EARLY EXPOSURE TO PARENTAL BIPOLAR ILLNESS AND RISK OF MOOD DISORDER

by

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

The objective of this thesis was to determine the association between exposure to parental BD during childhood and risk of mood disorder. Offspring of one parent with BD completed annual clinical assessments as part of a 16-year prospective cohort study. Clinical data in the parents from Ottawa and Halifax were mapped onto the first decade of their offspring's life to estimate the timing, duration and severity of exposure to their illness. The duration of parental BD was associated with a 2 to 2.5 fold increased risk of any psychopathology (HR: 1.9, 95%CI: 1.0-4.0), and unipolar depression (HR: 2.6, 95%CI: 0.9-7.5), and a 7 fold increased risk of substance use disorders (HR: 7.1, 95%CI: 1.8-37.0). A longer duration of exposure to parental BD may be an important indicator of mood and non-mood psychopathology risk in offspring. This has implications for early intervention and preventive efforts in high-risk youth.

LIST OF ABBREVIATIONS USED

AMI	Affective Morbidity Index
BD	Bipolar disorder
CECA.Q	Childhood Experiences of Care and Abuse Questionnaire
CI	Confidence interval
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders – 4th edition twice revised
EAS	Early Adolescent Temperament Scale
HPA	Hypothalamic pituitary axis
HR	Hazard ratio
KSADS-PL	Kiddie Schedule for Affective Disorders – Present and Lifetime Version
LEQ	Life Events Questionnaire
NOS	Not otherwise specified
SADS-PL	Schedule for Affective Disorders – Present and Lifetime Version
SD	Standard deviation
SES	Socioeconomic status

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CHAPTER 1 INTRODUCTION

1.1 INTRODUCTION

Bipolar disorder (BD) is a devastating, lifelong psychiatric illness associated with severe, individual, familial, and societal burden[1-3]. There is a lack of understanding of the development of BD, and as a result, it is often misdiagnosed[4]. In Canada, adults diagnosed with BD spend on average ten years in the healthcare system before receiving the correct diagnosis[5]. Delayed or inappropriate treatment is a burden on the individual and frequent physician visits are costly to the healthcare system. Of most concern to individuals affected with BD is the poor quality of life and increased risk of suicide[6-8].

The strong genetic contribution to BD is well established with heritability rate estimates of up to 85% [9, 10], meaning that offspring of a parent with BD are at substantially increased risk of developing BD and mood disorders later in life[11]. High heritability rates aside, the full etiology of BD is not well understood. Bipolar disorder likely develops from a complex interaction of genetic and other non-genetic risk factors[12,13 20]. There are environmental and psychosocial stressors connected to living with a psychiatrically ill parent, particularly early in development, which are associated with mood disorders including BD[14-18]. In particular, parental postnatal depressive illness is associated with major depression in their offspring later in adolescence[15, 18].

To date, no published study has examined prospectively the impact of parental bipolar illness on any psychopathological outcome in offspring. Research in this area is important for the development of preventive and early intervention strategies for youth at risk for BD. By identifying stressors that significantly increase risk, it may be possible to target high-risk youth before the development of full-blown BD.

Structure of Thesis

This thesis is in manuscript form. The format of this thesis is as follows: (1) background, (2) formatted manuscript ready to submit for publication which replaces the methods and results section, (3) general discussion, (4) policy implications, (5) future directions, (6) references and (7) appendices.

CHAPTER 2 BACKGROUND

2.1 BIPOLAR DISORDER

Bipolar disorder is a severe, heterogeneous psychiatric illness characterized by the presence of one or more (hypo) manic episodes often in combination with one or more depressive episodes[19]. The prevalence of BD in Canada is estimated to be 2.2%[4]. Bipolar disorder is a complex diagnosis and is difficult to detect, which is evident from the reported high rates of misdiagnosis[5]. Findings from a Canadian national survey in 2000[5] reported a 69% rate of misdiagnosis among individuals with BD. In turn, BD is associated with frequent physician visits and high costs to the healthcare system. Bipolar disorder is also difficult to treat due to the variable treatment response across patients[20-22]. There is substantial functional and interpersonal impairment, and an increased risk of suicide among patients with BD, which is a burden not only to the individual affected but also to their families[1-3, 6]. There are also high rates of absenteeism at work among individuals with BD, increasing costs associated with the diagnosis[1,2]. The estimated cost of lifetime BD in the United States (US) that began in 1998 is $24 billion USD[23].

Offspring of a parent with BD (high-risk offspring) have a 20-fold increased risk of developing major mood disorders including BD compared to offspring of psychiatrically well parents[24]. A staging model of BD has recently been proposed from evidence showing that the disorder evolves in a predictable sequence of prodromal stages in high-risk offspring[25]. The early clinical course in childhood consists of non-mood symptoms including anxiety and sleep disorders, progressing to mood disorders, typically depressive

in polarity[25-27]. The high-risk period of BD onset is in late adolescence[11, 25, 27]. Many high-risk offspring with a depressive disorder early in adolescence develop full blown BD later in adolescence as they move through this high-risk period[25-27].

The age of onset of BD has been generally reported in adolescence by retrospective studies of adult patients with BD and high-risk cohort studies[25-27]. However, some American studies have reported an earlier age of onset, diagnosing episodes of mania in young children[28]. It is important to note that these studies had high rates of comorbid personality and substance use disorders in the parents, which may have influenced the development of psychopathology in their offspring through factors in the early environment. For example, substance use in parents is significantly associated with oppositional defiant disorder, conduct problems, and major depression in their children[29]. In the majority of high-risk studies with minimal comorbidity in the biological parents, the age of onset of BD in high-risk offspring was after the age of ten years [11, 25-27].

In addition to population differences, high-risk offspring studies vary in methodology[30]. The measurement of the affected parent diagnosis and offspring diagnosis is essential to the high-risk study design. Diagnoses made by expert clinicians using systematic, semi-structured interviews are preferred. In addition, as the diagnosis of BD is complex, a best estimate diagnostic procedure which involves a consensus review using additional all available clinical information strengthens the validity of the diagnosis[30]. Studies using non-clinician trained raters and structured interviews to confirm diagnoses have reported conflicting findings compared to expert opinion[30].

2.2 GENETICS OF BIPOLAR DISORDER

Bipolar disorder has the highest estimated heritability (~85%) of all major psychiatric disorders[10]; therefore, offspring of a first degree relative with BD are at an increased risk of developing mood disorders. Many susceptibility genes of small effect size have been identified as contributing to the risk of BD. However, replication of these findings has been challenging[10, 31]. Genetic studies suggest that BD likely results from multiple susceptibility genes interacting with one another and with other risk factors, making the mapping of phenotype to genotype, and vice versa, complex[10, 13, 31].

Response to long-term lithium treatment in individuals with BD has also been shown to have a genetic influence where parental lithium response is associated with offspring lithium response[20-22]. Prophylactic lithium response is a good indicator of clinical course, for example, patients who respond well to lithium tend to have episodic, full remitting episodes with minimal residual symptoms in contrast to patients who do not respond to lithium who tend to have a chronic fluctuating clinical course with higher rates of psychotic symptoms[20-22].

It is important to keep in mind that not all individuals who are genetically susceptible towards BD become ill. As with many diseases, genetic inheritance is necessary but not sufficient to explain the complex interaction of risk factors that determine the risk of BD[12, 13].

2.3 Environmental and Psychosocial Risk Factors

Several demographic factors including socio-economic status (SES), age of offspring and affected parent, and sex of offspring and affected parent have been shown to influence the risk of developing BD in high-risk offspring[32]. Other neurobiological and psychosocial influences including hypothalamic pituitary adrenal (HPA) axis dysregulation, temperament, life stress, and clinical features of the affected parents[33-35] are also important risk factors in the development of BD among high-risk offspring.

HPA axis dysregulation is one of the most robust biological correlates of mood disorders[36, 37]. HPA axis dysfunction as measured through daytime cortisol levels predicts the onset and recurrence of major depressive episodes[38, 39] and BD episodes[40]. The cortisol awakening response refers to the natural rise in cortisol (a stress hormone) that all individuals experience upon awakening. Offspring at genetic risk for BD display a higher peak in the early morning cortisol rise post awakening compared to control offspring, suggesting that cortisol may reflect a trait marker in the development of BD[41-44]. In addition, early morning cortisol measured in adolescence significantly mediates the relationship between postnatal depression and adolescent offspring depression[39], suggesting that elevated cortisol may in part explain the association between exposure to parental depressive illness and major depression later in life.

Temperament, and specifically high emotionality, is associated with major depression[45] and BD among high-risk offspring of a bipolar parent[34, 46]. Temperament is important in personality formation and success in interpersonal relationships. Problems in interpersonal functioning form part of the substantial morbidity associated with BD in adults with established illness[47]. In the offspring of bipolar parents, the genetic diathesis may in part be reflected in temperament or temperament may be an independent risk factor for subsequent mood disorder.

Stressful life events are strongly associated with the onset and recurrence of mood disorders, including BD[48-50]. Also, it has been shown that individuals with major depression tend to experience more recent negative life events, and show a higher sensitivity to life events[51, 52]. Genetic vulnerability towards BD is associated with negative life events[34, 53], and negative life events have been shown to moderate the relationship between temperament and risk of psychopathology[34].

Clinical features in parents with BD have been shown to increase the risk of insecure attachment in their high-risk offspring[54], which in turn, is strongly correlated with depression[55, 56]. Specifically, a higher severity of illness in the parent as indexed by more psychotic symptoms, higher number of illness episodes, more hospitalizations, and rapid cycling are all significantly associated with insecure attachment in their offspring[54]. It has been prospectively shown that clinical features of affected parents, including duration, timing and severity of illness, are associated with offspring mood disorders in populations at risk for unipolar depression[15-18] while factors such as family adversity and

cortisol, may modify the relationship between parental clinical features and offspring mood disorders[17, 18] (figure a).

Little is known about the contribution of environmental and psychosocial risk factors to the risk of BD in individuals at genetic risk. Investigators examining risk factors for BD have been unable to disentangle the interplay between genetics, environment and other psychosocial intermediate factors as the study designs have been largely cross-sectional, failed to include a comparison group and failed to account for other important risk factors. In addition, many studies have suffered from measurement issues where the diagnosis of BD in the parents was not confirmed by clinician, which compromises the validity of the diagnosis[30]. This was also a problem when diagnosing BD in the high-risk offspring, and in some cases, these diagnoses were based on only parent report[57], which are known to agree poorly with clinician diagnoses[58, 59]. Another limitation of high-risk offspring studies are the high rates of comorbid psychopathology in the affected parents (probands) or non-proband parents which has been shown to impact the psychopathological outcomes and ages of onset of illness in their children[30].

Despite the evidence demonstrating an important role of early exposure to parental depressive illness on psychiatric outcomes in their offspring[15-18], less is known about the impact of early exposure to parental BD on offspring outcomes. This association is potentially influenced by other variables including morning cortisol, emotionality, life stress, family adversity and other socio-demographic factors (figure a).

