YOUTH SUICIDE-RELATED THOUGHTS AND ATTEMPTS IN CANADA: EXPLAINING THE ROLE OF CHILDHOOD EXPOSURE TO MATERNAL DEPRESSION

by

Sarah Margaret Goodday

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Department of Public Health Sciences
University of Toronto

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Sarah Margaret Goodday
Doctor of Philosophy
Department of Public Health Sciences
Dalla Lana School of Public Health
University of Toronto
2018

Abstract

Objectives: Objectives of this thesis were to: 1) determine the cumulative incidence of suicide-related thoughts (SRT) and attempts (SA) in Canadian youth and young adults; 2) estimate the association between exposure to maternal depressive symptoms during the first decade of life and subsequent SRT and SA; and 3) identify possible moderators (sex, family structure, maternal social support and social cohesion) and mediators (child psychiatric symptoms) of this association in Canadian youth and young adults.

Methods: A cohort was constructed by linking all cycles from the National Longitudinal Survey of Children and Youth, a nationally representative survey, from 1994-2009 in respondents 0-25 years. Exposure to maternal-reported depressive symptoms and moderators were measured when offspring were between 0-10 years, while mediators were measured when offspring were between 6-10 years. Offspring self-reported incident and recurrent SRT and SA were measured between 11-25 years. Time-to-event models under a counting process framework were used to estimate cumulative incidence, measures of associations and 95% confidence intervals (CI).
Results: The incidence of SRT between 11-25 years was 29% (95% CI: 26-31%) in females and 19% (95% CI: 16-23%) in males, and the incidence of SA between 11-25 years was 16% (95% CI: 14-19%) in females and 7% (95% CI: 6-8%) in males. The risk of incident and recurrent SRT and SA was significantly elevated among females exposed to maternal depressive symptoms, but not in males. Hyperactivity/inattention and psychiatric comorbidity were significant mediators, explaining 60% of the association with SRT and SA, and 50% of the association with SA, respectively.

Conclusions: These findings have implications for earlier age implementation of suicide prevention programs and upstream selective approaches. Family-based preventions targeting families where a mother is depressed, prenatal screening, and clinician monitoring of high-risk families could reduce the risk of entering the trajectory towards suicide.
Acknowledgments

I would like to give sincere thanks to Anne Rhodes, Susan Bondy, Rinku Sutradhar and Hilary Brown. Your supportive guidance, timely feedback, and kindness throughout this process made this an extremely valuable and enjoyable experience. It was a pleasure to work with all of you. A special thanks to Anne. I learned an immense amount working with you and your attention to detail and thoughtfulness is something to be admired.

I would also like to thank my PhD epidemiology colleagues for sticking it out and keeping spirits high, and the Ontario Graduate Scholarship program for continued funding throughout my PhD. Further, thank-you to my colleagues from the Flourish Mood Disorders Research Clinic for your continued support of my personal academic development and general inspiration to keep doing good research.

Finally, I would like to thank my family for their continued support and motivation to achieve this goal. Your subtle nudges to make certain decisions along my academic trajectory have undoubtedly contributed to where I am today, and I attribute my success to your support.
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Chapter 1
Introduction

1 Introduction

Suicide has a significant negative impact on individuals, families and societies. What is particularly concerning is its prominence in young populations relative to older ages. In Canada, suicide is the second leading cause of death in ten to 24-year olds. Suicide-related thoughts (SRT) and attempts (SA) are among the strongest predictors of suicide and the rates of suicide post-hospitalization for suicide-related behaviour are very high. This underscores the importance of studying and intervening in younger populations before individuals start to experience these behaviours and reach a crisis. Despite the high proportion of deaths due to suicide in young populations compared to other causes, we still have little understanding of the frequency, at what age and why young individuals start to report thoughts about suicide and SA in the population. Further, while some independent risk factors for SRT and SA have been identified, the nature of these associations have not been well defined. These research gaps stem from in part: 1) reliance on health administrative data to estimate incidence; 2) a focus on those presenting for treatment, or already in crisis; 3) poor measurement of childhood exposures; and 4) little investigation of effect modifiers and mediators, which are helpful for guiding preventive interventions.

Incidence rates of SRT and first SA in young Canadians are not well-defined owing to limitations in data records using International Classification of Disease (ICD) codes which do not capture SRT or confirm suicidal intent for self-inflicted events and only include those seen in hospital. As such, this approach includes populations of youth already exhibiting severe suicide-related behaviours and excludes those not presenting to the hospital. Further, using hospital administrative data as a measure of suicide-related behaviour limits the ability to study socio-demographic, familial or psychosocial antecedents as these types of variables are typically not collected systematically within the population, or longitudinally. There is a wealth of knowledge on the profound and lasting impact that early childhood exposures have on an individual’s emotional, and psychiatric health later in life, and there is a large body of evidence supporting lasting negative
emotional and behavioural effects among offspring of a mother with a major mood disorder. Yet, there has been a disproportionate lack of research on how exposure to maternal depression impacts offspring risk of suicide-related behaviour, and the available research is limited methodologically. Further, an important, yet missed focus of research to date on how maternal mood disorder impacts mental health outcomes in offspring is the question: for whom and why? Not all children of mothers with major mood disorders develop psychopathology, and there has been little investigation into effect modifying influences of variables that might buffer this association or mediating pathways that might explain this association. Investigation of protective factors and intermediate pathways of this association could be useful for preventive strategies targeting families to reach youth before they progress to more lethal behaviours.

1.1 Research aim and objectives

Aim: The aims of this thesis are to estimate the risk of and at what age young Canadians start to think about suicide and report attempts, and to determine the nature of the association between an important, potentially modifiable antecedent, maternal depression in childhood and youth and young adult SRT and SA. This aim was achieved using data from National Longitudinal Survey of Children and Youth (NLSCY), a nationally representative survey in Canada, conducted from 1994 to 2009 in respondents followed from birth to 25 years of age.

Objective 1: To determine the cumulative incidence of self-reported SRT and SA in Canadian youth and young adults (11 to 25 years) from 1996 to 2009.

Objective 2: To estimate the association between exposure to maternal depressive symptoms during the first decade of life and self-reported SRT and SA in Canadian youth and young adults (11 to 25 years) followed from 1994 to 2009.

Objective 3: To identify possible mediators (offspring psychiatric symptom(s)) and moderators (sex, family structure, maternal social support and cohesion) of the associations between exposure
to maternal depressive symptoms during the first decade of life and self-reported SRT and SA in Canadian youth and young adults (11 to 25 years) followed from 1994 to 2009.

1.1.1 Student role

In collaboration and under supervision of the PhD thesis committee, the conceptualization, design, statistical analysis and write-up of this thesis was conducted by the student independently. This project was a secondary analysis of data collected by Statistics Canada, and as such, the student was not involved in data collection.

1.1.2 Thesis format

This thesis is presented in paper series format with a comprehensive, common background, followed by three manuscripts which comprise this thesis methods section. Manuscripts are followed by a common discussion, limitations, and public health implications section. Paper one addresses objective one and is accepted for publication in the Canadian Journal of Psychiatry; paper two addresses objective two and effect modifying influences from objective three and is in review with the Journal of Social Psychiatry and Psychiatric Epidemiology; and paper three addresses mediating pathways from objective three and is in review with the Journal of Epidemiology and Psychiatric Sciences.
Chapter 2
Background

2 Background

2.1 Suicide-related thoughts and behaviour

Suicide is the second leading cause of death in 10 to 24-year-olds in Canada\(^2\), substantially contributing to potentially preventable years of life lost. Suicide at any age is a devastating outcome, but it is particularly concerning, that relative to other causes of death, it is prominent at younger ages. SRT and SA manifest in adolescence and are strong predictors of suicide\(^3\). While suicide rates are higher in males compared to females, SRT and SA are more common in females\(^10\), \(^11\), and these differences are more pronounced under the age of 20\(^12\).

The nomenclature in suicidal phenomena literature varies greatly, contributing to debate and confusion among researchers\(^13\). In this thesis, the terms used to describe different suicidal phenomena are in keeping with the definitions outlined by Silverman et al\(^14\). Herein, SRT refer to any thoughts or ideas pertaining to ending one’s life; SA refers to self-inflicted, potentially injurious behaviours with some intent to end one’s life; and suicide-related behaviour refers to acts that are irrespective of intent\(^14\). The distinction of suicidal intent is important. The Diagnostic and Statistical Manual for Mental Disorders (DSM)-V recognizes SA and self-harm (defined as non-suicidal self-injury in DSM nomenclature) as separate events\(^15\). There is evidence of different characteristics among populations who attempt suicide compared to those who self-harm and these two different populations may have separate etiologies. For example, those who report SA compared to self-harm have significantly greater risks of anxiety and depressive disorders and low educational attainment\(^16\), \(^17\). Further, higher IQ has been reported as a risk factor for self-harm, while lower IQ a risk factor for SA\(^16\). Ignoring the specification of intent could lead to an inaccurate portrayal of two different populations.
2.2 Measurement: Self-report versus health administrative data

Suicide-related outcomes can be measured through self-report measures and hospital and ambulatory administrative data systems. Both approaches have advantages and disadvantages. Self-reported measures have the benefit of capturing suicide-related behaviours that occur independently from a hospital setting. Further, self-report measures capture the individual’s interpretation of their suicide-related behaviour, reducing risk of misclassification by informant reports or clinicians. However, self-report measures of suicide-related behaviour increase the risk of potential misreporting. Factors that significantly contribute to inaccurate estimates of self-reported SRT and behaviours in adolescents include: lack of anonymity\textsuperscript{11}, long recall periods\textsuperscript{18}, and misunderstanding of the terminology used and the concept of suicidal intent\textsuperscript{19}, and social desirability\textsuperscript{20}.

Benefits of hospital and ambulatory administrative estimates of suicide-related behaviour include that these estimates are available internationally in populations. However, disadvantages include that health administrative data systems do not routinely record patient thoughts about suicide. Further, self-inflicted injury and self-poisoning ICD codes do not require the specification of intent and exclude those who do not go to the hospital. Therefore, these estimates refer to suicide-related behaviours (a mix of suicidal and non-suicidal behaviours) and excludes populations not presenting to the hospital and most adolescents admitted report prior SA that did not lead to hospitalization\textsuperscript{21}. Hospitals also vary according to recording procedures and misclassify events by inaccurate ICD-code entry\textsuperscript{1}. For example it has been estimated that approximately 75% of actual SA cases in adults admitted to the emergency department are missed by the use of self-inflicted ICD-10 codes\textsuperscript{22}.

2.3 Incidence

Understanding when SRT and SA first occur is important for intervening at the appropriate time to halt progression to suicide. SRT and SA are reported to start to occur in adolescence\textsuperscript{3}, although the exact age at which these thoughts and attempts first onset is less clear, as most reported estimates are based on prevalence and are derived from health administrative data. Moreover, there
is high heterogeneity of prevalence estimates between studies and countries\textsuperscript{11}. A meta-analysis of population based studies indicated that the lifetime prevalence of SA and self-reported SRT in 12 to 20 year-olds is 9.7\%, and 29.9\%, respectively\textsuperscript{11}. Recent findings from the 2012 Canadian Community Mental Health Survey, indicated that the lifetime prevalence of self-reported SRT in 15 to 25 year-olds was 16.2\% in females and 12\% in males\textsuperscript{23}. In Canada, the annual prevalence rate of suicide-related behaviour derived from hospital inpatient and emergency department visits, in girls and boys (aged 10 to 19 years) was 164/100,000 and 32/100,000, in 2013 to 2014, respectively\textsuperscript{24}.

Estimating incidence from community and national surveys poses analytical challenges relating to discontinuous risk intervals. Discontinuous risk intervals are gaps in respondent follow-up time which can be present by research design or participant drop-out. Many surveys use a one-year cut off as a look back window to reduce risk of recall bias\textsuperscript{25}, and if assessments are spaced more than one year apart, the time outside the one-year look back window (since last assessment) reflects a gap in time where the event status is unknown. Further, it is possible for respondents to drop-out of a survey at one point in time yet participate at a later time, also producing a period of time where the event status is unknown. These scenarios lead to varied discontinuous risk intervals. Analytic techniques that average across these discontinuous risk intervals for each individual or reduce samples down to complete follow-up are often employed strategies, and as such may be underestimating the true incidence owing to an inflated denominator.

Existing incidence studies primarily stem from health administrative data. For example, in Ontario youth aged 12 to 17 years, the incidence rate for emergency department based suicide-related behaviour was 474.5/100,000 for females and 174.6/100,000 for males from 2002 to 2007\textsuperscript{26}. Further, in the United States (US), the annual incidence rate of emergency department visits for suicide-related behaviour from 2006 to 2013 peaked in females from 15 to 19 (459/100,000) and in males, peaked between 20 to 24 years (270/100,000)\textsuperscript{27}.

Most adolescents admitted to the hospital for suicide-related behaviour report prior SAs that did not lead to hospitalization\textsuperscript{21}, and, two-thirds who present to the emergency department with suicide-related behaviour express suicidal intent\textsuperscript{28, 29}. Based on estimates from survey and
hospitalization data, few 15 to 17 year-olds self-reporting suicide-related behaviour present to the hospital\textsuperscript{30}. As such, studies reporting on hospital presentations for suicide-related behaviour using ICD codes likely underestimate SA incidence. Accordingly, we have a limited understanding of how many young individuals in the population, first think about suicide and attempt suicide with the actual intent to die, irrespective of a hospital setting. In Canada, the US, and other countries, this information is not systematically collected longitudinally.

### 2.4 Risk factors

SRT and SA are complex phenomena, and likely have underpinnings throughout the lifespan, beginning very early in life, that interact with genetic susceptibility\textsuperscript{31}. Several risk factors for SRT and SA have been identified from cross-sectional, retrospective and some longitudinal studies\textsuperscript{3, 32, 33}. These risk factors can be conceptualized into the following categories: genetics, family-related factors (parental psychopathology, family attachments, structure and functioning), environmental (abuse, exposure to suicide, and stressors), and individual (psychiatric symptoms).

#### 2.4.1 Genetics

Twin and genetic studies show that a family history of suicide-related behaviour and psychiatric disorder substantially increases the risk of suicide-related behaviours in offspring\textsuperscript{31, 34}. There is some evidence that this transmission is mediated by other phenotypes such as impulsive-aggressive traits\textsuperscript{31}. While genetics indeed play an important role in creating susceptibility for suicide-related behaviours, studies to date have only been able to explain a small proportion of the overall risk, implying an important role for other environmental factors\textsuperscript{31}.

#### 2.4.2 Family-related factors

Maternal psychopathology has been linked to offspring SRT and SA\textsuperscript{6}, but the nature of this relationship is not well understood. While the genetic transmission of psychopathology from mother to child indeed explains some of this association, part of this association may also be
explained through exposure to the maternal illness early in life when children are neurodevelopmentally and emotionally sensitive, increasing risk via attachment and biological mechanisms, or a combination of both. Findings from twin studies have shown independent effects of parental psychopathology on offspring psychiatric disorder later in life, beyond genetic vulnerability. Early life exposures during increased periods of neural plasticity may render individuals more vulnerable to the effects of stress later in life. Lack of expected experiences necessary for normal brain development during these critical periods (e.g., consistent parental care) may interfere with emotional maturation, and manifest as a vulnerable phenotype later in life. Accumulating evidence from animal and neurobiological studies in humans support this theory. Different brain regions are particularly susceptible during different childhood and adolescent sensitive windows. For example, the hypothalamic pituitary adrenal (HPA) axis, central in regulating emotional responses, rapidly matures during the first year of life, and develops normally in response to parental nurturance and emotional reactions, while other regions such as the prefrontal cortex are still developing later in childhood. Exposures during these critical periods can have lasting and permanent effects on neuroendocrine programming. For example, there is evidence that maternal anxiety and depression eight weeks postpartum is associated with increases in sympathetic nervous system reactivity and lower recovery in response to stress, and a blunted HPA axis response in male adolescents. Taken together, there is evidence of the biological plausibility of a temporal association between exposure to maternal psychopathology in childhood and subsequent suicide-related behaviour that may differ by sex and age of exposure.

A recent systematic review synthesizing studies up until March 2017, indicated that investigations of the association between parental mood disorder and offspring SRT and SA have yielded mixed findings, although most studies to date suffer from important methodological limitations, with 80% of included studies meeting criteria for serious or critical risk of bias. The search used in this systematic review was updated on February 15th, 2018 yielding no new studies meeting inclusion criteria. The review reported that approximately 70% of studies did not verify if the exposure to parental mood disorder occurred in childhood. The few prospective studies confirming this exposure support an elevated risk of SRT and SA compared to adolescent offspring of well mothers and of mothers with sub-clinical depressive symptoms. Few studies examined paternal psychopathology explicitly, and among the few studies examining how this exposure in
fathers impacts SRT and SA risk in offspring yielded mixed findings. This review concluded key areas for future research relate to: improved measurement of parental mood disorder and consideration of moderating and mediating variables.

Not all children of parents with mood disorders develop psychopathology and there has been little investigation into effect modifying influences of variables that might buffer this association\(^6\). There is evidence that the risk of hospital presentation of suicide-related behaviour among offspring exposed to parental psychopathology is higher among those coming from non-intact families compared to intact families\(^45\). Low offspring perceived social support increases risk for adolescent SRT and SA\(^46,47\), and the relative contribution of perceived support from parents has been found more strongly related to SRT and SA compared to support from peers\(^47\). Further, there is evidence that the protective effect of parental secure attachment on adolescent SA risk is enhanced among families reporting high social cohesion within their neighborhood\(^48\). However, it is unclear how parental perceived social support or cohesiveness might buffer the risk of SRT and SA in their children among parents who are depressed. The timing of maternal mood disorder in childhood might modify risk for SRT and SA, although no study has specifically tested this. However, studies have examined the effects of timing of parental psychopathology on other outcomes such as emotional disorder\(^49\) at age 12/13 years and psychopathology in adolescence and young adulthood\(^50\), and have provided preliminary support that exposure earlier in childhood (i.e., before five years), compared to later in childhood, is associated with a greater risk.

There has been considerable research conducted supporting associations between other family related factors involving adverse family environments and adolescent SRT and SA. For example, findings from the Christchurch birth cohort study indicated that insecure family attachments, parental alcohol abuse, and divorce or separation occurring before age 16 years significantly elevates risk of SRT and SA between 15 to 21 years\(^51\). Further, findings from a British birth cohort study found that parental death and divorce or separation at age seven, in addition to other factors (e.g., domestic disputes, contact with social services and bullying) was significantly associated with risk of lifetime suicide\(^52\). Family functioning and parental psychopathology may be related in some circumstances depending on whether one or both parents are affected and may jointly contribute to offspring SRT and SA\(^45,53\). A small number of studies have reported both
mediation\textsuperscript{53}, and effect modification\textsuperscript{45} of parent and offspring reported family functioning, and family intactness, respectively, on the association between parental psychopathology and offspring SA, as well as an independent association between parental divorce and offspring adult suicide in males after adjusting for parental depression\textsuperscript{54}. However, most studies examined these factors as separate independent predictors.

\subsection*{2.4.3 Environmental}

Childhood abuse and neglect are significantly associated with a greater risk of SA in 12 to 18 year olds\textsuperscript{55} and suicide in 15 to 29 year olds\textsuperscript{56} and the impact of some forms of childhood abuse may be stronger in children and adolescents compared to adults\textsuperscript{55}. While these latter findings are supported by several systematic reviews and meta-analyses\textsuperscript{55, 57, 58}, findings have been highly heterogeneous across studies, and are likely confounded, mediated and moderated by several other psychosocial and family variables that have been given little attention.

Exposure to suicide or suicide-related behaviours by family members and non-family members suggesting an imitation effect has been posited to increase risk of suicide-related behaviours, however, the evidence is unclear\textsuperscript{49}. Studies linking exposure to suicide-related behaviour in family members to increased risk in children or kin have not been able to disentangle possible imitation effects from bereavement or grief\textsuperscript{59}. Moreover, studies examining the effects of exposure to non-family member suicides have not adequately controlled for prior exposure to suicide-related behaviour by family members, and it may be that vulnerable individuals cluster together in part explaining this phenomenon\textsuperscript{60}. Further, studies reporting on associations between media reports of suicide with individual suicides, and suicide rates have yielded inconsistent findings\textsuperscript{61}.

Studies support associations between adverse early environments including social deprivation, low socio-economic status, and certain negative life events with suicide\textsuperscript{33}. A systematic review found that life stressors are generally related to SRT and SA, however, several included studies were cross-sectional, making the disentangling of these associations difficult, and among the longitudinal studies establishing temporality, the methodological quality was low\textsuperscript{62}. Further, this review did not distinguish between life stressors in comparison to significant life events such as
trauma, or abuse, which may have differential effects on SRT and SA risk. Finally, studies were underrepresented by childhood samples\textsuperscript{62}. However, there is some evidence from two birth cohort studies\textsuperscript{51, 52} that childhood and adolescent life events such as serious illnesses/accidents, death of a loved one, or major conflict are associated with adolescent SA, and adult suicide, and increasing number of life events was associated with a greater magnitude of risk.

2.4.4 Individual

One of the strongest and most studied risk factors for suicide-related behaviour and death by suicide is the presence of a psychiatric disorder. Psychological autopsy studies report that approximately 90\% of individuals who die by suicide had a prior psychiatric diagnosis\textsuperscript{63} and community-based surveys of younger populations (14-25 years) with SA report similar findings, where approximately 90\%\textsuperscript{64} report prior psychiatric disorders. However, 40\% of youth who die by suicide under age 16 years do not meet full diagnostic criteria for a psychiatric disorder\textsuperscript{3}. The nature of the psychiatric disorder-suicide relationship remains ill-defined and only recently have suicide-related behaviours been recognized as independent of psychiatric illness\textsuperscript{65}.

Trajectory-based studies have shown that externalizing symptoms and depression at age 11 to 12 years predict high-risk trajectories of SRT up to age 15 years\textsuperscript{66}, and anxiousness and disruptiveness in kindergarten children predicts SA between 15 and 24 years\textsuperscript{67}. A common finding across studies is that psychiatric comorbidity (two or more co-occurring psychiatric diagnoses) appears to heighten risk of both SRT and SA in adolescence and young adulthood\textsuperscript{64, 68, 69}, where higher numbers of diagnoses together predict a greater risk, compared to individual diagnoses alone.

