

MOOD AND ANXIETY SYMPTOMS: POTENTIAL RISK INDICATORS  
FOR MAJOR MOOD DISORDERS AMONG HIGH-RISK OFFSPRING OF BIPOLAR PARENTS

by

Courtney Grace Heisler

Submitted in partial fulfilment of the requirements  
for the degree of Master of Science

at

Dalhousie University  
Halifax, Nova Scotia  
August 2017

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## **ABSTRACT**

**Background:** Bipolar disorder refers to a heterogeneous group of mood disorders, affecting approximately 2% of the Canadian population. Family, twin, and adoption studies provide evidence of a strong genetic contribution, making children of affected parents an identifiable high-risk group. Other than a positive family history, there have been no reliable indicators to identify those who will develop illness. Longitudinal high-risk studies have shown that a significant proportion of offspring manifest antecedent internalizing symptoms such as anxiety and depressive symptoms in early childhood, years prior to the first diagnosable mood episode. Furthermore, the first few full-threshold mood episodes of emerging bipolar disorder are often depressive in polarity. There has been little systematic study of the strength and timing of the association between these antecedent clinical symptoms and the development of syndromal mood disorders in high-risk individuals. This could be important to improve earlier detection and identify targets for prevention.

**Objectives:** The objective of this study was to determine whether the presence of clinically significant childhood depressive and anxiety symptoms predicts the risk and age of onset of a subsequent mood episode. To address this objective, the following research questions were explored: i) Does the presence of clinically significant childhood anxiety and depressive symptoms influence the risk and timing of onset of major mood episodes (hypomania, mania, major depression)? ii) Does the presence of clinically significant childhood anxiety and depressive symptoms influence the risk and timing of any (major or minor) diagnosable mood episode (hypomania, mania, major depression, depression NOS, BDNOS, cyclothymia, dysthymia)?

**Methods:** The exposure to the risk indicator (presence of clinically significant childhood anxiety and depressive symptoms) and the primary and secondary outcomes (major mood episode and any diagnosable mood episode, respectively) were analyzed using discrete time survival analysis. We

assessed clinically significant anxiety and depressive symptoms in childhood prior to age 15 years (given that the median age of onset of mood disorders in high-risk offspring studies peaks in mid to late adolescence) on the risk and timing of DSM-IV criteria for a diagnosable mood episode based on both clinician-assessment (KSADS-PL clinical research interviews) and symptom-rating scales (HAM-A and BDI-II).

**Results:** The study included 286 participants (40.7% male) from the Flourish High Risk Offspring Cohort. The mean age of participants at baseline interview was 15.4 years (SD=5.6 years), and 22.91 years (SD=7.2 years) at the final assessment. Of the 286 participants with primary risk indicator data, 50 (17.5%) were determined to have clinically significant mood or anxiety symptoms based on semi-structured clinician interview and consensus review by expert clinicians. Among those meeting criteria for clinically significant symptoms, as per the KSADS-PL interview, the mean age of exposure was 10.3 years (SD=3.3). Depressive and anxiety symptoms measured by symptom rating scales were available for 262 participants under the age of 15 years. Individuals with clinically significant internalizing symptoms measured by the KSADS-PL interview were significantly more likely to develop a major mood episode (HR=2.2,  $p<0.05$ , 1.2-3.9) and any diagnosable mood episode (HR=2.1,  $p<0.05$ , 1.2-3.7) compared to those without these antecedents. There was no significant association found between antecedent symptoms measured by symptom rating scales and major episodes (HR=1.3,  $p>0.05$ , 0.4-4.4) or diagnosable mood episodes (HR=2.0,  $p>0.05$ , 0.8-5.2).

**Discussion:** This study demonstrated clinically significant internalizing symptoms determined by clinician assessment predict the risk of mood episodes later in life in youth at confirmed familial risk. However, symptoms assessed by validated rating scales were not significant predictors of subsequent mood episodes.

**Conclusions:** Clinically significant childhood mood and anxiety symptoms in youth at confirmed familial

risk were predictive of future mood episodes in adulthood. However, symptoms without the clinical context of a full psychiatric assessment appear to have limited predictive value. Other work has shown similar results which taken together suggests that the profile of symptoms taking into account change from baseline, context, persistence, and severity may be important for understanding the natural trajectory of mood disorders. Future work in this area should continue to follow this cohort over a longer length of time to allow for greater insight into the influences of clinically significant symptoms on future psychopathology in high-risk groups. By gaining greater insight into the natural history of major mood disorders and the significance of clinically significant symptoms in children at identifiable familial risk, we hope to help provide information pertinent to screening in order to facilitate earlier identification of mood disorders in high risk and to identify potential early intervention and even prevention targets.

**Key words:** Mood disorders, clinically significant internalizing symptoms, high-risk, family history, risk, depressive disorders, bipolar disorders



## LIST OF ABBREVIATIONS USED

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<b>Abbreviation</b>	<b>Full Term</b>
MDD	Major depressive disorder
BD	Bipolar disorder
BDI	Bipolar disorder – Type I
BDII	Bipolar disorder – Type II
BDNOS	Bipolar disorder – Not otherwise specified
Depression NOS	Depression – Not otherwise specified
SES	Socioeconomic status
KSADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime
SADS-L	Schedule for Affective Disorders and Schizophrenia-Lifetime
FH-RDC	Family history – research diagnostic criteria
HAM-A	Hamilton Anxiety Rating Scale
BDI-II	Beck Depression Inventory-II

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## **ACKNOWLEDGEMENTS**

I would like to thank my thesis committee (Drs. Anne Duffy, Adrian Levy, and Scott Patten) for their unwavering support and mentorship throughout my Master's program. Special thank you to Dr. Anne Duffy for her encouragement throughout this process and for the use of the Flourish Mood Disorders High risk database for this project. Also, thank you to Sarah Goodday, PhD candidate, for her amazing support throughout this project.

## **CHAPTER 1. INTRODUCTION**

Bipolar disorder (BD) is a major mood disorder affecting approximately 2% of the Canadian population, typically onsetting in late adolescence and early adulthood (1,2). Individuals with BD face high relapse rates, increased vulnerability for substance use, chronic use of health services, underemployment, and increased dependence on public assistance (2,3). In addition, BD is associated with a very high risk of suicide and significant decreased life expectancy (4). On average, accurate diagnosis does not occur until 10 years after the individual has sought treatment, and much longer since impairing and distressing (clinically significant) symptoms first began (5). Family, twin, and adoption studies provide strong evidence of a genetic contribution, making children of parents with BD an important identifiable high-risk group for developing depressive and bipolar disorders (6). Other than a positive family history, there are currently no known factors to identify who will develop the illness. Furthermore, diagnosis is based on the manifestation of a manic or hypomanic episode, as defined by the Diagnostic and Statistical Manual (DSM-5) (7), despite the fact that in an estimated 30% of high-risk offspring impairing and distressing antecedent childhood internalizing symptoms precede the onset of diagnosable mood disorders (8–11). However, little research to date has investigated the nature of the relationship between clinical symptoms and the development of major mood disorders in high-risk offspring.

Structure of thesis: background, formatted manuscript, general discussion, future directions, references, and appendices.

## **CHAPTER 2. BACKGROUND**

### **2.1. WHY IS RISK PREDICTION IMPORTANT?**

Mood disorders are associated with substantial mental, physical, and financial difficulties. Overall, mental illness costs the Canadian economy approximately \$33 billion annually (12). Mood disorders are currently the fastest growing disability category in Canada, and are the leading cause of disability-adjusted life years (DALYs) worldwide (13). Canadians with mood disorders face unemployment rates up to 90%, with nearly 70% of all disability claims in Canada related to mental illness (14,15).

The presence of mood disorders in adolescence and early adulthood has ripple effects throughout the lifespan. Research has shown the incidence proportion of newly diagnosed depression increases from 1-2% at age 13 years, to 7% at age 15 years (16). Incidence of depression continues to increase into early adulthood (17). Anxiety disorders also frequently begin in adolescence and early adulthood. The incidence proportion of anxiety disorders increases when moving from adolescence to adulthood, 5% to 6% respectively (18). Individuals with anxiety disorders have an elevated lifetime risk of depressive and bipolar disorders (19–22). To date, BD and Major Depressive Disorder (MDD) have had overall lifetime prevalence rates of 2% and 11% respectively (1,2,23). Furthermore, high-risk and clinical studies have shown that BD often debuts with depressive episodes (24–27).

The burden of mood disorders is compounded by co-morbid illness. Research has identified that patients with major mood disorders have a higher risk for developing cardiovascular disease,

diabetes, and obesity (28–31), as well as for hypertension, hyperglycaemia, angina, dyslipidemia, metabolic syndrome, pain disorders, impulse control disorders, and personality disorders (32–35). Further complicating the course of illness, patients with mood disorders have a significantly increased risk for developing substance use disorders (36). In turn, comorbid illness is associated with higher rates and longer duration of hospitalization in patients with mood disorders (37,38) and higher rates of mortality (37,39–41).

Increases in suicidal ideation, attempts, and completions are documented among individuals with major mood disorders (37,39–41). Suicide accounts for 20% of all deaths among Canadians aged 15-25 years, the typical age range for onset of mood disorders (42). Furthermore, over 90% of individuals who committed suicide are estimated to have suffered from psychiatric illness, mainly mood disorders, with an estimated 60% of suicides occurring in individuals before the age of 20 years (43,44). It is important to note that these values are likely higher than reported due to underestimation from often limited information regarding an individual's psychiatric history and overall sense of well-being prior to suicide (45).

## **2.2. RISK FACTORS**

Genetic heritability plays a substantial role in the risk of developing a mood disorder that persists and recurs through adolescence and adulthood. It has been suggested that the heritability of BD is around 80%- the highest among psychiatric illnesses (46). The strength of the heritability component places offspring of an affected parent at a substantially increased risk of

developing a related mood disorder (BD or depressive). Furthermore, a family history of major mood disorders has been associated with earlier age of illness onset, higher recurrence rates, greater severity, and longer duration of illness (36). Evidence has suggested there are major genetic contributions to BD, with family history being the strongest single risk factor (47). However, the majority of children of affected parents will not develop illness. Studies report an 8 to 10-fold increased risk of BD and 2 to 3-fold increased risk of unipolar disorders in children of affected parents (24). Risk determination on an individual basis is a research and public health priority that would inform those suitable for closer surveillance and preventative/early intervention.

Developmental stage and age have also been associated with the risk of developing mood disorders. Nearly 75% of diagnosable mood disorders onset between early adolescence and early adulthood (48–53). Females who have experienced early maturation and males who have experienced late maturation are at an increased risk for developing mood disorders (54). Pre-pubertal males less than 12 years of age have been shown to have higher prevalence of depressive symptoms (1.3%), when compared to their female counterparts (0.08%) (48). After puberty, the risk of depressive disorder shifts so that females have 2-fold the risk compared to males. While, BD has equal risk between males and females, females with BD have more preponderance of depressive episodes (55). After puberty, women are twice as likely to experience and subsequently be hospitalized for a mood disorder (55,56).

Individual factors related to mood disorders are well-documented (30–32). Socioeconomic status (SES) has been documented as a risk factor for primarily depressive disorders (58). Early

adversity and trauma seems to be an important risk exposure for both BD and depressive disorder (60–62). Also linked to SES, research has demonstrated social and non-social stress to be associated with major mood disorders (59).

### **2.3. CHALLENGES OF DIAGNOSIS EARLY IN THE COURSE OF ILLNESS**

MDD and BD are diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) (63) (Appendix A). A major depressive episode is marked by a change in normal functioning characterized by feelings of sadness or depressed mood for most of the day, nearly every day; loss of interest and pleasure in usual activities; changes in activity levels; difficulty sleeping; fluctuations in eating and weight gain; loss of energy, great fatigue; negative self-concept, self-reproach and self-blame, feelings of worthlessness, and guilt; difficulty concentrating; and recurrent thoughts of suicide or death. These symptoms must persist for at least two weeks. A diagnosis of MDD requires two or more major depressive episodes (63).

BD can be subdivided into BD Type I and BD Type II. BD Type I is characterized by at least one episode of mania with or without alternating episodes of mania and depression as the primary symptom presentation. However, the clinical presentation for BD Type II is defined by at least one hypomanic episode with or without alternating depressive episodes (63). Manic episodes are severe often requiring hospitalization and characterized by lack of insight and judgment,

increased self-esteem or grandiosity, decreased need for sleep, pressured speech, flight of ideas or subjective experience that thoughts are racing, distractibility, increases in goal-directed activity, psychomotor agitation, and impulsivity (63). Hypomanic episodes are milder changes from normal functioning. This classification system changed drastically from earlier version of DSM (earlier than the III version) in which recurrent manic and depressive disorders were considered part of the manic-depressive illness construct (the precursor to current BD classification). This reflected the fact that manic-depressive illness often began with depressive episodes years prior to the index manic/hypomanic episode and that relatives of BD probands with a shared genetic diathesis had an increased risk of MDD and BD (6).

In order to apply diagnostic criteria (Appendix A), a psychiatrist may interview an individual and significant family members on multiple occasions to gather a comprehensive psychiatric history (63). Clinical interviews also provide the opportunity to gather detailed information about psychopathology and context (i.e. individual change, evidence of altered insight and judgment, substance use), which may be missed through the simple questionnaires (64–69). The interview is a comprehensive assessment of an individual's psychiatric and medical history.



### **2.3.1. DIAGNOSTIC DELAY**

There is often a delay between the onset of a major mood disorder and an accurate diagnosis, which can negatively impact the prognosis of the individual (70). The more time that passes between disease onset and accessing appropriate treatment, the greater the possibility of increased burden and illness refractoriness (70). As symptoms become more severe, the risk of medical and psychiatric co-morbidity and subsequent decline in prognosis becomes an increasing concern. Nearly 60% of individuals never seek treatment for mood disorder (71). The least well served and least likely sector of the Canadian population to seek psychiatric help is those aged 15-25 years which is the highest risk age group for the onset of major mood disorders (72).

One obstacle to seeking treatment is fear of stigma. Stigma is shown to decrease self-efficacy and self-esteem, and increase reluctance to seek psychiatric help for mental illness, including major mood disorders (73). Further fear of discrimination is also shown to prevent individuals from seeking care for psychiatric illnesses (73). Furthermore, both lower education levels and the presence of co-morbid conditions are related to diagnostic delay (74). With wait times to see a psychiatrist ranging from weeks to months, even individuals who seek treatment, despite fears of stigma, may have to wait months for help (75).