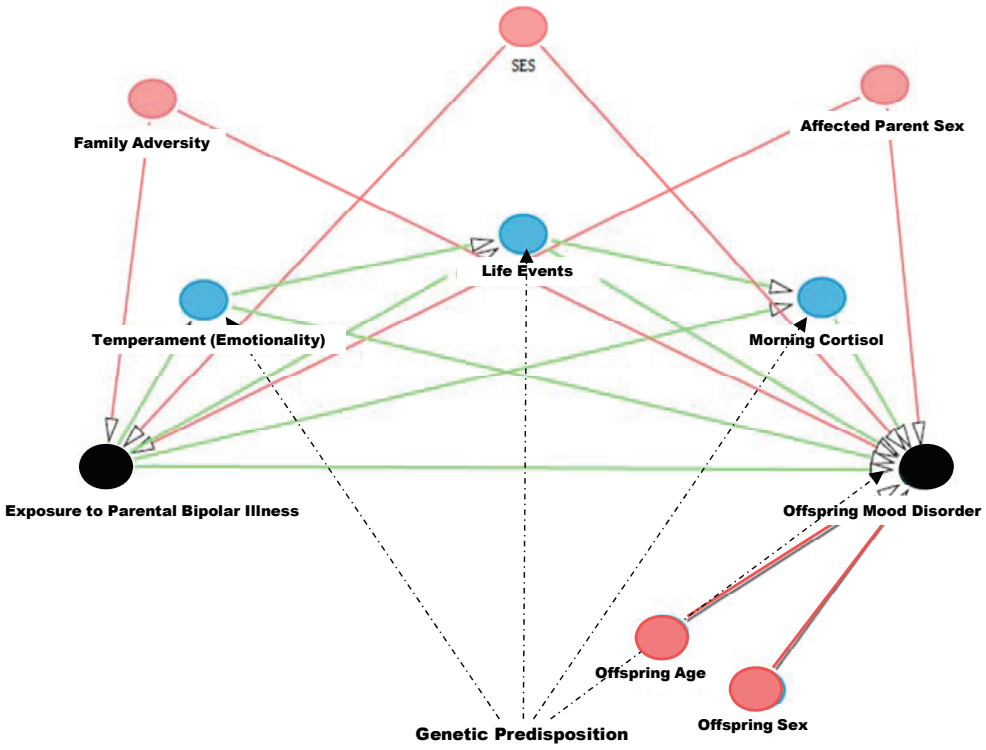

Figure a. Causal pathways towards the development of BD

Directed Acyclic Graph[60]: Green lines indicate the potential causal pathway while red lines and circles depict potential biasing pathways. Black dotted lines are genetic pathways. Blue circles are potential moderating or mediating variables.

2.4 Exposure to Parental Illness

In addition to genetic predisposition towards mood disorders, high-risk offspring of BD parents are also exposed to a different early environment compared to children of psychiatrically well parents. Depending on the duration, severity and timing of the parental clinical course, children of an affected parent may be exposed to an irritable, agitated parent during a manic episode, and a sad, distracted, and sometimes suicidal parent during a depressive episode. Furthermore, there may be emotional loss associated

with parental separation as well as associated stressors related to reduced family income and/or school disruption, such as if the parent loses the ability to work or is hospitalized.

Twin studies have demonstrated an important role of early environmental stressors beyond genetic factors in predicting adolescent and adult depression[61-63]. The mechanism through which early life adversity increases the risk of psychiatric outcomes later in life may be the result of stress during increased periods of neural plasticity and changes in a number of different neural systems[12, 64]. This in turn renders individuals more vulnerable to the effects of stress later in life[12, 64]. The first few years of life are particularly important in the neuro-maturation of emotional processes[65]. Lack of expected experiences necessary for normal brain development during these critical periods may interfere with emotional maturation rendering the individual vulnerable to illness later in life[12].

Many studies indicate an important role of postnatal maternal depression on subsequent infant and child emotional and behavioral problems[66]. However, there have only been a few prospective cohort studies examining this association on adolescent psychiatric outcomes. Findings from the few conducted studies have shown significant associations between longer duration[15, 18, 67], higher severity[15, 17] and different timing[16, 67] of maternal depression and adolescent offspring depression.

The evidence around the timing of parental depressive illness and subsequent offspring depression is mixed and the interpretation of many studies is limited by small sample

sizes. Some studies have found a significant effect of exposure to maternal depression between two and five years and not during the postpartum year (0-1 years), or older than age six[16, 67], while other studies have found no significant effect of timing on offspring depression[15]. In addition, many authors failed to take into account the duration, severity and timing of parental illness together. These three characteristics confound and potentially interact with each other. For example, a shorter in duration but highly severe illness may be more predictive of offspring major depression compared to a longer duration but less severe illness.

The few authors who have examined duration, severity, and timing of parental illness together have reported conflicting findings and their interpretation were limited by small sample sizes[15, 17]. Another limitation of all of these studies is that depression in the offspring was measured only until mid-adolescence. The high-risk period of depression onset extends from adolescence into adulthood[68]. In light of this, many of the children from these studies may have gone on to develop depression. Many studies also only examined the influence of maternal depression, not paternal depression. Paternal postnatal depression is also associated with offspring childhood psychiatric outcomes[69, 70], but has not been examined on adolescent outcomes. Although postnatal depression is more common in mothers than in fathers, it is not yet clear that maternal and not paternal postnatal depression is more strongly associated with offspring depression[71, 72]. In light of these limitations, it remains unclear whether the duration, severity or timing of parental illness, or a combination of the three, is associated with offspring adolescent depression.

2.5 ATTACHMENT AND BIPOLAR DISORDER

To date, no published study has examined postnatal bipolar illness and its impact on offspring. Research on parent-child interactions and the risk of psychopathology in the offspring of BD parents is limited. A few investigators have examined attachment that is intimately tied to the quality of the early environment and rearing[65]. Early critical periods, particularly during the first few years of life are especially important for emotional, neurological and sociological development in children[12]. Attachment is characterized by the level and consistency of care from a child's primary caregiver[65]. In the general population, early adversity including parental neglect, abuse, and parental psychiatric illness is associated with insecure attachment later in life[14, 73, 74]. Insecure attachment is in turn a strong predictor of subsequent mood disorder[75]. Two studies in Canada and the Netherlands found that perceived attachment does not differentiate high-risk offspring from control offspring[76] or from the general population[77], which is in contrast to findings from populations at risk for unipolar depression[14, 73, 74]. An important limitation in these studies is the use of self-report measures of perceived attachment. This type of measure may not be sensitive enough to take into account the heterogeneity in duration, timing and severity of parental acute episodes and the quality of the remissions. In keeping with attachment theory, there would be drastic differences in attachment among offspring exposed to an affected parent with a milder, remitting illness who may have not had an episode during their early development compared to an affected parent with a chronic, non-remitting course with high residual symptoms. This underscores the importance of quantifying exposure to parental illness during the early development in

this population. Specifically, the nature of bipolar parental illness whether it be duration, timing, or severity, may be important risk factors in the development of BD among offspring already genetically predisposed.

To conclude

Bipolar disorder is recognized as one of the leading causes of disability worldwide[78]. While the genetic loading of BD is well established, the contribution of other non-genetic factors is less understood[12]. The extant literature has emphasized the profound importance of our early environment on risk of psychiatric and psychosocial problems later in life. In particular, exposure to parental psychiatric illness early in life is associated with later psychiatric and psychosocial difficulties[15-18]. Prospective cohort studies of a well characterized high-risk sample are uniquely placed to lend knowledge on these early influences which is the primary aim of this study.

2.6 OBJECTIVE

The objective of this thesis was to determine the association between duration, severity and timing of parental bipolar illness during the first ten years of life and mood disorder after the age of ten years in offspring.

CHAPTER 3 MANUSCRIPT

Title: Early Exposure to Parental Bipolar Illness and Risk of Mood Disorder in Offspring: Findings from a 16-year Prospective Cohort Study

4.1 INTRODUCTION

Bipolar disorder (BD) is a lifelong, major psychiatric illness that typically begins in late adolescence (Angst & Gamma, 2008) and is among the leading causes of morbidity and mortality worldwide (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). The prevalence of BD in Canada is estimated to be 2.2% (Schaffer, Cairney, Cheung, Veldhuizen, & Levitt, 2005). Bipolar Disorder is associated with substantial societal, familial and individual burden from high healthcare costs due to frequent physician visits, psychosocial decline in affected individuals and of most concern, a high risk of suicide (Dean, Gerner & Gerner, 2004; Judd et al., 2005; Kozloff et al., 2010). Bipolar disorder has one of the highest heritability rates among all major psychiatric disorders (McGuffin et al., 2003). Offspring of a biological parent with BD have an estimated 20-fold increased risk of developing mood disorders compared to offspring of psychiatrically well parents (Duffy, Grof, Robertson, & Alda, 2000), and are also at high risk for non-mood psychopathology including anxiety and substance use disorders (Duffy, Alda, Hajek, Sherry, & Grof, 2010). In light of this, high-risk offspring are an important population to investigate.

The development of BD is the result of interplay between genetic and environmental factors. Early adversity is a significant predictor of the development of BD in offspring at genetic risk (Goldstein et al., 2010). The population attributable risk of mood disorders due to childhood adversities including parental illness is 57.1% in childhood (Green et al., 2010). It has been prospectively shown that clinical features of affected parents, including duration, timing and severity of their depressive illness are significantly associated with their offspring's risk of mood disorder (Fergusson, Horwood & Lynskey, 1995; Halligan, Muuray, Martin, Cooper & 2007; Hammen & Brennan, 2003; Naicker, Wickham & Colman, 2012), while factors such as family adversity, stress, and cortisol may modify this relationship (Fergusson et al., 1995; Halligan, Herbert, Goodyer, Murray, 2007). The findings regarding the timing of parental illness have been mixed, with some studies reporting exposure later in childhood predictive of mood disorder and some reporting earlier exposure predictive of mood disorder. However, many of these studies failed to consider the severity or duration of the parental illness which may have confounded the findings. Exposure to a more severe or longer duration of parental illness may impact offspring development differently, regardless of the specific timing.

Twin studies have demonstrated an important role of early environmental stressors beyond genetic factors in predicting adolescent and adult depression (Kendler et al., 2000; Nelson et al., 2002; Silberg, Maes & Eaves, 2010). The mechanism through which early life adversity increases the risk of psychiatric outcomes later in life may be the result of exposure to stress during increased periods of neural plasticity and the associated changes in a number of different neural systems (Heim & Binder, 2012; Paus

et al., 1999). This, in turn, may render individuals more vulnerable to the effects of stress later in life. The first few years of life are particularly important in the neuro-maturation of emotional processes (Bowlby, 1977). Lack of expected experiences necessary for normal brain development during these critical periods may interfere with emotional maturation and may have persisting effects (Heim et al., 2012).

High-risk offspring born to and raised by a parent with BD likely are exposed to a very different early environment compared to children of healthy parents depending on the nature and timing of their parent's illness episodes and quality of remission. This may in part explain why some offspring of a parent with BD express high emotional temperamental profiles and go on to develop mood disorders and other psychopathology (Duffy, Alda, Crawford, Milin, & Grof, 2007a; Duffy et al., 2007b). Attachment is a potential indicator of reduced or inconsistent parenting early in life. There is evidence that offspring of parents with psychiatric disorders such as unipolar depression (Coyl, Roggman, & Newland, 2002; Goodman & Tully, 2006) or borderline personality disorder (Herr, Hammen, & Brennan, 2008) are at an increased risk of insecure attachment and other psychosocial difficulties later in life. However, the literature pertaining to offspring of parents with BD reports contradictory results. For example, findings from two independent studies of a similar population of offspring at familial risk for BD found no difference in self-reported attachment or perceptions of parents in high-risk compared to control offspring (Doucette, Horrocks, Grof, Keown-Stoneman, & Duffy, 2013; Riechart et al., 2007), while some earlier studies using observational measures of attachment found higher insecure attachment in high-risk offspring compared to offspring of well

parents (DeMulder, & Radkey-Yarrow, 1991; Radke-Yarrow, Cummings, Kuczynski, & Chapman, 1985; Zahn-Waxler, Chapman, & Cummings, 1984). The heterogeneous nature of BD in the parents may in part help to explain these contradictory findings.