Externalizing disorders may be more strongly related to SA, primarily through impulsivity\textsuperscript{70}, while internalizing disorders may be more related to SRT via the symptom of hopelessness\textsuperscript{71}. In support of this, there is evidence that ADHD at age 15 is associated with SA but not SRT at age 16\textsuperscript{72}. Further, adolescents who die by suicide are more likely than community controls to meet criteria for cluster B and C personality disorders associated with impulsivity, avoidant attachments, and aggression\textsuperscript{73}. Genetic studies also support that the genetic transmission of SA risk, but not SRT is
mediated by genetic transmission of impulsive-aggressive traits. There is also some evidence that these associations are sex-specific, however research is limited, particularly in younger ages.

There is some evidence that adolescent psychiatric symptoms mediate the association between exposure to maternal depression in childhood and adolescent SRT and SA. This notion seems plausible given that maternal depression is associated with a broad range of offspring psychopathology, that differ by sex, and that psychiatric symptoms and disorders are among the strongest predictors of adolescent SA, yet only one study has specifically tested this hypothesis. Hammerton et al reported that offspring symptoms of major depressive disorder, generalized anxiety disorder, and disruptive behaviour disorder, but not attention deficit hyperactivity disorder at age 15 significantly mediated the association between chronic and severe, and even moderate maternal depression from zero to 11 years of age and offspring SRT at age 16. Moreover, in the same study, the same set of psychiatric symptoms in addition to attention deficit hyperactivity disorder were found to mediate the association between maternal depression and offspring SA at age 16. However, follow-up was short, with adolescent psychiatric symptoms measured at age 15 and SRT and SA at age 16.

2.5 Knowledge gap

Accurate estimates of how many young individuals’ first start to think about suicide and attempt suicide with intent to die in the population, irrespective of a hospital setting are unknown. Such information would be useful for guiding the age implementation of suicide prevention programs. Further, knowledge of antecedent pathways leading to SRT and SA is needed to inform these preventive strategies. Suicide prevention studies and much of the extant research have been dominated by studies of populations of youth identified via treatment settings and tend to exclude those not going to the hospital. However, the implementation and evaluation of family-based interventions, that support high-risk families before children get to a crisis stage in the field of suicide prevention is growing, and there is a need to further inform, develop, and systematically test these prevention strategies. Maternal depression is a major public health concern, affecting up to 20% of mothers, and in new mothers, one third report depressive
symptoms well beyond the post-partum year. Further, it has been suggested that less than 50% of mothers with post-partum depression recommended for treatment actually receive or seek treatment. Maternal depression is associated with a host of negative outcomes in children and adolescents that differ by sex, although question remains about exact mechanisms. Therefore, prevention strategies targeting families where a mother is depressed could have lasting protective effects throughout the lifespan. Addressing this particular exposure could maximize suicide prevention efforts given that it is associated with a broad range of risk factors, several of which are also risk factors for suicide-related behaviours. Research on sex-specific moderating and mediating pathways explaining the association between maternal depression and offspring SRT and SA risk would be useful for this purpose.
Chapter 3

Paper 1: The cumulative incidence of self-reported suicide-related thoughts and attempts in young Canadians

3 Paper 1

A version of this manuscript is published in the Canadian Journal of Psychiatry

The cumulative incidence of self-reported suicide-related thoughts and attempts in young Canadians

Sarah M. Goodday¹, Susan Bondy¹, Rinku Sutradhar²,³, Hilary K. Brown¹,⁴, Anne Rhodes¹,⁴,⁵

¹University of Toronto, Department of Epidemiology, Dalla Lana School of Public Health
²University of Toronto, Department of Biostatistics, Dalla Lana School of Public Health
³Institute for Clinical Evaluative Sciences
⁴University of Toronto, Department of Psychiatry, Dalla Lana School of Public Health
⁵McMaster University, The Offord Centre for Child Studies
Abstract

Objective: To estimate the cumulative incidence of self-reported suicide-related thoughts (SRT) and attempts (SA) in male and female youth and young adults in Canada.

Methods: A cohort study was conducted using the National Longitudinal Survey of Children and Youth, a representative survey of Canadians aged 11-25 years conducted from 1996-2009. The cumulative incidence of SRT and SA from 11-25 years was estimated in males and females using a counting process approach to account for discontinuous risk-intervals.

Results: The risk of SRT was 29% (95% CI: 26-31%) in females and 19% (95% CI: 16-23%) in males by age 25. The risk of SA was 16% (95% CI: 14-19%) in females and 7% (95% CI: 6-8%) in males by age 25. Over 70% of SRT and SA first occur between 11-16 years of age, and 30% between 11-13 years of age, respectively.

Conclusions: The risk of SRT and SA is high in young Canadians with most events first occurring in early to mid-adolescence, earlier than reported peaks in hospital presentations for suicide-related behaviours. Females are at a higher risk compared to males. This research underscores the need for earlier implementation of suicide prevention programs and better longitudinal surveillance of suicide attempts in the population.
Introduction

Suicide is the second leading cause of death in 15 to 29-year-olds globally\(^1\). Suicide-related thoughts and behaviour\(^2\) manifest in adolescence and are strong predictors of suicide\(^3\). While suicide rates are higher in males compared to females, suicide-related thoughts (SRT) and suicide attempts (SA) are more common in females\(^4,5\), and these differences are more pronounced under the age of 20\(^6\). To our knowledge, there is little understanding of the onset and frequency of SRT or SA with the intent to die in children and adolescents. This is the result of: 1) reliance on healthcare administrative data to estimate suicide-related behaviour incidence, which excludes suicide-related thoughts, and individuals who did not access a hospital, and where suicide-related behavior measures are irrespective of intent\(^2\), and 2) lack of longitudinal and nationally representative surveys including SRT and SA measures in young populations. Such knowledge would provide important information necessary for developing and implementing age-specific prevention strategies. Thus, the objective of this study was to estimate the cumulative incidence of self-reported SRT and SA in males and females from 11 to 25 years of age.

Several studies involving school and community surveys have reported the prevalence of suicidal phenomena in youth, although high heterogeneity between studies and countries exists\(^5\). A meta-analysis of population-based studies indicated that the lifetime prevalence of SA, self-harm (irrespective of intent), and SRT in 12 to 20-year-olds was 9.7%, 13.2% and 29.9%, respectively\(^5\). Recent findings from the 2012 Canadian Community Mental Health Survey indicated that the lifetime prevalence of SRT in 15 to 25-year-olds was 16.2% in females and 12% in males\(^7\).

Studies have also reported the prevalence of suicide-related behaviour using health administrative data. For example, in Canada, the annual prevalence rate derived from hospital inpatient and emergency department visits, in girls and boys (aged 10 to 19 years) was 164/100,000 and 32/100,000, in 2013-2014, respectively\(^8\). Few population-based incidence studies of suicidal phenomena have been conducted. Most existing studies also stem from health administrative data. In particular, in Ontario youth aged 12 to 17 years, the incidence rate for emergency department based self-harm was 474.5/100,000 for females and 174.6/100,000 for males from 2002 to 2007\(^9\). Further, in the Canadian Province of Newfoundland and Labrador, among youth aged 15 to 19
years, the inpatient-based incidence rate for self-harm was 189.1/100,000 in females and 98.6/100,000 for males, and among ten to 14-year-olds, was 75.0/100,000 in females and 24.5/100,000 in males\textsuperscript{10}. In the United States (US), the annual incidence rate of emergency department visits for self-harm from 2006 to 2013 peaked in females from 15 to 19 (459/100,000) and in males, peaked between 20 to 24 years (270/100,000)\textsuperscript{11}.

While hospital and ambulatory administrative estimates of suicide-related behaviour are available internationally, such self-inflicted injury and self-poisoning International Classification of Disease (ICD) codes do not require the specification of intent and exclude those who do not go to the hospital. Therefore, these estimates include patients with a mix of suicidal and non-suicidal behaviours. Nevertheless, most adolescents admitted to the hospital for suicide-related behaviour report prior SA that did not lead to hospitalization\textsuperscript{12}, and, two-thirds who present to the emergency department with suicide-related behaviour express suicidal intent\textsuperscript{13, 14}. These hospital presentations may reflect a progression in behaviours, which could have been previously halted\textsuperscript{15}. Based on estimates from survey and hospitalization data, few 15 to 17-year-olds self-reporting suicide-related behaviour present to the hospital\textsuperscript{16}. As such, studies reporting on hospital admissions for suicide-related behaviour likely underestimate SA incidence. Further, across all ages, it has been estimated that approximately 75\% of actual SA cases admitted to the emergency department are missed by the use of self-inflicted ICD-10 codes\textsuperscript{15}.

Accordingly, we have a limited understanding of how many young individuals in the population, first think about suicide and attempt suicide with the actual intent to die. In Canada, the US, and other countries, this information is not systematically collected longitudinally. In this study, we employed the National Longitudinal Survey of Children and Youth (NLSCY) to estimate the cumulative incidence of self-reported SRT and SA in Canada. This survey is comprehensive and nationally representative and was conducted in all provinces from 1996 to 2009.

\textbf{Methods}

\textit{Data source}
The NLSCY of Statistics Canada was a longitudinal cohort study (panel) for which Canadian children, initially zero to 11 years of age, were followed to young adulthood. The sampling frame for the NLSCY was based on the Statistics Canada Labor Force Surveys (LFS)\textsuperscript{17}. Briefly, the LFS is a household survey covering approximately 97\% of the Canadian population using multistage probability samples stratified by geographic areas. The LFS excludes full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian Reserves\textsuperscript{a}.

\textit{Study population}

The original longitudinal cohort in cycle one of the survey was comprised of 22,831 children aged zero to 11 years of age in 1994/1995. Child respondents were followed up biennially until 2008/2009 with a maximum of eight cycles of data collection. The outcome of interest, SRT and SA, became available in cycle two; thus, for this study, cycles two to eight were linked by individual unique identifiers. Respondents who were below the age appropriate to complete the SRT and SA (<11 years), and those who did not complete at least one cycle between cycles two to eight were excluded from the study. Due to Statistics Canada budget cuts and to reduce respondent burden, the sample from cycle one to two was cut by 5928 respondents. All respondents from households additionally participating in the National Population Health Study were omitted, and the number of respondents in the same household were cut from four to two. The remaining respondents were randomly selected and accurately reflected the survey population\textsuperscript{17}. Thus, the study population used in this study was comprised of 16,903 NLSCY respondents between the ages of 11 and 25 years of age (Figure 3.1). This study was approved by the research ethics board at the University of Toronto.

\textsuperscript{a} The term “Indian Reserve” is used throughout in keeping with the description used in the NLSCY population description\textsuperscript{17}
Procedure

Interviews for the NLSCY were completed in person or by telephone using computer assisted interviewing by Statistics Canada trained personnel or by self-report in schools for the child and youth questionnaires in age-appropriate respondents (11 to 17 years). In cycles six to eight, to accommodate the aging cohort, in 18 to 25-year-olds, the youth survey was completed by computer assisted telephone interview, to capture those respondents who were no longer in school. The parent respondent completed informed consent for their child, while young adults completing computer assisted interviewing completed their own informed consent.

Outcome measures

SRT were measured by the item: “During the past 12 months, did you seriously consider attempting suicide? SA were measured by the item: “During the past 12 months, how many times did you attempt suicide?” Respondents were asked to indicate yes or no. Outcomes were coded as time to first event variables. The wording of the SRT and SA were different in cycle two compared to later cycles. In cycle two, the phrase “try to kill yourself” was used instead of “attempt suicide”. These outcome measures derived from questions from the Youth Risk Behaviour Survey in the United States and research has supported their acceptable two-week test-retest reliability and convergent and discriminant validity.

Statistical analysis

To calculate the cumulative incidence of first reported SRT and SA over follow-up in males and females, a counting process framework was used, with age in year at interview as the time scale. Because of the NLSCY response structure, discontinuous risk intervals (gaps in a respondent’s follow-up) were present. Two forms of discontinuous risk intervals were present: 1) by design; and 2) by participant drop-out and re-entry into the survey. The NLSCY assessments were spaced every two years, while the response format for suicide-related outcomes was during a one-year look back window producing one-year gaps in time following each assessment where the outcome status is unknown. There were also cases where respondents dropped out of the survey at one cycle.
and re-entered at a later cycle, and the time elapsed between assessments reflects another form of discontinuous risk interval. To account for discontinuous risk intervals by participant drop-out and re-entry and design, a counting process approach was used\textsuperscript{20}. Herein, each respondent contributes a row of data with a start and stop time reflecting each time interval they were observed as at risk, until they report the outcome, and among those not reporting the outcome, until their last assessment. We estimated the cumulative incidence of SRT and SA both accounting for and not accounting for the discontinuous risk intervals by design. However, primary results are presented without accounting for these gaps, making the assumption that the event did not occur in the year prior to each cycle. These discontinuous risk intervals were consistent every cycle for every participant (depending on the number of cycles participated in), therefore omitting them from the risk set cuts the time at-risk approximately in half inflating the incidence. Implications of both approaches are discussed. Sensitivity analyses were conducted to determine if individuals with one or two cycles of non-response compared to those with complete response across all cycles differed significantly in main outcomes.

The NLSCY involved a complex survey design which requires the use of probability sampling weights and design-based methods to estimate variances and perform statistical tests. To produce unbiased estimates of the population, all reported estimates are weighted using the longitudinal weights provided by Statistics Canada\textsuperscript{17}. The design weights reflect the inverse probability of selection and account for post stratification and non-response. To estimate the frequencies of first captured SRT and SA, SAS procedures for complex surveys were used to estimate weighted frequencies. Variances were estimated using the bootstrap weights provided by Statistic Canada using the balanced repeated replication method. All analyses were performed using SAS software (version 9.4).

**Results**

The original longitudinal cohort at cycle two was comprised of 16,903 individual respondents (Figure 3.1). There were 828 respondents classified as out of scope, indicating that they either died, moved out of province, or to an Indian Reserve, or their age was out of range. As such, less than 3.6\% of the original longitudinal sample died during the study follow-up. From the cohort
sampled at cycle two (16,903), there were 3734 (22%) cases where respondents did not contribute
to cycles two to eight and were excluded either due to non-response, or not being age appropriate
for the outcome measures (Figure 3.1). The final sample analyzed included 13,169 respondents
(6601 females and 6568 males) with a weighted total of 3,745,388 respondents and 25,743,458
number of observations.

Among Canadians aged 11 to 25 years reporting SRT, the highest proportion first occurred
between 14 and 16 years of age in both males and females. The proportion reporting these thoughts
from 11 to 13 years of age was 32% in both females and males. When attempts occurred, the peak
times were at a later age in females compared to males, where the highest proportion of attempts
occurred between 14 to 16 years in females (52%) and between 11 to 13 years in males (38%)
(Table 3.1).

The cumulative incidence of SRT in males and females by 11-to 25-years of age was 19% (95%
CI: 16, 23) and 29% (95% CI: 26, 31), respectively (Figure 3.2). The cumulative incidence of SA
was 7% (95% CI: 6, 8) in males and 16% (95% CI: 14, 19) in females (Figure 3.2). In both females
and males, the cumulative incidence of SRT more than doubled from 11 to 13 years of age
(females: 8% [95% CI: 7, 9]); males: 4% [95% CI: 3,5]) to 11 to 16 years of age (females: 21%
[95% CI: 19, 23]; males: 10% [95% CI: 9, 11]) (Figure 3.2). In females, the cumulative incidence
of having a SA was approximately 4% (95% CI: 3, 5) from 11 to 13 years, and by age 16, this risk
tripled to 12% (95% CI: 11, 13). In males, the cumulative incidence of SA from 11 to 13 years,
and from 11 to 16 years was 2% (95% CI: 2, 3) and 4% (95% CI: 3, 5), respectively (Figure 3.3).

Sensitivity analyses to determine the impact of cycle non-response on cumulative incidence
estimates did not reveal major differences. For example, the 11 to 25-year cumulative incidence
of SA changed from 7% to 6% for males and 16% to 14% in females, while the cumulative
incidence of SRT changed from 19% to 18% in males, and 29% to 27% in females (Table 3.2
Supplemental).

The cumulative incidence of both outcomes was estimated while additionally accounting for the
discontinuous risk intervals by design. That is, the intervals where respondents were not observed
as at-risk were omitted from the time at-risk. Using this approach, the cumulative incidence of SRT between 11 to 25 years of age in females and males was 50% (95% CI: 44-55) and 34% (95% CI: 29-37), respectively, while the cumulative incidence of SA between 11 to 25 years of age was 28% (95% CI: 26-31) and 13% (95% CI: 11-16), respectively.

**Discussion**

The incidence of thinking about suicide in males and females by 11-to-25 years of age was high, 29% in females and 19% in males, with estimates possibly as high as 50% and 34%, respectively. Further, the incidence of attempting suicide by age 25 was 16% in females and 7% in males with estimates possibly as high as 28% and 13%, respectively. It is challenging to compare these estimates to other published reports because existing incidence studies are largely of ICD coded hospital presentations, where as expected, the incidence over adolescence and young adulthood is much smaller, typically under 1% (Appendix A). Moreover, among the few conducted incidence studies of self-reported SRT and SA, the age range was narrower, typically not reported below 12 years, and incidence estimates were annual rates\(^{21}\), rather than cumulative or studies used long recall periods\(^{22,23}\) increasing risk of recall biases. As such, the cumulative incidence reported here is higher than prior published incidence reports. In terms of prevalence, the 11 to 25-year cumulative incidence of SRT in this study is consistent with the average lifetime prevalence estimate from a meta-analysis of population-based studies of 12 to 20-year-olds synthesizing studies up until the year 2000\(^5\). This meta-analysis reported an average prevalence of SA in 12 to 20-year-olds of approximately 10% in males and females which could be comparable to our cumulative incidence estimate of SA, given that we reported these risk in males and females separately. However, our cumulative incidence estimates of both SRT and SA are higher than other more recent lifetime prevalence studies\(^7,24-26\) and annual prevalence studies\(^{27-29}\) in youth and young adults between 12 and 25 years of age. Lifetime prevalence studies are limited by recall biases that have been shown to underestimate incidence\(^{30}\) where youth are likely recalling the most severe past events. Further, some of these studies measured SRT and SA in the context of major depression\(^{24}\), and it has been shown that cases of SRT and SA are missed among respondents not meeting criteria for depression-related gate questions\(^{31}\).
In light of the methodological limitations of existing incidence and prevalence studies of SRT and SA, the current evidence base has likely been underestimating the true incidence of these thoughts and behaviours in the population. Further, no study has employed the method used in this study to more accurately estimate the time at-risk. We estimated the 11 to 25-year cumulative incidence two different ways; not accounting for the discontinuous risk intervals by design (which makes the assumption that events did not occur in the year after each cycle) leading to a possibility of underestimating incidence; and 2) accounting for the discontinuous risk intervals by design (which cuts the time at-risk by almost one half) leading to a possibility of overestimating incidence. On one hand, some respondents in the NLSCY could have recalled events since last assessment (rather than the past year look back window), which would reflect a two-year window. If this were true, it would be acceptable to assume that the outcome did not occur during these one-year gaps, making it appropriate to make this assumption, while on the other hand, we may be missing events during these gap years. Ultimately, the risk of SRT and SA is likely somewhere in between the two reported scenarios, both of which indicate that these outcomes are common in the population, much more so than previously reported.

**Sex differences**

The risks of SRT and SA from 11 to 25 years of age were 1.5 times and 2.3 times higher in females compared to males, respectively, with non-overlapping 95% CIs indicating statistically significant differences. These findings are consistent with the extant literature showing higher rates of these phenomena in females compared to males in adolescence and early adulthood\(^5\). The pattern of first captured events from age 11 years on were similar between males and females for SRT, where the majority of first reported thoughts were observed between 11 to 16 years with the peak time for these events to start between 14 and 16 years. More males (38%) reported first attempting suicide earlier (between the ages of 11 to 13 years) compared to females (30%), although the pattern of first captured event times for males was quite similar across all age categories. This is inconsistent with other population-based incidence studies of hospital presentations for suicide-related behaviour reporting peaks at later ages, from 15 to 19 years of age in females and even later in males, between 20 to 24 years of age\(^6\). Suicide-related behaviour may be less lethal
in adolescents compared to adults\textsuperscript{39}, which could, in part, explain this discrepancy. However, this hypothesis assumes that hospital presentations are in fact more serious than self-reported SA which may not always be true. Some portion of the latter group may be quite suicidal or engage in more lethal behaviours, yet never seek formal care. The concern is that without broader and early prevention strategies that reach these youth, they may progress to more lethal behaviours.

Nevertheless, there were dramatic jumps in risk of SRT and SA from 11 to 16 years of age in both males and females. SRT and SA begin to appear in parallel with pubertal changes, which may in part explain dramatic increases in risk during this time\textsuperscript{30}. It is less clear why certain adolescents reporting these thoughts and behaviours continue to attempt suicide and die by suicide. It is not currently possible to link many population survey data sources to mortality registries, such as the case of the NLSCY, making it challenging to decipher which young individuals endorsing SRT and SA die by suicide. Further, differences in the meaning and severity of thoughts, and lethality of attempts, and how these differ by sex would lend important insight into potential risk trajectories toward suicide.

\textit{Strengths and limitations}

This study used a novel application of a counting process approach to estimate cumulative incidence. The design of the NLSCY, similar to many other panel surveys, poses analytical challenges including: loss to follow-up, and discontinuous risk intervals. The approach applied in this study was able to use all available data from the NLSCY, and appropriately estimate time at risk among participants dropping out and re-entering the survey. Another concern relating to these longitudinal data are potential biases associated with attrition. However, our sensitivity analyses confirmed that the cumulative incidence from 11 to 25 years of age did not significantly change after excluding those with incomplete follow-up. We were unable to examine potential differences among those dropped from cycle one to two, however, the majority of these cases were dropped intentionally by Statistics Canada, and this was done randomly, to reduce potential selection biases\textsuperscript{36}. 
Another concern is that these estimates are outdated, covering a time-period between 1996 to 2009. As such, these estimates may not reflect the cumulative incidence of SRT and SA among 11 to 25-year-olds in the present date. However, there are no newer Canadian, nationally representative longitudinal studies.