### **2.3.2. CLINICALLY SIGNIFICANT SYMPTOMS**

The influence of psychopathology at the symptom rather than the syndrome level on the risk and timing of subsequent major mood disorder onset has not been well understood in the literature. However, it has been well established that the presence of clinically significant anxiety and depressive (internalizing) symptoms can have long-term consequences (76,77). Among school populations, clinically significant anxiety symptoms have independently predicted future occurrences of anxiety disorders and the combination of a history of anxiety, as well as clinically significant anxiety at baseline, were predictive of a subsequent depressive disorder (78). Similar patterns were found in high-risk populations (79,80). Furthermore, increasing severity of depressive symptoms were associated with subsequent mood disorder onset (70,77,81). In a community-based study, depressive symptoms were reported by 41% of adolescents who later met the criteria for a major mood disorder when reassessed in young adulthood (82).

There is little guidance as to what qualifies as clinically significant mood and anxiety symptoms, making the classification of these symptoms vulnerable to misclassification bias. For example, previous research has reported that the majority of the general population of adolescents report hypomanic-like symptoms, which is the majority of cases represents a transient normative experience (83). Furthermore, potential misclassification of clinically significant symptoms, or incorrect identification of symptoms, may lead to false positives and incorrect diagnoses. In order to qualify for a diagnosis of BD, an individual must experience at least one episode of mania or hypomania. Major depressive episodes often precede the onset of

the first activated episode (84). However, if the manic episode is misclassified or simply not reported, as is common with milder hypomania, a diagnosis of major depression is given. Treatment with antidepressants alone and/or in high doses can cause paradoxical worsening (85–87). The threat of misclassification should be acknowledged in research studies of major mood disorders, and every effort should be taken to minimize its presence through stringent clinical interviews, such as the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (KSADS-PL) (88).

## **2.4. CLINICAL IMPLICATIONS**

Prevention is important in the mitigation of chronic diseases. In Canada, there are many interventions available for individuals with major mood disorders ranging from community-based mental health services to specialized and subspecialized out-patient and in-patient psychiatric services. Interventions with a focus on primary prevention can be useful in stemming the progression of symptoms. As discussed above, research has shown individuals with mood symptoms are at a heightened risk of developing full-blown mood and co-morbid psychiatric disorders (36,38,45,89). By acknowledging the risk of antecedent symptoms, individuals at risk of developing mood disorders may also benefit from anxiety-reduction practices thereby approaching psychopathology from a developmental and a dimensional perspective facilitating clinicians to assess and subsequently treat mental illness as a spectrum, rather than the categorical presence or absence of illness, as well as prevent the onset of full blown illness.

Secondary prevention focuses on reduction of disease prevalence through early detection. It aims to shorten the duration or progression of a disease, increase survival rates, and/or improve quality of life (90). Meanwhile, the goal of primary prevention is to reduce exposure to risk factors, thus leading to a decrease in disease incidence, which is not possible for the current observational study where participants are selected based their high-risk status (90). The focus of this study is therefore on secondary prevention, with the aim to increase the understanding of prognostic features of clinically significant childhood anxiety and depressive symptoms (risk indicator) and the development of mood episodes (outcome). By gaining insight into this hypothesized association, we seek to better inform clinicians on the importance of clinically significant symptoms prior to diagnostic conversion at the syndromal level. Through the identification and study of individuals at high-risk for major mood disorders, we can gain greater understanding of risk indicators and develop interventions for modifying such risks to reduce harm to the individual. With high incidence rates of major mood disorders into adolescence and early adulthood, identification of risk indicators in those age groups can help reduce the burden of illness and ensure efficient resource allocation to those who need it most (16).

## **2.5. OBJECTIVE**

The objective of this study was to determine whether the presence of clinically significant childhood depressive and anxiety symptoms predicts the risk and age of onset of a subsequent mood episode. To address this objective, the following research questions were explored:

- 1) Does the presence of clinically significant childhood anxiety and depressive symptoms influence the risk and timing of a major mood episode defined as an episode of hypomania, mania or major depression?
  
- 2) Does the presence of clinically significant childhood anxiety and depressive symptoms influence the risk and timing of any diagnosable mood disorder defined as hypomania, mania, major depression, depression NOS, BDI, BDII, BDNOS, cyclothymia, dysthymia?

## **CHAPTER 3. MANUSCRIPT**

### **3.1. INTRODUCTION**

Bipolar disorder (BD) represents a heterogeneous group of mood disorders affecting approximately 2% of the Canadian population, and typically beginning during late adolescence and early adulthood (1,2). BD typically has a highly recurrent course and is associated with substantially increased risk of substance use, medical comorbidity, chronic use of health services, underemployment, and increased dependence on public assistance (2,3). In addition, BD is associated with a very high risk of suicide. On average, accurate diagnosis does not occur until 10 years after the individual has sought treatment, and much longer still since clinically significant symptoms first began (5). Family, twin, and adoption studies provide evidence of a strong genetic contribution, making children of parents with BD an important and identifiable high-risk group (91,92). Other than a positive family history, there are currently no known factors to help identify who will develop the illness. Furthermore, diagnosis is based on a manic or hypomanic episode, as defined by the Diagnostic and Statistical Manual (DSM-5) (7), despite that the illness often begins with antecedent symptoms and depressive episodes. For example, previous research has provided evidence of childhood mood and anxiety symptoms in an estimate 30% of high-risk offspring (8–11). Little research has been completed to date on the relationship between important clinically significant affective symptoms and the development of diagnosable mood disorders in high-risk offspring. The objective of this study is to determine whether the presence of clinically significant childhood anxiety and depressive symptoms predicts the risk and age of onset of DSM mood disorders in offspring of a parent with confirmed bipolar disorder (BD).

## **3.2. METHODS**

### **STUDY DESIGN**

Data were drawn from the Canadian Flourish high-risk offspring study, a longitudinal dynamic cohort study following offspring of a well-characterized biological parent with BDI or II for up to 20 years (43). These data were used to assess clinically significant anxiety and depressive symptoms in childhood on the risk and timing of developing full DSM-IV criteria for mood episodes using clinician-assessed symptoms (based on KSADS-PL format semi-structured interviews) and validated symptom-rating scales (HAM-A, BDI-II). As mood disorders typically onset in late adolescence and early adulthood, limiting symptom onset prior to the age of 15 years allowed for individuals at with childhood affective symptoms time to experience diagnostic conversion to full threshold mood episodes (94). Assessment of demographic variables was also collected at baseline and during follow-up interviews where appropriate.

### **PARTICIPANTS**

Eligible participants were identified from Flourish high-risk offspring study recruited from families participating in neurobiological research in the Maritime Provinces and Ontario between 1996 to the present date as published previously (27). Briefly, BD parents were identified from specialty adult mood disorders programs and based on SADS-L interviews and best estimate diagnosis including a wealth of longitudinal clinical data were determined on blind consensus

review by at least two psychiatrists to meet DSM criteria for BD I or II. All consenting children from these families were enrolled in a prospective study involving annual assessments by semi-structured KSADS-PL format interviews conducted by a research psychiatrist.

High-risk participant inclusion for the current study was dependent on three criteria: i) one parent meeting DSM diagnostic criteria for BD I or II at baseline; ii) the other parent must be unaffected for lifetime Axis Major Psychiatric Disorder at study entry. The comparison group was included in the study if they did not have a biological parent with BD and had not been diagnosed with a major mood disorder at the time of study entry. The comparison offspring were selected from families in which neither parent (based on direct clinical research interview of at least one parent) met DSM-IV diagnostic criteria for any major psychiatric illness at the time of enrollment (mood, substance use or psychotic disorder). Participants who experienced clinically significant symptoms after the age of 15 or had exposure to one of the risk indicators that predated the outcome were excluded from analyses. Participants who are unable to comprehend the study protocol were not included in this study.

## **PROCEDURE**

For the Flourish high-risk study, eligible parents were approached regarding the participation of their child/children, and consenting/assenting parents and children were included into the study (11). In the majority of cases, at least one of the offspring's parents was interviewed directly by a psychiatrist about the offspring's early development and emotional



health. A psychiatrist clinically assessed offspring annually. DSM-IV-TR diagnoses and ages of onset were captured over follow-up. Baseline assessments were completed with all participants involved in the study by an experienced child psychiatrist using the Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime (KSADS-PL) semi-structured format (88). DSM-IV-TR diagnoses were made on blind consensus review by two additional research psychiatrists of all research interviews and any other available clinical reports. Any disagreements were settled in one of two ways: additional information was gathered from the patient or the patient's guardian, or an independently conducted re-interview took place. The latter option was employed with a single participant, who was reviewed following this protocol. All offspring in the study were re-interviewed using the KSADS-PL/SADS-L format annually. If a participant was not available for an annual study visit, every effort was made to conduct a telephone/video call interview.

As part of the ongoing longitudinal study, the risk indicators and outcomes were assessed annually using both clinician-assessed (KSADS-PL/SADS-L interview) symptoms (indicating either the presence or absence of clinically significant symptoms), and symptom-ratings on validated measures. Mood episodes were diagnosed using DSM-IV-TR criteria (63). This study was approved by the IWK Health Center Research Ethics Board (Halifax, Nova Scotia) and the local Ottawa Institutional Review Board (16,50).

## **RISK INDICATOR MEASUREMENT**

### ***Primary Risk Indicator: Clinically significant symptoms as measured by the KSADS-PL interview***

The KSADS-PL is the gold standard semi-structured research interview for assessing current and lifetime psychopathology in children and adolescents (95). The assessment allows for the use of replicable, pre-determined questions and the ability to gather both quantitative and qualitative data (95). However, due to the degree of skill required to properly administer the KSADS-PL, the interview requires trained clinicians to conduct the interview. The KSADS-PL has demonstrated strong psychometric properties for use in clinical settings (88). It has good to excellent test-retest reliability, high internal consistency (Cronbach's alpha = 0.94), and inter-rater reliability intra-class correlation coefficient of 0.97 between two raters (88,95). Individuals who experienced the outcome prior to exposure to the primary risk indicator were excluded from the analyses.

An individual met clinically significant depressive symptoms based on the following criteria: i) participant endorsed a minimum of three DSM-IV depressive symptoms one of which included depressed mood, but did not meet full criteria for major depressive episode or depression not otherwise specified based on symptom duration or severity; ii) symptoms represented a clear change from normal functioning, endorsed by self and others who knew the person well; and iii) no evidence of major impairment.

Clinically significant anxiety symptoms were based on the following criteria: i) participant endorsed a minimum of three DSM-IV anxiety symptoms, one of which was feeling anxious, but did not meet full criteria for an anxiety disorder or anxiety not otherwise specified based on symptom duration or severity; ii) symptoms represented a clear change from normal functioning, endorsed by self and others who knew the person well; and iii) no evidence of major impairment.

***Secondary Risk Indicator: Clinically significant symptoms as measured by symptom-rating scales***

Validated symptom-rating scales were used to quantify symptoms using self-report measures. Specifically, the Hamilton Anxiety Rating Scale (HAM-A) a 14-item clinician-rated measure assesses the severity of anxiety symptoms of both somatic and psychic anxiety (e.g., mental agitation) (96). The range of the scale is 0 to 56, with each item on the scale scored between 0 (not present) to 4 (severe) (96). The scale is well-suited in clinical settings for its ability to be used from childhood to adulthood, and its minimal time requirement to administer (96). The Beck Depression Inventory (BDI-II/youth version) is a 21-item self-report measure of depressive symptoms (65,66,97). Responses range from 0 (absence of the depressive trait) to 3 (presence of the depressive trait), with a total range of 0 to 63. The BDI-II is well validated in both adolescent and adult populations (65,66). Individuals who experienced the outcome prior to exposure to the secondary risk indicator were excluded from the analyses.

## ***Sensitivity Analyses***

To further explore the predictive ability of symptom-rating scales on subsequent mood episodes, sensitivity analyses were completed on a range of cut-off scores for both the BDI and HAMA scales. In addition to using the standardized BDI clinical cut-off score of 14, we examined BDI cut-off scores of 10 and 16. Previous studies have used a variety of non-standardized cut-off scores for the BDI, with a range of 7 to 31 (98). However, among non-clinical samples, a cut-off score of 10 (99,100) demonstrated overall high sensitivity and specificity. Similar sensitivity and specificity levels were demonstrated with a cut-off score of 16 (101).

With the HAMA scale, in addition to the standardized cut-off score of 18, we also evaluated the predictive ability of using 15 and 23 as cut-off scores. Previous research found a score range of 15 to 23 to be an optimal cut off range for moderate anxiety symptoms for the HAMA in clinical populations (102). Due to limited published literature in HAMA cut off scores in non-clinical populations, 15 and 23 were chosen as cut-off scores for the sensitivity analyses.

## **OUTCOME MEASUREMENT**

The primary outcome was the onset of a major mood episode, involving a diagnosis of major depression, hypomania, or mania according to DSM-IV-TR criteria (Appendix A). The secondary outcome was the onset of any diagnosable mood episode, defined as major depression, hypomania, mania, BDI, BDII, Depression NOS, BDNOS, cyclothymia, or dysthymia according to DSM-IV-TR criteria (63) in order to include a broader phenotype and increase

statistical power. Mood episodes were selected as outcomes to capture offspring in the early course of BD as often the depressive episode precede the onset of diagnosable activated episodes by years (24–27,103,104).

## **COVARIATES**

All models were adjusted for sex of the offspring and SES was measured using the Hollingshead SES Scale (105). The Hollingshead SES Scale measures education and occupation levels of working spouses. Scores on the scale range from 1 to 5, with 1 being the lowest SES category and 5 being the highest SES category (105). The scale has shown high inter-rater reliability ( $r=0.91$ ), and good convergent validity (106).

## **STATISTICAL ANALYSIS**

### ***Primary Risk Indicator Coding***

The primary risk indicator was the presence of clinically significant anxiety and depressive symptoms assessed using the semi-structured clinical research interview (KSADS-PL) The research interviews were completed on an annual basis and covered psychopathology between assessments. Onset of mood episodes were dated to the nearest month based on history and consensus review resulting in any clinically significant symptoms being time-stamped (timing of risk indicator). Results from KSADS-PL interview were coded into a binary rating where 0

indicated the absence clinically significant anxiety or depressive symptoms and 1 indicated the presence of the symptoms, as determined by the clinician (risk indicator severity). Only the first occurrence of the primary exposure was used. Thus, once a participant had experienced the presence of clinically significant affective symptoms, they were not able to be unexposed at another time point. Duration was determined from the time of exposure onset to the outcome.