Despite the literature linking parental depressive illness to mood disorders in their offspring, this association has never been examined in offspring of a parent with BD. The objective of this study was to investigate the association between the duration, severity and timing of parental bipolar illness during childhood and subsequent risk of mood disorder and other psychopathology in their offspring using prospectively captured clinical information in both affected parents and offspring.

4.2 METHODS

Design

This study used data from the first 16 years of an ongoing prospective cohort study conducted from 1996 to 2012 from Ottawa and Halifax. Two-hundred and thirty-three offspring were identified from parents with BD recruited from specialty clinics. Offspring were recruited between the ages of 7 and 19 years. Clinical assessments of the offspring were conducted annually. Measurements of demographic variables, temperament, early adversity and salivary cortisol were collected during the study period. Clinical data in the affected parents of the offspring were collected prospectively from the parent's involvement in associated clinical and neurobiological studies in BD (Turecki et al., 1998; Turecki et al., 2001). The timing of this data collection in the parents overlapped

with the first decade of their offspring's life. The clinical data of the affected parent's bipolar illness was coded by a research psychiatrist in order to gauge the duration, severity and timing of their acute episodes and remissions.

Recruitment

Offspring were eligible if they had one parent with a confirmed DSM-IV-TR diagnosis of BDI or II and no other major psychiatric comorbidity at baseline. Their other biological parent had to have no history of any DSM-IV-TR major axis one psychiatric disorder. Their diagnosis was confirmed using the Schedule for Affective Disorders –Lifetime Version (SADS-L; Endicott & Spitzer, 1978) format interview conducted by research psychiatrists. Clinical diagnoses in the parents were verified through a consensus review meeting with the interviewing psychiatrist and at least two additional research psychiatrists blinded to family clinical history taking into account all available clinical information. Offspring were excluded if they were unable to comprehend the study protocol. To identify a more homogenous sample, offspring were divided based on their parental long term response to lithium mono-therapy using standardized criteria from a validated response scale (Garnham et al., 2007; Turecki et al 1998).

Procedure

Consenting offspring were clinically assessed upon recruitment and then during follow-up clinical assessments annually. Clinical interviews were conducted by child and adolescent research psychiatrists using Kiddie Schedule for Affective Disorders-Present and Lifetime Version (KSADS-PL; Axelson et al., 2003)/SADS-L; Garnham et al.,

2007) format interviews. Interviewing psychiatrists were blinded to affected parent diagnosis and lithium response during the baseline interview. All clinical diagnoses in the offspring were confirmed through a consensus review meeting with the interviewing psychiatrist and two additional research psychiatrists blind to family clinical history taking into account all available clinical information. Offspring also completed demographic and self-report psychosocial measures and a subset provided salivary cortisol samples (see Appendix A). This study was approved at the local research ethics boards in Ottawa and in Halifax.

Exposure: Parental Bipolar Illness

The prospective clinical data in the affected parents was coded using the Affective Morbidity Index (AMI; Coppen et al., 1971) which is 4-item systematic clinician rated ordinal scale designed to quantify the severity of major mood episodes in patients with affective disorders. The scale ranges from zero (no conspicuous affective disturbance) to three (severe depression or mania). The criteria used to assign the score is as follows: a score of one indicates presence of symptoms that do not require therapeutic action, a score of two indicates presence of symptoms that require either psychotherapy or pharmacological treatment, however can be managed at an outpatient level, a score of three indicates symptoms that require inpatient treatment. A research psychiatrist assigned an AMI score, describing the parents clinical course status for every month of the offspring's first ten years of life. The first ten years of the offspring's life was used as mood episodes typically begin after this age in high-risk offspring (DelBello & Geller, 2001; Duffy et al., 2010; Hillegers et al., 2005). Acute relapses, recurrences, and the

quality of remissions of the affected parent's illness were coded. If the affected parents were not acutely ill and were completely remitted with no residual symptoms during their offspring's first decade of life, an AMI score of zero was assigned. The AMI scores were confirmed through a consensual review meeting with the psychiatrist conducting the interview and two research psychiatrists blind to family clinical history, taking into account all available clinical information which included past general practitioner reports, discharge summaries or counseling/psychiatrist reports.

Outcome: Offspring Mood Disorder

The primary outcome of this study was offspring mood disorder defined as any DSM-IV-TR diagnosable mood spectrum diagnosis (major depression, dysthymia, cyclothymia, depression not otherwise specified (nos), BD I, BD II, BDnos, and Schizoaffective BD) diagnosed during the study period. A diagnosis of any DSM-IV-TR BD spectrum disorder (BD I, BD II, BDnos, Schizoaffective BD), substance use disorder and anxiety disorder were used as a secondary outcomes. Some lifetime anxiety disorders started before ten years of age. In all of these cases, the age of onset was systematically assigned at age ten in keeping with the assumption of the survival models. Mood disorders were used as the primary outcome as the first episode of BD is most often depressive in polarity (Duffy et al., 2010), meaning that many high-risk offspring with a diagnosis of a unipolar mood disorder may go on to develop BD. The primary outcome was defined to capture those affected offspring early in the course of developing BD (Duffy et al., 2010; Hillegers et al., 2005).

Covariates

Demographic information including age and sex of affected parents and offspring were collected. Socio-economic status (SES) was captured in the parents using the Hollingshead SES scale (Hollingshead, 1970) which is a composite measure of education and occupation of both working spouses where one equals the lowest SES category and five equals the highest. Emotionality was self-reported by the offspring using the Early Adolescent Temperament Scale (Buss & Plomin, 1984). The Childhood Experiences of Care and Abuse Questionnaire (Bilfuco, Brown & Harris, 1994) was used to measure the prevalence of physical and sexual abuse in offspring as well as measure perceived neglect and antipathy from parents. This measure was self-reported by the offspring. Life stress in offspring was measured using the Life Events Questionnaire (Goodyer, Herbert, Tamplin, Secher, & Pearson, 1997; Goodyer, Wright & Altham, 1990) which is a clinician-rated measure. All measures have demonstrated acceptable reliability and validity (please see Appendix A for a review). In a subset of offspring, the cortisol awakening response was measured using salivary samples collected upon awakening and 30 minutes later, repeated over three days (Appendix A).

Statistical Analysis

Exposure coding: *Timing of exposure* to parental BD was calculated as the duration (total months ill) of moderate or severe parental BD (AMI score of 2 or 3) during birth to two years, two to five years, and five to ten years. Both depressive and activated episodes were defined as parental BD. For example, if a parent had a severe manic episode (AMI=3) lasting one month, and a moderate depressive episode (AMI=2) lasting five

months during the first year of their offspring's life with no residual symptoms and no other episodes for the offspring's next nine years of life, the exposure score for birth to two years would be six and the exposure score would be zero for two to five, and for five to ten years. By calculating exposure in this way, we are able to examine a composite measure of duration and severity of parental BD during different developmental time periods. That is, we are able to estimate the impact of timing of parental BD while taking into account the duration and severity of the illness. Three binary timing variables were created indicating exposure to parental BD (AMI=1 to 3) during birth to two years, two to five years and five to ten years. These variables were created as covariates to adjust for timing while examining the independent effects of duration and severity. *Duration of exposure* to parental BD was coded as a binary variable based on whether the total months of exposure to parental illness (AMI=1 to 3) were above or below the median. Total duration of mild to severe parental BD was also examined. *Severity of exposure* to parental BD was coded as highest AMI score during the first decade of life.

Demographic statistics were calculated using chi-square, Fisher's exact tests and Student t-tests where appropriate. Survival analysis was used to estimate the association between duration of exposure to parental BD during the first decade of life and risk of mood disorder and other psychopathology. Adjusted Cox Proportional Hazard models and 95% Confidence Intervals (CI) were computed to examine the association between timing, duration and severity of parental BD and offspring mood disorder and other psychopathology. Sex of offspring and SES were included as covariates in all models. In addition, all models were adjusted for sibling correlation which adjusts the standard

errors to take into account clustering within families using the methods of Lin and Wei (1989). When examining the independent effect of duration of parental BD, additional covariates were included to take into account severity and timing. Similarly, when examining the independent effect of severity of parental BD, the other two characteristics of parental illness were included as covariates. All models were checked for proportionality. Statistical analyses were performed in SAS Software (Version 9.3). Power estimates were calculated using Power and Sample Size Software (Version 3.0.14) and indicated that the study had approximately 82% power to detect a hazard ratio (HR) of 2.0 and 44% power to detect a HR of 1.5 with a sample size of 200 participants using an alpha of 0.05.

4.3 RESULTS

Characteristics of Offspring

Characteristics of the sample can be found in table 1. This analysis included 233 high-risk offspring from 116 parents with BD. The mean age at first assessment was 16.6 years (SD: 5.6) and at last assessment was 23.3 years (SD: 6.9). Sixty percent of offspring were female. Mean follow-up time was 6.7 years with a range of 0 to 16.8 years. As described in prior publications (Duffy et al., 2010), in 13.3% of cases (31/233), offspring came from a parent with a recurrent major depressive disorder who was a first degree relative of a proband with BD. Approximately 86% of the sample came from middle to high socio-economic status (SES) families as per a composite score of four and five on the Hollingshead SES scale. The prevalence of physical and sexual abuse was 19.7% and is

comparable to general population estimates (Briere & Elliott, 2003). The majority of the sample (75.8%) came from intact families defined as biological parents not separated or divorced. One hundred percent of the sample reported that they were raised by their biological parents during their first decade of life while 5.1% reported that in addition to their biological parents, they were raised by another figure that included a relative or family friend. Offspring-reported neglect and antipathy from parents was relatively low compared to the established cutoff scores for moderate neglect and antipathy which is a subscale score of over 22 (Bilfuco et al., 1994; 2005) (table 1). Demographic characteristics were examined by city (Halifax and Ottawa) and no statistically significant differences were found at $p<0.05$ (Appendix B). Loss to follow-up was less than five percent. Reported reasons for dropping out consisted of location challenges such as offspring moving away, too busy to participate, or no longer interested.

Exposure: Parental BD during the first decade of offspring's life

Exposure to parental illness data was available in 189 offspring. Approximately 77% (145/189) of offspring were exposed to their parental BD during their first decade of life while 23% were never exposed to active illness. The quantity of exposure to parental BD varied, with most exposure (total months of mild to severe parental BD) occurring during five to ten years of age with an annual mean duration of 5.0 months (SD: 5.6) and the least amount of exposure occurring between birth and two years of age with an annual mean duration of 4.5 months (SD: 3.8). The annual mean duration of parental BD between two and five years was 4.8 months (SD: 5.6). The mean number of parental acute mood episodes during offspring's first decade of life was 2.2 (SD: 2.4). The total

duration of exposure to mild to severe parental BD was 59.8 months during the offspring's first decade of life (SD: 54.5).