The outcomes reported are based on self-report, thereby increasing the risk of misreporting. Factors that significantly contribute to inaccurate estimates of self-reported suicidal phenomena in adolescents include: lack of anonymity, long recall periods, misunderstanding of the definition used and social desirability. The questions used in the NLSCY explicitly describe the suicidal act, thereby reducing potential confusion over SA with intent to die compared to non-suicidal self-injury. The youth survey was paper and pencil, and youth respondents were ensured confidentiality from their parents and teachers when completing the measure. Further, the recall period was one-year.

The NLSCY did not include a measure of suicide. However, the number of longitudinal respondents who died due to any cause over the course of the study was less than 3.6%. Therefore, the competing risk of death is unlikely to have altered estimates appreciably. The NLSCY also does not provide information on lifetime SRT and SA. As a result, we were unable to determine if there were events occurring prior to baseline, below the age of ten years. However, suicidal phenomena are very rare under the age of ten, and we expect that most events reported here were the first occurrence. Finally, the NLSCY excludes some important populations, at high-risk for suicide including individuals residing on Indian reserves, and prison populations. Further research is necessary to also understand when SRT and SA start to occur in these populations.

Public health implications

The risk of thinking about suicide and attempting suicide with the intent to die is common in Canada, particularly in females. These thoughts and behaviours start to occur in early to mid-adolescence, earlier than reported rates of hospital presentations for suicide-related behaviour suggesting that there is a need for better surveillance of suicide-related behaviours in the population. Internationally, the incidence of self-reported SA with intent has been understudied,
possibly due to few large, longitudinal surveys and the application of methods to account for survey design limitations. This study used a novel application of a counting process survival model to estimate cumulative incidence using a methodologically complex survey. This approach could be applied to other longitudinal surveys that suffer from the same methodological limitations such as discontinuous risk intervals, contributing to improved surveillance of SRT and SA.

It is crucial to understand when SRT and SA start to occur to inform the age of implementation of suicide prevention strategies to prevent the onset and progression to repeat and possibly more lethal attempts and reduce the social and economic costs associated with these thoughts and behaviours. Findings from a recent systematic review demonstrated that school-based prevention programs have been effective in reducing the risk of SA\textsuperscript{40}, Yet, most programs target the mid to late adolescent population\textsuperscript{41-43}. Future and ongoing programs may consider targeting younger ages, as a high proportion of youth think about suicide and first report SA in early adolescence.
References


**Figure 3.1** Study sample flow diagram

*Original Longitudinal Cohort*

**Age in years**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Cycle Details</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11</td>
<td>Cycle 1 (1994/1995) 22,831</td>
<td><em>5928 omitted for budget</em></td>
</tr>
<tr>
<td>4-15</td>
<td>Cycle 3 (1998/1999)</td>
<td></td>
</tr>
<tr>
<td>6-17</td>
<td>Cycle 4 (2000/2001)</td>
<td></td>
</tr>
<tr>
<td>12-23</td>
<td>Cycle 7 (2006/2007)</td>
<td></td>
</tr>
</tbody>
</table>

Suicide-related thoughts and behaviour items available in 11+ year-olds

Cycles 2-8 merged

3734 omitted: dropped out before they were age appropriate for the outcome measures OR missing outcome data for all cycles

Final sample

Individual respondents: **13,169**

Number of observations: **91,138**

*Households from the National Population Health Survey and max number of children per household cut from 4 to 2*
Table 3.1 Frequencies of incident suicide-related thoughts and attempts in males and females by age from 1996 to 2009, weighted\textsuperscript{a} to reflect the Canadian general population

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Suicide-related thoughts = yes\textsuperscript{b}</th>
<th>Suicide attempts = yes\textsuperscript{b}</th>
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<tr>
<td></td>
<td>Weighted %</td>
<td>Weighted %</td>
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<tr>
<td>Females</td>
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<tr>
<td>11-13 years</td>
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<tr>
<td>Total responding yes</td>
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<td>100</td>
</tr>
<tr>
<td>Males</td>
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</tr>
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</table>

\textsuperscript{a}Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves

\textsuperscript{b}Column percentages reflect the total percent of respondents (weighted to the Canadian population) from the NLSCY indicating yes for the first time on suicide-related thoughts and attempts measures by age category
Figure 3.2 Cumulative incidence\(^a\) of suicide-related thoughts in males and females from 1996 to 2009, weighted\(^b\) to reflect the Canadian general population.

\(^a\)Cumulative incidence was estimated as 1-survival, calculated from a counting process model. The upper tail end was collapsed in keeping with Statistics Canada release guidelines.

\(^b\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.
Figure 3.3 Cumulative incidence\(^a\) of suicide attempts in males and females from 1996 to 2009, weighted\(^b\) to reflect the Canadian general population

\(^a\)Cumulative incidence was estimated as 1-survival, calculated from a counting process model. The upper tail end was collapsed in keeping with Statistics Canada release guidelines

\(^b\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves
### Table 3.2 Supplemental - Sensitivity analysis: 11 to 25-year cumulative incidence of suicide-related thoughts and attempts by cycle non-response

<table>
<thead>
<tr>
<th></th>
<th>Entire sample</th>
<th>Excluding respondents with 2 or more cycles of NR</th>
<th>Excluding respondents with 1 or more cycles of NR</th>
<th>Excluding respondents with any cycle NR</th>
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</thead>
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<td>Females</td>
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<td>0.28</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>SA</td>
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</tbody>
</table>

SA: suicide attempts; SRT: suicide-related thoughts; NR: non-response
Chapter 4
Paper 2: Exposure to maternal depressive symptoms in childhood and suicide-related thoughts and attempts in Canadian youth: Test of effect modifying factors

4 Paper 2

A version of this manuscript is in review with Social Psychiatry and Psychiatric Epidemiology
Exposure to maternal depressive symptoms in childhood and suicide-related thoughts and attempts in Canadian youth: Test of effect modifying factors

Sarah M. Goodday¹, Susan Bondy¹, Rinku Sutradhar²,³, Hilary K. Brown¹,⁴, Anne Rhodes¹,⁴,⁵

¹University of Toronto, Department of Epidemiology, Dalla Lana School of Public Health
²University of Toronto, Department of Biostatistics, Dalla Lana School of Public Health
³Institute for Clinical Evaluative Sciences
⁴University of Toronto, Department of Psychiatry, Dalla Lana School of Public Health
⁵McMaster University, The Offord Centre for Child Studies
Abstract

**Background:** The association between maternal depression and offspring psychopathology has been studied extensively; however, less is known about its impact on offspring suicide-related thoughts (SRT) and attempts (SA), particularly in a general population sample. Our aims were to examine the association between exposure to maternal depressive symptoms and offspring SRT and SA in youth and to identify effect measure modifiers (offspring sex, family structure, maternal perceived social support and social cohesion) of this association.

**Method:** A cohort was constructed by linking all cycles from the National Longitudinal Survey of Children and Youth, a Canadian nationally representative survey, from 1994-2009 in subjects 0-25 years. Exposure to maternal-reported depressive symptoms was measured when offspring were between 0-10 years. Offspring self-reported incident and recurrent SRT and SA were measured between 11-25 years. Time-to-event models under a counting process framework were used to estimate adjusted hazard ratios (HR) and relative rates (RR) and 95% confidence intervals (CI). Effect measure modifiers were examined across stratum-specific estimates.

**Results:** In offspring exposed to maternal depressive symptoms, the adjusted rates of incident SRT and SA (HR: 1.67, 95% CI: 1.37, 2.08; HR: 1.93, 95% CI: 1.43, 2.50) and of recurrent SRT and SA (RR: 1.61, 95% CI: 1.33, 1.96; RR: 1.87, 95% CI: 1.40, 2.36) were significantly elevated compared to non-exposed offspring. The stratum-specific rates of incident and recurrent SRT and SA were significantly elevated in females but not in males.

**Conclusions:** Girls exposed to maternal depressive symptoms in childhood are a target group for childhood preventive strategies. However, we need to further study the context of these strategies to support high-risk families.
**Introduction**

Suicide is the second leading cause of death among 15 to 29-year-olds, globally. Suicide-related thoughts (SRT) and behaviours are among the strongest predictors of suicide. Lifetime prevalence estimates between 12 to 20 years of SRT and suicide attempts (SA) are approximately 30% and 10%, respectively. Despite the high burden of suicide among youth, we lack strong evidence about the nature, timing and impact of specific exposures on the onset and persistence of SRT and SA. This stems in part from poor measurement of childhood exposures, and little investigation of effect modifiers, which are helpful for guiding preventive interventions.

Some studies have linked maternal psychopathology to offspring SRT and SA and an earlier age of onset, but the nature of this relationship is not well-understood. The association may in part be due to shared genetic susceptibility, or it may be that exposure to maternal illness when children are neurodevelopmentally and emotionally sensitive increases risk through neuroendocrine programming involving the hypothalamic pituitary adrenal axis. While genetics indeed play an important role in creating susceptibility for SA, they likely act in concert with environmental exposures surrounding family upbringing, stressful life events and other social factors.

A recent systematic review indicated that investigations of the association between parental psychopathology and offspring SRT and SA have yielded mixed findings with most studies meeting high-risk of bias. Further, this review reported that approximately 70% of studies did not verify if the exposure to parental psychopathology occurred in childhood. The few prospective studies confirming childhood exposure to parental mood disorder support an elevated risk of SRT and SA compared to adolescent offspring of well mothers, even of mothers with sub-clinical depressive symptoms.

An important, yet missed focus of research to date on how maternal mood disorder impacts mental health outcomes in offspring is the question: for whom and why? Not all children of mothers with major mood disorders develop psychopathology, and there has been little investigation into effect modifying influences of variables that might buffer this association. There is evidence that the
risk of hospital presentation of suicide-related behaviour among offspring exposed to parental psychopathology is higher among those coming from non-intact families compared to intact families. Low offspring perceived social support increases risk for adolescent SRT and SA and the relative contribution of perceived social support from parents has been found to be more strongly related to SRT and SA compared to support from peers. Further, there is evidence that the protective effect of parental secure attachment on adolescent SA risk is enhanced among families reporting high social cohesion within their neighborhood. However, it is unclear how parental perceived social support or cohesiveness might buffer the risk of SRT and SA in their children among parents who are depressed. Sex may also act as an effect measure modifier of this association, but few studies have examined sex differences, and among published studies the findings are mixed. Examining effect measure modifiers of the association between parental depression and offspring SRT and SA risk could be beneficial for preventive strategies involving the identification of target groups and improving knowledge for mothers with major mood disorders to reduce perceived burden and anxiety about imposed risk on children. This line of research is important because, informing parents with a major mood disorder that the risk of mental health problems is elevated in their children is associated with increases in parental anxiety and distress.

The objectives of this study were to examine the association between maternal depressive symptoms in childhood and offspring self-reported SRT and SA in Canadian youth and young adults, and to identify possible effect measure modifiers of this association including family structure, maternal reported social support and cohesion, and offspring sex, using the National Longitudinal Survey of Children and Youth (NLSCY).

Methods

Data source

The NLSCY is a nationally representative cohort panel survey conducted by Statistics Canada for which Canadian children (herein referred to as offspring) and the parent respondent of each
participating household were followed from 1994 to 2009. The survey included a maximum of eight cycles of data collection spaced every two years. Children were between zero and 11 years of age at cycle one and were followed into young adulthood, up to age 25. The NLSCY sampling frame was based on Statistics Canada Labor Force Surveys, which cover approximately 97% of the Canadian population and exclude residents of Yukon, Nunavut, Northwest Territories and Indian Reserves\(^b\), full-time members of the Canadian Armed Forces, and inmates of institutions\(^20\). All NLSCY cycles were linked using unique personal identifiers.

**Study population**

This study used the original longitudinal cohort from the NLSCY, which was comprised of 22,831 children initially sampled in 1994/1995. Twenty-six percent of the original longitudinal sample (n=5928) were omitted after cycle one due to Statistics Canada budget cuts and to reduce subject burden (Figure 1). These excluded individuals were randomly selected to reduce potential selection biases, and the remaining sample accurately reflected the survey population\(^20\). The study population used in this study therefore included 16,903 offspring between the ages of 11 to 25 years of age (Figure 1). This study was approved by the Research Ethics Board at the University of Toronto (#00032787).

**Procedure**

The NLSCY includes both parent respondent and offspring reported measures. Offspring age-appropriate for the child and youth questionnaires (11 to 17 years, starting in cycle two) completed self-reported measures in schools. When offspring reached 18 years of age, the youth survey was completed by computer-assisted telephone interview to accommodate the aging cohort and capture those no longer in school. Parent respondents were the biological mother in >90% of cases and are

\(^b\) The term “Indian Reserve” is used throughout in keeping with the description used in the NLSCY population description\(^17\)
herein referred to as mothers\textsuperscript{20}. Mothers were interviewed either in person or by telephone using computer-assisted interviewing by Statistics Canada trained personnel at every cycle. The mother completed informed consent for their child offspring in the study, and offspring completed informed consents when they became of age to complete the computer assisted interviewing\textsuperscript{20}.

**Measures**

The exposure in this study was exposure to maternal-reported depressive symptoms in childhood. This measure was drawn from cycles one to six of the NLSCY when offspring were between zero and ten years of age as this was hypothesized as a biologically plausible exposure period, encompassing childhood critical periods when children are neurodevelopmentally sensitive\textsuperscript{9}. The NLSCY included the 12-item short form of the Center for Epidemiologic Studies Depression Scale (CES-D)\textsuperscript{21}, designed to assesses the frequency and severity of past-week depressive symptoms. The sensitivity and specificity of the original CES-D using the cut-off of 16 to detect cases of diagnostic and statistical manual criteria major depression have been reported at 0.87, and 0.70, respectively\textsuperscript{22}. A score of nine has been identified as a cut-off on this shortened CES-D version that is indicative of elevated levels of depression\textsuperscript{23}. A measure of exposure was derived from the repeated maternal-reported measures, constructed by dividing total scores at each cycle by number of cycles participated in, and then dichotomizing these average scores to $\geq$ nine and $< $ nine (Table 4.3 Supplemental). The exposure was coded as an average to ensure mothers different numbers of cycle participation were accounted for. This was necessary to reduce the risk of selection biases where offspring could have had a greater likelihood of being exposed if mothers had more cycles of non-response compared to those with less.

The outcomes in this study were incident and recurrent SRT and SA from 11 to 25 years of age measured between cycles two to eight. SRT and SA were measured by asking offspring: “During the past 12 months, did you seriously consider attempting suicide?” and “During the past 12 months, how many times did you attempt suicide?”\textsuperscript{20} Outcomes were coded as time to event variables reflecting time to incident (first reported event) and subsequent recurrent events corresponding to age at each cycle. Both incident and recurrent events were examined to determine
the association between the exposure and the development and persistence of events over adolescence and young adulthood.

Potential effect measure modifiers were identified a priori from the literature, including: maternal reported social cohesiveness and social support, family structure, and offspring sex. All of these variables were coded as time-fixed, dichotomous variables with some variables deriving from repeated measures reflecting an average over the offspring’s first decade of life. Detailed information on all these variables and rationale for their selection can be found in Table 4.3 Supplemental. Maternal-reported social cohesiveness at cycle one was measured by a revised version of the Simcha-Fagan Neighborhood Questionnaire\textsuperscript{24}, designed to assess perceived social cohesion within the mother’s neighborhood. Maternal-reported social support at cycle one was measured by a shortened six-item version of Weiss’s Social Provisions Model\textsuperscript{25}. Only cycle one measures of social support and cohesion were used (reflecting a time period when offspring were between zero and ten years of age) as these measures were dropped at cycle two and changed during subsequent cycles\textsuperscript{26}. Family structure was derived from the marital status variable that was repeated each cycle. A non-intact family was coded as presence of divorce, separation or single parent, while an intact family was coded as offspring living with parents who were married or common-law when offspring were between the ages of zero and ten years. Offspring sex was measured by asking mothers if their children in the study were male or female.

Confounders were also identified a priori from the literature and included: offspring sex, offspring participation in religious activities (time varying from 11 to 21 years of age), offspring stressful life events (4 to 10 years of age), maternal and spouse binge drinking (when offspring were between 0 to 10 years) and socio-economic status (SES) (see Table 4.3 Supplemental for confounder selection rationale).

\textit{Statistical analysis}

Differences in baseline descriptive characteristics between exposed and non-exposed offspring were estimated using standardized differences, which can be interpreted as small (0.20), medium (0.50) and large (0.80) effect sizes\textsuperscript{27}, that are invariant to large sample sizes\textsuperscript{28}. 
Unadjusted rates of incident SRT and SA between exposed and non-exposed were estimated, and the mean cumulative number of recurrent SRT and SA was estimated by using the mean cumulative function approach, where calculations were conducted as a function of age. Hazards and rates of incident and recurrent SRT and SA among youth were modeled, and hazard ratios and relative rates (HR, RR) and their corresponding 95% confidence intervals (CI) were estimated for offspring exposed to maternal depressive symptoms (vs. not).

Herein, a counting process framework was employed, with age in year at interview as the time scale (11 to 25 years). Owing to the NLSCY response structure, discontinuous risk intervals (e.g., gaps in respondent time) were present. These gaps in time were present both by design, because the NLSCY assessments were spaced every two years, while the outcome measure of SRT and SA reflect a one-year look back window, and by participant drop-out and re-entry into the survey at a later time. A counting process framework was used to account for both of these types of discontinuous risk intervals, which uses a time variable with a start and stop time, representing the specific time periods each offspring was observed as at risk. A survival model was used to estimate the risk of incident outcome, while risk of recurrent outcome was estimated using an Anderson-Gill recurrent event model. Recurrent event models were adjusted for potential within-subject correlation and dependency of events over time using a robust sandwich estimator and adjusting for prior events, respectively.

All models are adjusted for confounders identified a priori from the literature including: sex (also tested as an effect measure modifier), offspring age in years at baseline, offspring participation in religious activities (time varying), offspring stressful life event, SES, and maternal and paternal binge drinking. Statistical interaction and effect measure modification was tested by adding interaction terms to models and using adjusted stratum-specific effect estimates that reflect the adjusted effect of the exposure on the outcome within each level of the effect measure modifier.

To account for the NLSCY’s complex survey design, the longitudinal weights, and bootstrap weights provided by Statistics Canada were used to calculate point estimates and variances to produce unbiased estimates of the Canadian population and account for post-stratification and non-
response, respectively. Survival model assumptions were verified graphically. In particular, the proportional hazards assumption was verified through visual checks of log-log survival curves of all unadjusted and adjusted incident and recurrent time-to-event models. All analyses were performed using SAS software (version 9.4).

Results

Characteristics of the sample

The final study sample comprised 11,960 offspring after excluding 3734 (22%) and 1209 (7%) offspring with missing outcome or exposure measurements, respectively (Figure 4.1). 75.4% of offspring had complete follow-up data, or no more than two instances of cycle non-response, where they missed a cycle and re-entered the survey at a subsequent cycle. Cycle non-response was associated with offspring stressful life events and baseline age (Table 4.4 Supplemental), and these variables were adjusted for in multivariable models.

14.4% of offspring were exposed to maternal depressive symptoms between zero and ten years of age. There was a higher proportion of exposed compared to non-exposed offspring coming from families with lower SES (standardized difference=0.36; Table 4.1). Further, there was a higher proportion of exposed offspring reporting significant stressful life events from four to ten years of age (standardized difference=0.32), coming from non-intact families (standardized difference=0.57), and coming from families whose mothers reported low social support (standardized difference=0.32) compared to non-exposed offspring.

Hazard of SRT and SA

The unadjusted proportion of exposed offspring reporting at least one instance of SRT was 20.6% compared to 13.0% of non-exposed offspring from 11 to 25 years of age. Further, among exposed offspring, 13.2% reported at least one instance of SA, while 6.3% of non-exposed offspring reported SA from 11 to 25 years of age. The mean cumulative number of SRT recurrences was
higher in the exposed compared to non-exposed at all ages (Figure 4.3 Supplemental). By age 17 years, the cumulative number of SRT recurrences per 100 persons was 75 in exposed, and 49 in non-exposed, while the cumulative number of SA recurrences was 36 in exposed and 19 in non-exposed (Figure 4.3 Supplemental).

At any given age between 11 to 25 years, the incident hazard rates of SRT and SA in exposed offspring were significantly elevated by 1.7 times (95% CI: 1.51, 2.14) and 2.2 times (95% CI: 1.81, 2.86), respectively compared to non-exposed offspring. After adjustment for confounders, these hazard rates remained significantly elevated among exposed compared to non-exposed offspring (SRT adjusted HR: 1.67 95% CI: 1.37, 2.08) and (SA adjusted HR: 1.93 95% CI: 1.43, 2.05), (Table 4.2). The pattern of findings was similar in models predicting recurrent SRT and SA (Table 4.2). Primary associations were estimated in a sub-set of the sample excluding offspring with any instance of cycle non-response. The primary associations remained similar, and statistically significant among this subset with effect estimates attenuating slightly (Table 4.5 Supplemental).

Interaction and effect measure modification

The proportion of offspring residing with intact families between zero to ten years of age was 84.3%, while the proportion of offspring with mothers reporting high social support, and cohesion (=>90th percentile) was 24.5%, and 10.7%, respectively. There was no significant evidence of statistical interaction between any of the potential effect measure modifiers predicting either incident or recurrent SRT and SA (all p>0.05). Among males, the stratum-specific adjusted hazard of SRT and SA was not significantly different in exposed versus non-exposed, while among females, the stratum-specific adjusted hazards of incident SRT and SA were significantly elevated (HR: 1.67 95% CI: 1.44, 2.19) and (HR: 1.93 95% CI: 1.43, 2.50), respectively (Figure 4.2) and (Table 4.6 Supplemental). The stratum-specific adjusted hazards of incident SA were not statistically significant among offspring whose mothers reported high social cohesion or support, or coming from intact families, while the hazards were statistically significantly elevated among offspring whose mothers reported low social cohesion, social support, or coming from non-intact.
families (Figure 4.2). The pattern of interaction and effect modification findings for recurrent SRT and SA was similar to the incident SRT and SA findings (Table 4.6 Supplemental).