### ***Secondary Risk Indicator Coding***

The secondary risk indicator was a composite measure of two rating scales: HAM-A and BDI-II scales. The presence of the secondary risk indicator was defined as those who met the standardized cut-off scores for *at least one* of the two scales (score of 18 and 14 on the HAM-A or BDI, respectively), denoting the severity of secondary risk indicator and thus differentiating clinically significant psychopathology. This resulted in a binary coding of the secondary risk indicator: a score of 0 indicated the absence of at least one score above the standardized cut-off point for any of the two scales; 1 indicated the presence of at least one score above the standardize cut-off point for any of the two scales. To determine the positive presence of the secondary risk indicator, the cut-off scores for the HAMA, and BDI-II are  $\geq 18$ , and  $\geq 14$ , respectively (65,88,96,107). A score above 18 on the HAMA or 14 on the BDI-II is indicative of symptoms that are more severe than 'mild' symptomology (65,88,96,107). The timing of the secondary risk indicator was measured as the date the participant first scored above the defined cut-off score on the BDI or HAM-A. The duration of the secondary risk indicator was determined

from the time of exposure onset (the date of first exceeded the cut-off of either the BDI or HAM-A) to the outcome.

### ***Demographics***

Descriptive analyses were calculated to provide descriptive statistics for each predictor (e.g. mean follow up time, mean age at first assessment and last assessment). Graphical techniques were used to detect extreme variations in the data (e.g. data entry errors, out of bounds values). Means, medians, and 95% confidence intervals were also used to describe the study sample. Further descriptive statistics were calculated using chi-square tests and mean survival times were calculated for participants with no clinically significant symptoms, and those with depressive and anxiety symptoms combined.

### ***Survival Model***

To examine the time to mood episode onset, a discrete-time survival model was used. Discrete time periods were counted in years. Time of exposure was used as the baseline time point. Individuals who experienced the outcome prior to the exposure were excluded. To account for immortal time bias, all participants were initially coded as unexposed to the risk indicator. Immortal time bias refers to the inability of an individual to experience an outcome in the absence of the exposure in question (108,109). When a participant experienced the risk indicator,

they were then coded as exposed (Figure 1). If there was no exposure to the risk indicator, they were coded as unexposed (Figure 1). Person-time was counted in years since the baseline time point. Time of enrollment and person-time in years since enrollment accounted for variable onset and duration of the risk indicator using time-stamped clinical assessments. To account for different ages at enrollment, we adjusted for age at enrollment as a variable and potential confounder in the analysis. All models were adjusted for sex, SES, age of enrollment, and status (high-risk and comparison groups). Proportional hazards assumptions were tested with likelihood ratio tests. Power estimates indicated the study had approximately 99.9% power to detect a hazard ratio of 2.0, and 89.67% power to detect a hazard ratio of 1.5 with an alpha of 0.05 and a sample size of 365. This calculation was based on an assumed hazard rate of approximately 5% among the non-exposed participants. All analyses were completed with Stata 13 (110).

### **3.3. RESULTS**

#### ***Participant Characteristics***

The study included 286 participants (42.31% male) from the Flourish Longitudinal High-Risk study database (Table 1). The mean age of participants at the baseline interview was 15.4 years (SD=5.6 years), and 22.9 years (SD=7.2 years) at the final interview. Participants included in this analysis were followed annually on average for 7.5 years (SD=4.7 years). The majority of participants were from middle to high SES, with an average 4.4/5 (SD=0.8) Hollingshead score. Demographic characteristics are described in Table 1.



## ***Risk Indicators***

### Clinically Significant Symptoms based on KSADS-PL interview (primary risk indicator):

Primary risk indicator data (based on KSADS-PL interview) was available for 286 participants under the age of 15 years (Table 2). Of the 286 participants, 50 (17.5%) were considered to have clinically significant affective symptoms and were therefore exposed to the primary risk indicator and 236 (82.5%) were unexposed. The mean age of exposure was 10.7 years (SD=3.5 years), with a total range of 3.0 to 15.0 years.

Clinically Significant Symptoms based on symptom-rating scales (secondary risk indicator): Secondary risk indicator data (symptom-rating scales) was available for 256 participants under the age of 15 years (Table 2). Of the 256 participants, 31 (12.1%) met cut-off scale score criteria and were considered exposed to the secondary risk indicator and 225 (87.9%) were unexposed. During the initial interview, the mean age of completing the baseline symptom-rating scale at was 11.9 years (SD=3.2 years), with a total range of 6.8 to 15.0 years.

## ***Outcomes***

Primary Outcome: Major mood episodes (hypomania, mania, or major depression) were diagnosed in 91 of the 286 participants (31.5%) up until the last follow-up assessment (Table 3). One participant was dropped from the analysis due to experiencing the outcome prior to the exposure. Of the remaining 90 participants, the mean age of onset for a major mood episode was 17.9 years (SD =4.2 years), with a range of 7.1 to 29.4 years of age.

Secondary Outcome: Any diagnosable mood disorder (hypomania, mania, or major depression, BDI/II/NOS, depression NOS, cyclothymia, or dysthymia) were diagnosed in 108 of the 286 participants (37.8%) (Table 3). Mean age of onset for a diagnosable mood disorder was 17.2 years (SD=4.5), with a range of 7.1 to 29.3 years of age.

***Exposure to clinically significant symptoms (primary risk indicator) and major mood episodes***

Of the 50 participants who were determined to have clinically significant antecedent affective symptoms based on the KSADS-PL assessment, 19 (38%) eventually developed a major mood episode (Table 4). The mean time between exposure to clinically significant internalizing symptoms and the development of a major mood episode was 6.3 years (SD=2.9) (Figure 2). Individuals with antecedent symptoms were significantly more likely to develop a subsequent major mood episode (HR=2.2,  $p<0.05$ , 1.2-3.9). The significant association was maintained when adjusting for sex, SES, status (high risk versus comparison groups), and age at enrollment (HR=2.0,  $p<0.05$ , 1.1-3.7) (Table 6). When restricting the model to include only the high-risk group, there may have been insufficient power to observe a significant association between clinically significant symptoms and major mood episodes (HR=1.9,  $p>0.05$ , 1.0-3.4).

### ***Exposure to clinically significant symptoms (primary risk indicator) and diagnosable mood episodes***

Of the 50 participants who were determined to have clinically significant symptoms (based on KSADS-PL interviews), 21 (42.0%) developed any diagnosable mood disorder (Table 5). The mean time between onset of clinically significant internalizing symptoms and the development of a diagnosable mood disorder was 5.6 (SD=3.0) (Figure 3). Individuals with clinically significant symptoms were significantly more likely to develop a diagnosable mood episode (HR=2.1,  $p<0.05$ , 1.2-3.7). The direction of the association remained when adjusting for sex, SES, status (high-risk versus comparison groups), and age at enrollment (HR=1.9,  $p<0.05$ , 1.1-3.4) (Table 6). After restricting the model to the high-risk group, there may have been insufficient power to detect a significant association between clinically significant symptoms and diagnosable mood episodes (HR=1.7,  $p>0.05$ , 1.0-3.1).

### ***Exposure to clinically significant symptoms (secondary risk indicator) and major mood episodes***

Of the 31 participants who met criteria for the secondary risk indicator, 7 (22.6%) eventually developed a major mood episode (Table 4). The mean time between clinically significant symptoms as measured by symptom rating scales and the development of a major mood episode was 6.8 years (SD=2.2 years) (Figure 4). However, there was no significant association detected in individuals with clinically significant symptoms and subsequent major mood episodes

compared to individuals without antecedent symptoms (HR=1.3,  $p>0.05$ , 0.4-4.4). Similar results, with slightly less precision, were obtained when adjusting for SES, sex, status (high-risk versus comparison groups), and age at enrollment (HR=1.2,  $p>0.05$ , 0.3-4.6) (Table 6). Little change was observed in the point estimate when restricting the model to high-risk offspring group (HR=1.0,  $p>0.05$ , 0.2-4.4).

The association continued to overlap the null value when conducting sensitivity analyses for the lower cut off scores (score of 10 on the BDI and 15 on the HAMA) (Unadjusted model: HR=1.5,  $p>0.05$ , 0.5-4.5; Adjusted model: HR=1.7,  $p>0.05$ , 0.5-6.1). Similar findings were also evident in the sensitivity analyses for higher cut off scores (score of 16 on the BDI and 23 on the HAMA) (Unadjusted model: HR=0.8,  $p>0.05$ , 0.1-5.7; Adjusted model: HR=0.7,  $p>0.05$ , 0.1-5.2).

### ***Exposure to clinically significant symptoms (secondary risk indicator) and diagnosable mood episodes***

Of the 31 participants who met exhibited clinically significant symptoms based on the symptom-rating scales, 9 (29.0%) eventually developed any diagnosable mood episode (Table 5). The mean time between clinically significant symptom onset and the development of a diagnosable mood episode was 5.8 years (SD=3.4 years) (Figure 5). Individuals meeting criteria for clinically significant symptoms were more likely to develop any diagnosable mood episode, however the 95% confidence interval overlapped the null value (HR=2.0,  $p>0.05$ , 0.8-5.2). The direction of the association remained when adjusting for sex, SES, status (high-risk versus

comparison groups), and age at enrollment (HR=1.6,  $p>0.05$ , 0.5-4.9) (Table 6). Similarly, little change in the point estimate was observed when the model was restricted to only the high-risk offspring group (HR=1.3,  $p>0.05$ , 0.4-4.2).

The association continued to overlap the null value when conducting sensitivity analyses for the lower cut off scores (score of 10 on the BDI and 15 on the HAMA) (Unadjusted model: HR=1.7,  $p>0.05$ , 0.7-4.3; Adjusted model: HR=1.3,  $p>0.05$ , 0.4-3.8). Similar findings were also evident in the sensitivity analyses for higher cut off scores (score of 16 on the BDI and 23 on the HAMA) (Unadjusted model: HR=1.5,  $p>0.05$ , 0.4-6.5; Adjusted model: HR=1.2,  $p>0.05$ , 0.3-5.7).

### **3.4. DISCUSSION**

The main finding from this study was that clinically significant depressive and anxiety symptoms were associated with an increased risk of developing mood episodes in youth. As the time to major and diagnosable mood onset once clinically significant symptoms were identified was on average 6.3 and 5.6 years, respectively, this can help inform future work on the natural history of mood episodes among those at familial risk who will develop mood episodes. This finding further supports existing literature on childhood affective symptoms and their importance for understanding mood disorder trajectories throughout the lifespan (11,26,41,111,112). Further, there was evidence that the clinically-determined risk status (KSADS-PL interview) is a stronger measure than using standardized cut-off scores from validated symptom rating scales. The semi-structured clinical assessment showed stronger associations for

subsequent mood disorders, particularly for the broader phenotype which included a spectrum of mood diagnoses.

Interestingly, clinically significant symptoms as measured by the symptom-rating scales and using standardized cut-off scores did not predict future mood episodes in the population. This finding may relate to the fact that cut-off scores for these scales derived from studies of patients and were designed to identify subgroups suitable for pharmacological intervention. Therefore, the cut-off scores may not be appropriate for screening even within a high-risk population. Furthermore, the number of “exposed” or identified high-risk youth identified as symptom positive by using these cut-off scores was quite low, and therefore limited power may have precluded statistical significance.

The current study used longitudinal data from the longest and one of the largest high-risk offspring cohorts in existence. The prospective cohort design allowed for clarification of temporal sequences of events, as well as facilitated the study of rare events and outcomes. Furthermore, the study was protected from information/misclassification bias. For each interview, the clinician was blinded to participant membership status and each subsequent annual assessment was subjected to blind diagnostic consensus review by an additional clinician who was not aware of the risk indicator status of the participant. In addition, the use of a composite measure for the secondary risk indicator allowed for avoidance of issues of multiplicity (potential for Type I error) and allowed for greater interpretability of results within a clinical setting. The composite measure increased clinical interpretability as it could identify an abnormality (in this case, exceeding at

least one standardized cut-off score), which may be informative in its own right when clinical interviews are not possible (e.g. as a screening).

A limitation of the current study was the risk of selection bias as the study did not contain information on affected parents who declined participation. In addition, there was potential for the inability to recall or unwillingness to disclose information during the interviews. Furthermore, the study used both self- and clinician-reported symptom rating scales. There is a possibility that one may have been better at predicting subsequent outcomes. However, the two measures were grouped together as a composite variable for the purposes of clinical utility and power. The use of cut-off scores and subsequent lower numbers of participants who met the cut-off scores may have limited the ability of the composite symptom-rating scale measure and subsequently predict subsequent mood episodes. Another limitation is the use of the comparison group, which was strictly drawn from Ontario. While the group can be used to inform additional research to a greater segment of the general population, it cannot be used to generalize the findings to multiple Canadian provinces at this time.

Given the longitudinal nature of the study, attrition bias may be introduced. Reasons for dropping out of the study included the participant moving away, being too busy to participate, or were no longer interested in participation. There is a possibility loss of participants could have also resulted from individuals becoming more unwell than those who remained in the study. In this event, the loss of these individuals from the cohort could have attenuated the associations found between risk indicator exposure and outcomes. However, if the loss to follow up resulted from relocation, lack of free time, or lack of interest, the effects of this attrition on clinically

significant symptoms and subsequent mood episodes is not certain.

Future work in this area should continue to follow this cohort over a longer length of time to allow for greater insight into the influences of clinically significant symptoms on future psychopathology in high-risk groups. Additional follow up would also increase participation numbers and the associations found in this study may prove to be more information with greater power. Understanding the pathway from clinically significant symptoms to development of subsequent mood episodes can help inform clinical care guidelines and improve overall patient quality of life.

## **CONCLUSIONS**

This longitudinal study allowed for the examination of the risk of developing a mood episode with the presence of antecedent clinically significant symptoms. Identifying early clinical stages of major mood disorders is paramount for screening, as these disorders typically onset during developmentally critical periods and result in distressing chronic consequences. Due to incomplete understanding of the natural history of major mood disorders and associated heterogeneity, there is still much work to be done among these high-risk populations. Continued investigation into high-risk groups can lead to greater understanding of the natural history of major mood disorders.