Outcome: Psychopathology in offspring

A DSM-IV-TR diagnosable lifetime mood disorder was confirmed in 44.2% (103/233) of offspring over follow-up. In this sample, all cases of mood disorders began after the age of ten years with a mean age onset of 19.8 years (SD: 6.4). DSM-IV-TR diagnosable lifetime BD, anxiety and substance use disorders were confirmed in 14.2% (33/233), 21.9% (51/233), and 23.2% (54/233) of offspring. All cases of substance use disorders began after the age of ten years.

Offspring with a mood disorder diagnosis were significantly older ($p<0.01$). Sex of affected parent and SES were not significantly different between offspring with compared to those without a mood disorder ($p=0.59$; $p=0.13$) (table 2.) Psychosocial characteristics of offspring with and without a mood disorder can be found in table 2. Mean cortisol awakening response over the three sampling days was higher in offspring with a mood disorder (0.1, SD: 0.1) compared to those without a mood disorder (0.0, SD: 0.1; $p=0.05$).

Exposure to parental BD and offspring psychopathology

The mean number of acute mood episodes in parents over the first decade of their offspring's life was similar between offspring with (2.2, SD=2.6) compared to without a mood disorder (2.2, SD=2.2; $p=0.9$). Although not statistically significant, the total

duration of mild to severe illness (AMI = 1 to 3) in months during the first decade of life was higher in offspring with a mood disorder (63.0, SD: 54.8) than in offspring without a mood disorder (57.0, SD: 54.5; p=0.46). The total duration of mild to severe illness was also higher in offspring with other diagnosable psychopathology, however, not statistically significant. Specifically, offspring with a substance use disorder were exposed to 14.9 more months of illness compared to offspring without a substance use disorder (p=0.11) and offspring with an anxiety disorder were exposed to 17.2 more months of illness compared to offspring without an anxiety disorder (p=0.07) (table 3). Duration of moderate or severe parental BD (AMI=2 or 3) during the first decade of life was not different between offspring with and without a mood disorder and other psychopathology with the exception of being significantly higher in offspring with an anxiety disorder compared to no anxiety disorder (p=0.07) (Appendix D). Highest AMI score (severity) over the first decade of life was not significantly different between offspring with compared to those without a mood disorder (p=0.49). Similarly, severity was not significantly different in offspring with and without BD, anxiety or substance use disorders (all p>0.05). Offspring with a mood disorder were exposed to an annual mean duration of 2.0 months (SD: 3.8) of moderate or severe parental BD during birth to two years compared to 1.5 months (SD: 7.6) in offspring without a mood disorder (p=0.33). (table 4)

Using survival analysis, high exposure to parental BD during the first decade of life defined as total duration of mild to severe parental BD (total months ill) over the median duration of the sample was not significantly associated with a higher risk of mood

disorder (logrank, p=0.27). However, high exposure during the first decade of life was significantly associated with the risk of unipolar depression (logrank, p=0.01), and substance use disorders (logrank, p=0.02) while the risk of BD, anxiety disorders and any psychopathology was increased but not statistically significant (figures 1a-1f).

Timing: Using Cox Proportional Hazard Models, the unadjusted duration of moderate or severe parental BD during birth to two years and two to five years was significantly, and marginally significantly associated with the hazard of mood disorder in offspring (HR: 1.03, 95%CI: 1.00-1.05; HR: 1.01, 95%CI: 0.99-1.03) while exposure during five to ten years was not (HR: 0.99, 95%CI: 0.99-1.01) (table 5). After adjustment, taking into account duration of moderate to severe parental BD during the other time periods and offspring sex, SES and sibling correlation, the duration of moderate to severe parental BD during birth to two years was still significantly associated with the hazard of mood disorder, although it only increased by a small percentage. For example, for every month of moderate to severe parental BD during birth to two years, the hazard of mood disorder increased by 0.4%. The unadjusted duration of parental BD during birth to two years and two to five years was significantly associated with the hazard of unipolar depression (HR: 1.06, 95%CI: 1.02-1.09; HR: 1.04, 95%CI: 1.01-1.06) while the adjusted hazard of duration of moderate to severe parental BD during birth to two years in particular was marginally significantly associated with the hazard of unipolar depression (HR: 1.03, 95%CI: 0.99-1.08) (table 5).

Duration: The adjusted duration of mild to severe parental BD during the first decade of life was suggestive of an increased risk of mood disorders, however, was not statistically significant (HR: 1.4, 95%CI: 0.7-3.2) (table 6). The adjusted duration of mild to severe parental BD was significantly associated with the hazard of unipolar depression (HR: 2.6, 95%CI: 1.0-7.5), and any psychopathology (HR: 1.9, 95%CI: 1.0-4.0) and was strongly significantly associated with the hazard of substance use disorders (HR: 7.1, 95%CI: 1.8-37.0) (table 6).

Severity: The independent effect of severity of parental BD defined as highest AMI score during the first decade of life was not significantly associated with the hazard of mood disorder or other psychopathology (table 6).

An alternative measure of exposure was coded as offspring age at first exposure × severity of first parental episode, however, was not significantly associated with the adjusted hazard of mood disorder (HR: 1.0, 95% CI: 1.0-1.1).

Psychosocial and demographic predictors: While adjusting for other important demographic and psychosocial factors including parent age and sex, offspring emotionality, mean number of significant undesirable life events, and reported parental neglect and antipathy, high duration of mild to severe parental BD during the first decade of life was not statistically associated with the hazard of mood disorder (HR: 0.8, 95%CI: 0.4-1.5) (table 7). However, for every one unit increase in self-reported mother neglect score, there was a 20% increase in the hazard of mood disorder (HR: 1.2, 95%CI: 1.1-

1.3). Offspring undesirable life events also significantly increased the hazard of mood disorder, where for every life event, the hazard of mood disorder increased by 20% (HR: 1.2, 95%CI: 1.0-1.6). Offspring emotionality also significantly increased the hazard of mood disorder, however, only by a small proportion (HR: 1.1, 95%CI: 1.0-1.1) (table 7). An interaction term of neglect from mother and sex of affected parent was included in the model and was non-significant (p=0.11) indicating that the reported neglect from mother was not dependent on whether the affected parent was female, however, this finding may reflect low power. The influence of offspring cortisol awakening response was examined, however, due to a low sample size (n=32), and very high variation in cortisol estimates, this variable was dropped from the model.

There was no significant evidence of interaction between sex of affected parent with duration of moderate to severe parental BD in predicting mood disorder and other psychopathology (Appendix C).

4.4 Discussion

To our knowledge, this is the first study to examine the association between early exposure to parental bipolar illness and risk of subsequent mood disorder in high-risk offspring. After examining the independent effects of duration, timing and severity of parental BD during the first decade of life, it appears that the duration and timing of parental BD may be significant factors influencing risk of psychopathology in high-risk offspring. Exposure to a longer duration of parental BD during the first decade of life was

significantly associated with the hazard of unipolar mood and non-mood psychopathology. In addition, the pattern of findings suggests that earlier exposure to parental BD in childhood may be influential in the development of mood disorders.

Offspring with psychopathology were exposed to a substantially longer duration of parental bipolar illness during their first ten years of life compared to offspring without psychopathology, ranging from 4.1 to 17.2 more months of illness. While offspring with all forms of psychopathology had more exposure to parental BD, after adjustment, the hazard of unipolar depression, substance use disorders and any psychopathology in particular were significantly increased. The duration of illness has been shown in previous studies to increase risk of depression in offspring of depressed parents (Halligan et al., 2007; Hammen et al., 2003).

Both unadjusted and adjusted hazard ratios for mood disorder suggest that exposure earlier in life from birth to five years is more strongly associated with mood disorders than at ages five to ten years. These findings remained consistent after adjusting for exposure to parental illness during the other time intervals. In addition, the duration and severity of the parent's illness during each time interval was taken into account. This is consistent with other studies of offspring of depressed parents (Murray et al., 2011; Naicker et al., 2012). The first few years of life are a particularly vulnerable time for children as they are undergoing major neurodevelopment changes in the brain, important for emotional processing (Heim et al., 2012).

Severity of parental illness, defined as highest AMI score over the first decade of life, was not associated with the hazard of mood disorder. This variable was based on a 4-point scale and may have not been sensitive enough to detect important differences in the experienced severity of parental illness.

Exposure to parental BD was varied over the first decade of life and the timing of exposure was different in offspring with and without psychopathology. In addition, 23% of the sample were never exposed to their parents' illness. That is, these parents were completely stabilized and in remission during their offspring's first decade of life. This is an important descriptive finding as it highlights the heterogeneity of BD in parents and may help to explain the contradictory findings regarding psychosocial functioning among offspring of parents with BD compared to offspring of parents of other major psychiatric disorders (Coyl et al., 2002; Goodman et al., 2006; Herr et al., 2008). That is, not all offspring are exposed to active illness in their parents during their early critical years for emotional and neural development.

Perceived neglect from the mother, in particular, was a significant predictor of mood disorders in offspring. This is consistent with the literature of offspring of depressed mothers (Bilfuco et al., 2002; Goodman, & Gotlib, 1999). Contrary to expected, the reported neglect from mother was not dependent on the mother being affected with BD. Therefore regardless of sex of affected parent, perceived neglect from mother may be an important indicator of mood disorder risk in high-risk offspring. Future research should

explore this association further, as it is still unknown if the reported perceptions of neglect were influenced by the offspring having experienced a mood disorder.

For every significant reported life event, offspring risk of developing a mood disorder increased by 20%. Duffy et al (2007b) have shown that offspring of parents with BD report more life events compared to offspring of well parents. In addition, it has been shown that offspring of a parent with BD report more severe life events, as well as interpersonal and non interpersonal stress compared to offspring of well parents (Ostiguy et al., 2009). Offspring at high risk for BD and related mood disorders may be more vulnerable to the effects of life stress compared to control populations. It is still unclear if this vulnerability stems from genetic influences related to BD, differential early exposures, or from a combination of the two.

Strengths and limitations: This study used a refined and novel approach to quantify early exposure to parental bipolar illness and used gold standard diagnostic approaches to confirm clinical diagnoses in both offspring and parents. However, these findings should be interpreted with the following limitations in mind. Firstly, the AMI is an ordinal scale. Differences in scores between one to two and two to three may be very different and can be difficult to interpret. This potential bias may have attenuated this study's findings and may in part explain the non-significant findings regarding severity of parental BD in predicting offspring mood disorder. Secondly, the measure of temperament and parental neglect and antipathy were self-reported by the offspring and in some offspring were completed after the diagnosis of a mood disorder. Although all offspring were in

remission while completing these measures, the burden of having been ill (i.e., diagnosed with a prior mood disorder) may impact the offspring's perceptions of themselves, and their relationships with their parents. In addition, the combined effect of mother and father neglect and antipathy was not examined due to limitations of the measure. These potential biases may either attenuate or strengthen the study findings; however, the likelihood of this is low as these measures were only used in exploratory analyses and not in primary analyses. In addition, all self-report measure used have well established reliability and validity (Appendix A). Thirdly, there was potentially recall bias as participants entered the study at different ages, therefore there was an aspect of retrospective data collection in some participants. In addition some of the parental clinical course data was missing, and the parents had to be recalled for an interview. This bias could have both attenuated or strengthened the study's findings, however, to reduce the likelihood of this impacting the results, all diagnoses in both offspring and parents were confirmed using a best estimate diagnostic approach using already collected prospective data (in the affected parents) and using all available clinical information. Fourthly, we were unable to examine the impact of polarity of parental episode on risk of offspring mood disorder. As some of the parents had mixed manic episodes as well as mixed residual symptoms during remission, it was difficult to quantify proportion of depressed versus activated episodes. Early exposure to activated episodes, and particularly severe psychotic manic episodes may be more strongly associated with the offspring's risk of mood disorder. On the other hand severe suicidal depressive episodes may impact offspring's risk of mood disorder similarly. Fifthly, there are unmeasured potential risk or protective factors that may have influenced this study's findings. The

education of the non-affected parent would likely impact the offspring's early environment. While we did not directly take the non-affected parents education into account, the measure of SES accounts for both parents level of education and occupation. Due to the strong study design and well characterized sample, the likelihood of unmeasured confounding factors either attenuating or strengthening this study's findings is relatively low. Finally, the majority of the sample derived from middle to high SES families. Therefore these findings are only generalizable to relatively intact high SES families where parents are seeking treatment.