Discussion

This study reports on prospective associations between maternal depressive symptoms in childhood and offspring SRT and SA in adolescence and young adulthood, using nationally representative data from the NLSCY with up to 25 years follow-up in some offspring. Exposure to maternal depressive symptoms in childhood was associated with an almost doubled hazard of SA between 11 and 25 years of age and a 70% increased hazard of SRT relative to non-exposed offspring. Exposure to maternal depressive symptoms also increased the rate of recurrent SA and SRT between 11 and 25 years by approximately 90% and 60%, respectively. These associations remained statistically significant after adjustments for offspring stressful life event(s), maternal and spouse drinking behaviour, offspring religious activity involvement, and household SES.

Further, we found these associations were modified by offspring sex, such that these associations were significant among females and not males. Consistent with these findings, Tsypes et al\textsuperscript{18} reported an elevated risk of SRT in females exposed to maternal major depression but not in males. In contrast, Hammerton et al.\textsuperscript{13} did not find any sex differences in the association between maternal depression in childhood and adolescent SRT. Others have reported on associations between maternal depression and other offspring outcomes (e.g., depression, externalizing symptoms) by sex with mixed findings\textsuperscript{31-33}. Still, the mechanisms linking maternal depression to offspring SRT and SA may differ from those leading to other outcomes, and by age. Plausible explanations for an association between maternal depression and SRT and SA in females but not in males could be linked to neurodevelopmental differences during exposure to maternal depression where females are more vulnerable to these effects in comparison to males\textsuperscript{9}. Further, gender-specific responses to child behaviour by parents might also explain these sex differences. It has been suggested that female offspring of depressed mothers are at a greater risk for SRT and emotional problems than boys, as they are more sensitive to the stressors associated with maternal depression such as relationship strain\textsuperscript{34}. Our findings also suggest possible protective effects of residing with intact
families, where the hazard of offspring SRT and SA in exposed compared to non-exposed became non-significant among offspring residing with both parents in childhood.

Strengths and limitations

This study took advantage of a comprehensive, nationally representative survey with up to 25 years of follow-up in some offspring starting from zero years of age. The application of a survival model under a counting process framework to estimate rates for incident and recurrent SRT and SA accounting for discontinuous risk intervals from survey design and participant cycle non-response was unique. However, the following limitations should be considered.

Measures were based on self-report, which could lead to misreporting; however, offspring were ensured confidentiality and anonymity when completing measures. Further, by using a self-reported outcome, we were able to determine how maternal depressive symptoms are associated with SRT (an outcome not systematically collected in health administrative data) and SA, irrespective of hospitalization.

The main exposure in this study varied by offspring by age of entry at baseline and number of cycles participated in. In turn, the number of measurements available by age varied. While accounted for, exposure misclassification may still be possible, where older non-exposed offspring at cycle one could have been exposed at earlier ages. However, this misclassification would likely be non-differential because the proportion of exposed offspring between zero to ten years of age was relatively stable (Appendix D). Further, the numbers were too low to restrict the sample to those who were zero at cycle one, i.e., a birth cohort; therefore, the influence of timing of exposure could not be explored, which could lend important insight into developmentally sensitive windows, useful for the timing of preventive strategies.

There is no measure of family or parental history for suicide-related behaviour in the NLSCY; therefore, we were unable to examine their roles. Maternal SA is indeed linked to offspring SA\(^4\); however, there is evidence of independent pathways from maternal depression to offspring SRT and SA risk\(^{35}\). There is also no specific measure of childhood abuse in the NLSCY. This is an
established risk factor for suicide-related behaviour and depending on the timing may be associated with maternal depression. However, the stressful life event variable encompassed a summary variable that included a question about abuse\textsuperscript{20}, although numbers were too low to isolate this item. Finally, most variables were maternal reported, and there is limited paternal information available from the NLSCY. The lack of available paternal information is a limitation of many national surveys and more efforts should be focused on collecting paternal information.

Implications

There is an established link between exposure to maternal depression in childhood and psychiatric disorders in offspring\textsuperscript{36}, and findings from this study confirm an association with the development of and persistence of SRT and SA in female youth. This information is helpful for guiding preventive efforts in terms of identifying high-risk groups, and for clinician monitoring of high-risk children; however, without understanding of the context of this association, we lack necessary information to inform such prevention strategies. Suicide intervention studies have been dominated by studies of populations of youth identified via treatment settings or already in crisis and tend to exclude those not going to the hospital\textsuperscript{37}. However, the implementation and evaluation of family-based interventions, that support high-risk families before children get to a crisis stage in the field of suicide prevention is growing\textsuperscript{38-40}, and there is a need to further inform and develop these prevention strategies. Research on sex-specific moderating and mediating pathways explaining the association between maternal depression and offspring SRT and SA risk would be useful for this purpose.

Conclusions

Exposure to maternal depressive symptoms before age 11 in girls significantly elevates the risk of the development and persistence of thinking about suicide and reporting attempts before 25 years of age. These individuals reflect a target group for early preventive strategies and clinician monitoring. A shift in research focus to family protective factors of SRT and SA risk among offspring of depressed mothers could be useful in informing future effective preventions that
support families and their high-risk children before the onset of offspring suicide-related behaviour, halting progression towards suicide.
References


**Figure 4.1** Flow diagram of sample selection from the National Longitudinal Survey of Children and Youth, 1994 – 2009

- **Original Longitudinal Cohort**

  - **Age in years**
    - 0-11
      - Cycle 1 (1994/1995) 22,831
    - 2-13
    - 4-15
      - Cycle 3 (1998/1999)
    - 6-17
      - Cycle 4 (2000/2001)
    - 8-19
    - 10-21
    - 12-23
      - Cycle 7 (2006/2007)
    - 14-25
      - Cycle 8 (2008/2009)

- **Exposure coverage 0-10 years**
- **Outcome coverage 11-25 years**

- *5928 omitted for budget*

- Suicide-related thoughts and behaviour items available in 11+ year-olds

- Cycles 1-8 merged

- Missing outcome data: 3734
  Missing exposure data: 1209

- Final sample analyzed: 11,960

*Households from the National Population Health Survey and max number of children per household cut from 4 to 2
Figure 4.2 Stratum-specific adjusted hazard ratios and 95% confidence intervals of suicide-related thoughts and attempts in 11 to 25-year-old offspring exposed versus non-exposed to maternal depressive symptoms in childhood, weighted to reflect the Canadian general population.

*Adjusted for sex (not in models testing effect modification of sex), socio-economic status, offspring participation in religious activities (time varying), maternal and spouse binge drinking (0-10 years), child stressful life event (4-10 years), and offspring age at cycle one

*Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.

x-asis is on the log10 scale

Hazard ratios and 95% confidence intervals
Table 4.1 Standardized differences between proportions of sample characteristics in offspring exposed and non-exposed to maternal depressive symptoms in childhood, weighted to reflect the Canadian general population

<table>
<thead>
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<th>Offspring sex</th>
<th>Male</th>
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<th>Non-exposed</th>
<th>SD (^h)</th>
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<td>49.16</td>
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<th>Exposed</th>
<th>Non-exposed</th>
<th>SD (^h)</th>
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<tr>
<td>1 - at least once</td>
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<td>22.45</td>
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<tr>
<td>2 - at least once a month</td>
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<td>13.04</td>
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<tr>
<td>3 - at least 3 or 4 times a year</td>
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<td>13.13</td>
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<th>Non-exposed</th>
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<th>SD (^h)</th>
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<th>Maternal reported social support (baseline)</th>
<th>High</th>
<th>Exposed</th>
<th>Non-exposed</th>
<th>SD (^h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>13.22</td>
<td>26.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>85.46</td>
<td>72.75</td>
<td>0.32</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal reported</th>
<th>High</th>
<th>Exposed</th>
<th>Non-exposed</th>
<th>SD (^h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>7.62</td>
<td>11.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>82.74</td>
<td>81.10</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>social cohesion (baseline)</td>
<td>Missing</td>
<td>9.65</td>
<td>7.69</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>Offspring stressful life event (4-10 years)</td>
<td>No</td>
<td>17.89</td>
<td>31.30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>82.11</td>
<td>68.69</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0.00</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

SD: standardized differences

a) Presented as offspring participation in religious activities at first available cycle (cycle two). In multivariable models, this variable reflects a time varying measure from offspring age 11-21 years.

b) Socio-economic status corresponding categories are presented in supplementary table 1

c) Represents proportion of maternal and spouse binge drinking occasions over ten when offspring were between 0-10 years.

d) Family intact: married or common law for entire first 10 years of offspring’s life; Not intact, at least one report of divorced widowed, separated or single never married

e) Yes reflects any maternal report of child offspring experiencing a stressful life event from 4-10 years of age

f) The offspring participation in religious activities was only measured in 11-19-year-olds. 92% of the missing values for this variable reflects valid skips of offspring over 19 years of age.

g) Absolute values of 0.2=small, 0.5=medium, and 0.8=large effect sizes

h) Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves
### Table 4.2 Hazard ratios, relative rates and 95% confidence intervals of suicide-related thoughts and attempts in 11 to 25-year-olds among those exposed and non-exposed to maternal depressive symptoms in childhood, weighted\(^c\) to reflect the Canadian general population

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted(^a)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95%CI(^b)</td>
<td>#observations (unweighted)</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>SRT incident</td>
<td>1.74</td>
<td>1.51</td>
<td>2.14</td>
<td>29772</td>
</tr>
<tr>
<td>SA incident</td>
<td>2.24</td>
<td>1.81</td>
<td>2.86</td>
<td>40182</td>
</tr>
<tr>
<td></td>
<td>Relative rate</td>
<td>95%CI(^b)</td>
<td>#observations (unweighted)</td>
<td>Relative rate</td>
</tr>
<tr>
<td>SRT recurrent</td>
<td>1.67</td>
<td>1.28</td>
<td>2.00</td>
<td>32187</td>
</tr>
<tr>
<td>SA recurrent</td>
<td>2.00</td>
<td>1.45</td>
<td>2.54</td>
<td>41889</td>
</tr>
</tbody>
</table>

CI: confident intervals; SA: suicide attempt; SRT: suicide-related thoughts

\(^a\)Adjusted for sex, socio-economic status, offspring participation in religious activities (time varying), maternal and spouse binge drinking (0-10 years), child stressful life event (4-10 years), and offspring age at cycle one

\(^b\)Estimated using Statistics Canada Bootstrap weights

\(^c\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves
### Table 4.3 Supplemental - Description of study measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Description</th>
<th>Coding</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Maternal depressive symptoms    | Cycles 1 to 6 (when offspring were 0 to 10 years) | Average exposure to maternal depressive symptoms, indicative of depression when offspring were between the ages of 0 to 10 years | Average total CES-D score: total scores at each cycle/number of cycles participated in  
1=Average total score ≥9  
0=Average total score <9 | To account for different numbers of cycle participation, total scores were divided by number of cycles participated in. Age at baseline (cycle 1) was adjusted for in all multivariable models |
|                                 |                                           | The short form of the CES-D has been shown to be internally consistent (Cronbach’s α=0.86). The CES-D is not a diagnostic measure, but rather a screening tool to identify individuals endorsing high levels of depressive symptoms that are related to the diagnosis of major depression |                                                                        |                                                                           |
| **Confounders**                 |                                           |                                                                                                       |                                                                        |                                                                           |
| Maternal/spouse binge drinking occasions | Cycles 1 to 6 (when offspring were 0 to 10 years) | Average exposure to mother/spouse binge drinking when offspring were between the ages of 0 to 10 years  
Spouse binge drinking was reported by the mother | Average total number of past year binge drinking occasions (5 or more drinks on 1 occasion): total occasions/number of cycles participated in  
1=Average total occasions ≥10  
0=Average total occasions <10 | The maternal and spouse binge drinking items were highly skewed to the right with a high number of zeros across all cycles. This variable was dichotomized to above and below the 90th percentile (10 binge drinking occasions)  
To account for different numbers of cycle participation, total occasions were divided by number of cycles participated in. |
These variables were selected given their association with offspring suicide attempts, and a plausible association with maternal depression. These variables were selected given their association with offspring suicide attempts, and a plausible association with maternal depression. The SES composite score was not available in all NLSCY cycles and socio-economic environment of families in childhood was the measure of interest (not later in adolescence), therefore only a baseline measure of SES was used. This variable was selected given the differences in suicide attempts and psychopathology by SES group.

| Maternal reported SES continuous (used in multivariable models) | Cycle 1 (when offspring were 0 to 11 years) | Composite score derived from maternal and spouse highest level of education, occupation and household income | Continuous score ranging from -2.0 to 1.75 | The SES composite score was not available in all NLSCY cycles and socio-economic environment of families in childhood was the measure of interest (not later in adolescence), therefore only a baseline measure of SES was used. This variable was selected given the differences in suicide attempts and psychopathology by SES group. |
| Maternal reported SES categorical (for descriptive purposes only) | 5: Both the mother and spouse have a university degree (BA/BSc), are employed professionals, household income is $80,000 | SES composite scores ≥1.5 |
| | 4: Mother has a university degree (BA/BSc) and spouse has grade 13, mother is employed as a semi-professional and spouse employed in a semi-skilled clerical position, household income is $65,000 | SES composite scores <1.5≥0.5 |
| | 3: Mother has grade 13 and spouse grade 12. Spouse is employed in a semi-skilled manual position and mother has a semi-skilled clerical position or is not in the labour force, household income is $55,000 | SES composite scores <0.5≥0.0 |
| | 2: Mother and spouse completed high-school, mother is employed in a semi-skilled manual position and spouse in an unskilled manual position, household income is $30,000 | SES composite scores <0.0≥-0.5 |
| | 1: Mother and spouse did not complete high-school, mother is | SES composite scores <0.5 |
| Offspring participation in religious events | Cycles 2 to 8 (when offspring were 11 to 21 years) | Offspring participation in religious events (maternal reported in 11-15-year old’s, self-reported in 16-21-year old’s): “Other than on special occasions (such as weddings, funerals or baptisms), how often did your child attend religious services or meetings in the past 12 months?” | Time varying covariate indicating: 0=None at all 1=At least once a week 2=At least once a month 3=At least 3-4 times a year 4=At least once a year | It was expected that participation in religious events from 11 to 21 years of age might change when offspring become older, therefore this variable was examined as time-varying. This variable was selected because participation in religious activities are significantly related to lower suicide rates and depression. |
| Offspring stressful life event | Cycles 1 to 6 (when offspring were 4 to 10 years) | Offspring significant stressful events (maternal reported in 4-10-year-olds): “Has ... ever experienced any event or situation that has caused him/her a great amount of worry or unhappiness?” | 1 = Yes 0 = No | This variable was only measured in offspring =>4 years and was only derived from cycles 1 to 6 to capture the exposure time of interest (between 0 to 10 years of age). This variable was selected as offspring stressful experiences such as a loss, illness/injury, or separation from parents are associated with suicide attempts in adolescents and likely exacerbate psychiatric symptoms in parents. |
| Offspring Sex | Cycle 1 | Maternal reported sex of their child offspring | 1=Male 0=Female | Sex was expected to be both a confounder and an effect measure modifier There was no measure of self-reported gender in the NLSCY |

Effect measure modifiers
<table>
<thead>
<tr>
<th>Offspring Sex</th>
<th>Cycle 1</th>
<th>Maternal reported sex of their child offspring</th>
<th>1=Male 0=Female</th>
<th>Sex was expected to be both a confounder and an effect measure modifier. There was no measure of self-reported gender in the NLSCY.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal social support</td>
<td>Cycle 1 (when offspring when 0 to 10 years)</td>
<td>6-item maternal reported social support continuous scale (based on the Social Provisions Scale) designed to assess perceived support from family, friends and others (Cronbach’s alpha’s &gt;0.90)</td>
<td>1=Total score at cycle 1&gt;18 0=total score at cycle 1≤18</td>
<td>This measure was dichotomized to above and below the 90th percentile (18) to effectively test for effect measure modification. This measure was dropped from the NLSCY in cycle 2 and changed with subsequent cycles and maternal social support when offspring were young was of interest (not when offspring were in adolescence), therefore only the baseline measure was used. This variable was selected given its potential as an upstream preventive target for youth suicide prevention.</td>
</tr>
<tr>
<td>Maternal social cohesion</td>
<td>Cycle 1 (when offspring when 0 to 10 years)</td>
<td>5-item maternal reported social cohesion continuous scale (based on the Simcha-Fagan Neighbourhood Questionnaire) designed to assess perceived social cohesion with the neighbourhood (Cronbach’s alpha’s &gt;0.90)</td>
<td>1=Total score at cycle 1&gt;15 0=total score at cycle 1≤15</td>
<td>This measure was dichotomized to above and below the 90th percentile (15) to effectively test for effect measure modification. This measure was dropped from the NLSCY in cycle 2 and changed with subsequent cycles and maternal social cohesion when offspring were young was of interest (not when offspring were in adolescence), therefore only the baseline measure was used.</td>
</tr>
</tbody>
</table>
Family structure | Cycles 1 to 6 (when offspring where 0 to 10 years) | Family intactness derived from maternal reported repeated marital status categories: Non-intact: presence of non-intactness during first 10 years of offspring’s life Intact: Completely intact during first 10 years of offspring’s life | 1 (intact) = married, living with partner or common-law 0 (non-intact) = single, never married, separated, divorced, widowed | Family structure when offspring were young (during the exposure time 0 to 10 years) was of interest, therefore this measure was derived only from cycles 1 to 6 to cover the appropriate age periods. This variable was selected given its potential as an upstream preventive target for youth suicide prevention7.

References

Table 4.4 Supplemental - Standardized differences between covariates in offspring with and without cycle non-response, weighted\textsuperscript{b} to reflect the Canadian general population

<table>
<thead>
<tr>
<th></th>
<th>Cycle non-response yes\textsuperscript{a}</th>
<th>Cycle non-response no\textsuperscript{b}</th>
<th>SD\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%\textsuperscript{d}</td>
<td>%\textsuperscript{d}</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>82.11</td>
<td>68.69</td>
<td>0.11</td>
</tr>
<tr>
<td>Male</td>
<td>47.57</td>
<td>53.03</td>
<td></td>
</tr>
<tr>
<td>Socio-economic status\textsuperscript{e}</td>
<td>1 - lowest</td>
<td>10.07</td>
<td>6.36</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>16.93</td>
<td>12.82</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>29.23</td>
<td>26.91</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>22.93</td>
<td>24.62</td>
</tr>
<tr>
<td></td>
<td>5 - highest</td>
<td>20.14</td>
<td>28.07</td>
</tr>
<tr>
<td>Offspring participation in religious activities\textsuperscript{d}</td>
<td>0 - not at all</td>
<td>18.68</td>
<td>22.51</td>
</tr>
<tr>
<td></td>
<td>1 - at least once</td>
<td>22.53</td>
<td>22.29</td>
</tr>
<tr>
<td></td>
<td>2 - at least once a month</td>
<td>12.40</td>
<td>13.17</td>
</tr>
<tr>
<td></td>
<td>3 - at least 3-4 times/year</td>
<td>12.72</td>
<td>14.48</td>
</tr>
<tr>
<td></td>
<td>4 - at least once a year</td>
<td>7.67</td>
<td>8.74</td>
</tr>
<tr>
<td>Age at baseline in years</td>
<td>0-2</td>
<td>14.05</td>
<td>31.27</td>
</tr>
<tr>
<td></td>
<td>3-5</td>
<td>21.97</td>
<td>29.43</td>
</tr>
<tr>
<td></td>
<td>6-8</td>
<td>29.77</td>
<td>19.50</td>
</tr>
<tr>
<td></td>
<td>9-11</td>
<td>34.49</td>
<td>19.30</td>
</tr>
<tr>
<td>Offspring stressful life event (4-10 years)\textsuperscript{e}</td>
<td>Yes</td>
<td>67.91</td>
<td>26.25</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>32.33</td>
<td>73.26</td>
</tr>
<tr>
<td>Maternal binge drinking (0-10 years)\textsuperscript{f}</td>
<td>Yes</td>
<td>4.27</td>
<td>3.33</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>83.77</td>
<td>89.73</td>
</tr>
<tr>
<td>Spouse binge drinking (0-10 years)\textsuperscript{f}</td>
<td>Yes</td>
<td>8.06</td>
<td>10.14</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>79.24</td>
<td>82.65</td>
</tr>
<tr>
<td>Suicide attempt (11-25 years)</td>
<td>Yes</td>
<td>7.87</td>
<td>7.37</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>92.41</td>
<td>92.13</td>
</tr>
<tr>
<td>Suicide-related thoughts (11-25 years)</td>
<td>Yes</td>
<td>13.58</td>
<td>16.83</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>86.70</td>
<td>82.68</td>
</tr>
<tr>
<td>Maternal depressive symptoms (0-10 years)</td>
<td>Yes</td>
<td>14.80</td>
<td>9.43</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>72.89</td>
<td>83.49</td>
</tr>
</tbody>
</table>
SD: standardized difference  
\(^a\) Offspring with one or more instance of cycle non-response  
\(^b\) Offspring with complete follow-up  
\(^c\) Socio-economic status corresponding categories are presented in Table 4.3 Supplemental  
\(^d\) Presented as offspring participation in religious activities at first available cycle (cycle 2). In multivariable models, this variable reflects a time varying measure from offspring age 11-9 years.  
\(^e\) Yes: Any maternal report of child distressing stress from 4-10 years of age  
\(^f\) Represents proportion of maternal and spouse binge drinking occasions over ten when offspring were between 0-10 years.  
\(^g\) Absolute values of 0.2=small, 0.5=medium, and 0.8=large effect sizes  
\(^h\) Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves  
\(^i\) Some frequencies do not amount to 100 owing to missing data on specific covariates
### Table 4.5 Supplemental - Sensitivity analysis: Primary unadjusted and adjusted associations among those with no cycle non-response, weighted\(^c\) to reflect the Canadian general population

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted(^a)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95%CI(^b)</td>
<td>#observations (unweighted)</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>Incident SRT</td>
<td>1.54</td>
<td>1.18</td>
<td>2.13</td>
<td>14328</td>
</tr>
<tr>
<td>Incident SA</td>
<td>2.00</td>
<td>1.22</td>
<td>2.95</td>
<td>18619</td>
</tr>
</tbody>
</table>