### 3.5. REFERENCES

1. Schaffer A, Cairney J, Cheung A, Veldhuizen S, Levitt A. Community Survey of Bipolar Disorder in Canada: Lifetime Prevalence and Illness Characteristics. [Enquête dans la collectivité sur le trouble bipolaire au Canada: Prévalence à vie et caractéristiques de la maladie.]. *Can J Psychiatry / La Rev Can Psychiatr.* 2006;51(1):9–16.
2. Fagiolini A, Forgione R, Maccari M, Cuomo A, Morana B, Dell’Osso MC, et al. Prevalence, chronicity, burden and borders of bipolar disorder. *J Affect Disord.* 2013;148(2–3):161–9.
3. Müller-Oerlinghausen B, Felber W, Berghöfer A, Lauterbach E, Ahrens B. The impact of lithium long-term medication on suicidal behavior and mortality of bipolar patients. *Arch Suicide Res.* 2005;9(3):307–19.
4. Kessing L, Vradi E, Andersen P. Life Expectancy in bipolar disorder. *Bipolar Disord.* 2015;17:543–8.
5. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry.* 2003 Mar;60(3):261–9.
6. Craddock N, Sklar P. Bipolar Disorder 1 - Genetics of bipolar disorder. *Lancet* [Internet]. 2013;381(9878):1654–62. Available from: [http://dx.doi.org/10.1016/S0140-6736\(13\)60855-7](http://dx.doi.org/10.1016/S0140-6736(13)60855-7)

7. Association AP. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington: American Psychiatric Pub Inc; 2013.
8. Juli G, Juli MR, Juli L. Involvement of genetic factors in bipolar disorders: Current status. *Psychiatr Danub*. 2012;24(SUPPL. 1):112–6.
9. Tijssen MJ, Van Os J, Wittchen HU, Lieb R, Beesdo K, Wichers M. Risk factors predicting onset and persistence of subthreshold expression of bipolar psychopathology among youth from the community. *Acta Psychiatr Scand*. 2010 Sep;122(3):255–66.
10. Shaw J a, Egeland J a, Endicott J, Allen CR, Hostetter AM. A 10-year prospective study of prodromal patterns for bipolar disorder among Amish youth. *J Am Acad Child Adolesc Psychiatry*. 2005;44(11):1104–11.
11. Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar disorder. *J Affect Disord*. 2010;121(1–2):127–35.
12. Lim, K., Jacobs, P., Ohinmaa, A., Schopflocher, D., & Dewa CS. A new population based measure of the economic burden of mental illness in Canada. *Chronic Dis Can*. 2008;28(3):92–8.
13. Whiteford H a., Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;382(9904):1575–86.

14. Dewa CS, Chau N, Dermer S. Examining the comparative incidence and costs of physical and mental health-related disabilities in an employed population. *J Occup Environ Med.* 2010;52(7):758–62.
15. Marwaha S, Johnson S. Schizophrenia and employment: A review. *Soc Psychiatry Psychiatr Epidemiol.* 2004;39(5):337–49.
16. Lewinsohn P, Duncan E, Stanton A, Hautzinger M. Age at first onset for nonbipolar depression. *J Abnorm Psychol.* 1986;95:378–83.
17. Lewinsohn P, Moerk K, Klein D. Epidemiology of adolescent depression. *Econ Neurosci.* 2000;2:52–68.
18. Statistics Canada. Canadian Community Health Survey 2009. 2009.
19. Bittner A, Goodwin R, Wittchen H, Beesdo K, Höfler M, Lieb R. What Characteristics of Primary Anxiety Disorders Predict Subsequent Major Depressive Disorder? *J Clin Psychiatry.* 2004;65(5):618–26.
20. Bittner A, Egger H, Erkanli A, Costello E, Foley D, Angold A. What do childhood anxiety disorders predict? (2007). Antje Bittner, Helen L. Egger, Alaattin Erkanli, E. Jane Costello, Debra L. Foley, Adrian Angold. *Journal of Child Psychology and Psychiatry;* 48(12), 1174-1183. *J Child Psychol Psychiatry.* 2007;48(12):1174–83.
21. Sareen S, Cox B, Afifi T, de Graaf R, Asmundson G, ten Have M, et al. Anxiety Disorders and Risk for Suicidal Ideation and Suicide Attempts A Population-Based Longitudinal Study of Adults (2005). *Arch Gen Psychiatry.* 2005;62:1249–57.

22. Simon N, Zalta A, Otto M, Ostacher M, Fischmann D, Chow C, et al. The association of comorbid anxiety disorders with suicide attempts and suicidal ideation in outpatients with bipolar disorder. *J Psychiatr Res.* 2007;41(3–4):255–64.
23. Pearson C, Janz T, Ali J. Mental and substance use disorders in Canada. *Stat Canada Cat no 82-624-X.* 2013;
24. Duffy A, Grof P, Robertson C, Alda M. The implications of genetics studies of major mood disorders for clinical practice. *J Clin Psychiatry.* 2000;61(9):630–7.
25. Duffy A. The early natural history of bipolar disorder: what we have learned from longitudinal high-risk research. *Can J psychiatry.* 2010;55(8):477–85.
26. Duffy A. Early identification of recurrent mood disorders in youth: the importance of a developmental approach. *Evid Based Ment Health.* 2015;18(1):7–9.
27. Duffy A, Horrocks J, Doucette S, Keown-Stoneman C, McCloskey S, Grof P. The developmental trajectory of bipolar disorder. *Br J Psychiatry.* 2014;204(2):122–8.
28. Scott K, de Jonge P, Alonso J, Viana M, Liu Z, O’Neill S, et al. Associations between DSM-IV mental disorders and subsequent heart disease onset: beyond depression. *Int J Cardiol.* 2014;168(6):1–16.
29. Williams MM, Clouse RE, Lustman PJ. Treating Depression to Prevent Diabetes. 2006;24(2):79–86.

30. Richardson L, Davis R, Poulton R, McCauley E, Moffitt T, Caspi A, et al. A longitudinal evaluation of adolescent depression and adult obesity. *Arch Pediatr Adolesc Med*. 2003;157(8):739–45.
31. Goodman E, Whitaker R. A prospective study of the role of depression in the development and persistence of adolescent obesity. *Pediatrics*. 2002;110:498–504.
32. Kilbourne A, Cornelius J, Han X, Pincus H, Shad M, Salloum I, et al. Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord*. 2004;6:368–73.
33. McIntyre R, Konarski J, Yatham L. Comorbidity in bipolar disorder: a framework for rational treatment selection. *Hum Psychopharmacol*. 2004;19:369–86.
34. Oswald P, Souery D, Kasper S, Lecrubier Y, Montgomery S, Wyckaert S, et al. Current issues in bipolar disorder: a critical review. *Eur Neuropsychopharmacol*. 2007;17(687–695).
35. Centorrino F, Mark T, Talamo A, Oh K, Chang J. Health and economic burden of metabolic comorbidity among individuals with bipolar disorder. *J Clin Psychopharmacol*. 2009;29:595–600.
36. Holma KM, Melartin TK, Holma I a K, Paunio T, Isometsä ET. Family history of psychiatric disorders and the outcome of psychiatric patients with DSM-IV major depressive disorder. *J Affect Disord [Internet]*. 2011;131(1–3):251–9. Available from: <http://dx.doi.org/10.1016/j.jad.2010.12.016>

37. Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*. 2006;63(10):1139–48.
38. Parker G, McCraw S, Hadzi-Pavlovic D, Fletcher K. Costs of the principal mood disorders: A study of comparative direct and indirect costs incurred by those with bipolar I, bipolar II and unipolar disorders. *J Affect Disord* [Internet]. 2013;149(1–3):46–55. Available from: <http://dx.doi.org/10.1016/j.jad.2012.10.002>
39. Ferrari AJ, Norman RE, Freedman G, Baxter AJ, Pirkis JE, Harris MG, et al. The burden attributable to mental and substance use disorders as risk factors for suicide: Findings from the Global Burden of Disease Study 2010. *PLoS One*. 2014;9(4).
40. Latham L. *Mental Health in Atlantic Canada : A Snapshot*. 2012.
41. Duffy A, Alda M, Hajek T, Grof P. Early course of bipolar disorder in high-risk offspring: Prospective study. *Br J Psychiatry*. 2009;195(5):457–8.
42. Pan SY, Desmeules M, Morrison H, Semenciw R, Ugnat AM, Thompson W, et al. Adolescent Injury Deaths and Hospitalization in Canada: Magnitude and Temporal Trends (1979-2003). *J Adolesc Heal*. 2007;41(1):84–92.
43. Bertolote J, Fleischmann A. Suicide and psychiatric diagnosis: a worldwide perspective. *World Psychiatry*. 2012;13(3):181–5.
44. Shaffer D, Gould M, Fisher P, Trautman P, Moreau D, Kleinman M, et al. Psychiatric Diagnosis in Child and Adolescent Suicide. *Arch Gen Psychiatry*. 1996;53(4):339–48.

45. Luppá M, Heinrich S, Angermeyer MC, König H-H, Riedel-Heller SG. Cost-of-illness studies of depression: a systematic review. *J Affect Disord.* 2007;98(1–2):29–43.
46. Smoller J, Finn C. Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet.* 2003;123C:48–58.
47. Gottesman I, Laursen T, Bertelsen A, Mortensen P. Severe mental disorders in offspring with 2 psychiatrically ill parents. *Arch Gen Psychiatry.* 2010;67:252–7.
48. Douglas J, Scott J. A systematic review of gender-specific rates of unipolar and bipolar disorders in community studies of pre-pubertal children. *Bipolar Disord.* 2014;16(1):5–15.
49. Duffy A, Doucette S, Lewitzka U, Alda M, Hajek T, Grof P. Findings from bipolar offspring studies: Methodology matters. *Early Interv Psychiatry.* 2011;5(3):181–91.
50. Scott J. Bipolar disorder: From early identification to personalized treatment. *Early Interv Psychiatry.* 2011;5(2):89–90.
51. Martino DJ, Marengo E, Igoa A, Scapola M, Ais ED, Perinot L, et al. Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. *J Affect Disord.* 2009 Jul;116(1–2):37–42.
52. Van Meter A, Moreira A, Youngstrom E. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *J Clin Psychiatry.* 2011;72(9):1250–6.

53. Bellivier F, Etain B, Malafosse A, Henry C, Kahn J-P, Elgrabli-Wajsbrodt O, et al. Age at onset in bipolar I affective disorder in the USA and Europe. *World J Biol Psychiatry*. 2011;2975(September 2015):1–8.
54. Laitinen-Krispijn S, Jan van der E, Verhulst FC. The role of pubertal progress in the development of depression in early adolescence. *J Affect Disord*. 1999;54(1–2):211–5.
55. Angst J. The Course of Affective Disorders II: Typology of Bipolar-Manic Depressive Illness. *Arch Psychiatry Neurol Sci*. 1978;226:65073.
56. Roy-Byrne P, Post RM, Uhde TW, Porcu T, Davis D. The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. *Acta Psychiatr Scand Suppl*. 1985;317(317):1–34.
57. Cuijpers P, Beekman A, Smit F, Deeg D. Predicting the onset of major depressive disorder and dysthymia in older adults with subthreshold depression: A community based study. *Int J Geriatr Psychiatry*. 2006;21(9):811–8.
58. Ibrahim AK, Kelly SJ, Glazebrook C. Socioeconomic status and the risk of depression among UK higher education students. *Soc Psychiatry Psychiatr Epidemiol*. 2013;48(9):1491–501.
59. Raposa EB, Hammen CL, Brennan P a, O’Callaghan F, Najman JM. Early adversity and health outcomes in young adulthood: the role of ongoing stress. *Health Psychol* [Internet]. 2014;33(5):410–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23730716>



60. Aas M, Henry C, Andreassen OA, Bellivier F, Melle I, Etain B. The role of childhood trauma in bipolar disorders. *Int J bipolar Disord* [Internet]. 2016;4(1):2. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4712184&tool=pmcentrez&rendertype=abstract>
61. Bifuico A, Brown W, Adler Z. Early sexual abuse and clinical depression in adult life. *Br J Psychiatry*. 1991;159:115–222.
62. Goodyer I, Altham P. Lifetime exit events and recent social and family adversities in anxious and depressed school-age children and adolescents - I. *J Affect Disord*. 1991;21:219–28.
63. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC; 2000.
64. Kent L, Vostanis P, Feehan C. Detection of Major and Minor Depression in Children and Adolescents: Evaluation of the Moods and Feelings Questionnaire. *J Child Psychol Psychiatry Allied Discip*. 1997;38(5):565–73.
65. Olsson G, von Knorring L. Beck's Depression Inventory as a screening instrument for adolescent depression in Sweden: gender differences. *Acta Psychiatr Scand*. 1997;95(4):277–82.
66. Steer R, Ball R, Ranieri W, Beck A. Further evidence for the construct validity of the Beck Depression Inventory-II with psychiatric outpatients. *Psychol Rep*. 1997;80(2):443–6.

67. Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, et al. The HCL-32: Towards a self-assessment tool for hypomanic symptoms in outpatients. *J Affect Disord.* 2005;88(2):217–33.
68. Rosenberg M. *Conceiving the Self.* Malabar, FL: Krieger; 1986.
69. Coric V, Stock EG, Pultz J, Marcus R, Sheehan D V. Sheehan Suicidality Tracking Scale (Sheehan-STS): Preliminary Results from a Multicenter Clinical Trial in Generalized Anxiety Disorder. *Psychiatry (Edgmont).* 2009;6(1):26–31.
70. Axelson D a., Birmaher B, Strober M a., Goldstein BI, Ha W, Gill MK, et al. Course of subthreshold bipolar disorder in youth: Diagnostic progression from bipolar disorder not otherwise specified. *J Am Acad Child Adolesc Psychiatry.* 2011;50(10).
71. Kohn R, Saxena S, Levav I, Saraceno B. The Treatment Gap in Mental Health Care. *Bull World Health Organ.* 2002;82:858–66.
72. Burgess PM, Pirkis JE, Slade TN, Johnston AK, Meadows GN, Gunn JM. Service use for mental health problems: findings from the 2007 National Survey of Mental Health and Wellbeing. *Aust N Z J Psychiatry.* 2009;43(7):615–23.
73. Pattyn E, Verhaeghe M, Sercu C, Bracke P. Public stigma and self-stigma: differential association with attitudes toward formal and informal help seeking. *Psychiatr Serv.* 2014;65(2):232–8.

74. Huerta-Ramírez R, Bertsch J, Cabello M, Roca M, Haro JM, Ayuso-Mateos JL. Diagnosis delay in first episodes of major depression: A study of primary care patients in Spain. *J Affect Disord*. 2013;150(3):1247–50.
75. Canadian Institute for Health Information. *Health Care in Canada , 2012 A Focus on Wait Times Our Vision*. 2012;108.
76. Ayuso-Mateos JL, Nuevo R, Verdes E, Naidoo N, Chatterji S. From depressive symptoms to depressive disorders: The relevance of thresholds. *Br J Psychiatry*. 2010;196(5):365–71.
77. Lewinsohn PM, Solomon a, Seeley JR, Zeiss a. Clinical implications of “subthreshold” depressive symptoms. *J Abnorm Psychol*. 2000;109(2):345–51.
78. Karsten J, Hartman CA, Smit JH, Zitman FG, Beekman AT, Cuijpers P, et al. Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. *Br J psychiatry*. 2011 Mar;198(3):206–12.
79. Nurnberger JI. Genetics of bipolar disorder: Where we are and where we are going. *Depress Anxiety*. 2012;29(12):991–3.
80. Duffy A. Toward effective early intervention and prevention strategies for major affective disorders: a review of antecedents and risk factors. *Can J psychiatry*. 2000 May;45(4):340–8.
81. Duffy A. Does bipolar disorder exist in children? A selected review. *Can J psychiatry Revue Can Psychiatr*. 2007 Jul;52(7):409–17.