4.5 Conclusions

Exposure to a longer duration of parental BD during the first decade of life is associated with an increased hazard of unipolar mood and non-mood psychopathology in offspring. An earlier timing of exposure (birth to five years) to parental BD during the first decade of life may influence the development of mood disorders. This research contributes to the knowledge surrounding the etiology of BD, and has implications for early intervention and prevention targets in high-risk individuals.

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Table 1. Demographic, psychosocial and parent characteristics of high-risk offspring from Ottawa and Halifax followed between 1996 to 2012

		Total (N=233)	
		N	%
Region	Ottawa	160	68.7
	Halifax	73	31.3
Sex Offspring	Male	94	40.3
	Female	139	59.7
Sex Parent	Male	113	48.5
	Female	120	51.5
SES[a]	1 – Low	1	0.4
	2	4	1.7
	3	29	12.5
	4	71	30.5
	5 - High	128	54.9
Abuse[b]	Yes	27	19.7
	No	110	80.3
Family Intact[c]	Yes	175	75.8
	No	56	24.2
Parent Primary Diagnosis	BD I	95	41.8
	BD II	98	43.2
	MD	31	13.7
	Schizo BD	3	1.3
Parent Lithium Response	LiR	95	40.9
	LiNr	137	59.1
		Mean	SD
Age Offspring[d]		26.9	7.2
Age Parent[d]		57.9	7.3
Mean No. Siblings in Study		2.5	1.1
Parental Neglect Score[e]	Mother	11.3	3.9
	Father	14.0	5.8
Parental Antipathy Score[e]	Mother	13.9	5.7
	Father	14.9	6.2
Mean No. Life Events[f]		1.2	1.1

Offspring Emotionality Score[g]	12.4	4.5

BD: bipolar disorder; MD: major depression; LiR: lithium responder; LiNr: lithium non-responder
[a]Hollingshead Socio-economic Status (SES) scale
[b]Physical and sexual abuse during the first decade of life
[c]Family intact: Parents living together vs. separated or divorced at any time during first decade of offspring's life
[d]Mean age at time of analysis (June 2013)
[e]Parental neglect and antipathy score reported by offspring using the Childhood Experiences of Care and Abuse Scale
[f]Mean number of undesirable life events over study follow-up according to the Life Events Questionnaire
[g]Subscale total score from the Early Adolescent Temperament Scale
Note: Frequencies may not sum to total offspring due to missing data

Table 2. Univariate analyses of demographic and psychosocial characteristics of high-risk offspring with and without a mood disorder from Ottawa and Halifax followed between 1996 to 2012

		Mood[c] (N=103)		No Mood (N=130)		*p-value*
		N	%	n	%	
Sex Offspring	Male	35	34.0	59	45.4	0.08[g]
	Female	68	66.0	71	54.6	
Sex Affected Parent	Male	52	50.5	61	46.9	0.59[g]
	Female	51	49.5	69	53.1	
SES[a]	1 - Low	0	0.0	1	0.7	0.13[h]
	2	1	1.0	3	2.3	
	3	12	11.6	17	13.1	
	4	28	27.2	43	33.1	
	5 - High	62	60.2	66	50.8	
Parent Lithium Response	LiR	38	37.2	57	43.8	0.31[g]
	LiNr	64	62.8	73	56.2	
		Mean	SD	Mean	SD	
Age Offspring[b]		29.2	5.6	24.9	7.8	<0.01[i]
Age Parent[b]		59.4	6.7	56.7	7.6	<0.01[i]
Parental Neglect Score[d]	Mother	12.0	5.0	10.7	2.6	0.05[i]
	Father	15.4	6.6	14.4	4.9	0.28[i]
Parental Antipathy Score[d]	Mother	15.0	6.1	13.0	5.2	0.04[i]
	Father	15.9	6.9	13.8	5.3	0.05[i]
Mean No. Life Events[e]		1.3	1.1	1.1	1.1	0.12[i]
Offspring emotionality Score[f]		13.2	4.1	11.7	4.7	0.01[i]

[a]Hollingshead Socio-economic Status (SES) scale
[b]Mean age at time of analysis (June 2013)
[c]Mood includes: major depression, BD I, II, NOS, schizoaffective BD, depression not otherwise specified, dysthymia, & cyclothymia
[d]Parental neglect and antipathy score reported by offspring using the Childhood Experiences of Care and Abuse Scale
[e]Mean number of undesirable life events over study follow-up according to the Life Events Questionnaire
[f]Subscale total score from the Early Adolescent Temperament Scale
[g]Chi-square test
[h]Mantel haenszel Chi-Square test for trend
[i]T-test
Note: Frequencies may not sum to total offspring due to missing data

Table 3. Duration of exposure to mild to severe parental bipolar illness during the first decade of life in high-risk offspring with and without psychopathology from Ottawa and Halifax followed between 1996 to 2012

Outcome		Total (N=189)		
		Mean	SD	*p-value*[g]
Mood[a] n=103	Yes	63.0	54.8	0.46
	No	57.0	54.5	
Unipolar Depression[b] n=71	Yes	62.7	54.2	0.61
	No	58.4	54.9	
Bipolar Disorder[c] n=33	Yes	65.7	43.1	0.54
	No	58.8	54.2	
Substance Use Disorder[d] n=54	Yes	71.2	56.3	0.11
	No	56.3	53.7	
Anxiety Disorder[e] n=51	Yes	73.0	54.0	0.07
	No	55.9	54.3	
Any Psychopathology[f] n=140	Yes	63.3	55.2	0.27
	No	54.3	53.4	

[a]Mood includes: major depression, BD I, II, NOS, schizoaffective BD, depression not otherwise specified, dysthymia,& cyclothymia
[b]Unipolar includes: major depression, depression not otherwise specified, and dysthymia
[c]Bipolar (BD) includes: BD I, BD II, BD not otherwise specified, Schizoaffective BD
[d]Substance includes: any DSM-IV-TR criteria substance abuse/dependence disorder
[e]Anxiety includes: any DSM-IV-TR criteria anxiety disorder
[f]Any Psychopathology includes: any mood disorder, substance use disorder or anxiety disorder
[g]T-test

Table 4. Mean duration of exposure to moderate to severe parental bipolar illness during the first decade of life in high-risk offspring with and without a mood disorder from Ottawa and Halifax followed between 1996 to 2012

	Mood[a] (n=88)		No Mood (n=101)	
	Mean	SD	Mean	SD
0<2 yr exposure	2.0	3.8	1.5	3.4
2<5 yr exposure	1.9	3.8	1.8	3.6
5≤10 yr exposure	1.9	3.7	2.2	4.1

[a]Mood includes: major depression, BD I, II, NOS, schizoaffective BD, depression not otherwise specified, dysthymia, & cyclothymia

Table 5. Exposure to moderate to severe parental bipolar illness during birth to two years, two to five years and five to ten years and hazard of psychopathology in high-risk offspring from Ottawa and Halifax followed between 1996 to 2012

Outcome		Predictor	Unadjusted		Adjusted[a]		Adjusted[b]	
			Hazard Ratio	*95% CI*	Hazard Ratio	*95% CI*	Hazard Ratio	*95% CI*
Primary								
Mood[c]		*0<2 yr exposure*	1.03	1.00-1.05	1.04	0.99-1.08	1.04	1.00-1.08
		2<5 yr exposure	1.01	0.99-1.03	1.03	0.98-1.07	1.03	0.99-1.07
		5≤10 yr exposure	0.99	0.99-1.01	0.98	0.95-1.00	0.98	0.95-1.00
	Unipolar[d]	*0<2 yr exposure*	1.06	1.02-1.09	1.04	0.99-1.08	1.03	0.99-1.08
		2<5 yr exposure	1.04	1.01-1.06	1.01	0.97-1.05	1.01	0.97-1.06
		5≤10 yr exposure	1.02	1.00-1.03	1.01	0.98-1.03	1.00	0.98-1.02
	Bipolar[e]	*0<2 yr exposure*	1.02	0.96-1.06	1.02	0.94-1.09	1.02	0.94-1.10
		2<5 yr exposure	1.01	0.97-1.04	1.04	0.97-1.10	1.03	0.97-1.09
		5≤10 yr exposure	0.99	0.97-1.01	0.97	0.94-1.01	0.97	0.94-1.01
Secondary								
Substance[f]		*0<2 -yr exposure*	0.97	0.91-1.01	0.98	0.91-1.06	0.99	0.91-1.06
		2<5 yr exposure	0.98	0.94-1.01	0.98	0.92-1.04	0.97	0.91-1.03
		5≤10 yr exposure	0.99	0.97-1.01	1.00	0.98-1.02	1.01	0.98-1.03
Anxiety[g]		0<2 yr exposure	1.03	0.99-1.06	1.01	0.95-1.07	1.00	0.94-1.06
		2<5 yr exposure	1.02	0.99-1.04	1.01	0.96-1.06	1.02	0.96-1.07
		5≤10 yr exposure	1.01	1.00-1.02	1.00	0.98-1.02	1.00	0.98-1.02
Any Psychopathology[h]		*0<2 yr exposure*	1.01	0.99-1.04	1.00	0.96-1.04	1.02	0.96-1.04
		2<5 yr exposure	1.01	0.99-1.02	1.01	0.98-1.05	1.02	0.98-1.05
		5≤10 yr exposure	1.00	0.99-1.01	1.00	0.98-1.01	1.00	0.98-1.01

[a]Adjusted for duration of moderate to severe exposure during the two other time intervals
[b]Additionally adjusted for sex of offspring, SES, and sibling correlation
[c]Mood includes: major depression, BD I, II, NOS, schizoaffective BD, depression not otherwise specified, dysthymia, & cyclothymia
[d]Unipolar includes: major depression, depression not otherwise specified, and dysthymia

[e]Bipolar (BD) includes: BD I, BD II, BD not otherwise specified, Schizoaffective BD
[f]Substance include: any DSM-IV-TR criteria substance abuse/dependence disorder
[g]Anxiety include: any DSM-IV-TR criteria anxiety disorder, any anxiety disorder beginning before age 10 was systematically assigned an age onset of 10 years
[h]Any Psychopathology includes: any mood disorder, substance use disorder or anxiety disorder
Note: Estimates were kept at 2 decimal places due to a small unit of analysis (month). Using 1 decimal place would have omitted important patterns.