CI: confident intervals; SA: suicide attempts; SRT: suicide related thoughts
\(^a\)Adjusted for sex, socio-economic status, offspring participation in religious activities (time varying), maternal and spouse binge drinking during each indicated time period, offspring stressful life event (4-10yrs), offspring age at baseline
\(^b\)Estimated using Statistics Canada Bootstrap weights
\(^c\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves
Table 4.6 Supplemental - Stratum specific adjusted\(^a\) hazard ratios of effect modifying variables of associations between maternal depressive symptoms in childhood and offspring recurrent suicide-related thoughts and attempts from 11-25 years of age, weighted\(^c\) to reflect the Canadian general population

<table>
<thead>
<tr>
<th>Effect measure modifiers</th>
<th>Incident suicide-related thoughts</th>
<th>Incident suicide attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95%CI(^b))</td>
<td>Hazard ratio (95%CI(^b))</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.89 (0.68, 1.19)</td>
<td>0.77 (0.54, 1.15)</td>
</tr>
<tr>
<td>Female</td>
<td>1.67 (1.44, 2.19)</td>
<td>1.93 (1.43, 2.50)</td>
</tr>
<tr>
<td>Family intactness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.36 (0.95, 1.82)</td>
<td>1.16 (0.71, 1.63)</td>
</tr>
<tr>
<td>No</td>
<td>1.62 (1.32, 1.98)</td>
<td>1.77 (1.31, 2.26)</td>
</tr>
<tr>
<td>Maternal social support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.71 (1.26, 2.37)</td>
<td>1.67 (1.03, 2.66)</td>
</tr>
<tr>
<td>Low</td>
<td>1.70 (1.35, 2.06)</td>
<td>1.88 (1.42, 2.47)</td>
</tr>
<tr>
<td>Maternal social cohesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.56 (1.03, 2.13)</td>
<td>1.67 (0.93, 2.49)</td>
</tr>
<tr>
<td>Low</td>
<td>1.70 (1.39, 2.15)</td>
<td>1.95 (1.45, 2.59)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Recurrent suicide-related thoughts</th>
<th>Recurrent suicide attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative rate (95%CI(^b))</td>
<td>Relative rate (95%CI(^b))</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.84 (0.62, 1.08)</td>
<td>0.74 (0.52, 1.09)</td>
</tr>
<tr>
<td>Female</td>
<td>1.61 (1.33, 1.96)</td>
<td>1.87 (1.40, 2.36)</td>
</tr>
<tr>
<td>Family intactness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.40 (0.96, 1.85)</td>
<td>1.20 (0.71, 1.68)</td>
</tr>
<tr>
<td>No</td>
<td>1.58 (1.28, 1.90)</td>
<td>1.74 (1.29, 2.20)</td>
</tr>
<tr>
<td>Maternal social support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.69 (1.25, 2.28)</td>
<td>1.62 (1.03, 2.49)</td>
</tr>
<tr>
<td>Low</td>
<td>1.60 (1.32, 1.96)</td>
<td>1.82 (1.36, 2.33)</td>
</tr>
<tr>
<td>Maternal social cohesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.51 (0.99, 1.97)</td>
<td>1.61 (0.90, 2.39)</td>
</tr>
<tr>
<td>Low</td>
<td>1.63 (1.33, 2.00)</td>
<td>1.88 (1.41, 2.41)</td>
</tr>
</tbody>
</table>

CI: confidence interval
\(^a\)Adjusted for socio-economic status, offspring participation in religious activities (time varying), maternal binge drinking, spouse binge drinking and sex (only in models not examining sex as an effect modifier) and past suicide-related thoughts and attempts (only in models with suicide attempt outcomes)
\(^b\)Estimated using Statistics Canada Bootstrap weights
\(^c\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of
institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves
Figure 4.3 Supplemental - Cumulative mean function for recurrent suicide-related thoughts (A) and attempts (B) by age in offspring exposed and non-exposed to maternal depressive symptoms in childhood, weighted to reflect the Canadian general population.

A. Suicide-related thoughts

B. Suicide attempts
Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.

Owing to Statistics Canada release guidelines, the entire age range (11-25 years) was collapsed to 12-18 years.
Chapter 5
Paper 3: Exposure to maternal depressive symptoms in childhood and adolescent suicide-related thoughts and attempts: Mediation by child psychiatric symptoms

5 Paper 3

A version of this manuscript is in review with Epidemiology and Psychiatric Sciences
Exposure to maternal depressive symptoms in childhood and adolescent suicide-related thoughts and attempts – Mediation by child psychiatric symptoms

Sarah M. Goodday¹, Susan Bondy¹, Hilary K. Brown¹,³, Rinku Sutradhar²,⁴, Anne Rhodes¹,⁴,⁵

¹University of Toronto, Department of Epidemiology, Dalla Lana School of Public Health
²University of Toronto, Department of Biostatistics, Dalla Lana School of Public Health
³University of Toronto, Department of Psychiatry, Dalla Lana School of Public Health
⁴Institute for Clinical Evaluative Sciences
⁵McMaster University, The Offord Centre for Child Studies
Abstract

Objectives: To assess whether child psychiatric symptoms from six to ten years of age mediate the association between exposure to maternal depressive symptoms in childhood and offspring suicide-related thoughts (SRT) and attempts (SA) in adolescence.

Methods: A cohort study was constructed by linking all eight cycles from the National Longitudinal Survey of Children and Youth (NLSCY), a nationally representative Canadian panel survey conducted from 1994-2009. Self-reported maternal depressive symptoms were measured when offspring were between zero to five years. Maternal-reported child psychiatric symptoms and comorbidity were measured from six to ten years, and offspring self-reported SRT and SA were measured between 11 to 19 years. Indirect effects, the effect proportion mediated, and their corresponding bootstrapped 95% confidence intervals (CI) were estimated.

Results: Hyperactivity and inattention significantly mediated the association between maternal depressive symptoms in childhood and risk of both SRT and SA from 11 to 19 years, where approximately 60% (SRT 95% CI: 23, 94%; SA 95% CI: 27, 95%) of this association was explained by hyperactivity and inattention. Psychiatric comorbidity significantly mediated this relationship with SA only, accounting for 50% (95% CI: 18, 81%) of this association.

Conclusions: Targeting hyperactivity and inattention and co-occurring psychiatric symptoms in offspring of mothers exhibiting depressive symptoms could reduce risk of SRT, eventual SA, and halt progression towards suicide. However, further understanding of comorbid psychiatric symptoms in childhood that most strongly predict adolescent SA is needed.
Introduction

Suicide-related behavior begins in adolescence, and is strongly associated with the progression to suicide\(^1\), exacting a heavy toll in young populations. Psychological autopsy studies report that approximately 90% of individuals who die by suicide had a prior psychiatric diagnosis\(^2\), and community-based surveys of younger populations (14 to 25 years) with suicide attempts (SA) report prior psychiatric disorders in approximately 90% of cases\(^3\). However, 40% of youth who die by suicide under age 16 years do not meet full diagnostic criteria for a psychiatric disorder\(^1\). The nature of the psychiatric disorder-suicide relationship remains ill-defined and only recently have suicide-related behaviors been recognized as separate from psychiatric illness\(^4\). Further, there is evidence that psychiatric symptoms, in part, explain associations between adverse early environments and (SA) risk\(^5, 6\). Knowledge of other antecedent risk factors of both suicide-related behaviors and psychiatric symptoms and mediating pathways are needed to understand the etiology of suicide-related behavior onset to inform preventive strategies.

Exposure to maternal depression in childhood is a risk factor for a broad range of psychopathology including internalizing and externalizing disorders in offspring occurring from early childhood to late adolescence\(^7\). Some studies also support that maternal depression is associated with offspring suicide-related behavior\(^8\), although the nature of this association is understudied. Hypothesized mechanisms linking maternal depression to offspring psychiatric problems in addition to or interacting with genetics, involve disruptions in neuro-programming of important emotional systems during sensitive windows in childhood. These disruptions in turn, can have lasting influences on emotional functioning evident as early as childhood, producing a psychological vulnerability\(^9\). Psychiatric symptoms may reflect a vulnerable phenotype resulting from maternal depression that in turn predicts SRT and SA.

Trajectory-based studies have shown that externalizing symptoms and depression at age 11 to 12 years predict high-risk trajectories of SRT up to age 15 years\(^10\) and anxiousness and disruptiveness in kindergarten children predicts SA between 15 and 24 years\(^11\). A common finding across studies is that psychiatric comorbidity (co-occurring psychiatric diagnoses) appears to heighten risk of both SRT and SA in adolescence and young adulthood\(^3, 12, 13\), where multiple psychiatric diagnoses

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\(^13\) Reference
together predict a greater risk, compared to individual diagnoses alone. Externalizing disorders may be more strongly related to SA, primarily through impulsivity\textsuperscript{14}, while internalizing disorders may be more related to SRT via the symptom of hopelessness\textsuperscript{15}. In support of this, there is evidence that attention deficit hyperactivity disorder at age 15 years is associated with SA but not SRT at age 16\textsuperscript{16}, and genetic studies also support that the transmission of SA risk but not SRT is mediated by genetic transmission of impulsive-aggressive traits\textsuperscript{17}. There is also some evidence that these associations are sex/gender specific, however research is limited, particularly in younger ages\textsuperscript{18}.

Few studies have specifically tested whether child or adolescent psychiatric symptoms mediate the association between exposure to maternal depression and SRT and SA\textsuperscript{8}. Hammerton et al\textsuperscript{16} reported that symptoms of major depression, generalized anxiety disorder, and disruptive behavior disorder, but not attention deficit hyperactivity disorder at age 15 significantly mediated the association between chronic and severe, and even moderate maternal depression from zero to 11 years of age and offspring SRT at age 16. In the same study, the same set of psychiatric symptoms in addition to attention deficit hyperactivity disorder were found to mediate the association between maternal depression and offspring SA at age 16\textsuperscript{16}.

Knowledge of pathways to incident SRT and SA could be useful for understanding their etiology and for informing the development and implementation of preventive interventions. Our objective was to test whether child psychiatric symptoms from six to ten years of age mediate the association between exposure to maternal depressive symptoms from zero to five years of age and adolescent SRT and SA from 11 to 19 years of age, using prospectively captured data from the National Longitudinal Survey of Children and Youth (NLSCY).

**Methods**

*Data source and study population*

The NLSCY was a nationally representative longitudinal survey with a maximum of eight cycles, spaced every two years, conducted by Statistics Canada. The sampling frame was based on the Labor Force Surveys, which includes approximately 97% of the Canadian population excluding full-time members of the Canadian Armed Forces, inmates of institutions, and residents of Indian
Reserves\(^c\), Yukon, Nunavut, and the Northwest Territories\(^{19}\). Children (herein referred to as offspring) and the parent respondent of each participating household were followed from 1994 to 2009 including respondents between zero and 11 years of age at baseline (cycle one) and up to age 25 years by the last cycle. In 90\% of cases, the parent respondent was the biological mother and hereafter is referred to as the mother\(^{19}\). All NLSCY cycles (one to eight) were linked using unique personal identifiers.

This study included offspring who participated in the original NLSCY longitudinal cohort, which was comprised of 22,831 children, first sampled in 1994/1995. Due to Statistics Canada budget cuts and to reduce respondent burden on families with several participating respondents, 26\% of the baseline longitudinal sample were randomly excluded after cycle one (Figure 5.1). However, the remaining sample accurately reflected the survey population (n=16,903)\(^{19}\). For this analysis, the sample was reduced to offspring with outcome data, no cycle non-response, and to those offspring who were between zero to five years of age at baseline. The resulting study population included 3123 offspring between zero and 19 years of age (Figure 5.1). The proportion of missing data that reflected “not stated” for the exposure, mediators and other covariates was low (<5\%).

*Procedure*

The NLSCY included both maternal and offspring-reported measures conducted through computer assisted phone interviews by Statistics Canada trained personnel or through school self-report questionnaires. The mothers were interviewed either in person or by telephone, while youth offspring between 11 and 17 years completed self-reported measures in schools. When offspring reached 18 years of age, the youth survey was completed by computer assisted phone interview, to accommodate the aging cohort and capture those no longer in school. Informed consent was completed by young adult respondents when completing computer assisted interviewing, while the

\(^c\) The term “Indian Reserve” is used throughout in keeping with the description used in the NLSCY population description\(^{17}\)
mother completed informed consent for their children and adolescents in the study\textsuperscript{19}. This study was approved by the Research Ethics Board at the University of Toronto (#00032787).

\textit{Measures}

Specific time periods of measurement were chosen to ensure temporal order between the exposure, mediator and outcomes.

Exposure to maternal depressive symptoms when offspring were between zero and five years of age was the main exposure. Maternal depressive symptoms were measured from the 12-item short form of the Center for Epidemiologic Studies Depression Scale (CES-D)\textsuperscript{20} designed to assess the frequency and severity of past-week depressive symptoms (Cronbach’s $\alpha=0.86$)\textsuperscript{21}. For each offspring, total scores were averaged across repeated assessments and then coded over an established cut-off of nine reflected elevated depressive symptoms indicative of possible cases of major depression\textsuperscript{22}. Producing an average score was necessary to account for different numbers of cycle participation by mothers, while the dichotomy using the clinical cut-off was necessary to deal with considerable floor effects of this measure. The exposure was self-reported by the mother.

Incident SRT and SA occurring between 11 and 19 years of age were our main outcomes and self-reported by the offspring. SRT and SA were measured by asking offspring: “During the past 12 months, did you seriously consider attempting suicide?” and “During the past 12 months, how many times did you attempt suicide?”\textsuperscript{19}. Both SRT and SA measures were coded as binary variables indicating yes or no.

Child psychiatric symptoms, when offspring were between six and ten years of age, were examined as mediators and reported by the mother. These measures were derived from the NLSCY parent-reported behaviors scale for four to 11-year-olds, designed to assess psychiatric symptoms that map onto Diagnostic and Statistical Manual – III – Revised and IV criteria\textsuperscript{19}. These maternal-reported scales were originally derived from the Child Behavior Checklist\textsuperscript{23}. These measures have been shown to be internally consistent, and valid\textsuperscript{20, 24}. The subscales from the Behaviours Scale included: emotion-anxiety (internalizing), hyperactivity-inattention, conduct-physical aggression,
and indirect aggression. Total scores for each subscale were averaged across measurements when offspring were between six and ten years of age and then coded to reflect an average score over the 75th percentile, suggestive of moderate symptoms for each separate subscale. The Behaviours Scale subscale scores were positively skewed with substantial floor effects, making their dichotomy into percentiles necessary, as suggested by others. A measure reflecting psychiatric comorbidity was also derived from these measures reflecting two or more subscales meeting the cut-off of > 75th percentile (where 1=two or more symptoms indicative of comorbid diagnoses, and 0=None).

Potential confounders (see Table 5.3 Supplemental which includes the rationale for each included confounder) were identified a priori from the literature relevant to the exposure-mediator, mediator-outcome and exposure-outcome level. These included maternal-reported offspring stressful life events occurring between four and ten years of age (the age range when this measure was available), maternal and spouse binge drinking when offspring were between zero and ten years of age, socio-economic status (SES) measured at baseline (when offspring were between zero to ten years of age), and offspring sex.

Statistical analysis

Differences in descriptive characteristics between offspring exposed and non-exposed to maternal depressive symptoms were estimated using standardized differences. Standardized differences are invariant to large sample sizes and can be interpreted as small (0.20), medium (0.50) and large (0.80) effect sizes.

Methods outlined by Shrout and Bolger and others guided the mediation approach (Methods 1S). Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated to quantify the magnitude of each path A (exposure – mediator), B (mediator - outcome), and C (total effect) (Step 1: Methods 1S). Several mediation models were estimated, quantifying the mediating effect of each independent psychiatric symptom subscale and psychiatric comorbidity on both outcomes separately. Specifically, unadjusted and adjusted beta-coefficients (regression coefficients) and their corresponding 95% CIs, and p-values were estimated to quantify the
indirect, and direct effects through a series of univariate and multivariable logistic regression models (Step 2: Supp. Methods 1). All models were adjusted for the same potential confounders: offspring age in years at baseline, offspring stressful life event, SES, maternal and paternal binge drinking and offspring sex. Offspring sex was also included as an interaction term with the exposure to account for the heterogeneity in these associations between males and females as unweighted numbers were too low to stratify by sex. The effect proportion mediated (EPM) and corresponding 95% CIs were calculated where appropriate (indirect effects/(direct effects + indirect effects)) to quantify the percent of the total effect that is accounted for by the pathway through the mediator (Step 3: Methods 1S). To ensure all models included the same number of observations at the outset, individuals with missing data on the mediator variables (<5%) were excluded.

To reduce risk of bias in mediation models we performed several sensitivity analyses testing for: 1) exposure-mediator interaction; 2) whether the exposure is related to mediator-outcome controlled confounding variables; and 3) whether adjusted beta coefficients differ in those with and without cycle non-response.

To account for the NLSCY’s complex survey design, the longitudinal weights, and bootstrap weights provided by Statistics Canada were used to calculate beta-coefficients and variances using SAS survey procedures. The weights were used to produce unbiased estimates of the Canadian population and account for post stratification and non-response. All analyses were performed using SAS software (version 9.4).

**Results**

**Characteristics the sample**

This analysis included 3,123 offspring with a weighted total of 816,140. Differences in sample characteristics in exposed and non-exposed offspring can be found in Table 5.1. Briefly, the proportion of females was similar in exposed (52%) and non-exposed (53%) offspring.
(standardized difference: 0.02). There was a higher proportion of exposed offspring coming from low SES households compared to non-exposed offspring (standardized difference: 0.31). Exposed offspring were more likely to have experienced a stressful life event between four and ten years of age compared to non-exposed offspring (standardized difference: 0.19) (Table 5.1).

Quantifying exposure – mediator (A), mediator – outcome (B) and total effects (C)

Unadjusted paths A, B and C can be found in Figures 5.4 and 5.5 Supplemental. Exposure to maternal depressive symptoms occurring from zero to five years of age significantly increased the adjusted odds of internalizing (OR: 2.85, 95% CI: 1.69, 4.83), hyperactivity (OR: 2.82, 95% CI: 1.62, 4.90), conduct (OR: 1.97, 95% CI: 1.17, 3.31) and psychiatric comorbidity (OR: 2.77, 95% CI: 1.61, 4.74), but not indirect aggression (Table 5.4 Supplemental). None of the subscales significantly increased the unadjusted or adjusted odds of SRT, while the adjusted odds of SA were significantly elevated among offspring with hyperactivity compared to no hyperactivity (OR: 1.97, 95% CI: 1.09, 3.54). The odds of SA were elevated in offspring with compared to without psychiatric comorbidity, although this did not reach statistical significance (OR: 1.61, 95% CI: 0.94, 2.76) (Table 5.5 Supplemental). While not statistically significant, the path from indirect aggression to both SRT and SA was opposite in sign to the other subscales providing some evidence of suppression (e.g., when path coefficients are opposite in sign)\textsuperscript{28}. The unadjusted and adjusted total effect (the association between exposure to maternal depressive symptoms and offspring SRT and SA) was not statistically significant, although in both cases were suggestive of an increased risk (SRT adjusted OR: 1.45, 95% CI: 0.84, 2.51) and (SA adjusted OR: 1.75, 95% CI: 0.82, 3.73), respectively (Figures 5.2, and 5.3).

Mediation analyses

Mediation analyses were conducted only for the hyperactivity subscale and psychiatric comorbidity (only for SA) as these were the only two intermediate variables that met criteria for possible mediation. Table 5.2 presents the indirect effects, the EPM, and their corresponding 95% CI’s. The indirect effect through hyperactivity predicting SRT was statistically significant (b=0.43, 95% CI: 0.30, 0.55). Further, the indirect effect through hyperactivity predicting SA was
statistically significant and larger in magnitude than SRT (b=0.70, 95% CI, 0.54, 0.87). The indirect effects through psychiatric comorbidity predicting SA was also statistically significant (Table 2). 58% (95% CI: 23, 94%) and 61% (95% CI: 27, 95%) of the association between exposure to maternal depressive symptoms and offspring SRT and SA was accounted for by hyperactivity symptoms, while 50% (95% CI: 18, 81%) of the association was accounted for by psychiatric comorbidity, respectively (Table 5.2).

Sensitivity analyses

Exposure-mediator interaction was not statistically significant (p > 0.05) for all subscales except for indirect aggression. Specifically, there was a statistically significant interaction between exposure to maternal depressive symptoms and indirect aggression (p=0.02) and this product term significantly contributed to the model predicting both SRT and SA according to the likelihood ratio test.

Unadjusted associations between exposure to maternal depressive symptoms and mediator-outcome controlled confounders were not statistically significant for maternal binge drinking (OR: 1.21, 95% CI: 0.55, 2.66), however, just reached statistical significance for spouse binge drinking (OR: 1.87, 95% CI: 1.09, 3.21), and offspring stressful life events (OR: 1.61, 95% CI: 1.02, 2.55). However, unadjusted and adjusted path beta coefficients were similar (Figures 5.4 and 5.5 Supplemental).

In models including all offspring, irrespective of cycle non-response, beta coefficients became slightly stronger in magnitude and more statistically significant, as the sample size increased substantially (Figures 5.6 and 5.7 Supplemental). Indirect effects and EPM’s for hyperactivity and psychiatric comorbidity were similar (Table 5.6 Supplemental). Those with cycle non-response were less likely to come from households of high SES (standardized difference: 0.23) and were older age at cycle one (standardized difference: 0.21) and these covariates are adjusted for in all multivariable models (Table 5.7 Supplemental).

Discussion
This study examined the mediating role of child psychiatric symptoms in the association between exposure to maternal depressive symptoms in childhood and adolescent SRT and SA using data from a Canadian population-based cohort. Symptoms of hyperactivity and inattention significantly mediated the association between maternal depressive symptoms in childhood and risk of both SRT and SA from 11 to 19 years of age, where approximately 60% of this association was explained by hyperactivity and inattention. Psychiatric comorbidity, indicating the presence of two or more psychiatric symptom dimensions also significantly mediated this relationship with SA accounting for 50% of this association. This study extends previous research both by being prospective and nationally representative, and by clarifying the mediating role of child psychiatric symptoms occurring between six and ten years of age specifically in comparison to other studies examining symptoms later in adolescence16.