82. Axelson D a., Birmaher B, Strober M a., Goldstein BI, Ha W, Gill MK, et al. Course of subthreshold bipolar disorder in youth: Diagnostic progression from bipolar disorder not otherwise specified. *J Am Acad Child Adolesc Psychiatry*. 2011;50(10).
83. Tjissen MJ a, Van Os J, Wittchen HU, Lieb R, Beesdo K, Mengelers R, et al. Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. *Br J Psychiatry*. 2010;196(2):102–8.
84. Keown-stoneman C, Horrocks J, Darlington G, Goodday S, Grof P, Duffy A. Multi-state models for investigating possible stages leading to bipolar disorder. *Int J Bipolar Disord*. 2015;3(5):1–8.
85. Damluji N. Paradoxical worsening of depressive symptomatology caused by antidepressants. *J Clin Psychopharmacol*. 8AD;5(347–349).
86. Jick H, Kaye J, Susan S, Jick S. Antidepressants and the Risk of Suicidal Behaviors. *JAMA*. 2004;292(2):338–43.
87. El-Mallakh R, Vöhringer P, Ostacher M, Baldassano C, Holtzman N, Whitham E, et al. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. *J Affect Disord*. 2015;184:318–21.
88. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980–9.

89. Smith SM, Stinson FS, Dawson D a, Goldstein R, Huang B, Grant BF. Race/ethnic differences in the prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychol Med.* 2006;36(7):987–98.
90. Porta M, Greenland S, Hernan M, dos Santos Silva I, Last JM. A dictionary of epidemiology (Sixth edition). Vol. 1. Toronto: Oxford University Press; 2014.
91. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: A naturalistic study. *J Clin Psychiatry.* 2000;61(10):804–8.
92. Craddock N, Skylar P. Genetics of bipolar disorder. *Lancet.* 2013;381:1656–62.
93. Duffy A. The early course of bipolar disorder in youth at familial risk. *J Can Acad Child Adolesc Psychiatry.* 2009;18(3):200–5.
94. Kessler RC, Wang PS. The Descriptive Epidemiology of Commonly Occurring Mental Disorders in the United States. *Annu Rev Public Health [Internet].* 2008;29(1):115–29. Available from: <http://www.annualreviews.org/doi/10.1146/annurev.publhealth.29.020907.090847>
95. Axelson D, Birmaher BJ, Brent D, Wassick S, Hoover C, Bridge J, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. *J Child Adolesc Psychopharmacol.* 2003;13(4):463–70.

96. Hamilton M. The assessment of anxiety states by rating. *British Journal of Medical Psychology*. Br J Med Psychol. 1959;
97. Beck, A. T., Steer, R. A., Ball, R. & Ranieri WF. Comparison of Beck Depression Inventories-I and-II in psychiatric outpatients. *J Pers Assess*. 1996;67(588–597).
98. Wang Y, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Rev Bras Psiquiatr*. 2013;35:416–31.
99. Osman A, Kopper B, Barrios F, Gutierrez P, Bagge C. Reliability and validity of the Beck Depression Inventory-II with adolescent psychiatric inpatients. *Psychol Assess*. 2004;16:120–32.
100. Shean G, Baldwin G. Sensitivity and specificity of depression questionnaires in a college-age sample. *J Genet Psychol*. 2008;169:281–8.
101. Sprinkle S, Lurie D, Insko S, Atkinson G, Jones G, Logan A, et al. Validity, severity cut scores, and test-retest reliability of the Beck Depression Inventory-II in a University counseling center sample. *J Couns Psychol*. 2002;49:381–5.
102. Matza L, Morlock R, Sexton C, Malley K, Feltner D. Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder. *Int J Methods Psychiatr Res*. 2010;19(4):223–32.
103. Wals M, Hillegers M, Reichart C, Ormel J, Nolen W, Verhulst F. Prevalence of psychopathology in children of a bipolar parent. *J Am Acad Child Adolesc Psychiatry*. 2001;40(9):1094–102.

104. Mesman E, Nolen W, Reichart C, Wals M, Hillegers M. The Dutch bipolar offspring study: 12-year follow-up. *Am J Psychiatry*. 2013;170(5):542–9.
105. Hollingshead A. Commentary on the indiscriminate state of social class measurement. *Soc Forces*. 1970;49(563).
106. Cirino P, Chin C, Sevcik R. Measuring socioeconomic status reliability and preliminary validity for different approaches. *Assessment*. 2002;9(2):145–55.
107. Spence SH. A measure of anxiety symptoms among children. *Behav Res Ther*. 1998;36(5):545–66.
108. Walker A. *Observation and inference: an introduction to the methods of epidemiology*. Newton Lower Falls, MA: Epidemiology Resources Inc; 1991.
109. Rothman K, Greenland S. *Modern epidemiology*. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1998.
110. StataCorp. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP; 2013.
111. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev Psychopathol*. 2006;18(4):1023–35.
112. Hafeman DM, Merranko J, Axelson D, Goldstein BI, Goldstein T, Monk K, et al. Toward the definition of a bipolar prodrome: Dimensional predictors of bipolar spectrum disorders in at-risk youths. *Am J Psychiatry*. 2016;173(7):695–704.

113. Suissa S. Immortal time bias in pharmacoepidemiology. *Am J Epidemiol.* 2008;167(4):492–9.



## CHAPTER 4. DISCUSSION

Few studies have examined the association between these clinical symptoms and the development of mood disorders in high-risk offspring with and without antecedent internalizing symptoms. The current study highlighted the clinical importance of clinically significant symptoms during childhood and their impact on subsequent mood episodes later in life. This finding supports the need to identify and address childhood psychopathology so that secondary prevention efforts may take place. Participants in the study became exposed to the primary and secondary indicators, on average, before the age of 11 years. This finding further supports existing literature on childhood affective symptoms and their importance for understanding mood disorder trajectories throughout the lifespan (11,26,41,111,112). Clinically significant symptoms in childhood assessed using the KSADS-PL interview appeared to indicate an increase in the individual's risk of developing a mood episode later in life, particular that of a diagnosable mood episode. As such, it is important to acknowledge childhood events can have lasting effects throughout the lifespan and attempt to reduce the harm of such events whenever possible.

While clinically significant symptoms, as measured by the KSADS-PL interview, were found to be predictor of subsequent mood episodes, the same was not found when compared with the composite symptom rating scale measure. This may be explained by use of cut-off scores for these scales derived from studies of patients and were designed to identify subgroups suitable for pharmacological intervention. As a result, the cut-off scores for these scales may not be appropriate for screening even within a high-risk population. Lastly, the low number of "exposed"

individuals identified as symptom positive by using these cut-off scores may have limited the power to reach statistical significance.

### ***Strengths and Limitations***

The current study used longitudinal data from the largest high-risk offspring cohort in the world. The prospective cohort design allowed for clarification of temporal sequences of events, as well as facilitates the study of rare events and outcomes when they occur. The study design allowed for diagnostic assessment of diagnoses in both parents and offspring, thus allowing for a comprehensive family history background.

The study is well-protected against information/misclassification bias. At the time of intake interviews, the clinician was blinded to participant membership status. While it was true that raters would come to know the risk indicator status of the participant over time, each annual assessment was subjected to blind diagnostic consensus review by an additional clinician who was not aware of the risk indicator status of the participant. At no point were risk indicator or outcome ratings changed retroactively during the course of the study. With the use of blind consensus, any bias can be assumed to be non-differential and in the direction of the null value. This form of bias will not threaten the validity of observed positive results.

The use of a composite measure for the secondary risk indicator allowed for avoidance of issues of multiplicity (potential for Type I error) and permitted for greater interpretability of results within a clinical setting. The applicability within clinical settings increased clinical

interpretability. Specifically, the composite measure could be used to identify an abnormality (in this case, exceeding at least one standardized cut-off score), which may be informative at times when clinical interviews are not possible (e.g. as a screening). While the use of the composite measure was used to increase clinical applicability and power, both self- and clinician-reported symptom rating scales were used. It is possible one of the scales may have been better at predicting subsequent outcomes. The use of cut-off scores, which led to lower numbers of participants who met the cut-off scores, may have reduced the ability of the composite measure and subsequently predict subsequent mood episodes. The cut-off scores of the BDI and HAM-A are typically used to indexing severity of symptoms rather than for predicting future disorders. Another limitation is the recruitment of the comparison group was only conducted in Ontario. While the group can be used to informed additional research to a greater segment of the general population, it should not be used to generalize the findings to multiple Canadian provinces.

There was risk of selection bias, or the selection of individuals not representative of the target population. All participants were selected using the same inclusion/exclusion criteria. However, it is possible individuals who refused to participant or who were not well enough to participate could lead to selection bias. Unfortunately, the study does not contain information on affected parents who declined participation. Limitations on external validity must also be considered as the high-risk participants may be higher-functioning as the sample was recruiting from parents receiving treatment for this illness in specialty clinics. Further, for inclusion into the Flourish database, only one parent had a psychiatric illness while the other parent did not. This recruitment method has the potential to create a study population that may be healthier (both parents are not ill, exclusion of personality disorders, substance-used disorders, etc.) than the

general population.

A limitation to the current study is the potential for recall bias on the part of the participant when providing information during the annual KSADS-PL interview. Given that the annual assessments require participants to report their psychological states over the past year, there is potential for the inability to recall or unwillingness to disclose information during the interviews. Furthermore, recall or reporting bias may also be introduced into the current study through the use of self-report measures. However, given the clinical diagnoses are dependant first and foremost on psychiatric assessment interviews (KSADS-PL), self-report measures provide additional information for clinicians but do not form the basis for diagnoses. Still, this method of measurement is considered the gold standard, and surpasses other methodologies through the use of a best estimate diagnostic approach (supplementing with all available clinical information).

In addition, as with any self-report measure, there is the potential for social desirability bias. Anxiety and depressive symptoms were measured using HAM-A and BDI-II (96,97,107). It is possible participants may have completed the measures in a manner that they felt was viewed favourably by others by minimizing negative behaviours and maximizing positive behaviours.

Survival time (or unmeasured time) bias must also be considered when selecting an exposure-based cohort. This bias refers to a period of time during the study where the outcome could not have occurred (113). A participant could enter the study and become exposed shortly after entry. Without accounting for the time the participant was 'unexposed', the individual would be misclassified as always exposed, thus leading to the immortal time bias. To account for this bias,

we initially coded each participant as unexposed. If a participant became exposed, they were then re-coded as exposed.

### ***Future Directions***

Using a well-characterized high-risk offspring dataset provides a powerful strategy to determine the risk and amount of time between clinically important symptoms and major mood disorders. Results are expected to lead to new insights concerning the natural history of BD, the importance of clinically significant symptoms. This information has the potential to advance early identification of major mood disorders in youth, inform early intervention studies, and influence clinical care decisions. While the symptom-rating scales did not show an association with subsequent mood episodes, it would be interesting to take multiple measures of the scales to examine their stability over time, rather than employing a 'once exposed, always exposed' method for coding the presence/absence of the clinically significant symptoms in the sample.

Future work in this area should continue to highlight the importance of studying high-risk groups to garner further insight and enable subsequent secondary prevention and prediction efforts. By investigating an identifiable at-risk group of individuals at confirmed familial risk, research efforts can employ a more refined focus for studying mood disorders. With limited healthcare resources, this focused approach could facilitate targeted resource allocation and utilization by individuals that may need it most. Additional work focusing on the natural history of mood disorders and the trajectory of these disorders throughout the lifespan is paramount.

With greater understanding of these phenomena, secondary prevention and prediction efforts can be implemented. These efforts could also encourage collaboration between clinical science and population health and health services. By supporting existing continuing care models, this project and future endeavors can provide a unique opportunity to improve understanding of clinically significant symptoms and the long-term implications these conditions have on individuals living in Nova Scotia. Additional follow up of this cohort over a longer length of time will allow for greater insight into the influences of clinically significant symptoms on future psychopathology in high-risk groups. Continued follow up would also increase participation numbers and the associations found in this study may prove to be more information with greater power. Understanding the pathway from clinically significant symptoms to development of subsequent mood episodes can help inform clinical care guidelines and improve overall patient quality of life.

## REFERENCES

1. Schaffer A, Cairney J, Cheung A, Veldhuizen S, Levitt A. Community Survey of Bipolar Disorder in Canada: Lifetime Prevalence and Illness Characteristics. [Enquête dans la collectivité sur le trouble bipolaire au Canada: Prévalence à vie et caractéristiques de la maladie.]. *Can J Psychiatry / La Rev Can Psychiatr.* 2006;51(1):9–16.
2. Fagiolini A, Forgiione R, Maccari M, Cuomo A, Morana B, Dell’Osso MC, et al. Prevalence, chronicity, burden and borders of bipolar disorder. *J Affect Disord.* 2013;148(2–3):161–9.
3. Müller-Oerlinghausen B, Felber W, Berghöfer A, Lauterbach E, Ahrens B. The impact of lithium long-term medication on suicidal behavior and mortality of bipolar patients. *Arch Suicide Res.* 2005;9(3):307–19.
4. Kessing L, Vradi E, Andersen P. Life Expectancy in bipolar disorder. *Bipolar Disord.* 2015;17:543–8.
5. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry.* 2003 Mar;60(3):261–9.
6. Craddock N, Sklar P. Bipolar Disorder 1 - Genetics of bipolar disorder. *Lancet* [Internet]. 2013;381(9878):1654–62. Available from: [http://dx.doi.org/10.1016/S0140-6736\(13\)60855-7](http://dx.doi.org/10.1016/S0140-6736(13)60855-7)

7. Association AP. Diagnostic and statistical manual of mental disorders (5th ed.).  
Arlington: American Psychiatric Pub Inc; 2013.
8. Juli G, Juli MR, Juli L. Involvement of genetic factors in bipolar disorders: Current  
status. *Psychiatr Danub*. 2012;24(SUPPL. 1):112–6.
9. Tijssen MJ, Van Os J, Wittchen HU, Lieb R, Beesdo K, Wichers M. Risk factors predicting  
onset and persistence of subthreshold expression of bipolar psychopathology among  
youth from the community. *Acta Psychiatr Scand*. 2010 Sep;122(3):255–66.
10. Shaw J a, Egeland J a, Endicott J, Allen CR, Hostetter AM. A 10-year prospective study  
of prodromal patterns for bipolar disorder among Amish youth. *J Am Acad Child  
Adolesc Psychiatry*. 2005;44(11):1104–11.
11. Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar  
disorder. *J Affect Disord*. 2010;121(1–2):127–35.
12. Lim, K., Jacobs, P., Ohinmaa, A., Schopflocher, D., & Dewa CS. A new popula–tion based  
measure of the economic burden of mental illness in Canada. *Chronic Dis Can*.  
2008;28(3):92–8.
13. Whiteford H a., Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global  
burden of disease attributable to mental and substance use disorders: Findings from  
the Global Burden of Disease Study 2010. *Lancet*. 2013;382(9904):1575–86.