Table 6. Duration and severity of exposure to parental bipolar illness during the first decade of life and hazard of psychopathology in high-risk offspring from Ottawa and Halifax followed between 1996 to 2012

Outcome	Predictor		Unadjusted		Adjusted[a]		Adjusted[b]	
			Hazard Ratio	*95% CI*	Hazard Ratio	*95% CI*	Hazard Ratio	*95% CI*
Primary								
Mood[c]		Duration	1.3	0.8-1.9	1.4	0.7-3.1	1.4	0.7-3.2
		Severity	0.9	0.8-1.1	0.8	0.6-1.1	0.8	0.6-1.1
	Unipolar[d]	Duration	1.9	1.1-3.2	2.4	0.9-7.2	2.6	1.0-7.5
		Severity	1.1	0.9-1.3	1.0	0.7-1.4	1.0	0.7-1.5
	Bipolar[e]	Duration	1.3	0.6-2.8	0.9	0.3-3.9	0.9	0.2-3.7
		Severity	1.0	0.7-1.3	0.6	0.3-1.0	0.6	0.3-1.0
Secondary								
Substance[f]		Duration	1.9	1.1-3.6	7.0	1.8-36.2	7.1	1.8-37.0
		Severity	1.0	0.8-1.2	1.0	0.7-1.6	1.0	0.7-1.6
Anxiety[g]		Duration	1.6	0.9-3.0	1.1	0.5-3.2	1.3	0.5-3.6
		Severity	1.2	0.9-1.6	1.0	0.7-1.6	1.1	0.7-1.6
Any Psychopathology[h]		Duration	1.4	1.0-2.0	1.9	1.0-3.9	1.9	1.0-4.0
		Severity	1.0	0.9-1.0	1.0	0.8-1.3	1.0	0.8-1.3

[a]Adjusted for duration, severity and timing as defined as presence of parental illness during 0-2yrs, 2-5yrs and 5-10yrs
[b]Additionally adjusted for sex of offspring, SES, and sibling correlation
[c]Mood includes: major depression, BD I, II, NOS, schizoaffective BD, depression not otherwise specified, dysthymia,& cyclothymia
[d]Unipolar includes: major depression, depression not otherwise specified, and dysthymia
[e]Bipolar (BD) includes: BD I, BD II, BD not otherwise specified, Schizoaffective BD
[f]Substance includes: any DSM-IV-TR criteria substance abuse/dependence disorder
[g]Anxiety includes: any DSM-IV-TR criteria anxiety disorder
[h]Any Psychopathology includes: any mood disorder, substance use disorder or anxiety disorder

Table 7. Psychosocial predictors of mood disorder in high-risk offspring from Ottawa and Halifax followed between 1996 to 2012

Predictor		Unadjusted		Adjusted[a]		Adjusted[b]	
		Hazard Ratio	*95% CI*	Hazard Ratio	*95% CI*	Hazard Ratio	*95% CI*
Duration of Exposure to Parental BD[c]		1.3	0.8-1.9	0.7	0.4-1.4	0.8	0.4-1.5
Offspring Emotionality Score[d]		1.1	1.0-1.1	1.1	1.0-1.1	1.1	1.0-1.1
Mean No. of Life Events[e]		1.2	1.0-1.4	1.2	1.0-1.6	1.2	1.0-1.6
Parental Neglect Score[f]	Mother	1.1	1.0-1.2	1.2	1.1-1.3	1.2	1.1-1.3
	Father	1.0	1.0-1.1	1.0	0.9-1.1	1.0	0.9-1.1
Parental Antipathy Score[f]	Mother	1.0	1.0-1.1	1.0	0.9-1.0	1.0	0.9-1.0
	Father	1.0	1.0-1.1	1.0	0.9-1.1	1.0	0.9-1.1
Affected Parent Sex		1.2	0.8-1.7	0.9	0.5-1.4	0.9	0.5-1.5
Affected Parent Age		1.0	0.9-1.0	1.0	0.9-1.0	1.0	0.9-1.0

[a]Adjusted for all variables in model
[b]Additionally adjusted for sex of offspring, SES, and sibling correlation
[c]High duration of mild to severe parental BD (total duration over the median duration of the sample compared to below the median duration of the sample)
[d]Total emotionality subscale score from the Early Adolescent Temperament Scale
[e]Mean number of undesirable life events over study follow-up according to the Life Events Questionnaire
[f]Parental neglect and antipathy score reported by offspring using the Childhood Experiences of Care and Abuse Scale

Figure 1a. Time to mood disorders among offspring from Ottawa and Halifax followed from 1996 to 2012 with high (red) and low (blue) exposure to parental bipolar illness during the first decade of life

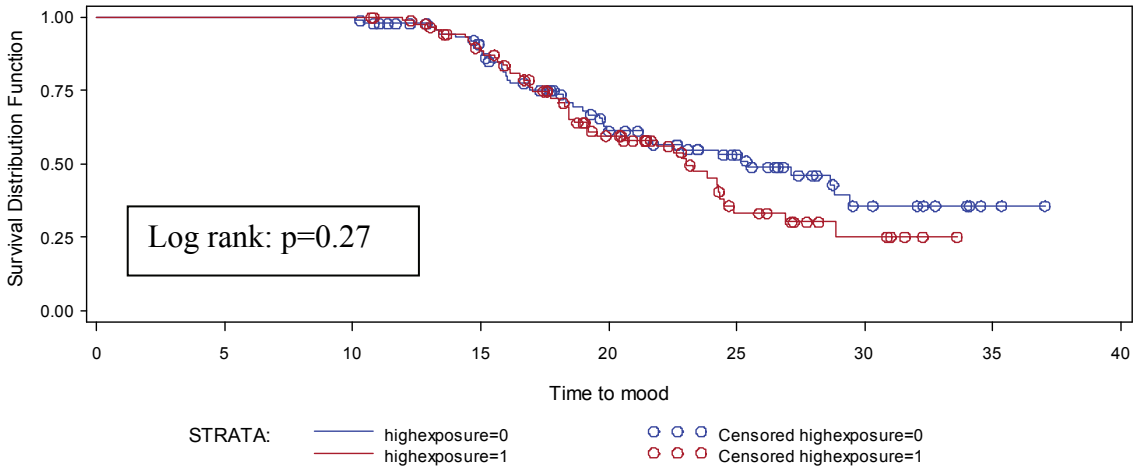


Figure 1b. Time to unipolar mood disorders among offspring from Ottawa and Halifax followed from 1996 to 2012 with high (red) and low (blue) exposure to parental bipolar illness during the first decade of life

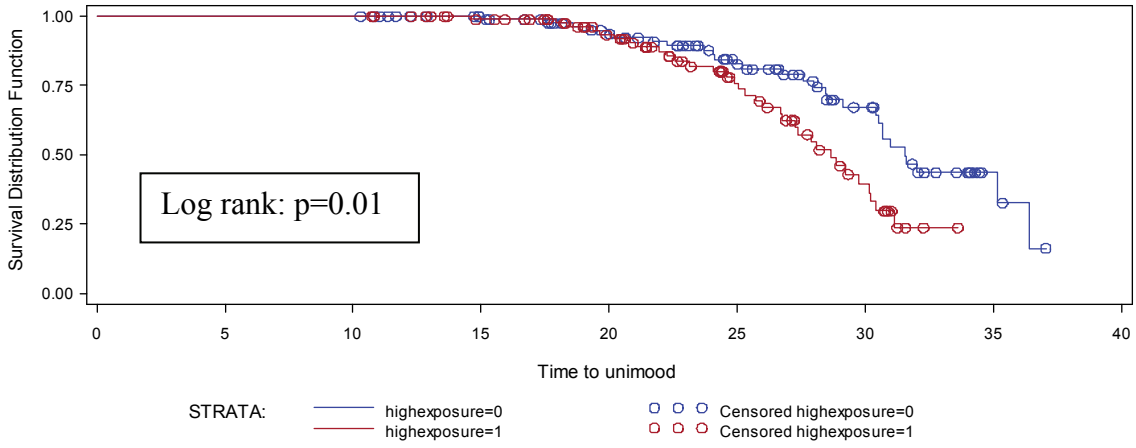


Figure 1c. Time to bipolar disorder among offspring from Ottawa and Halifax followed from 1996 to 2012with high (red) and low (blue) exposure to parental bipolar illness during the first decade of life

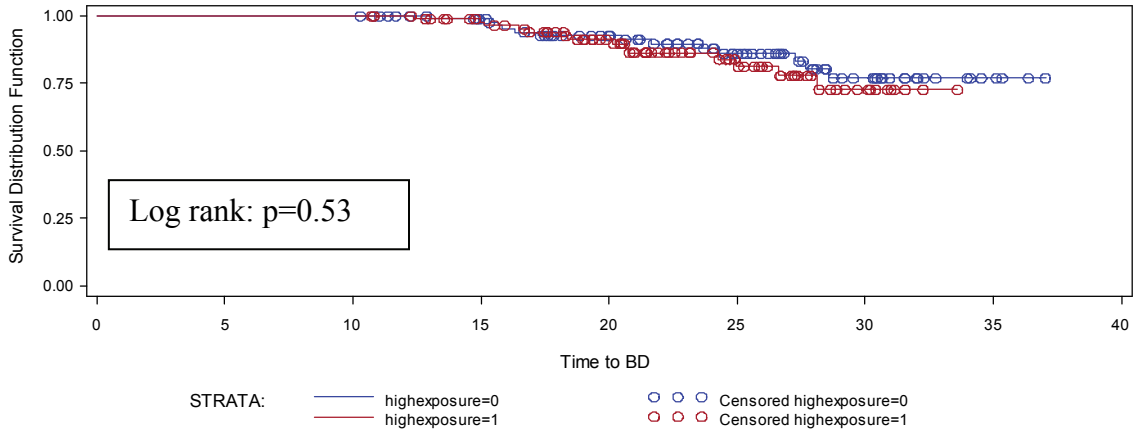


Figure 1d. Time to anxiety disorders among offspring from Ottawa and Halifax followed from 1996 to 2012 with high (red) and low (blue) exposure to parental bipolar illness during the first decade of life

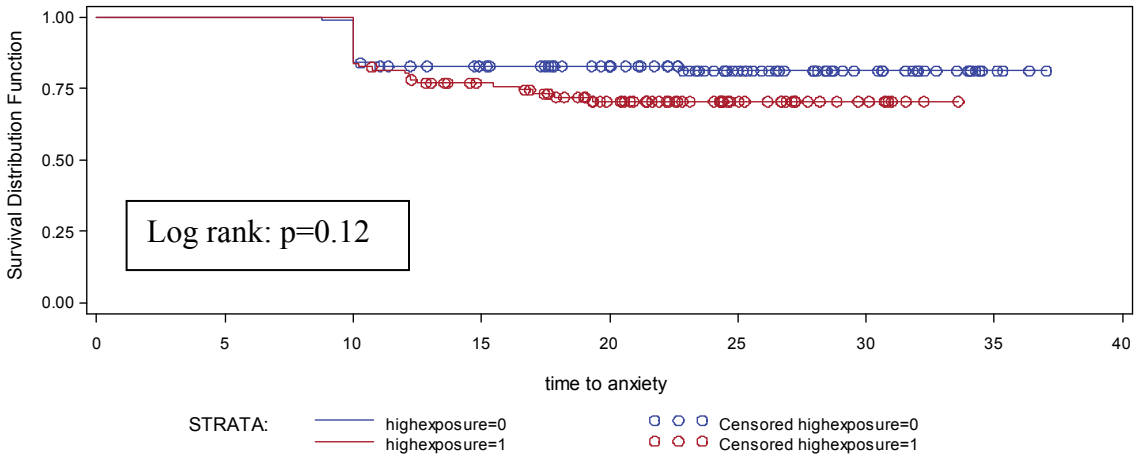


Figure 1e. Time to substance use disorders among offspring from Ottawa and Halifax followed from 1996 to 2012 with high (red) and low (blue) exposure to parental bipolar illness during the first decade of life