These findings are consistent with a study using data from the Avon Longitudinal Study finding that attention deficit hyperactivity disorder at age 15 years mediated the association between maternal depression symptoms occurring when offspring were zero to 11 years of age and offspring self-reported SA at age 1616. However, given the proximity of the mediator and outcome measurements in this other study, these symptoms could have acted more as an immediate trigger, rather than a variable causing development of these outcomes over time. This other study also found that major depression, generalized anxiety disorder and disruptive behavior disorder also mediated this association31. We found no evidence that internalizing, conduct, or indirect aggression were mediating pathways to SRT or SA, and indirect aggression, which can be conceptualized as a form of social manipulation to direct aggression toward another32, was suggestive of a non-significant protective effect, for SRT. However, in sensitivity analyses including the entire NLSCY cohort, irrespective of cycle non-response, this protective effect attenuated towards the null. In this study psychiatric symptoms were measured in childhood, not in adolescence and there may be differential effects by age33. Collectively, these findings support that symptoms of attention deficit hyperactivity disorder in childhood and adolescence partially explain the association between childhood exposure to maternal depression and offspring adolescent SA. These findings raise questions about the role of impulsivity in predicting SA. While there is debate among researchers as to the nature of the association between impulsivity and
suicide-related behaviors, with some authors suggesting most SA’s are impulsive in nature, while others argue that SA cases are planned\textsuperscript{34}. However, research has typically been conducted in older adolescents and adults. The association between impulsive characteristics in childhood with adolescent SA is unclear.

Although exposure to maternal depression in childhood is associated with a broad range of psychopathology in childhood and adolescence\textsuperscript{7}, further supported by this study, it appears as though there is specificity when it comes to which dimensions both indirectly or directly predict offspring SRT and SA. Studies linking specific psychiatric dimensions and diagnoses to suicide-related behavior have yielded mixed findings and are heterogeneous by age. While we did not find that conduct or internalizing subscales were associated with SRT or SA, in contrast to findings from other prospective studies of adolescents and young adults\textsuperscript{3, 10, 13, 35, 36}, this may reflect that in childhood these symptoms are less indicative of SA risk compared to adolescence, where these symptoms are more prevalent\textsuperscript{33}, and more proximal to the reported SA. Further, while depression is associated with SRT, some studies show that it is not associated with SA, and this is in keeping with theories surrounding the differential genetic transmission of SA in comparison to SRT\textsuperscript{17}. Therefore, including measures of internalizing symptoms of both depression and anxiety may wash out the effects of anxiety on SA risk, or depression on SRT risk.

What appears consistent across studies is that psychiatric comorbidity is associated with a greater risk of SA. Findings from this study support this observation, where psychiatric comorbidity indirectly explained the association between maternal depressive symptoms and offspring SA. In fact, several studies have reported findings showing that psychiatric comorbidity is more strongly related to suicide-related behavior compared to individual diagnoses alone\textsuperscript{3, 12, 13}. This may reflect that greater severity of psychiatric illness, associated with higher psychiatric comorbidity, is more predictive of SRT and SA. Still, specific patterns of psychiatric comorbidity remain unclear.

\textit{Limitations}

Maternal depressive symptoms and offspring psychiatric symptoms were reported by the mother. The CES-D is not a diagnostic tool, but rather a screening measure to identify possible cases of
depression. Therefore, the exposure used in this study reflects depressive symptoms indicative of a DSM diagnosis, and is not clinician-confirmed. On the other hand, this exposure is more reflective of maternal depressive symptoms seen in the general population. Maternal reports of child psychiatric symptoms have been shown to be rated more severe compared to youth reports\textsuperscript{37, 38}. As such, there is a potential risk of differential misclassification of the mediator among exposed compared to non-exposed. However, other studies support that there is inconsistent evidence that depressed mothers perceive behavior and emotional problems differently in their children compared to independent raters\textsuperscript{39, 40}. Outcomes were also self-reported, which could be underreported relating to their sensitive nature, however, offspring were ensured confidentiality and anonymity when completing measures.

Even though this study was population-based, we were still restricted by low unweighted numbers owing to the rarity of outcomes and were unable to stratify by sex. These mediating effects are likely different in girls and boys given differences in rates of both psychiatric symptoms and SA’s by sex. While we attempted to account for this heterogeneity by including sex and exposure interaction terms in our multivariable models, and it did improve their precision, we cannot speak to sex differences and sex-specific intermediate pathways.

While individual symptoms mapping onto each Behaviors Scale subscales were available from the NLSCY, the only validated subscales available included mixtures of symptoms (e.g., anxiety and depressive symptoms)\textsuperscript{19}. We were reluctant to pull the symptom-level items and examine them individually as they were not part of a validated scale. In light of the mixed findings pertaining to psychopathologic diagnoses and dimensions with offspring SA risk, future research should focus on unpacking categorical diagnoses.

It is established that childhood physical and sexual abuse are strong predictors of adolescent SA\textsuperscript{41}. We did not have a direct measure of abuse, although the life events measure we adjusted for included an item on abuse. We also did not have access to a measure of family history for suicide-related behavior and were unable to account for genetic transmission of risk; still, studies have provided evidence of independent associations between maternal depression and offspring SA risk\textsuperscript{16, 17}. 
Implications and conclusions

This research has implications for preventive and early intervention strategies for high-risk families where a mother is depressed. Assessing and appropriately treating hyperactivity and inattention symptoms, along with co-occurring psychiatric symptoms in offspring of depressed mothers could reduce risk of SRT, eventual SA, and halt progression towards suicide. However, further understanding of the dimensional patterns of psychopathology (e.g., groups of symptoms) in childhood that most strongly predict adolescent SA is needed. Family-based interventions and clinician monitoring targeting exposure to maternal depression when children are young aimed at increasing resiliency and reducing exposure during critical neurodevelopmental windows could have lasting influences on reducing vulnerability to psychiatric morbidity and SA risk. The strongest risk factor for death by suicide, and future SA is a prior SA; therefore, implementing preventive and early intervention strategies before youth reach crisis is crucial.

Symptoms of hyperactivity and inattention between six to ten years of age explain 60% of the association between exposure to maternal depressive symptoms early in childhood and adolescent SA. Still, 40% of this association is accounted for by other factors that require further study. Categorical diagnoses likely do not tap into the complexity of pathologies that predict adolescent SA both indirectly via maternal depression, and directly. More consideration of comorbid patterns of psychiatric symptoms is needed to fully understand this complex association.
References


Figure 5.1 Flow chart of study sample selection

Original Longitudinal Cohort
22,831

16,903

13,169

5004

Study sample:
3234

NLSCY Cycle 1

NLSCY Cycle 2

NLSCY Cycle 3

NLSCY Cycle 4

NLSCY Cycle 5

NLSCY Cycle 6

NLSCY Cycle 7

NLSCY Cycle 8

5928 omitted for budget reasons *

Cycles 1-8 merged

Missing outcome data or too young to complete measures: 3734

Had cycle non-response: 8165

Were over age 5 at cycle 1: 1770

*Households from the National Population Health Survey and max number of children per household cut from 4 to 2
Figure 5.2 Adjusted\(^a\) beta coefficients of the total effects, and exposure, mediator associations, and mediator, outcome associations with suicide-related thoughts as the outcome weighted\(^b\) to reflect the Canadian general population

\(^a\)Offspring age in years at baseline, offspring stressful life event (4-10 years), socio-economic status, maternal and paternal binge drinking (0-10 years), offspring sex, sex by exposure interaction

\(^b\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves
**Figure 5.3** Adjusted\(^a\) beta coefficients of the total effects, and exposure, mediator associations, and mediator outcome associations with suicide attempts as the outcome, weighted\(^b\) to reflect the Canadian general population.

\(^a\)Offspring age in years at baseline, offspring stressful life event (4-10 years), socio-economic status, maternal and paternal binge drinking (0-10 years), offspring sex, sex by exposure interaction

\(^b\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.
Table 5.1 Standardized differences between proportions of sample characteristics in offspring exposed and non-exposed to maternal depressive symptoms, weighted\(^a\) to reflect the Canadian general population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposed</th>
<th>Non-exposed</th>
<th>SD(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offspring sex</td>
<td>Male</td>
<td>48.27</td>
<td>47.22</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>51.73</td>
<td>52.78</td>
</tr>
<tr>
<td>Socio-economic status(^b)</td>
<td>1 – Lowest</td>
<td>14.25</td>
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</tr>
<tr>
<td></td>
<td>2</td>
<td>18.15</td>
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<td></td>
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<td>4</td>
<td>21.73</td>
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<tr>
<td></td>
<td>5 - Highest</td>
<td>15.28</td>
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<tr>
<td>Maternal binge drinking &gt; 10 occasions (0-10 years)(^c)</td>
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<td></td>
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<td></td>
<td>Yes</td>
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<tr>
<td>Offspring stressful life events (4-10 years)(^d)</td>
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<td>33.37</td>
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</tr>
</tbody>
</table>

SD: standardized difference

\(^a\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of
institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves

bSocio-economic status corresponding categories are presented in Table 5.3 Supplemental

cRepresents proportion of maternal and spouse binge drinking occasions over ten when offspring were between 0-10 years.

dYes reflects any maternal report of child offspring experiencing a stressful life event from 4-10 years of age

eAbsolute values of 0.2=small, 0.5=medium, and 0.8=large effect sizes\textsuperscript{27}
**Table 5.2** Adjusted\(^a\) direct and indirect effects and effect proportion mediated, weighted\(^b\) to reflect the Canadian general population

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Total effect</th>
<th>Direct effect</th>
<th>Indirect effect(^d)</th>
<th>Proportion mediated (EPM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI(^c)</td>
<td>β</td>
<td>95% CI(^c)</td>
</tr>
<tr>
<td>Suicide-related thoughts</td>
<td>Hyperactivity</td>
<td>0.37</td>
<td>-0.17, 0.92</td>
<td>0.31</td>
</tr>
<tr>
<td>Suicide attempts</td>
<td>Hyperactivity</td>
<td>0.56</td>
<td>-0.19, 1.32</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Psychiatric</td>
<td>0.56</td>
<td>-0.19, 1.32</td>
<td>0.49</td>
</tr>
</tbody>
</table>

\(^a\)Offspring age in years at baseline, offspring stressful life event (4-10 years), socio-economic status, maternal and paternal binge drinking (0-10 years), offspring sex, sex by exposure interaction

\(^b\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves

\(^c\)Estimated using Statistics Canada Bootstrap weights

\(^d\)beta coefficient from path a (exposure – mediator) multiplied by beta coefficient from path b (mediator – outcome)
Supplemental Methods 1. Mediation approach

**Mediation analytic procedure**
For each outcome (SRT or SA), multivariable logistic regression models were performed testing associations between exposure and mediator (A); mediator and outcome, controlling for exposure (B); exposure and outcome (C); exposure and outcome, controlling for mediator (C'), controlling for the same confounders in each model (Figure 1). Indirect effects were calculated by multiplying paths A and B.

*Figure 1. Mediation model*
Testing for presence of mediation

Step 1: Testing criteria for possible mediation
Paths A, B and C are considered significant given the following accepted exemptions\(^{1,2}\):

C is not significant but,

a. the effect estimate is suggestive of an association  
b. there is sufficient evidence from the literature that an association exists  
c. the association between the exposure and outcome is distal

A and B are not significant but,

d. the effect estimates are suggestive of an association  
e. there is sufficient evidence from the literature that these associations exist  
f. the p-value is close to significance: p ≤0.10

Step 2: Testing if mediation is present
Indirect effects are significant according to their bootstrapped 95% confidence intervals not spanning 0

Step 3: Quantifying magnitude of mediating effects
Calculate effect proportion mediated (EPM) and it’s corresponding bootstrapped 95% confidence intervals
EPM: Indirect effects / (Direct effect + Indirect effect) * 100

References:
Table 5.3 Supplemental - Information on confounding variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Coding</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal/spouse binge drinking occasions</td>
<td>Average exposure to maternal/spouse binge drinking when offspring were between the ages of 0 to 10 years (cycles 1-6)</td>
<td>Average total number of past year binge drinking occasions (5 or more drinks on 1 occasion): Total occasions/number of cycles participated in 1= Average total occasions ≥10 0= Average total occasions &lt;10</td>
<td>The maternal and spouse binge drinking item was highly right skewed. This variable was dichotomized to above and below the 90th percentile (10 binge drinking occasions). These variables were selected given their association with offspring suicide attempts, and a plausible association with maternal depression.</td>
</tr>
<tr>
<td>Household SES continuous (used in multivariable models)</td>
<td>Composite score derived from maternal and spouse highest level of education, occupation and household income when offspring were between 0 to 10 years (Cycle 1)</td>
<td>Continuous score ranging from -2.0 to 1.75  For descriptive purposes this score was categorized into the following according to Statistics Canada suggested categories: 5=≥1.5 4=&lt;1.5≥0.5 3=&lt;0.5=&gt;0.0 2=&lt;0.0=&gt;-0.5 1=&lt;-0.5</td>
<td>The SES composite score was not available in all NLSCY cycles and SES of families in childhood was the measure of interest. This variable was selected given the differences in suicide attempts and psychopathology by SES group.</td>
</tr>
<tr>
<td>Offspring stressful life event</td>
<td>Offspring stressful life events (maternal reported in 4-10-year-olds, cycles 1-6): “Has ... ever experienced any event or situation that has caused him/her a great amount of worry or unhappiness?”.</td>
<td>1 = Yes 0 = No</td>
<td>This variable was only measured in offspring =&gt;4 years and was only derived from cycles 1 to 6 to capture the exposure time of interest (between 0 to 10 years of age). This variable was selected as offspring stressful experiences such as a loss, illness/injury, or separation from parents are associated with suicide attempts in adolescents and likely exacerbate psychiatric symptoms in parents.</td>
</tr>
<tr>
<td>Offspring Sex</td>
<td>Maternal reported sex of their child offspring (cycle 1)</td>
<td>1=Male 0=Female</td>
<td>There was no measure of self-reported gender in the NLSCY</td>
</tr>
</tbody>
</table>

SES: socio-economic status; NLSCY: National Longitudinal Survey of Children and Youth

References:
Table 5.4 Supplemental - Risk of child psychiatric symptoms from 6-10 years of age in offspring exposed versus non-exposed to maternal depressive symptoms between 0-5 years of age, weighted\(^a\) to reflect the Canadian general population

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted(^b)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI(^c)</td>
<td>OR</td>
<td>95%CI(^c)</td>
</tr>
<tr>
<td>Internalizing</td>
<td>2.23</td>
<td>1.53</td>
<td>3.25</td>
<td>2.85</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>2.15</td>
<td>1.50</td>
<td>3.09</td>
<td>2.82</td>
</tr>
<tr>
<td>Indirect aggression</td>
<td>1.57</td>
<td>1.02</td>
<td>2.41</td>
<td>1.68</td>
</tr>
<tr>
<td>Conduct</td>
<td>1.46</td>
<td>1.03</td>
<td>2.08</td>
<td>1.97</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>2.05</td>
<td>1.38</td>
<td>3.03</td>
<td>2.77</td>
</tr>
</tbody>
</table>

CI: confidence interval; OR: odds ratio

\(^a\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves

\(^b\)Offspring age in years at baseline, offspring stressful life event (4-10 years), socio-economic status, maternal and paternal binge drinking (0-10 years), offspring sex, sex by exposure interaction

\(^c\)Estimated using Statistics Canada Bootstrap weights
Table 5.5 Supplemental - Risk of suicide-related thoughts and attempt from 11-19 years of age in individuals with and without psychiatric symptoms from 6-10 years, weighted\textsuperscript{a} to reflect the Canadian general population

<table>
<thead>
<tr>
<th></th>
<th>Suicide-related thoughts</th>
<th>Suicide-attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted\textsuperscript{b}</td>
</tr>
<tr>
<td>Internalizing</td>
<td>1.17</td>
<td>0.78</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>1.49</td>
<td>0.99</td>
</tr>
<tr>
<td>Indirect aggression</td>
<td>0.81</td>
<td>0.52</td>
</tr>
<tr>
<td>Conduct</td>
<td>1.15</td>
<td>0.78</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>1.36</td>
<td>0.91</td>
</tr>
</tbody>
</table>

CI: confidence interval; OR: odds ratio
\textsuperscript{a}Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves
\textsuperscript{b}Offspring age in years at baseline, offspring stressful life event (4-10 years), socio-economic status, maternal and paternal binge drinking (0-10 years), offspring sex, sex by exposure interaction
\textsuperscript{c}Estimated using Statistics Canada Bootstrap weights
**Table 5.6 Supplemental** - Sensitivity analysis: Adjusted\(^a\) direct and indirect effects and effect proportion mediated including offspring with cycle non-response, weighted\(^b\) to reflect the Canadian general population

<table>
<thead>
<tr>
<th></th>
<th>Hyperactivity</th>
<th>Indirect effects(^d)</th>
<th>95%CI(^c)</th>
<th>Effect proportion mediated</th>
<th>95%CI(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide-related thoughts</td>
<td></td>
<td>0.43</td>
<td>0.37 0.49</td>
<td>0.55</td>
<td>0.26 0.84</td>
</tr>
<tr>
<td>Suicide attempts</td>
<td>Hyperactivity</td>
<td>0.71</td>
<td>0.63 0.79</td>
<td>0.65</td>
<td>0.37 0.94</td>
</tr>
<tr>
<td></td>
<td>Comorbidity</td>
<td>0.58</td>
<td>0.50 0.65</td>
<td>0.62</td>
<td>0.35 0.88</td>
</tr>
</tbody>
</table>

CI: confidence interval

\(^a\)Offspring age in years at baseline, offspring stressful life event (4-10 years), socio-economic status, maternal and paternal binge drinking (0-10 years), offspring sex, sex by exposure interaction

\(^b\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves

\(^c\)Estimated using Statistics Canada Bootstrap weights

\(^d\)Beta coefficient from path a (exposure – mediator) multiplied by beta coefficient from path b (mediator – outcome)
Table 5.7 Supplemental - Sensitivity analysis: Standardized differences between covariates in offspring with and without cycle non-response, weighted\textsuperscript{a} to reflect the Canadian general population

<table>
<thead>
<tr>
<th></th>
<th>CNR Yes\textsuperscript{f}</th>
<th>CNR No\textsuperscript{g}</th>
<th>SD\textsuperscript{e}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46.95</td>
<td>52.65</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>53.05</td>
<td>47.35</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Socio-economic status\textsuperscript{b}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - lowest</td>
<td>10.83</td>
<td>6.01</td>
<td>0.17</td>
</tr>
<tr>
<td>2</td>
<td>17.92</td>
<td>13.04</td>
<td>0.14</td>
</tr>
<tr>
<td>3</td>
<td>28.88</td>
<td>26.43</td>
<td>0.05</td>
</tr>
<tr>
<td>4</td>
<td>22.54</td>
<td>24.71</td>
<td>0.05</td>
</tr>
<tr>
<td>5 - highest</td>
<td>19.20</td>
<td>28.87</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Suicide attempt</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>94.53</td>
<td>93.53</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>5.47</td>
<td>6.47</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Suicide-related thoughts</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>90.50</td>
<td>86.11</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>9.50</td>
<td>13.89</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Maternal binge drinking &gt;10 occasions (0-10 years)\textsuperscript{c}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>96.28</td>
<td>96.93</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>3.72</td>
<td>3.07</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Spouse binge drinking &gt;10 occasions (0-10 years)\textsuperscript{c}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>91.44</td>
<td>88.75</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>8.53</td>
<td>11.25</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Offspring stressful life event (4-10 years)\textsuperscript{d}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>28.68</td>
<td>25.09</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>71.27</td>
<td>74.91</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Maternal depressive symptoms (0-5 years)</strong></td>
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</tr>
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<td>no</td>
<td>82.11</td>
<td>88.31</td>
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<tr>
<td>yes</td>
<td>17.89</td>
<td>11.69</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Age at cycle one in years</strong></td>
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<td></td>
<td></td>
</tr>
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<td>0</td>
<td>11.30</td>
<td>17.12</td>
<td>0.17</td>
</tr>
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<td>1</td>
<td>11.55</td>
<td>17.51</td>
<td>0.17</td>
</tr>
<tr>
<td>2</td>
<td>16.43</td>
<td>17.16</td>
<td>0.02</td>
</tr>
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<td>3</td>
<td>15.13</td>
<td>17.78</td>
<td>0.07</td>
</tr>
<tr>
<td>4</td>
<td>22.64</td>
<td>15.51</td>
<td>0.18</td>
</tr>
<tr>
<td>5</td>
<td>22.95</td>
<td>14.92</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Internalizing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>75.40</td>
<td>80.24</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>18.61</td>
<td>18.55</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Hyperactivity</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>no</td>
<td>76.32</td>
<td>80.29</td>
<td></td>
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<td>16.22</td>
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</tr>
<tr>
<td></td>
<td>no</td>
<td>SD</td>
<td>yes</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Indirect aggression</td>
<td>69.27</td>
<td>77.56</td>
<td>24.64</td>
</tr>
<tr>
<td>Conduct</td>
<td>74.49</td>
<td>76.06</td>
<td>19.56</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>70.67</td>
<td>76.69</td>
<td>22.50</td>
</tr>
</tbody>
</table>

*d*: Yes: Any maternal report of child distressing stress from 4-10 years of age

e*: Absolute values of 0:2=small, 0:5=medium, and 0:8=large effect sizes

*f*: Offspring with one or more instance of cycle non-response

*g*: Offspring with complete follow-up

h*: Some frequencies do not amount to 100 owing to missing data on specific covariates
**Figure 5.4 Supplemental** - Unadjusted beta coefficients of the total effects, and exposure, mediator associations, and mediator, outcome associations with suicide-related thoughts as the outcome, weighted to reflect the Canadian general population

Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.
Figure 5.5 Supplemental - Unadjusted beta coefficients of the total effects, and exposure, mediator associations, and mediator outcome associations with suicide attempts as the outcome, weighted\textsuperscript{a} to reflect the Canadian general population.