14. Dewa CS, Chau N, Dermer S. Examining the comparative incidence and costs of physical and mental health-related disabilities in an employed population. *J Occup Environ Med.* 2010;52(7):758–62.
15. Marwaha S, Johnson S. Schizophrenia and employment: A review. *Soc Psychiatry Psychiatr Epidemiol.* 2004;39(5):337–49.
16. Lewinsohn P, Duncan E, Stanton A, Hautzinger M. Age at first onset for nonbipolar depression. *J Abnorm Psychol.* 1986;95:378–83.
17. Lewinsohn P, Moerk K, Klein D. Epidemiology of adolescent depression. *Econ Neurosci.* 2000;2:52–68.
18. Statistics Canada. Canadian Community Health Survey 2009. 2009.
19. Bittner A, Goodwin R, Wittchen H, Beesdo K, Höfler M, Lieb R. What Characteristics of Primary Anxiety Disorders Predict Subsequent Major Depressive Disorder? *J Clin Psychiatry.* 2004;65(5):618–26.
20. Bittner A, Egger H, Erkanli A, Costello E, Foley D, Angold A. What do childhood anxiety disorders predict? (2007). Antje Bittner, Helen L. Egger, Alaattin Erkanli, E. Jane Costello, Debra L. Foley, Adrian Angold. *Journal of Child Psychology and Psychiatry;* 48(12), 1174-1183. *J Child Psychol Psychiatry.* 2007;48(12):1174–83.
21. Sareen S, Cox B, Afifi T, de Graaf R, Asmundson G, ten Have M, et al. Anxiety Disorders and Risk for Suicidal Ideation and Suicide Attempts A Population-Based Longitudinal Study of Adults (2005). *Arch Gen Psychiatry.* 2005;62:1249–57.

22. Simon N, Zalta A, Otto M, Ostacher M, Fischmann D, Chow C, et al. The association of comorbid anxiety disorders with suicide attempts and suicidal ideation in outpatients with bipolar disorder. *J Psychiatr Res.* 2007;41(3–4):255–64.
23. Pearson C, Janz T, Ali J. Mental and substance use disorders in Canada. *Stat Canada Cat no 82-624-X.* 2013;
24. Duffy A, Grof P, Robertson C, Alda M. The implications of genetics studies of major mood disorders for clinical practice. *J Clin Psychiatry.* 2000;61(9):630–7.
25. Duffy A. The early natural history of bipolar disorder: what we have learned from longitudinal high-risk research. *Can J psychiatry.* 2010;55(8):477–85.
26. Duffy A. Early identification of recurrent mood disorders in youth: the importance of a developmental approach. *Evid Based Ment Health.* 2015;18(1):7–9.
27. Duffy A, Horrocks J, Doucette S, Keown-Stoneman C, McCloskey S, Grof P. The developmental trajectory of bipolar disorder. *Br J Psychiatry.* 2014;204(2):122–8.
28. Scott K, de Jonge P, Alonso J, Viana M, Liu Z, O’Neill S, et al. Associations between DSM-IV mental disorders and subsequent heart disease onset: beyond depression. *Int J Cardiol.* 2014;168(6):1–16.
29. Williams MM, Clouse RE, Lustman PJ. Treating Depression to Prevent Diabetes. 2006;24(2):79–86.

30. Richardson L, Davis R, Poulton R, McCauley E, Moffitt T, Caspi A, et al. A longitudinal evaluation of adolescent depression and adult obesity. *Arch Pediatr Adolesc Med*. 2003;157(8):739–45.
31. Goodman E, Whitaker R. A prospective study of the role of depression in the development and persistence of adolescent obesity. *Pediatrics*. 2002;110:498–504.
32. Kilbourne A, Cornelius J, Han X, Pincus H, Shad M, Salloum I, et al. Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord*. 2004;6:368–73.
33. McIntyre R, Konarski J, Yatham L. Comorbidity in bipolar disorder: a framework for rational treatment selection. *Hum Psychopharmacol*. 2004;19:369–86.
34. Oswald P, Souery D, Kasper S, Lecrubier Y, Montgomery S, Wyckaert S, et al. Current issues in bipolar disorder: a critical review. *Eur Neuropsychopharmacol*. 2007;17(687–695).
35. Centorrino F, Mark T, Talamo A, Oh K, Chang J. Health and economic burden of metabolic comorbidity among individuals with bipolar disorder. *J Clin Psychopharmacol*. 2009;29:595–600.
36. Holma KM, Melartin TK, Holma I a K, Paunio T, Isometsä ET. Family history of psychiatric disorders and the outcome of psychiatric patients with DSM-IV major depressive disorder. *J Affect Disord [Internet]*. 2011;131(1–3):251–9. Available from: <http://dx.doi.org/10.1016/j.jad.2010.12.016>

37. Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*. 2006;63(10):1139–48.
38. Parker G, McCraw S, Hadzi-Pavlovic D, Fletcher K. Costs of the principal mood disorders: A study of comparative direct and indirect costs incurred by those with bipolar I, bipolar II and unipolar disorders. *J Affect Disord* [Internet]. 2013;149(1–3):46–55. Available from: <http://dx.doi.org/10.1016/j.jad.2012.10.002>
39. Ferrari AJ, Norman RE, Freedman G, Baxter AJ, Pirkis JE, Harris MG, et al. The burden attributable to mental and substance use disorders as risk factors for suicide: Findings from the Global Burden of Disease Study 2010. *PLoS One*. 2014;9(4).
40. Latham L. *Mental Health in Atlantic Canada : A Snapshot*. 2012.
41. Duffy A, Alda M, Hajek T, Grof P. Early course of bipolar disorder in high-risk offspring: Prospective study. *Br J Psychiatry*. 2009;195(5):457–8.
42. Pan SY, Desmeules M, Morrison H, Semenciw R, Ugnat AM, Thompson W, et al. Adolescent Injury Deaths and Hospitalization in Canada: Magnitude and Temporal Trends (1979-2003). *J Adolesc Heal*. 2007;41(1):84–92.
43. Bertolote J, Fleischmann A. Suicide and psychiatric diagnosis: a worldwide perspective. *World Psychiatry*. 2012;13(3):181–5.
44. Shaffer D, Gould M, Fisher P, Trautman P, Moreau D, Kleinman M, et al. Psychiatric Diagnosis in Child and Adolescent Suicide. *Arch Gen Psychiatry*. 1996;53(4):339–48.

45. Luppá M, Heinrich S, Angermeyer MC, König H-H, Riedel-Heller SG. Cost-of-illness studies of depression: a systematic review. *J Affect Disord.* 2007;98(1–2):29–43.
46. Smoller J, Finn C. Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet.* 2003;123C:48–58.
47. Gottesman I, Laursen T, Bertelsen A, Mortensen P. Severe mental disorders in offspring with 2 psychiatrically ill parents. *Arch Gen Psychiatry.* 2010;67:252–7.
48. Douglas J, Scott J. A systematic review of gender-specific rates of unipolar and bipolar disorders in community studies of pre-pubertal children. *Bipolar Disord.* 2014;16(1):5–15.
49. Duffy A, Doucette S, Lewitzka U, Alda M, Hajek T, Grof P. Findings from bipolar offspring studies: Methodology matters. *Early Interv Psychiatry.* 2011;5(3):181–91.
50. Scott J. Bipolar disorder: From early identification to personalized treatment. *Early Interv Psychiatry.* 2011;5(2):89–90.
51. Martino DJ, Marengo E, Igoa A, Scapola M, Ais ED, Perinot L, et al. Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. *J Affect Disord.* 2009 Jul;116(1–2):37–42.
52. Van Meter A, Moreira A, Youngstrom E. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *J Clin Psychiatry.* 2011;72(9):1250–6.

53. Bellivier F, Etain B, Malafosse A, Henry C, Kahn J-P, Elgrabli-Wajsbrodt O, et al. Age at onset in bipolar I affective disorder in the USA and Europe. *World J Biol Psychiatry*. 2011;2975(September 2015):1–8.
54. Laitinen-Krispijn S, Jan van der E, Verhulst FC. The role of pubertal progress in the development of depression in early adolescence. *J Affect Disord*. 1999;54(1–2):211–5.
55. Angst J. The Course of Affective Disorders II: Typology of Bipolar-Manic Depressive Illness. *Arch Psychiatry Neurol Sci*. 1978;226:65073.
56. Roy-Byrne P, Post RM, Uhde TW, Porcu T, Davis D. The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. *Acta Psychiatr Scand Suppl*. 1985;317(317):1–34.
57. Cuijpers P, Beekman A, Smit F, Deeg D. Predicting the onset of major depressive disorder and dysthymia in older adults with subthreshold depression: A community based study. *Int J Geriatr Psychiatry*. 2006;21(9):811–8.
58. Ibrahim AK, Kelly SJ, Glazebrook C. Socioeconomic status and the risk of depression among UK higher education students. *Soc Psychiatry Psychiatr Epidemiol*. 2013;48(9):1491–501.
59. Raposa EB, Hammen CL, Brennan P a, O’Callaghan F, Najman JM. Early adversity and health outcomes in young adulthood: the role of ongoing stress. *Health Psychol* [Internet]. 2014;33(5):410–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23730716>

60. Aas M, Henry C, Andreassen OA, Bellivier F, Melle I, Etain B. The role of childhood trauma in bipolar disorders. *Int J bipolar Disord* [Internet]. 2016;4(1):2. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4712184&tool=pmcentrez&rendertype=abstract>
61. Bifuico A, Brown W, Adler Z. Early sexual abuse and clinical depression in adult life. *Br J Psychiatry*. 1991;159:115–222.
62. Goodyer I, Altham P. Lifetime exit events and recent social and family adversities in anxious and depressed school-age children and adolescents - I. *J Affect Disord*. 1991;21:219–28.
63. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC; 2000.
64. Kent L, Vostanis P, Feehan C. Detection of Major and Minor Depression in Children and Adolescents: Evaluation of the Moods and Feelings Questionnaire. *J Child Psychol Psychiatry Allied Discip*. 1997;38(5):565–73.
65. Olsson G, von Knorring a L. Beck's Depression Inventory as a screening instrument for adolescent depression in Sweden: gender differences. *Acta Psychiatr Scand*. 1997;95(4):277–82.
66. Steer R, Ball R, Ranieri W, Beck A. Further evidence for the construct validity of the Beck Depression Inventory-II with psychiatric outpatients. *Psychol Rep*. 1997;80(2):443–6.

67. Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, et al. The HCL-32: Towards a self-assessment tool for hypomanic symptoms in outpatients. *J Affect Disord.* 2005;88(2):217–33.
68. Rosenberg M. *Conceiving the Self.* Malabar, FL: Krieger; 1986.
69. Coric V, Stock EG, Pultz J, Marcus R, Sheehan D V. Sheehan Suicidality Tracking Scale (Sheehan-STSS): Preliminary Results from a Multicenter Clinical Trial in Generalized Anxiety Disorder. *Psychiatry (Edgmont).* 2009;6(1):26–31.
70. Axelson D a., Birmaher B, Strober M a., Goldstein BI, Ha W, Gill MK, et al. Course of subthreshold bipolar disorder in youth: Diagnostic progression from bipolar disorder not otherwise specified. *J Am Acad Child Adolesc Psychiatry.* 2011;50(10).
71. Kohn R, Saxena S, Levav I, Saraceno B. The Treatment Gap in Mental Health Care. *Bull World Health Organ.* 2002;82:858–66.
72. Burgess PM, Pirkis JE, Slade TN, Johnston AK, Meadows GN, Gunn JM. Service use for mental health problems: findings from the 2007 National Survey of Mental Health and Wellbeing. *Aust N Z J Psychiatry.* 2009;43(7):615–23.
73. Pattyn E, Verhaeghe M, Sercu C, Bracke P. Public stigma and self-stigma: differential association with attitudes toward formal and informal help seeking. *Psychiatr Serv.* 2014;65(2):232–8.



74. Huerta-Ramírez R, Bertsch J, Cabello M, Roca M, Haro JM, Ayuso-Mateos JL. Diagnosis delay in first episodes of major depression: A study of primary care patients in Spain. *J Affect Disord.* 2013;150(3):1247–50.
75. Canadian Institute for Health Information. Health Care in Canada , 2012 A Focus on Wait Times Our Vision. 2012;108.
76. Ayuso-Mateos JL, Nuevo R, Verdes E, Naidoo N, Chatterji S. From depressive symptoms to depressive disorders: The relevance of thresholds. *Br J Psychiatry.* 2010;196(5):365–71.
77. Lewinsohn PM, Solomon a, Seeley JR, Zeiss a. Clinical implications of “subthreshold” depressive symptoms. *J Abnorm Psychol.* 2000;109(2):345–51.
78. Karsten J, Hartman CA, Smit JH, Zitman FG, Beekman AT, Cuijpers P, et al. Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. *Br J psychiatry.* 2011 Mar;198(3):206–12.
79. Nurnberger JI. Genetics of bipolar disorder: Where we are and where we are going. *Depress Anxiety.* 2012;29(12):991–3.
80. Duffy A. Toward effective early intervention and prevention strategies for major affective disorders: a review of antecedents and risk factors. *Can J psychiatry.* 2000 May;45(4):340–8.
81. Duffy A. Does bipolar disorder exist in children? A selected review. *Can J psychiatryRevue Can Psychiatr.* 2007 Jul;52(7):409–17.

82. Axelson D a., Birmaher B, Strober M a., Goldstein BI, Ha W, Gill MK, et al. Course of subthreshold bipolar disorder in youth: Diagnostic progression from bipolar disorder not otherwise specified. *J Am Acad Child Adolesc Psychiatry*. 2011;50(10).
83. Tijssen MJ a, Van Os J, Wittchen HU, Lieb R, Beesdo K, Mengelers R, et al. Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. *Br J Psychiatry*. 2010;196(2):102–8.
84. Keown-stoneman C, Horrocks J, Darlington G, Goodday S, Grof P, Duffy A. Multi-state models for investigating possible stages leading to bipolar disorder. *Int J Bipolar Disord*. 2015;3(5):1–8.
85. Damluji N. Paradoxical worsening of depressive symptomatology caused by antidepressants. *J Clin Psychopharmacol*. 8AD;5(347–349).
86. Jick H, Kaye J, Susan S, Jick S. Antidepressants and the Risk of Suicidal Behaviors. *JAMA*. 2004;292(2):338–43.
87. El-Mallakh R, Vöhringer P, Ostacher M, Baldassano C, Holtzman N, Whitham E, et al. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. *J Affect Disord*. 2015;184:318–21.
88. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980–9.