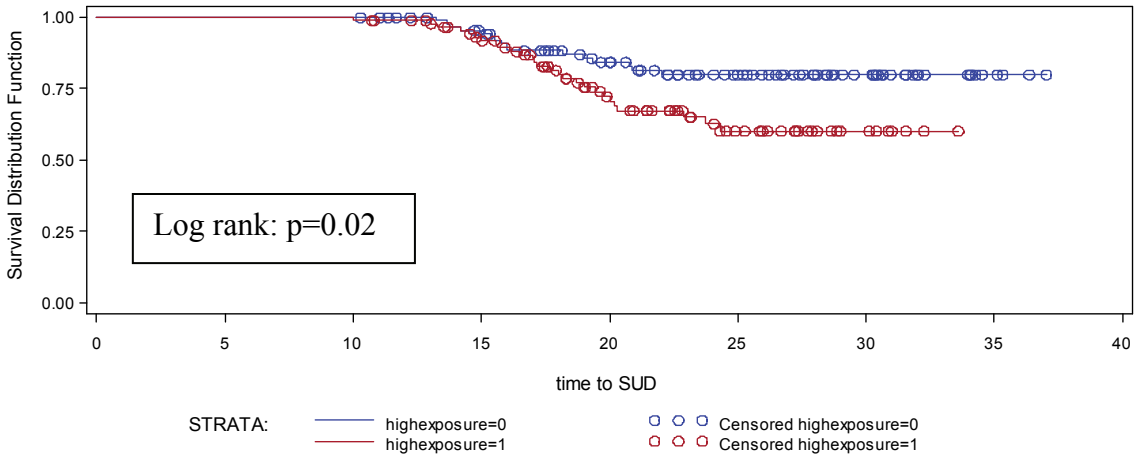
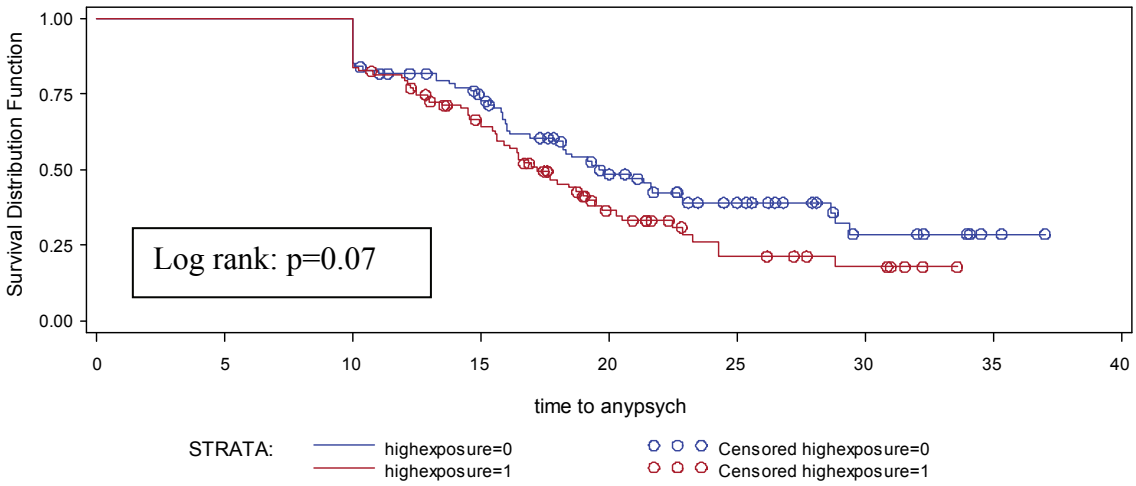


Figure 1f. Time to any psychopathology among offspring from Ottawa and Halifax followed from 1996 to 2012 with high (red) and low (blue) exposure to parental bipolar illness during the first decade of life



CHAPTER 4 DISCUSSION

5.1 DISCUSSION

While the genetic contribution of BD is well established, the intermediate pathways leading to illness onset among high-risk individuals are poorly understood. This study contributes knowledge of these pathways and is the first to prospectively examine the association between early exposure to parental bipolar illness and risk of subsequent mood disorder.

The duration and timing of parental BD may be important factors influencing risk of mood disorder and other psychopathology in high-risk offspring. Exposure to a longer duration of parental BD during the first decade of life was associated with the hazard of unipolar mood and non-mood psychopathology. In addition the pattern of findings suggests that earlier exposure in childhood (< 5 years) may be more influential in the development of mood disorders.

Offspring with psychopathology were exposed to a substantially longer duration of parental bipolar illness during their first ten years of life ranging from 4.1 to 17.2 more months of illness compared to offspring without psychopathology. While offspring with all forms of psychopathology had more exposure to parental BD, after adjustment, the hazard of unipolar depression, substance use disorders and any psychopathology showed the highest measures of association. The 95% confidence limits for the adjusted hazard ratios of duration of parental BD were wide, indicating a lack of precision. Length of

exposure to parental BD may be an important indicator or psychopathological risk in offspring already genetically predisposed towards mood disorders. But future research with larger samples is necessary to confirm this. The duration of illness has been shown in previous studies to increase risk of depression in offspring of depressed parents[15, 18, 67].

The pattern of findings regarding timing of parental BD found here are consistent with other studies of offspring of depressed parents[16, 66, 67] as well as with attachment theory suggesting that inconsistent or poor relationships with primary caregivers very early in life increases the risk of emotional disorders later in life[65]. The first few years of life are a particularly vulnerable time for children as they are undergoing major neuro-developmental changes which are important in emotional processing[12]. Exposure to severe parental BD during the first few years of life may be more detrimental to offspring's later development compared to exposure later in childhood.

There was differential exposure to parental BD during the first decade of life and the timing of quantity of exposure was different in offspring with and without psychopathology. In addition, 23% of the sample was never exposed to their parents' illness. That is, these parents were completely stabilized and in remission during their offspring's first decade of life. This is an important descriptive finding as it highlights the heterogeneity of BD in parents and helps explain the contradictory findings regarding psychosocial functioning among offspring of parents with BD compared to offspring of parents of other major psychiatric disorders. That is, not all offspring are exposed to

active bipolar illness in their parents during their early critical years for emotional and neuro-development.

In an exploratory analysis, some psychosocial factors were found to significantly predict the development of mood disorders in offspring after taking into account high exposure to parental BD during the first decade of life. Perceived neglect from mother in particular was a significant predictor of mood disorder. This is consistent with the literature of offspring of depressed mothers[79, 80]. This finding was not modified by sex of affected parent. Therefore, regardless of the mother being affected with BD, perceived neglect from mother may be an important indicator of mood disorder risk in high-risk offspring. For every significant reported life event, offspring risk of developing a mood disorder increased by 20%. Duffy et al[34] have shown that offspring of parents with BD report more recent life events compared to offspring of well parents. In addition, it has been shown that offspring of a parent with BD report more severe life events, as well as interpersonal and non interpersonal stress compared to offspring of well parents[53]. Offspring at high risk for BD and related mood disorders may be more vulnerable to the effects of life stress compared to control populations.

In addition to genetic susceptibility, the etiology of BD is the result of a complex interaction of environmental and psychosocial factors (figure a). The duration and timing of exposure to parental BD may be one piece of this complex interaction influencing the risk of mood disorders and other psychopathology in high-risk individuals while other

psychosocial factors including early relationships with the mother, life stress and possibly vulnerability towards life stress may also contribute[12].

5.2 Strengths and Limitations

This study used a novel method to quantify early exposure to parental bipolar illness and used gold standard diagnostic approaches to confirm clinical diagnoses in both offspring and parents. In addition, the sample of this study derived from well characterized families where affected parents with BD were confirmed to have no other major psychiatric disorders at baseline. The other biological parent was confirmed to have no major psychiatric disorder to reduce the potential for assortative mating. Therefore, the influence of genetic loading of other psychiatric disorders or associated family discord is minimal in this study compared to other high-risk studies with high rates of comorbidity in the parent.

Selection Bias: The target population of this study is offspring of a parent with BD raised in a developed country. All high-risk offspring were ascertained the same way based on the same exposure criteria; therefore there is minimal risk of systematic differences in ascertainment leading to participation biases. However, this study does not have information on affected parents who refused to participate, which raises concern of a potential selection bias. Participants who refused to participate may have been too ill to participate, or may have been very well and less motivated to participate. Therefore, this bias could potentially attenuate or strengthen the study results. These findings are only

generalizable to relatively intact high SES families where parents are seeking or receiving treatment for their illness. Therefore the sample population of this study does not directly generalize to its target population and this fact should be kept in mind when interpreting the findings.

Information Bias: The research psychiatrists conducting the clinical assessments in the high-risk offspring were blind to parental diagnosis and lithium response at the baseline interview. However, with subsequent interviews, the interviewing psychiatrist may have become familiar with the offspring's history leading to possible diagnostic suspicion biases. This bias has the potential to increase the magnitude of association between exposure and outcome, as the psychiatrists may have been more likely to diagnose mood disorders in offspring with more severely ill parents. However, all diagnoses in offspring were confirmed through a consensus review with the interviewing psychiatrist and two additional psychiatrists blind to family clinical history using a best estimate diagnostic approach, therefore, the likelihood of this bias impacting the findings is low.

The confirmation of AMI scores introduces a possible misclassification of exposure data. The consensual meetings may have not been completely blinded as the psychiatrists conducting the meetings worked together in the same clinics. This has the potential to overestimate the measures of association found. However, the AMI scores were based not only on research interviews, but all available clinical information in the parents including practitioner reports, discharge summaries or counseling reports from outside clinicians. The likelihood of this significantly impacting the findings is low.

There is always an aspect of recall bias with ongoing prospective cohort studies as participants are entering the study at different ages. In addition some of the parents used in this study had to be recalled for an interview due to incomplete data. This bias has the potential to either attenuate or strengthen this study's findings. To reduce the likelihood of this impacting the results, all diagnoses in both offspring and parents were confirmed using a best estimate diagnostic approach using already collected prospective data (in the affected parents) and using all available clinical information including past clinical interviews, general practitioner records, and hospital discharge reports. In addition, in some cases, multiple informants were used to ascertain information regarding specific episodes of illness in the affected parents. In light of this, our confidence of the diagnoses in both offspring and affected parents is high.

The nature of some of the measures used in this study may have introduced potential information biases. The AMI used to code exposure to parental BD is an ordinal scale. Differences in scores between one to two and two to three may be very different and can be difficult to interpret. This bias may have attenuated this study's findings and may in part explain the non-significant findings regarding severity of parental BD in predicting offspring mood disorder. I support of this, evidence of a ceiling effect was evident with 62% of AMI scores falling into the maximum (three) category. Also, the measure of temperament and parental neglect and antipathy were self-reported by the offspring and in some offspring were completed after the diagnosis of a mood disorder. The findings regarding these measures should be interpreted with caution as they introduce a potential

recall bias. In addition, although all offspring were in remission while completing these measures, the burden of having been ill (i.e., diagnosed with a prior mood disorder) may impact offspring perceptions of themselves, and their relationships with their parents. Also, the combined effect of neglect and antipathy from mother and father was not examined due to limitations of the measure used and may have contributed to the risk of mood disorder more than mother and father alone. These potential biases may either attenuate or strengthen the study findings; however, the likelihood of this is low as these measures were only used in exploratory analyses and not in primary analyses. In addition, all self-report measure used have well established reliability and validity (Appendix A).