\textsuperscript{a}Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.
Figure 5.6 Supplemental - Sensitivity analyses: Adjusted\(^a\) beta coefficients of the total effects, and exposure, mediator associations, and mediator outcome associations with suicide-related thoughts as the outcome among offspring with cycle non-response, weighted\(^b\) to reflect the Canadian general population.

\(^a\)Offspring age in years at baseline, offspring stressful life event (4-10 years), socio-economic status, maternal and paternal binge drinking (0-10 years), offspring sex, sex by exposure interaction

\(^b\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.
Figure 5.7 Supplemental - Sensitivity analyses: Adjusted\(^a\) beta coefficients of the total effects, and exposure, mediator associations, and mediator outcome associations with suicide-related thoughts as the outcome among offspring with cycle non-response, weighted\(^b\) to reflect the Canadian general population.

\(^a\)Offspring age in years at baseline, offspring stressful life event (4-10 years), socio-economic status, maternal and paternal binge drinking (0-10 years), offspring sex, sex by exposure interaction

\(^b\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.
Chapter 6
Discussion

6 Discussion

6.1 Main findings

The main findings of this research indicate that the risk of self-reporting thoughts about suicide (SRT) and suicide attempts (SA) was high in young Canadians between 1996 to 2009. By age 25, the cumulative incidence of SRT in females and males was 29% and 19%, and SA was 16% and 7%, respectively. Among Canadians reporting these thoughts and behaviours, a considerable number first occurred early in adolescence. Specifically, over 70% of SRT and SA were first reported between 11 to 16 years of age, and 30% between 11 to 13 years of age, respectively. The risk of first thinking about suicide and SA and persistence of these thoughts and attempts over adolescence into early adulthood was significantly elevated among females exposed to maternal depressive symptoms from birth to ten years of age, but not in males. Specific childhood psychiatric symptoms reflected an intermediate pathway of this association, with hyperactivity/inattention, and psychiatric comorbidity explaining approximately 60%, and 50% of the association, respectively.

These findings improve on previous research by: 1) being longitudinal and nationally representative, limiting recall biases, temporal biases, and low statistical power; 2) estimating for the first time the risk of SRT and SA (with confirmed suicidal intent), irrespective of a hospital setting in young Canadians; 3) developing a new application of a counting process framework to estimate incidence in survey data where discontinuous risk intervals are present; 4) identifying antecedent childhood risk factors that are potentially modifiable with implications for suicide preventive targets.
6.1.1 Incidence

The cumulative incidence estimates reported in this thesis are difficult to compare to other published reports because existing incidence studies are largely of International Classification of Disease (ICD)-coded hospital presentations, where as expected, the incidence over adolescence and young adulthood is much smaller, typically under 1%. In comparison to the few recent studies examining incidence and lifetime prevalence of SRT and SA in youth and young adults, the estimates reported here are higher (Appendix A and B). This may be due to limitations of existing studies involving long recall periods and measuring SRT and SA in the context of depression. Long recall periods have been shown to underestimate the frequency of suicide-related outcomes, where participants are likely remembering only the most salient events. Further, studies that assess suicide-related outcomes in the context of depression may also be underestimating events, particularly if gate questions are present that do not proceed to suicide-related items if depressive symptomatology is not present. Further, the degree to which suicide-related events are missed through the use of such depression measures is more pronounced in younger ages and in females.

Further, no study has employed the method used in this study to more accurately estimate the time at-risk. The decision to report primary results not accounting for discontinuous risk intervals by design was made to yield incidence estimates that are more in line with existing incidence and lifetime prevalence estimates (Appendix A and B). However, this approach did in fact estimate the denominator correctly and it may be that the true incidence of SRT and SA is much higher in the general youth and young adult population than typically thought. In particular, after accounting for the discontinuous risk intervals by design, the risk of SRT in females and males between 11 to 25 years of age was 50%, and 34%, respectively, while the risk of SA in females and males between 11 to 25 years of age was 28% and 12%, respectively. Because this approach to estimating population incidence has not been conducted before, and in light of the limitations of existing studies, we lack good comparisons and these methods require further exploration. It is also possible that respondents in the NLSCY recalled the outcomes since last assessment (rather than the past year look back window), which reflects a two-year window. If this is the case, it would be acceptable to assume that the outcome did not occur during these one-year discontinuous risk
intervals. However, we may also be missing events during these discontinuous yearly intervals after each cycle, underestimating incidence by assuming no events occurred during these gaps. The true risk of these outcomes likely lies somewhere in between the two reported estimates (accounting and not accounting for discontinuous risk intervals by design), with both approaches yielding high estimates, relative to what has been reported in the literature to date.

The majority of first reported SRTs were observed between 11 to 16 years with the peak time for these events to start between 14 and 16 years. This is inconsistent with other population-based incidence studies of hospital presentations for suicide-related behaviour reporting peaks at later ages, from 15 to 19 years of age in females and even later in males, between 20 to 24 years of age. Suicide-related behaviour may be less lethal in adolescents compared to adults, which could, in part, explain this discrepancy. However, this hypothesis assumes that hospital presentations are in fact more serious than self-reported SA which may not always be true and require further study. Some portion of the latter group may be quite suicidal and (or) engage in more lethal behaviours, yet never seek formal care. Taken together, there is a considerably large number of young adolescents self-reporting SAs in the general population, not captured by ambulatory and hospital administrative data with the majority of first reported attempts occurring by age 16 with peaks occurring earlier than reported by hospital presentations for suicide-related behaviour.

6.1.2 Exposure to maternal depressive symptoms

Exposure to maternal depressive symptoms in childhood was associated with an almost doubled hazard of SA between 11 and 25 years of age and a 70% increased hazard of SRT. Exposure to maternal depressive symptoms also increased the rate of recurrent SA and SRT between 11 and 25 years by approximately 70% and 60%, respectively. Others have reported associations between maternal depression and other offspring outcomes (e.g., depression, externalizing symptoms) by sex with mixed findings. Still, the mechanisms linking maternal depression to offspring SRT
and SA may differ from those leading to other outcomes, and by age. The timing of first exposure to maternal depressive symptoms over the first decade of life was also explored (Appendix Ci) indicating that first exposure from three to five years of age was suggestive a stronger risk for SRT and SA compared to first exposure from zero to two or six to ten years of age. However, to test this, the sample had to be reduced to offspring who were age zero at baseline, which drastically reduced the sample size, number of events and particularly, those exposed for the youngest time-period, therefore these findings should be interpreted cautiously.

Not all children of depressed mothers develop suicide-related behaviour or other psychopathology\textsuperscript{75}. The timing, duration and dose of exposure to maternal depression may account for this. Other studies have supported this notion, showing stronger associations between exposure to maternal depression in childhood and offspring SRT and SA when the illness was chronic and severe compared to moderate symptoms\textsuperscript{44}. Further, there is evidence that remission in mothers with a major depressive disorder over a nine-month period is associated with decreases in psychiatric symptoms in children, while maternal depression relapse is associated with increases in child symptoms\textsuperscript{91}. Taken together, there is increasing evidence, supported by findings from this study, that exposure, or other factors that co-occur with maternal acute depressive episodes do matter in predicting psychopathological risk in offspring\textsuperscript{92}.

6.1.3 Moderating pathways

The association between maternal depressive symptoms in childhood and offspring SRT and SA was modified by offspring sex, such that these associations were only found among females and not males. Consistent with these findings, Tsypes et al\textsuperscript{93} reported an elevated risk of SRT in females exposed to maternal major depression but not in males. In contrast, Hammerton et al.\textsuperscript{44} did not find any sex differences in the association between maternal depression in childhood and adolescent SRT or SA. It is clear that the sex-specific pathways from maternal depression to offspring mental health outcomes are complex and in need of refinement. Our findings also raise questions about possible protective effects of residing with intact families in childhood and
maternal perceived high social cohesion and support against SRT and SA among exposed offspring. The stratum specific hazard ratios predicting both SRT and SA indicated significant increases in risk among offspring coming from non-intact families, and whose mothers reported low social support or cohesion with non-significant stratum specific hazard ratios among offspring coming from intact families, and whose mothers reported high social cohesion. From a qualitative standpoint (e.g., considering differences in point estimates), these findings suggest that these factors might buffer risk in offspring of depressed mothers. The social support and cohesion variables were discontinued at cycle two, and changed in subsequent cycles in the NLSCY, thus, their measurement was restricted to the baseline measure. It was not possible to produce an average measure of these constructs over the first decade of life. This may have contributed to the overlapping 95% CIs, and smaller differences in point estimates. That is, these types of social influences might operate in a cumulative way over time, and if measured at one cross-section, might not be sensitive enough to detect true differences.

6.1.4 Mediating pathways

Specific psychiatric symptoms present between six to ten years of age reflected intermediate pathways of the association between maternal depressive symptoms between zero to five years of age and SRT and SA from 11 to 19 years of age. Namely, hyperactivity and inattention accounted for approximately 60% of the association with both SRT and SA, while psychiatric comorbidity accounted for 50% of this association with SA, respectively. Internalizing, conduct symptoms, and indirect aggression were not significant mediators of this association. These results are partially consistent with findings from a longitudinal study of data from the Avon Longitudinal Study of Parents and Children. This study reported that attention deficit hyperactivity disorder at age 15 significantly mediated the association between maternal depressive symptoms occurring when offspring were zero to 11 years of age and offspring self-reported SA at age 16. However, this study also found that major depressive disorder, generalized anxiety disorder and disruptive behaviour disorder also mediated this association, which was inconsistent with findings from this study, although, in this study, these symptoms were examined at a much younger age, and there
may be differential effects by age, as trajectories of psychiatric symptoms change from childhood to adolescence. These findings raise questions about the role of impulsivity in predicting SA. High impulsivity could reflect an early antecedent risk factor for SA and suicide and in light of the evidence supporting a high family loading for impulsive aggressive traits in first degree relatives of individuals reporting SA’s.

Studies linking specific psychiatric dimensions and diagnoses to suicide-related behaviour have yielded mixed findings; however, studies are heterogeneous when it comes to the specific age at which the dimensions and suicide-related behaviour are measured and in terms of the specific dimensions or diagnoses examined. For example, some prospective cohort studies support that depressive symptoms in adolescence are associated with SRT in males and females, and in conjunction with conduct symptoms are associated with SA in adolescence, while other prospective studies have reported that the highest risk for adolescent and young adult SA was predicted by anxiety disorders occurring in adolescence. Findings from this study did not support that conduct or internalizing subscales were associated with SRT or SA, or indirectly via maternal depressive symptoms. This could reflect that in childhood these symptoms are less indicative of SRT and SA risk compared to adolescence, where these symptoms are more prevalent, and more proximal to the reported SA. Further, while depression is associated with SRT, some studies show that it is not associated with SA and this is in keeping with theories surrounding the differential genetic transmission of SA in comparison to SRT. Therefore, including measures of internalizing symptoms of both depression and anxiety may wash out the effects of anxiety on SA risk, or depression on SRT risk. What appears consistent across studies is that comorbidity is associated with a greater risk of SA, and consistent with this where psychiatric comorbidity indirectly explained the association between maternal depressive symptoms and offspring SA. This may reflect that greater severity of psychiatric illness, associated with higher comorbidity, is more predictive of SRT and SA. Still, specific patterns of comorbidity remain unclear.
6.1.5 Sex/gender differences

The risks of SRT and SA from 11 to 25 years of age were 1.5 times and 2.3 times higher in females compared to males, respectively. Interestingly, more males (38%) reported first attempting suicide earlier (between the ages of 11 to 13 years) compared to females (30%). SRT and SA begin to onset in parallel with pubertal changes, which may in part explain more pronounced differences in incidence between females and males at younger ages as well as dramatic increases in risk during this time\textsuperscript{97}. Low rates of SA in males compared to females measured by self-report also raises the question about possible differential underreporting, where males might underreport more than females. This notion is consistent with differential underreporting of depressive symptoms between males and females\textsuperscript{98}. Given that the rates of SA are so low in males, this adds a challenge to detecting significant exposures due to statistical power issues. However, in this study, the finding of no association between maternal depressive symptoms and offspring SRT and SA in males was qualitatively different than in females, with the effect estimate yielding a paradoxical protective non-significant effect with adequate statistical power. Studies have reported inconsistent findings relating to the modifying influence of sex on this association\textsuperscript{44, 93}. Plausible explanations for an association between maternal depressive symptoms and SRT and SA in females but not in males could be linked to neurodevelopmental differences during exposure to maternal depression where females are more vulnerable to these effects in comparison to males\textsuperscript{99}. Further reasons for inconsistent findings could also be linked to differential age at exposure and the age of when the outcome is measured which is varied across existing studies.

Sex refers to the biological differences distinguishing males and females, while gender refers to the socially prescribed roles associated with sex, or a personal identification of sex\textsuperscript{100}. The NLSCY did not include measures of gender and only recently have national surveys included measures of gender. Gendered behavioural patterns and risk of depression and suicide-related behaviours have been well documented\textsuperscript{101, 102}; however, the association between maternal depression and sexual minority male and female youth compared to heterosexual youth has not been examined. Females have been posited to report more depression than males owing to differential early socialization responses. Specifically, parents exhibit gender-specific responses to child behaviour, in line with
traditional gender roles, where female children are encouraged to be more self-expressive and relationship-oriented, while boys are encouraged to be more strong and independent. It has been suggested that female offspring of depressed mothers are at a greater risk for SRT and emotional problems than boys, as they are more sensitive to the stressors associated with maternal depression such as relationship strain. These early gender-specific socializations may in part explain an association between exposure to maternal depression and SRT and SA risk in girls, but not in boys, but further study of these gendered specific associations is needed.

6.2 Limitations

6.2.1 Self- and maternal-reported measures

The NLSCY is based on self-reported data. As such, there are potential biases that could arise involving all variables examined. The exposure was measured by the CES-D, which is not a diagnostic tool, but rather a screening measure to identify possible cases of depression. Therefore, the exposure used in this study reflects depressive symptoms indicative of a DSM-IV diagnosis. While a semi-structured interview with a clinical interviewer would be ideal to confirm a DSM diagnosis of depression, this is not feasible in population-based studies. It has been suggested that mothers under-report post-partum depression owing to concerns about possible institutionalization, separation from their children and embarrassment. However, it is unclear if this under-reporting is more present in self-report measures compared to semi-structured or structured clinical interviews. Respondents from the NLSCY were ensured confidentiality and anonymity. The fact that the exposure was both self-reported and indicative of depressive symptoms, rather than a confirmed diagnosis is more reflective of maternal depressive symptoms seen in the general population, increasing external validity.

The outcome was self-reported in offspring, which could lead to misreporting. This may have been differential in females compared to males. Factors that significantly contribute to inaccurate estimates of SRT and SA in adolescents include: lack of anonymity, long recall periods,
misunderstanding of the term SRT and SA and the concept of intent to die\textsuperscript{19} and social desirability\textsuperscript{20}. The question used in the NLSCY explicitly describes the suicidal act, thereby reducing potential confusion over SA with intent to die compared to non-suicidal self injury\textsuperscript{104}. Moreover, the youth survey was paper and pencil, and youth respondents were ensured confidentiality from their parents and teachers when completing the measure. Acceptable reliability and validity of the suicide-related measures in the NLSCY has been established\textsuperscript{105,106}. Further, by using a self-reported outcome, we were able to determine how maternal depressive symptoms are associated with SRT (an outcome not systematically collected in health administrative data) and SA, irrespective of hospitalization. Suicidal intent is also not systematically captured by other hospital confirmed cases of SA measured through ICD codes. Also, several structured and some semi-structured clinical interviews measure SRT and SA in the context of depression, and some cases of SRT and SA are missed among respondents not meeting criteria for depression-related gate questions\textsuperscript{85}. While an assessment battery with several items would be ideal for the measurement of SRT and SA, this was not available through the NLSCY given that this is a population-based design.

Child psychiatric symptoms were maternal-reported. However, the validity and reliability of the parent reported Behaviours Scale used in the NLSCY has been shown to mirror the validity and reliability of the Diagnostic Interview for Children and Adolescents, a structured clinical interview as well as other structured clinical interviews\textsuperscript{107,108}. The mother’s own current functioning and level of psychopathology could have impacted her ratings. Some studies support that maternal reports of child psychiatric symptoms tend to be rated more severe compared to youth reports\textsuperscript{109,110}, leading to a potential risk of differential misclassification of the mediator among exposed compared to non-exposed. However, other studies have reported mixed findings pertaining to the depression-distortion hypothesis in term mother’s reports on child behaviours\textsuperscript{111,112}. The impact of the mother’s illness on her perceptions of offspring behaviour is likely influenced by illness severity and other associated characteristics.

The binge drinking variables, adjusted for as confounders, were also maternal-reported. Therefore, the mother reported on her spouse’s binge drinking behaviour. There is evidence supporting
acceptable reliability and validity of self-reported alcohol consumption in general population surveys\textsuperscript{113}, and self-report and collateral reports (such as spousal reports) have shown to converge\textsuperscript{114}. Although discrepancies in self-report compared to other informant reports may be present when the functioning of the self-reporting individual is poor\textsuperscript{114}. As such, maternal reports of spouse binge drinking may have been different in exposed versus non-exposed offspring.

6.2.2 Measurement

The exposure was coded as an average and then dichotomized because of design limitations in the NLSCY. However, the advantage of this approach is being able to determine the association between maternal depressive symptoms and childhood and offspring SRT and SA in a general population sample. The disadvantage of this is the possibility of misclassifying exposed and non-exposed individuals by averaging across scores. However, the total proportion exposed (reflecting a count of those ever exposed during the first decade of life) was quite stable across the exposure period (Appendix D) and was very similar to the proportion exposed (14.5\%) estimated through the averaging method used in primary analyses. Therefore, the level of exposure misclassification was not expected to be significant. The primary rationale for coding the exposure as an average value was to account for mother’s differential number of cycle participation to reduce risk of a higher likelihood of offspring being exposed among mothers with more cycles of response compared to those with less. Further, there were considerable floor effects of this measure, as expected in general population samples, leading to the measures dichotomy using a cut-off, rather than leaving this variable as continuous. Because of the NLSCY design and the rarity of the outcome examined, other measures of exposure pertaining to severity and duration were challenging to estimate.

The marital status measures which were used to derive the family structure variable could reflect misclassified cases. A self-report of being married or common-law is a crude measure of family intactness and there could have been cases where parents were married but not living together. Ideally, this measure would include questions about whether parents reside at home which would
reflect a more accurate portrayal of the family scenario, but this level of detail was not available from the NLSCY.

6.2.3 Selection bias

Attrition was present in the NLSCY (Appendix E), although, while several respondents had cycle non-response, many re-entered the survey at a later cycle. This was accounted for through the use of a counting process framework, taking into account these discontinuous risk intervals; however, this does not account for potential selection biases imposed by those with less cycles of data collection, or those who dropped out early. Selection biases were tested for in each analysis by estimating primary associations in those with and without cycle non-response. Effect estimates tended to be attenuated among the reduced sample with those with no cycle non-response compared to those with cycle non-response, yet the findings did not change appreciably, suggesting no evidence of selection bias. Information on individuals who refused to participate in the NLSCY was not available, although the provided Statistics Canada longitudinal and bootstrap weights were used in all analyses and account for non-response bias.

6.2.4 Generalizability

The NLSCY excluded certain groups: namely, full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves. Thus, reducing the generalizability of these findings to these particular groups of individuals. In light of this, this study is not truly generalizable to the entire Canadian population and excludes certain groups that are at ultra-high-risk for suicide.

The parent respondent participating in the NLSCY was the biological mother in > 90% of cases. The remainder of cases the parent respondent was the biological father or adoptive parents. Cases where the parent respondent was not indicated to be the biological mother were not excluded. Other studies using the NLSCY have used this same approach, while others omit respondents
whose parent respondent was not the biological mother\textsuperscript{49}. A sensitivity analysis was conducted excluding the cases where the parent respondent was not the mother, and primary results were very similar (Appendix C tables iv-vi), indicating that these results can be extended to mothers and that this decision did not alter the findings.

### 6.2.5 Confounding

The NLSCY is comprehensive; yet, there were still some potential confounding variables that were not measured. It is established that childhood physical and sexual abuse are strong predictors of adolescent SA\textsuperscript{55}. The NLSCY does not include a direct measure of abuse, although the life events measure adjusted for in all multivariable analyses included an item of abuse. The NLSCY also does not include a measure of family history for suicide-related behaviour; however, studies have provided evidence of independent associations between maternal depression and offspring SA risk, after accounting for family history for suicide-related behaviour\textsuperscript{31, 72}. Although ethnicity is associated with differences in suicide-related behaviour risk\textsuperscript{79}, the population captured by the NLSCY is 97% white, and there was very little variability in ethnicity in offspring reporting SRT and SA compared to no SRT or SA. Therefore, this variable was not accounted in multivariable models. It was also decided a priori to adjust for stressful life events as a confounder, and not test this variable as a mediator or moderator. While there is preliminary evidence that adolescent stressful life events in conjunction with adolescent psychiatric symptoms mediate the association between adverse early environments (including parental alcohol, dysfunctional attachment to parents and childhood sexual abuse) with SA occurring between 15 to 21 years\textsuperscript{51}, maternal reports of offspring stressful life events in childhood may capture a different construct. Maternal depression may be associated with offspring stress reactivity, but not necessarily an increased risk of experiencing stressful life events\textsuperscript{116}. Finally, the NLSCY did not have any measures of suicide. However, given the prevalence rates of suicide in youth, and the size of the sample used, the number of deaths by suicide was expected to be very low. While the competing risk of death from any cause was considered, the number of respondents who were out of scope (which included those who died during follow-up) was very small, (<3.6%), and as such, this was not expected to significantly impact the findings.
6.3 Future research directions

The NLSCY ended in 2009, and there are currently no nationally representative longitudinal surveys in young Canadians. The need for better surveillance of SRT and SA has been identified as an international priority. Recommended improvements surround establishing standard definitions and language of suicide-related behaviours, and adding important measures (socio-demographic, and more detailed information about the suicide-related event) to existing population data sources. Unfortunately, this relies on existing population data sources, most of which are cross-sectional and not nationally representative, or health administrative data that excludes those not accessing a healthcare setting. The development of new longitudinal surveys should be considered. Also, using the novel application of a counting process survival model to estimate cumulative incidence could be applied to other existing international longitudinal surveys that contain discontinuous risk intervals, contributing to improved surveillance.