89. Smith SM, Stinson FS, Dawson D a, Goldstein R, Huang B, Grant BF. Race/ethnic differences in the prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychol Med.* 2006;36(7):987–98.
90. Porta M, Greenland S, Hernan M, dos Santos Silva I, Last JM. *A dictionary of epidemiology (Sixth edition). Vol. 1.* Toronto: Oxford University Press; 2014.
91. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: A naturalistic study. *J Clin Psychiatry.* 2000;61(10):804–8.
92. Craddock N, Skylar P. Genetics of bipolar disorder. *Lancet.* 2013;381:1656–62.
93. Duffy A. The early course of bipolar disorder in youth at familial risk. *J Can Acad Child Adolesc Psychiatry.* 2009;18(3):200–5.
94. Kessler RC, Wang PS. The Descriptive Epidemiology of Commonly Occurring Mental Disorders in the United States. *Annu Rev Public Health [Internet].* 2008;29(1):115–29. Available from:  
<http://www.annualreviews.org/doi/10.1146/annurev.publhealth.29.020907.090847>
95. Axelson D, Birmaher BJ, Brent D, Wassick S, Hoover C, Bridge J, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. *J Child Adolesc Psychopharmacol.* 2003;13(4):463–70.

96. Hamilton M. The assessment of anxiety states by rating. *British Journal of Medical Psychology*. *Br J Med Psychol*. 1959;
97. Beck, A. T., Steer, R. A., Ball, R. & Ranieri WF. Comparison of Beck Depression Inventories-I and-II in psychiatric outpatients. *J Pers Assess*. 1996;67(588–597).
98. Wang Y, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Rev Bras Psiquiatr*. 2013;35:416–31.
99. Osman A, Kopper B, Barrios F, Gutierrez P, Bagge C. Reliability and validity of the Beck Depression Inventory-II with adolescent psychiatric inpatients. *Psychol Assess*. 2004;16:120–32.
100. Shean G, Baldwin G. Sensitivity and specificity of depression questionnaires in a college-age sample. *J Genet Psychol*. 2008;169:281–8.
101. Sprinkle S, Lurie D, Insko S, Atkinson G, Jones G, Logan A, et al. Validity, severity cut scores, and test-retest reliability of the Beck Depression Inventory-II in a University counseling center sample. *J Couns Psychol*. 2002;49:381–5.
102. Matza L, Morlock R, Sexton C, Malley K, Feltner D. Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder. *Int J Methods Psychiatr Res*. 2010;19(4):223–32.
103. Wals M, Hillegers M, Reichart C, Ormel J, Nolen W, Verhulst F. Prevalence of psychopathology in children of a bipolar parent. *J Am Acad Child Adolesc Psychiatry*. 2001;40(9):1094–102.

104. Mesman E, Nolen W, Reichart C, Wals M, Hillegers M. The Dutch bipolar offspring study: 12-year follow-up. *Am J Psychiatry*. 2013;170(5):542–9.
105. Hollingshead A. Commentary on the indiscriminate state of social class measurement. *Soc Forces*. 1970;49(563).
106. Cirino P, Chin C, Sevcik R. Measuring socioeconomic status reliability and preliminary validity for different approaches. *Assessment*. 2002;9(2):145–55.
107. Spence SH. A measure of anxiety symptoms among children. *Behav Res Ther*. 1998;36(5):545–66.
108. Walker A. *Observation and inference: an introduction to the methods of epidemiology*. Newton Lower Falls, MA: Epidemiology Resources Inc; 1991.
109. Rothman K, Greenland S. *Modern epidemiology*. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1998.
110. StataCorp. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP; 2013.
111. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev Psychopathol*. 2006;18(4):1023–35.
112. Hafeman DM, Merranko J, Axelson D, Goldstein BI, Goldstein T, Monk K, et al. Toward the definition of a bipolar prodrome: Dimensional predictors of bipolar spectrum disorders in at-risk youths. *Am J Psychiatry*. 2016;173(7):695–704.

113. Suissa S. Immortal time bias in pharmacoepidemiology. *Am J Epidemiol.* 2008;167(4):492–9.

## APPENDIX A: DSM-IV-DIAGNOSTIC CRITERIA

### Major Depression (MD)

A. Five (or more) of the following symptoms have been present during the same 2- week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

### Manic Episode<sup>2</sup>

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

- Inflated self-esteem or grandiosity
- decreased need for sleep (e.g., feels rested after only 3 hours of sleep)

- 
- More talkative than usual or pressure to keep talking
  - Flight of ideas or subjective experience that thoughts are racing
  - Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
  - Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
  - Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- C. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
- D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism). Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.
- 

<sup>1</sup>Adapted from the DSM-IV-TR (American Psychiatric Association, 2000).

<sup>2</sup> DSM-IV-TR MD criteria in conjunction with at least one DSM-IV-TR criteria manic episode is required for the diagnosis of BD.



## APPENDIX B: DESCRIPTIVE CHARACTERISTICS OF COHORT

**TABLE 1.** Descriptive characteristics of high-risk offspring and comparison groups from Ontario and the Maritimes from 1996 to 2014 (N=286).

	High-risk offspring (n=214)		Comparison group (n=72)		Total N = 286		P value
	n	%	n	%	n	%	
<b>Sex</b>							
Male	87	40.7	34	47.2	121	42.3	0.076 <sup>2</sup>
Female	127	59.3	38	52.8	165	57.7	
<b>Region</b>							
Maritimes	55	25.7	0	0.0	55	19.2	0.001 <sup>2</sup>
Ontario	159	74.3	72	100.0	231	80.8	
<b>Socioeconomic status<sup>1</sup></b>							
1 (low)	0	0.0	0	0.0	0	0.0	0.001 <sup>2</sup>
2	6	2.8	2	2.8	8	2.8	
3	24	11.2	1	1.4	25	8.7	
4	71	33.2	24	33.3	95	33.2	
5 (high)	113	52.8	45	62.5	158	55.3	
	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	<b>P value</b>
<b>Age at enrollment (years)</b>	15.8	6.2	14.2	2.3	15.4	5.6	0.001 <sup>3</sup>
<b>Study participation duration (years)</b>	8.1	4.9	5.7	3.1	7.5	4.7	0.001 <sup>3</sup>
<b>Person-Years contributed</b>	2308.1	1409.6	1616.7	882.7	2134.0	1330.2	0.001 <sup>3</sup>

<sup>1</sup> Hollingshead socioeconomic (SES) scale.

<sup>2</sup> Chi square test.

<sup>3</sup> Students t-test.

## APPENDIX C: PRESENTATION OF EXPOSURE TO RISK INDICATORS

**TABLE 2.** Presentation of exposure to risk indicators in high-risk offspring and comparison groups from Ontario and the Maritimes from 1996 to 2014.

	High Risk Offspring (n=214)		Comparison group (n=72)		P-value
	n	%	n	%	
Presence of exposure to KSADS-PL (primary) risk indicator <sup>1</sup>	45	21.0	5	6.9	0.006 <sup>3</sup>
	Mean	SD	Mean	SD	P-value
Age at exposure to KSADS-PL risk indicator (years) <sup>1</sup>	10.3	3.3	14.8	1.3	0.281 <sup>4</sup>
	High Risk Offspring (n=214)		Comparison group (n=72)		P-value
	n	%	n	%	
Presence of exposure to SRS (secondary) risk indicator <sup>2</sup>	20	9.4	11	15.3	0.359 <sup>3</sup>
	Mean	SD	Mean	SD	P-value
Age at exposure to SRS risk indicator (years) <sup>2</sup>	10.7	3.2	14.2	1.4	0.999 <sup>4</sup>

<sup>1</sup> KSADS-PL= Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (primary risk indicator);

<sup>2</sup> SRS=symptom-rating scales (secondary risk indicator). Only 262 participants were exposed to the secondary risk indicator prior to the age of 15.

<sup>3</sup> Chi square test.

<sup>4</sup> Students t-test.

## APPENDIX D: PRESENTATION OF OUTCOMES

**TABLE 3.** Presentation of outcomes in high-risk offspring and comparison groups from Ontario and the Maritimes from 1996 to 2014.

	High Risk Offspring (n=214)		Comparison group (n=72)		P-value
	n	%	n	%	
Presence of major mood episodes (primary) outcome <sup>1</sup>	87	40.7	3	4.2	0.001 <sup>3</sup>
	Mean	SD	Mean	SD	P-value
Age at major mood episode onset (years) <sup>1</sup>	17.9	4.3	19.6	1.0	0.758 <sup>4</sup>
	High Risk Offspring (n=214)		Comparison group (n=72)		P-value
	n	%	n	%	
Presence of any diagnosable mood episodes (secondary) outcome <sup>2</sup>	104	48.6	4	5.6	0.001 <sup>3</sup>
	Mean	SD	Mean	SD	P-value
Age at any diagnosable mood episode onset (years) <sup>2</sup>	17.2	4.6	17.4	2.5	0.374 <sup>4</sup>

<sup>1</sup> Major mood episode = hypomania, mania, or major depression.

<sup>2</sup> Diagnosable mood episode = hypomania, mania, major depression, depression NOS, bipolar disorder NOS, cyclothymia, or dysthymia.

<sup>3</sup> Chi square test.

<sup>4</sup> Students t-test.

## APPENDIX E: MAJOR MOOD EPISODES IN COHORT

**TABLE 4.** Major mood episodes in high-risk offspring and comparison groups from Ontario and the Maritimes from 1996 to 2014 (N=286).

	KSADS-PL Exposed <sup>1</sup> (n = 50)		KSADS-PL Unexposed <sup>1</sup> (n = 236)		P-value
	n	%	n	%	
Presence of major mood episode	19	38.0	71	30.1	0.274 <sup>3</sup>
	Mean	SD	Mean	SD	P-value
Age at major mood episode diagnosis (years)	17.2	3.2	18.1	4.5	0.190 <sup>4</sup>
	SRS Exposed <sup>2</sup> (n = 21)		SRS Unexposed <sup>2</sup> (n = 241)		P-value
	n	%	n	%	
Presence of major mood episode	7	33.3	59	24.5	0.664 <sup>4</sup>
	Mean	SD	Mean	SD	P-value
Age at major mood episode diagnosis (years)	14.5	5.6	18.5	4.5	0.013 <sup>4</sup>

KSADS-PL= Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (primary risk indicator); SRS=symptom-rating scales (secondary risk indicator).

<sup>1</sup> Exposed = exposure to primary risk indicator; Unexposed = absence of exposure to primary risk indicator.

<sup>2</sup> Exposed = exposure to secondary risk indicator; Unexposed = absence of exposure to secondary risk indicator.

Only 262 participants were exposed to the secondary risk indicator prior to the age of 15.

<sup>3</sup> Chi square test.

<sup>4</sup> Students t-test.

## APPENDIX F: DIAGNOSABLE MOOD EPISODES IN COHORT

**TABLE 5.** Diagnosable mood episodes in high-risk offspring and comparison groups from Ontario and the Maritimes from 1996 to 2014 (N=286).

	KSADS-PL Exposed <sup>1</sup> (n = 50)		KSADS-PL Unexposed <sup>1</sup> (n = 236)		<i>P</i> -value
	n	%	n	%	
<b>Presence of diagnosable mood episode</b>	21	42.0	87	36.9	0.496 <sup>3</sup>
	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	<b><i>P</i>-value</b>
<b>Age at diagnosable mood diagnosis (years)</b>	16.6	3.7	17.3	4.7	0.254 <sup>4</sup>
	SRS Exposed <sup>2</sup> (n = 21)		SRS Unexposed <sup>2</sup> (n = 241)		<i>P</i> -value
	n	%	n	%	
<b>Presence of diagnosable mood episode</b>	9	42.9	73	30.3	0.703 <sup>3</sup>
	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	<b><i>P</i>-value</b>
<b>Age at diagnosable mood diagnosis (years)</b>	15.0	6.2	17.8	4.8	0.055 <sup>4</sup>

KSADS-PL= Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (primary risk indicator); SRS=symptom-rating scales (secondary risk indicator).

<sup>1</sup> Exposed = exposure to primary risk indicator; Unexposed = absence of exposure to primary risk indicator.

<sup>2</sup> Exposed = exposure to secondary risk indicator; Unexposed = absence of exposure to secondary risk indicator.

<sup>3</sup> Chi square test.

<sup>4</sup> Students t-test.

## APPENDIX G: EXPOSURE TO CLINICALLY SIGNIFICANT SYMPTOMS AND SUBSEQUENT HAZARD OF MOOD EPISODE OUTCOMES IN COHORT

**TABLE 6.** Exposure to clinically significant symptoms and subsequent hazard of mood episode outcomes in high-risk offspring and comparison groups from Ontario and the Maritimes from 1996 to 2014 (N=286).

Outcome	Risk Indicator	Unadjusted		Adjusted <sup>1</sup>	
		Hazard Ratio	95% CI	Hazard Ratio	95% CI
<b>Primary</b>					
Major mood episode <sup>2</sup>	KSADS-PL interview <sup>4</sup>	<b>2.2*</b>	1.2-3.9	<b>2.0*</b>	1.1-3.7
	Symptom rating scales <sup>5</sup>	1.3	0.4-4.4	1.2	0.3-4.6
Diagnosable mood episode <sup>3</sup>	KSADS-PL interview <sup>4</sup>	<b>2.1*</b>	1.2-3.7	<b>1.9*</b>	1.1-3.4
	Symptom rating scales <sup>5</sup>	2.0	0.8-5.2	1.6	0.5-4.9

<sup>1</sup> Adjusted for sex, SES, and age at enrollment.

<sup>2</sup> Major mood episode = hypomania, mania, or major depression.

<sup>3</sup> Diagnosable mood episode = hypomania, mania, major depression, depression NOS, bipolar disorder NOS, cyclothymia, or dysthymia.

<sup>4</sup> Kiddie Schedule for Affective Disorders and Schizophrenia (Present and Lifetime version).

<sup>5</sup> Composite measure of the Hamilton Anxiety Rating Scale and the Beck Depression Inventory Version II (BDI-II).