Confounding: Several potential confounding factors were explored in this analysis. All models were adjusted for sex of offspring, SES and sibling correlation which takes into account clustering within families. In addition, exposure characteristics of parental illness including duration, severity and timing were taking into account while examining each variable independently. Psychosocial characteristics were also explored. Despite this, there may be unmeasured factors that could have influenced this study's findings. The education of the non-affected parent would likely impact the offspring's early environment. While we did not directly take the non-affected parents education into account, the measure of SES accounts for both parents level of education and occupation. In addition, the majority of the sample derived from high SES families. Offspring may have been exposed to other influences early in life either through other non-biological caregivers or family members. However, this is likely not a large problem in this analysis as 100 % of the sample reported that their biological parents were their primary

caregivers during their first decade of life. Another possible confounder is birth order. Although the mean number of siblings in the study is reported, information on some siblings who did not participate in the study was not available therefore we were unable to examine this variable. First born compared to second and third born may have an impact on risk of psychopathology later in life as well with relationships with parents.

We were unable to examine the impact of polarity of parental episode on risk of offspring mood disorder. As many of the parents had mixed acute episodes as well as mixed remissions, it was difficult to quantify proportion of depressed versus activated episodes. Early exposure to activated episodes, and particularly severe manic episodes may be more strongly associated with offspring risk of mood disorder due to the erratic behavior of the parent.

While these potential confounding factors may have either attenuated or strengthened this study's findings, due to the well characterized sample, and variables already reported and adjusted for in analyses, the likelihood of these factors significantly impacting the findings is relatively low.

5.3 Policy Implications

This proposed research adds to the body of literature aimed at understanding the etiology of BD. This research is primarily hypothesis generating, however, has potential implications for policy interventions. Although genetic susceptibility does not ensure the

development of an illness, individuals predisposed are more vulnerable to specific exposures which may trigger the eventual onset of psychopathology. By defining potential markers of illness, we can begin to develop targeted interventions or early prevention strategies for this high-risk population. In light of the already available literature, better support for parents suffering from major psychiatric illness particularly mood disorders is needed. Exposure to parental illness during the first few years of life may be particularly detrimental to the emotional development of high-risk offspring. Expecting families with one or both parents affected with BD may benefit from psycho-education on parenting and social support. Implications of this research also lie in clinical practice. Youth identified as high-risk should be monitored closely during periods of high stress as major life events are significant predictors of mood disorder in this population.

5.4 Future Directions

This research informs several areas for future research. As the current study was underpowered to adequately address some of its questions, replication with larger numbers is needed. In addition to replication, there are several areas needing improvement. For example, investigation into the impact of the polarity of parental episode on mood disorder risk is warranted, however, is challenging to quantify. A more refined sample with classical lithium responsive BD parents would be ideal to address this question as their clinical course is typically more episodic with clear acute episodes compared to lithium non-responsive parents whose course tends to be more chronic.

In light of this study's findings, quantity of exposure to parental BD early in life is an important variable to consider in future research in high-risk offspring. Mainly, quantity of exposure may confound associations between other variables such as environmental stressors in early childhood and risk of psychopathology later in life.

Future research also needs to clarify if psychosocial factors such as perceived neglect from mother, undesirable life events or high emotionality are true risk factors of mood disorder, or are the reflection of illness in the offspring. Longitudinal assessment of repeated measures of temperament, perceptions of parents and life stress before during and after the first episode of mood disorder would be necessary to confirm this. In addition, investigation into the time lag between life events and mood disorder would be important to better understand the nature of this relationship as well as inform preventive measures for clinicians.

Finally, future research in this high-risk population needs to refine better methodology to understand the nature of the association between early relationships with parents, psychosocial factors and risk of psychopathology in offspring. Studies of offspring of depressed mothers have examined in detail attachment relationships between mother and child and the influence of maternal depression on these associations and risk of emotional problems in offspring later in life (e.g., Murray et al.,[80]). Future researchers should adopt these methods in populations of offspring of a parent with BD.

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APPENDIX A Psychometric Properties of Self and Clinician Reported Measures

Hollingshead SES: The Hollingshead SES[82] scale is a composite measure of education and occupation of both working spouses where one equals the lowest SES category and five equals the highest. The Hollingshead SES scale has demonstrated high inter-rater reliability (r=.91)[83]. Although this measure has been criticized for being outdated compared to current social status scales, it demonstrates good convergent validity as evidenced by its correlations with other more recent SES scales including the Socioeconomic Index of Occupations (r=.81) and the Socioeconomic Index for Occupations in Canada (r=.86)[83]. For the purposes of this study, SES was captured during the first decade of offspring's life which in some cases dated back to the 1970's and therefore maps appropriately to the time frame of this measure.

Temperament: The Early Adolescent Temperament Scale (EAS)[84] is a 20-item measure composed of four subscales designed to assess emotionality, activity, sociability and shyness. The EAS is used as a self report measure in youth over 13 years of age, and a parent rated measure in youth below the age of 13. The validity of parent ratings of this measure has been established[85]. Higher scores on all subscales indicate higher levels of the construct measured. Research has established the reliability and validity of the EAS subscales[84-87].

Childhood Experiences of Care and Abuse (CECA.Q): The CECA.Q[88] is a self-reported measure of early adversity in youth over the age of 13 years. For the purposes of this study, offspring were asked to report based on events occurring during the first ten years of their life. The CECA.Q consists of three domains: abuse, parental neglect and antipathy. The abuse domain was coded into a binary variable indicating presence of physical or sexual abuse during the first decade of life. The neglect and antipathy scores are reported for mother and father separately where higher scores indicate higher levels of neglect and antipathy. The CECA.Q has demonstrated good reliability and validity in both community[89] and clinical samples[90].

Life events: The Recent Life Events and Difficulties Questionnaire[91, 92] is a 13-item semi-structured interview in children over the age of 13 years, designed to assess significant life events during the past year. Parents are interviewed in children under the age of 13 years. Events were counted as significant if they were rated as quite unpleasant or very unpleasant, and lasting for at least two weeks. Yearly total scores are calculated by summing the amount of significant life events. The LEQ has shown to be a reliable and valid instrument in both child and parent[92].

Affective Morbidity Index: The AMI[93] is a 4-item systematic clinician rated scale designed to quantify the severity of a major mood episodes in patients with affective disorders. The scale ranges from zero (no conspicuous affective disturbance) to three (severe depression or mania). The criteria used to assign the score is as follows: A score of one indicates presence of symptoms that do not require therapeutic action, a score of

two indicates presence of symptoms that require either psychotherapy or pharmacological treatment, however can be managed at an outpatient level, a score of three indicates symptoms that require inpatient treatment.

Salivary Cortisol Methodology: The salivary cortisol sample collection was consistent with methods from Goodyer et al[94, 95] and Ellenbogen et al[96]. During an annual research visit, offspring were instructed on the procedure of the cortisol collection. For the sample collection, offspring took sampling kits home and filled 5 ml sterile cryovials with saliva three times a day, time 0 (upon awakening), time 1 (30 minutes later) and time 1 (8:00pm) for three consecutive routine days. Routine days are used as sleep patterns and associated cortisol levels are variable on the weekend, also multiple days are necessary to account for day-to-day variation[95]. During the sampling collection, offspring were instructed to record their time of awakening, and time of spitting. Their samples were frozen immediately and were stored at either Halifax or Ottawa research sites. Offspring were generally compliant with the sampling protocol and did not have major issues with filling the vials with saliva. The cortisol awakening response was calculated by taking the mean of the difference between time 1 and time 0 samples over the three consecutive sampling days.

APPENDIX B Regional Differences

Regional differences between Ottawa and Halifax research sites in high-risk offspring from Ottawa and Halifax followed between 1996 to 2012

		Ottawa (N=160)		Halifax (N=73)		*p-value*
		n	%	n	%	
Sex Offspring	Male	70	43.7	24	32.9	0.12[d]
	Female	90	56.3	49	67.1	
Sex Parent	Male	84	52.5	29	39.7	0.07[d]
	Female	76	47.5	44	60.3	
SES[b]	1 – Low	1	0.6	0	0.0	0.26[e]
	2	3	1.9	1	1.4	
	3	23	14.4	6	8.2	
	4	47	29.4	24	32.9	
	5 - High	86	53.7	42	57.5	
Mood[c]	Yes	74	46.2	29	39.7	0.35[d]
	No	86	52.3	44	60.3	
		Mean	SD	Mean	SD	
Age Offspring[a]		27.1	7.6	26.1	6.1	0.28[f]
Age Parent[a]		58.4	7.6	56.8	6.4	0.12[f]

[a]Mean age at time of analysis (June 2013)
[b]Hollingshead Socio-economic Status (SES) scale
[c]Mood includes: major depression, bipolar disorder I, II, NOS, schizoaffective bipolar disorder, depression not otherwise specified, dysthymia, and cyclothymia
[d] Chi-square test
[e]Mantel-Haenszel chi-square
[f]t-test

APPENDIX C Interaction: Sex of Offspring and Affected Parent

After taking into account mean duration of moderate to severe parental BD during the first decade of life, offspring sex, SES and sibling correlation, sex of affected parent did not significantly increase the hazard of substance use disorders, (HR 1.32, 95%CI: 0.71-2.46) or bipolar disorder (HR: 0.48, 95%CI: 0.20-1.07), however, if the mother was the affected parent, this significantly increased the hazard of anxiety disorders by a factor of 2.55 (95%CI: 1.33-5.16) and marginally increased the hazard of unipolar depression by a factor of 1.78 (95%CI: 1.04-3.08). However, there was no significant evidence of interaction between sex of affected parent and mean exposure to parental BD during the first decade of life (all $p>0.05$). Sex of offspring did not significantly interact with mean duration of parental BD during the first decade of life ($p=0.68$) in predicting substance use disorder.

APPENDIX D Duration of Exposure to Moderate to Severe Parental Bipolar Illness in Offspring With and Without Psychopathology

Duration of exposure to moderate to severe parental bipolar disorder in offspring with and without psychopathology from Ottawa and Halifax followed between 1996-2012

Outcome		Total (N=189)		
		Mean	SD	*p-value*[g]
Mood[a]	Yes	22.6	37.7	0.59
	No	25.5	37.6	
Unipolar Depression[b]	Yes	25.2	15.1	0.78
	No	23.6	17.3	
Bipolar Disorder[c]	Yes	20.1	37.2	0.55
	No	24.8	18.9	
Substance Use Disorder[d]	Yes	15.5	27.0	0.03
	No	26.7	39.9	
Anxiety Disorder[e]	Yes	34.7	44.9	0.07
	No	21.0	34.6	
Any Psychopathology[f]	Yes	24.1	38.2	0.99
	No	24.1	36.7	

[a]Mood includes: major depression, BD I, II, NOS, schizoaffective BD, depression not otherwise specified, dysthymia,& cyclothymia
[b]Unipolar includes: major depression, depression not otherwise specified, and dysthymia
[c]Bipolar (BD) includes: BD I, BD II, BD not otherwise specified, Schizoaffective BD
[d]Substance includes: any DSM-IV-TR criteria substance abuse/dependence disorder
[e]Anxiety includes: any DSM-IV-TR criteria anxiety disorder
[f]Any Psychopathology includes: any mood disorder, substance use disorder or anxiety disorder
[g]T-test