help explain why we did not find a significantly elevated risk of psychopathology in these very young offspring.

In most pediatric studies, and especially with preschoolers, children were assessed without direct interviews and the main informants were the parents. As the child's psychopathology was ascertained through parental report, the parental psychiatric illnesses could have inflated the rates of reported psychopathology in offspring (Rothen et al., 2009). The strength of the present study is that all the children of our sample, even preschoolers, were directly interviewed using an appropriate instrument for their ages. Thus, using the Dominic, four-year olds' diagnoses were based on child report only. This contrasts with most previous studies reported in the literature. Our study is therefore noteworthy because on the one hand, it investigated psychopathology in very young children, which then represents the third high-risk controlled study until this day in such young children, and on the other hand, it assessed all children of the sample directly.

Our results must also be viewed in light of some methodological limitations. As mentioned, the small size of the sample limited the statistical power and may have been insufficient to detect meaningful differences in the rates of distinct disorders. Indeed, some odd's ratios greater than 2.0

were not statistically significant in our sample. Furthermore, difficulties related to the young age of the children may have contributed to overlooking potential psychopathology. The emotional and cognitive development level at this age may have hindered the detection of psychopathology. Above all, specific manic symptoms such as grandiosity and elation, or depressive symptoms, such as hopelessness and severe melancholia may have gone undetected as they require a certain level of abstraction that is not yet present at such a young age when we interview the children directly. If they were present, they were more difficult to ascertain at that age (Luby et al., 2006).

Despite these limitations, our study provides additional information on the initial manifestations of psychiatric disorders in childhood. Findings support the hypothesis that parental MDD represents a risk for child psychopathology. More particularly, seven-year old offspring of MDD proband are at an elevated risk for separation anxiety disorder. We can speculate then that separation anxiety might represent an early developmental marker of emotional dysregulation in high-risk offspring. This suggests that children presenting clinically significant anxiety symptoms ought to be carefully assessed. It appears also necessary to consider the psychiatric family history of these children. In addition to the treatment of the child, the depressed parent also needs clinical attention. One meta-analysis has shown that the psychological treatment of maternal depression, aside from improving the level of functioning in the parent, also has a beneficial effect on the mental health and functioning of the children (Cuijpers et al., 2015).

According to our findings and regarding preschool children, the absence of an increased risk of other psychopathology could be a window of opportunity for primary prevention in this high-risk population.

Although it seems difficult and it might be too early to diagnose any psychopathology in preschool offspring, findings from two previous studies (Hirschfeld-Becker et al., 2005; Birmaher et al., 2010) displayed significant psychopathology in pre-school children. However, both these studies are American and previous studies have generally found higher rates of psychopathology among American compared to European offspring (Mesman et al., 2016). Indeed, a comparison between offspring of bipolar parents from the study of Birmaher et al. in Pittsburg and those from the Dutch offspring study showed much higher rates of psychopathology and of non-mood disorders in particular in the American children (Mesman et al., 2016). It is therefore possible that the offspring from our Swiss sample are much less affected than their American peers, although significant psychopathology does tend to develop later on as was shown in previous analyses in our sample (Vandeleur et al., 2012; Preisig et al., 2016).

Moreover, offspring of the present analysis had not reached the age of highest risk for developing bipolar and major depressive disorders, and it has been consistently shown that the rate of these disorders is likely to increase with age (Birmaher et al., 2009; Weissman et al., 2006; 2016). Our own study showed a significant increase in BPD among offspring aged 20 years of bipolar parents with an early onset (Preisig et al., 2016). It is known that the beginning of the peak risk period for the onset of mood disorders starts in adolescence (Kessler et al., 2007). Further prospective studies of individuals at high-risk in larger sample are needed in order to properly explore early prodromes in a group well below the age of risk for mood disorder, to detect potential warning signs or to examine the way these psychopathologies develop and become manifest in children. In this regard, more extensive analyses of the signs and symptoms and not only of the disorders meeting full criteria in our sample of 4 and 7 year-old children are warranted.

Our results present the Dominic as a valid instrument to assess young children. More studies are needed to explore the Dominic in the identification of psychopathology in preschool children. One suggestion for further studies is to recommend the use the computer version, the Dominic Interactive. Indeed, graphic material and concrete examples presenting mental health problems in a format similar to a computer game would be decidedly more attractive for young children. Moreover, the development in information technologies gives an opportunity to reduce the influence of the evaluative process by removing an intermediate between the child and the final result.

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