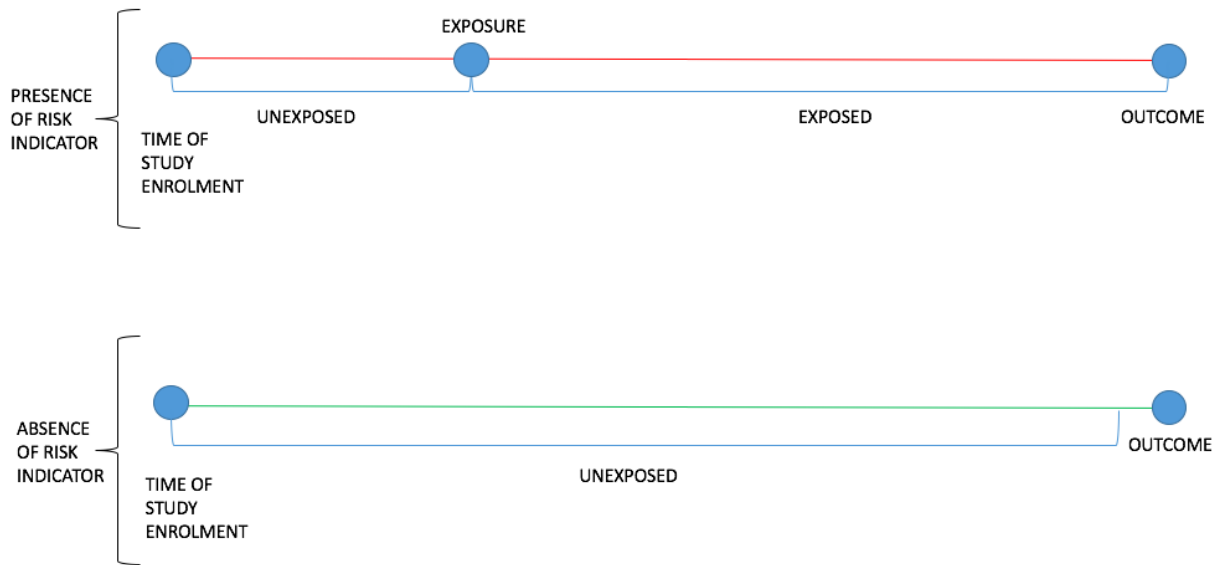
\*Significant at p<0.05.

Note: To test the assumption of proportional hazards, the model was repeated with interaction terms between the predictors and time (in years). This model was compared to the original model using likelihood ratio (LR) tests. Significant differences were not found between the two models (p>0.05).

Note: High-risk offspring and comparison groups were combined and adjusted for in the final model.

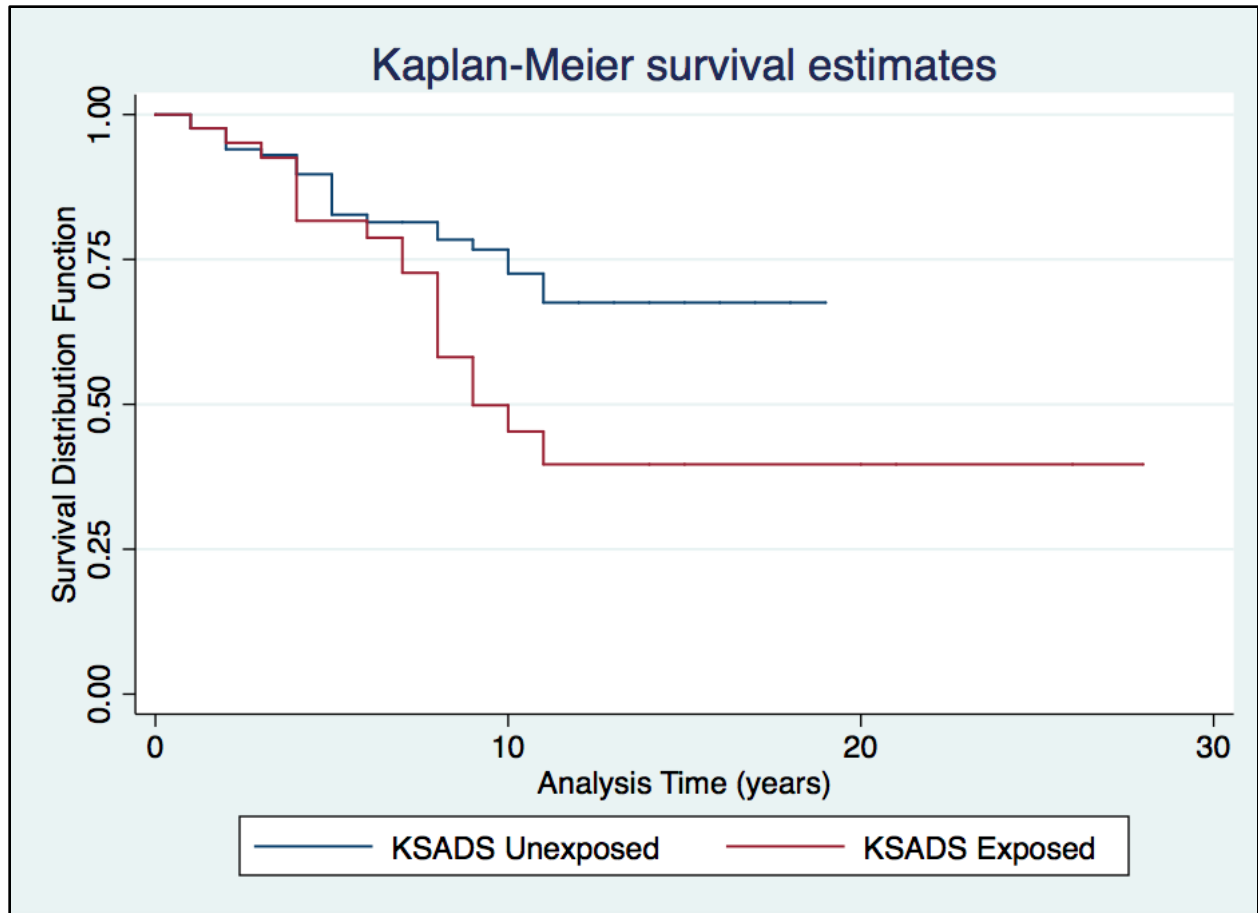
## APPENDIX H: DEPICTION OF CODING AT TIME OF ENROLLMENT

**Figure 1.** Depiction of exposed versus unexposed coding of participants at time of enrollment.



## APPENDIX I: TIME FROM PRIMARY RISK INDICATOR EXPOSURE TO MAJOR MOOD EPISODE

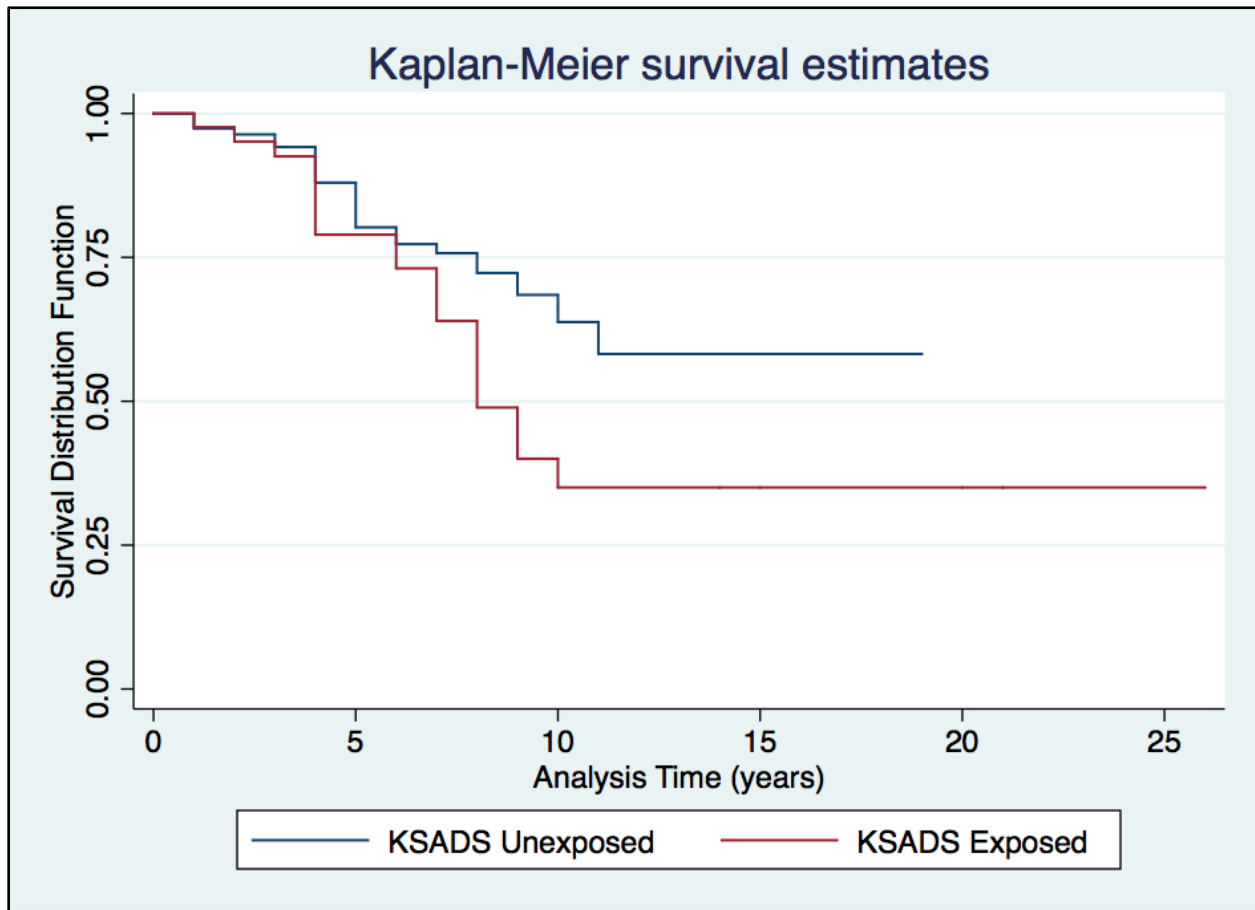
**Figure 2:** Time between primary risk indicator exposure to major mood episode in high-risk offspring and comparison groups from Ontario and the Maritimes from 1996 to 2014 (N=286).





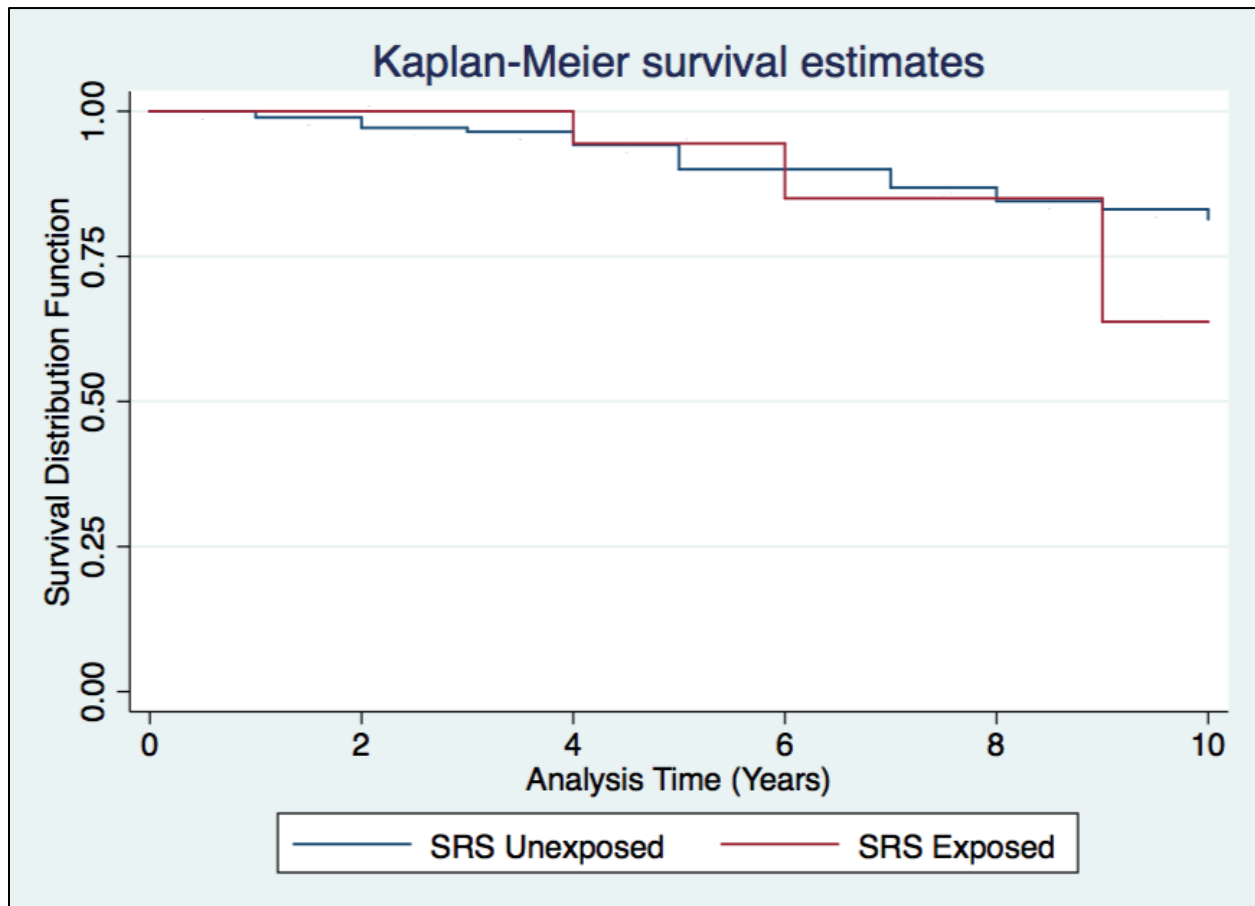
## APPENDIX J: TIME FROM PRIMARY RISK INDICATOR EXPOSURE TO DIAGNOSABLE MOOD EPISODE

**Figure 3:** Time between primary risk indicator exposure to diagnosable mood episode in high-risk offspring and comparison groups from Ontario and the Maritimes from 1996 to 2014 (N=286).



## APPENDIX K: TIME FROM SECONDARY RISK INDICATOR EXPOSURE TO MAJOR MOOD EPISODE

**Figure 4:** Time between secondary risk indicator exposure to major mood episode in high-risk offspring and comparison groups from Ontario and the Maritimes from 1996 to 2014 (N=286).



## APPENDIX L: TIME FROM SECONDARY RISK INDICATOR TO DIAGNOSABLE MOOD EPISODE

**Figure 5:** Time between secondary risk indicator exposure to diagnosable mood episode in high-risk offspring and comparison groups from Ontario and the Maritimes from 1996 to 2014 (N=286).