Findings from this thesis informed the nature of the association between maternal depressive symptoms in childhood and offspring SRT and SA risk from adolescence to young adulthood. However, question remains about earlier prenatal exposures, other effect modifying influences, and mediating pathways that require further study. Examining the impact of timing, severity, and duration of exposure to maternal depression in childhood could yield insight about critical windows that map onto different neurodevelopmental stages. There is evidence that prenatal maternal stress and major depression increases risk of emotional and behavioural problems in childhood and adolescence. Large prospective cohort studies following children prenatally into adolescence are costly but can lend important insight into the age specific effects of these exposures. Larger samples are also needed to have sufficient statistical power to stratify study samples and determine effect modification by sex and different genders to clarify moderating and mediating pathways by sex and gender. In light of the higher-risk of suicide in sexual minorities, the need to identify risk factors early in the development of suicide-related behaviour has been noted. Further, we still have little understanding as to why males report SA and die by suicide.
Given that males have higher rates of suicide than females\(^7\), it should be a priority to understand why. Specific psychiatric symptoms in childhood and adolescence may be differentially associated with SA in males compared to females and this area is in need of further study.

Understanding the patterns of psychopathology in childhood that most strongly predict adolescent SA and focusing on unpacking categorical diagnoses into dimensional symptoms is needed. Importantly, future research should put more consideration into effect measure modification by age at exposure, mediator and outcome variables. Differential age across studies might in part explain the discrepant findings pertaining to child psychiatric symptoms and SRT and SA risk. Given the conflicting evidence pertaining to specific psychiatric symptoms and diagnoses predicting SRT and SA in adolescence and adulthood and by age, a systematic review and meta-analysis would be very helpful in synthesizing these findings.

The lack of paternal information is a major limitation of most surveys. The need to inform paternal measures when studying child and adolescent psychiatric outcomes has been recognized\(^1\)\(^2\)-\(^3\), yet, we still lack good paternal measures. This may reflect the general perception of the lack of importance of paternal exposures on child development\(^2\), and issues relating to paternal engagement in research\(^3\). Nevertheless, there is some evidence that paternal postnatal depression is associated with psychiatric disorders at age seven in offspring, even after controlling for maternal depression\(^4\). Therefore, it is important to study the influence of mental health exposures in fathers in addition to mothers on offspring SRT and SA risk.

### 6.4 Suicide prevention strategies and implications

#### 6.4.1 Suicide prevention strategies

The World Health Organization (WHO)\(^1\) published a suicide prevention report in 2014 describing suicide prevention strategies in three forms: universal, selective and indicated. Universal suicide preventions focus on reducing access to means that increase risk of suicide-related behaviour, and increasing access to healthcare, and other protective factors. Selective suicide prevention strategies
target vulnerable groups characterized by known risk factors for suicide-related behaviours, and indicated strategies focus on symptom reduction in vulnerable groups already exhibiting suicide-related behaviour. Wilcox et al\textsuperscript{5} subsequently developed a framework for categorizing suicide prevention strategies, that largely overlap with the WHO framework involving: primary, secondary, and tertiary prevention strategies. Although, Wilcox et al\textsuperscript{5} suggests a crucial point that primary suicide preventions ideally should reach youth before the onset of suicide-related behaviour and even before youth reach the high-risk period for suicide-related behaviour and this criterion is not encompassed by all universal or primary prevention strategies.

Universal prevention strategies include educational programs aimed at strengthening skills that are protective for suicide-related behaviour and equip children with strategies to cope with stress. For example, the Good Behaviour Game is a school-based program that targets school-aged children and is aimed at increasing prosocial behaviour through an in-classroom game\textsuperscript{125}. Other forms of universal prevention strategies include increasing healthcare access and altering the environment to reduce access to means to attempt suicide. For example, means restriction limits access to means such as firearms via policy level changes; however, this approach does not reduce the causes of the underlying SRT and SA. Another example is primary prevention aimed at reducing stigma of psychiatric problems, and suicide-related behaviours, often conveyed through the form of social media campaigns and other forms of public health communication\textsuperscript{5}.

Gatekeeper training programs include a mix of selective and universal approaches towards suicide prevention, targeting suicide-related behaviour reduction for both high-risk groups (e.g., First Nations\textsuperscript{126}) and entire groups (e.g., high-school students)\textsuperscript{5}. Gatekeeper training aims to equip individuals with the skills to acknowledge and respond effectively to an individual in a suicide-related crisis. While there is a high volume of gatekeeper training programs currently implemented internationally, these programs are highly heterogenous making them difficult to compare\textsuperscript{5} and also do not consider the underlying factors leading to suicide-related behaviour. These types of programs rely on the individuals being trained and there are likely several factors (e.g., cultural, socio-economic, age and sex-related) that impact the effectiveness with implications for specific tailored programs. School-based prevention programs similarly include a mix of universal and
selective prevention approaches depending on the population targeted. The Saving and Empowering Young Lives in Europe\textsuperscript{127}, the Signs of Suicide\textsuperscript{128}, and the Sources of Strength\textsuperscript{129} programs all aim to increase protective factors in youth such as active coping strategies, knowledge about suicide, trust, and help-seeking behaviours with an ultimate goal to prevent the trajectory of suicide-related behaviours.

Indicated suicide prevention approaches involve active treatment of acute symptoms related to suicide-related behaviour to prevent suicide. These approaches wait until youth reach a suicidal crisis, most often when they access a health care setting for serious SRT, or self-harm. Psychotherapies such as cognitive behavioural therapy, or dialectical behaviour therapy are common indicated approaches that typically target patients either diagnosed with a psychiatric disorder or who are exhibiting serious SRT, or recently attempted suicide. Pharmacological treatment involving antidepressants, mood stabilizers, and anti-psychotics are other common indicated strategies employed to reduce risk of future SA and suicide in patients with existing psychiatric disorders\textsuperscript{5}. Debate remains about the effectiveness of antidepressants in light of the conflicting evidence of possible SRT and suicide-related behaviour side-effects associated with antidepressant use in young populations\textsuperscript{130}.

6.4.2 Effectiveness of suicide prevention strategies

The effectiveness of several selective and indicated suicide preventions such as pharmacological treatment, gatekeeper and general physician training, and post hospitalization follow-up has not been supported, although the heterogeneity across interventions, and low methodological quality of studies testing these interventions, limits interoperability\textsuperscript{80,131}. Despite these equivocal findings, suicide prevention studies and most implemented preventions have been dominated by selective and indicated preventions targeting populations of youth identified via treatment settings or already in crisis\textsuperscript{5}. Further, indicated suicide prevention programs are typically provided to youth who access healthcare settings and (or) personnel. Given that a large proportion of SRT and SA start to occur in early to mid-adolescence\textsuperscript{3}, this raises concern that without broader and early
prevention strategies that reach these youth, they may progress to more lethal behaviours. Cross-sectional findings from the National Comorbidity Survey – Replication Adolescent Supplement indicate that up to 73% of adolescents (13 to 18 years) in the United States receive some form of mental health treatment (primarily selective and indicated prevention programs) prior to the onset of their suicide-related behaviour; however, only approximately 50% received this treatment during the same year that their suicide-related behaviours occurred. These findings highlight two important points: 1) most adolescents report SAs after initial treatment raising questions about transitions in their care; and 2) we are not reaching almost 50% of adolescents currently exhibiting suicide-related behaviours.

A recent systematic evaluation of a gatekeeper training program in Manitoba, targeting First Nations on reserve community members did not show effectiveness in increasing the capacity to intervene a suicide-related crisis and suggested an increase of SRT in the individuals being trained as gatekeepers. Further, school-based gatekeeper training programs targeting high-school students and school staff have shown increases in positive attitudes towards and knowledge of suicide-related behaviours, but these programs have not shown to be effective in increasing actual behavioural outcomes in those trained (e.g., talking to students about suicide), nor have they shown effectiveness by increasing mental health service use.

There is some evidence that school based programs, typically targeting high-school aged youth, such as the Saving and Empowering Young Lives in Europe, the Signs of Suicide, and the Sources of Strength programs, are effective in reducing short-term risk of self-reported SA and related outcomes such as psychiatric symptoms and increase protective factors surrounding strategies to cope effectively with negative emotions and stress. However, more research systematically evaluating these programs is needed.

There has been increasing interest in family-based interventions, involving parents in suicide prevention efforts, and while there is a limited number of studies systematically testing effectiveness of these programs, some studies support their efficacy in reducing suicide-related behaviour. Further, it has been suggested that suicide interventions that involve parental
support and the strengthening of other protective factors in youth are most impactful in reducing suicide-related behaviour risk in youth. In particular, family-based preventions that target parent-child communication, problem-solving and parental monitoring. These types of family-oriented prevention strategies could also include discussions and/or treatment of parental psychiatric symptoms in addition to symptom reduction in youth.

It is already well established that suicide-related behaviour is a complex phenomenon resulting from genetic, individual, environmental and family-related factors and interactions of these factors throughout the lifespan. Intuitively, preventions that intersect throughout the lifespan, involving different approaches should be most effective. Further, certain selective and indicated preventions may not reach lower socio-economic status groups as they often require regular access to a healthcare setting, or access to high-income schools. On the other hand, universal preventions may not reach individuals at highest risk. In order to maximize the reduction of suicide and reach individuals across a broad socio-economic spectrum, several authors have recognized the need to take a multi-sectorial approach intervening on several different levels at several different times throughout the lifespan. This would likely involve the implementation of several different types of suicide prevention programs simultaneously.

6.4.3 Maternal depression in the context of offspring suicide prevention

Despite the extant literature linking maternal depression to a wide variety of negative health outcomes in offspring, this exposure is rarely considered as a basis for youth suicide prevention efforts. An individual level approach to treatment has been the norm, focusing solely on maternal depression, or solely on psychiatric outcomes in offspring when they occur. Researchers have noted the need for a paradigm shift, moving away from treating individuals towards treating families as a unit. Family-based interventions targeting offspring of depressed parents aimed at improving mother-child interactions, and involving cognitive based-therapies in families, and psychoeducation for mothers with depression have shown promising effects in the reduction of depression in offspring. Of note, these preventions target children before the onset of depressive symptoms. These types of programs have not been systematically evaluated and have not been
developed for the reduction of suicide-related behaviours; however, could be tailored for suicide prevention. Applying these approaches for suicide prevention could be promising in light of one of the main findings from this research showing significant increases in risk of both SRT and SA among offspring exposed to maternal depressive symptoms in childhood.

The majority of women in Canada receive some form of prenatal care, and in turn have some contact with the healthcare system. This could reflect an optimal time to reach mothers experiencing or who have experienced major depression. Most mothers who experience depression postnatally, also experienced symptoms during their pregnancy. Therefore, this could be a useful way of reaching potential high-risk families, where offspring are at increased risk for SA. The importance of perinatal depression screening has been highlighted, although the implementation of universal perinatal depression screening programs is controversial, and some authors suggest that perinatal screening could be harmful to mothers owing to false positives, and stigma. It has been reported that less than half of new mothers referred for treatment for major depression seek or receive treatment. Efforts to reduce stigma surrounding maternal depression would be useful, and may improve the effectiveness of prenatal screening programs which could contribute to offspring suicide prevention.

6.4.4 Public health implications

The results from this thesis have research and public health implications for: 1) the need for better surveillance of SRT and SA in populations; 2) the age implementation of suicide prevention programs; 3) informing the context of upstream selective suicide prevention strategies targeting youth before the peak high-risk period for suicide-related behaviour.

Findings from this thesis suggest that Canadians start to report thoughts about suicide, and attempt suicide at earlier ages and at much higher rates than reflected by population incidence estimates of hospital presented suicide-related behaviour. Among young individuals who report attempts, a large proportion first occur between 11 to 13 years of age, with most first events occurring by age
16. Firstly, this underscores the need for better surveillance of specifically self-reported SRT and SA in the population, as hospital presentations for suicide-related behaviours exclude a large proportion of youth reporting attempts and do not routinely collect information on SRT. Secondly, these findings suggest that suicide prevention programs targeting youth protective factors should be implemented earlier, as a considerable amount of youth are thinking about suicide and reporting attempts as early as age 11 and possibly earlier. Most school-based suicide prevention programs target the mid to late adolescent population\textsuperscript{127-129}.

These findings also have implications for several different selective suicide prevention strategies targeted for families where a mother is depressed involving: 1) family and school-based preventions; 2) clinician monitoring; and 3) prenatal depression screening. Families where a mother is depressed, and possibly where children are exposed to family-breakup are potential target groups for selective suicide preventions and could reach children before the onset of suicide-related behaviour. Specifically, family-based preventions involving support and psychoeducation for depressed mothers and cognitive-based therapies for mothers and children could serve as an upstream approach towards reducing vulnerability in offspring. Family-based preventions using such approaches have been developed to reduce offspring depression\textsuperscript{139, 140}, and could be tailored for the reduction of suicide-related behaviours. Further, both family and school-based suicide prevention programs targeting the reduction of childhood risky symptoms related to attention deficit hyperactivity disorder and co-occurring psychiatric symptoms in offspring of depressed mothers could also reduce risk of SA.

A shift in focus to the family unit, away from the individual, could be helpful in guiding clinician monitoring and treatment approaches for depressed mothers and their children. Reductions in acute maternal depression improves in parallel, offspring’s depressive symptoms, and these effects might extend to offspring SRT and SA reductions\textsuperscript{91}. As highlighted in section 6.4.3, prenatal screening could be an effective way to at least reach high-risk mothers who have experienced or who are experiencing depression and start the clinician monitoring process. Public health campaigns targeting stigma reduction relating to maternal depression in parallel to prenatal screening efforts could possibly improve effectiveness and subsequent uptake of treatment.
The future development of upstream selective suicide prevention strategies also need to consider important sex-specific differences in target groups, and symptoms. The risk of SRT and SA in offspring exposed to maternal depressive symptoms in childhood was only present in females, not males. Further, more females report SRT and SA compared to males. The prevention strategies suggested above may be more effective in females compare to males. Intermediate risk factors including childhood psychiatric symptoms likely differ in males and females and require further study and consideration to inform selective prevention strategies to maximize effectiveness.

Finally, the aforementioned suicide prevention strategies would be most impactful if implemented in conjunction with other forms of suicide preventions. The main findings from this thesis inform a few out of several pieces of the web of risk factors for youth and young adult SRT and SA, and these implications for selective preventions do not extend to all groups. An optimal approach towards suicide prevention that reaches the entire socio-economic status range, would be to implement evidence based preventions at universal, selective and indicated levels that compliment one another\textsuperscript{135}.

### 6.5 Conclusions

The strongest risk factor for death by suicide, and future SA is a prior SA\textsuperscript{3}, therefore, implementing upstream prevention strategies before youth reach crisis is crucial. Current selective and indicated suicide prevention strategies tend to target adolescents after the peak risk time for suicide-related behaviour onset. Selective preventions targeting support and psychoeducation for depressed mothers, and the reduction of maternal depressive symptoms and child risky psychiatric symptoms could help to build the necessary protective factors in children to reduce the risk of SRT, eventual SA, and halt progression towards suicide.
References


Appendices
## Appendix A. Suicide-related thoughts and attempts incidence studies

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</thead>
</table>
| Prosser et al., 2007 | USA     | All ages    | National Electronic Injury Surveillance System - All Injury Program (NEISS-AIP) | 2001-2004 Emergency department visits (intentional non-fatal poisonings) Yearly incidence rates/100,000 | 2001: 76 (95% CI 53 – 98) 2002: 75 (95% CI 58 – 92) 2003: 94 (95% CI 74 – 115) 2004: 93 (95% CI 74 – 112) | *Examined by sex, age, race, but did not report all age and sex specific estimates  
*Young (15-18), white females at highest risk (238/100,000)  
*Irrespective of suicidal intent |
| Benjet et al., 2017  | Mexico  | Wave 1: 12-17 years Wave 2: 19-26 years | Mexican Adolescent Mental Health Study – 2005 (2-wave longitudinal study) | WHO Composite International Diagnostic Interview: Suicide-related thoughts from 2005 – 2013 (12-26 years) | 2005-2013 (8-year cumulative incidence) SRT: 13.3% SRT with plan: 4.8% SA: 5.9% | *Did not report sex specific estimates  
*Not self-report (trained raters) |
| Canner et al., 2016  | USA     | All ages    | CDC’s National Electronic Injury Surveillance System-All Injury Program (NEISS-AIP) E-codes | 2006-2013 emergency department visits (annual incidence rates/100,000) | Age patterns for males and females were similar  
The peak for females (459/100,000 at age 15–19) is earlier and higher than the peak for males (270/100,000 at age 20–24) | *Did not report all estimates by sex and age  
*Irrespective of suicidal intent |
| Corcoran et al., 2004 | Europe  | 15+         | ICD-codes self-inflicted injury and poisonings and confirmed by research psychiatrists | Hospital treated suicide-related behaviours | F: 15-19 (433 per 100,000) M: 20–24 (374 per 100,000) | *Displayed most incidence estimates graphically  
*Irrespective of suicidal intent |
| Morthorst et al., 2016 | Denmark | 15-24       | ICD-codes self-inflicted injury and poisonings | Annual incidence rate/100,000 for suicide-related behaviours | 15-19 yrs  
F: 543/100,000  
DNR for M  
20-24 yrs  
F: 432.9/100,000  
M: 146.6/100,000 | *Displayed most incidence estimates graphically  
*Irrespective of suicidal intent |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Location</th>
<th>Year</th>
<th>Data Source</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
</table>
| McMahon et al., 2014    | Ireland                 | 15-17| National Registry of Deliberate self-harm and community school surveys       | Annual incidence rates/100,000 for hospital treated and community occurring suicide-related behaviours | hospital treated suicide-related behaviours (2003-2011)  
F: 438.1  
M: 256.2  
Self-reported suicide-related behaviour (2003-2004)  
F: 8900  
M: 2400  
*Estimated only 6% of self-reported SA resulted in hospitalization |
| Perry et al., 2012      | Ireland                 | 15-19| National Registry of Deliberate SH in Ireland                               | 2003-2009 average incidence rate for hospital treated suicide-related behaviours | F: 620/100,000  
M: 336/100,000  
*Irrespective of suicidal intent |
| Bethell et al., 2013    | Ontario, Canada         | 12-17| Emergency department visits (2002-2009)                                     | 7-year incidence rate/100,000 for hospital treated suicide-related behaviours   | F: 474.5  
(95% CI: 461.8-487.3)  
M: 174.6  
(95% CI: 169.5-179.7)  
*Irrespective of suicidal intent |
| Larsson et al., 2008    | Norway                  | 12-15| School survey                                                                | 1-year incidence rate of self-reported suicide attempts                        | F: 2.1%  
M: 1.2% |
| Kuo et al., 2001        | Baltimore, USA          | 18-29| Epidemiologic Catchment Area program                                        | Annual incidence/100,000 of self-reported suicide-related thoughts and suicide attempts | Suicide-related thoughts  
F: 688/100,000  
M: 550/100,000  
Suicide attempts  
F: 373/100,000  
M: 224/100,000  
*Based on very small numbers |
| Alaghehbandan et al., 2005 | Newfoundland and Labrador, Canada | 10-24| Inpatient ICD codes (1998-2000)                                            | Incidence rates/100,000 for hospital treated suicide-related behaviour         | F: 10-14: 75.0  
15-19: 189.1  
20-24: 96.7  
M: 10-14: 24.5  
*Irrespective of suicidal intent |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Location</th>
<th>Age Range (yr)</th>
<th>Data Source</th>
<th>Incidence/At-risk Estimates</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mok et al., 2015</td>
<td>Denmark</td>
<td>15-40</td>
<td>National patient register</td>
<td>Annual incidence and cumulative incidence of hospital presentations of suicide-related behaviour</td>
<td>Only provide figures (see paper) *Did no report age specific estimates only presented in figures</td>
</tr>
<tr>
<td>Peyre et al., 2017</td>
<td>USA</td>
<td>18+</td>
<td>National Epidemiologic Survey of Alcohol and Related Conditions</td>
<td>Lifetime incidence rates of self-reported suicide attempts</td>
<td>M/F: &lt;13 yrs: 0.27% 13 – 17 yrs: 1.22% &gt;17 yrs: 1.82% *Retrospective *Did not report sex specific estimates but did indicated a 1:4 ratio for males: females with no significant differences</td>
</tr>
</tbody>
</table>
## Appendix B. Suicide-related thoughts and attempts prevalence studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Age (years)</th>
<th>Data Source</th>
<th>Outcome</th>
<th>Prevalence</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Evans et al., 2005       | International    | 12-20       | Systematic review of population-based studies                               | Lifetime prevalence of self-reported suicide attempts, self-harm and suicide-related thoughts | Suicide attempts: 9.7%  
Self-harm: 13.2%  
Suicide-related thoughts: 29.9%, | *Did not report sex-specific estimates, but all estimates were significantly higher in females  
*High heterogeneity between studies |
| Findlay, 2017 (Health Reports) | Canada          | 15-25       | 2012 - Canadian Community Health Survey (CCHS) – Mental Health             | Prevalence of self-reported suicide-related thoughts and suicide attempts | Life-time  
Suicide-related thoughts  
M: 12%  
F: 16.2%  
M/F: 14.1%  
Suicide attempts  
M/F: 3.5%  
Past year  
Suicide-related thoughts  
M/F: 5.8%  
Suicide attempts  
M/F: 1% | *Did not report sex specific estimates for all outcomes |
| CIHI report, 2014        | Canada           | 10-19       | Hospital and emergency department visits                                   | Annual prevalence of suicide-related behaviours                           | M: 32/100,000  
F: 164/100,000 | *Irrespective of suicidal intent |
| Barzilay et al., 2017    | Europe           | 15          | Saving and Empowering Young Lives in Europe study (SEYLE)                   | Point prevalence of past week self-reported suicide-related thoughts and suicide attempts | Suicide-related thoughts  
M: 2.8%  
F: 4.3%  
Suicide attempts  
M: 1.9%  
F: 4.6% | |
| Peltzer et al., 2017     | International    | 13-15       | Global school-based survey from the 7 Association of Southeast Asian Nations (ASEAN) Countries | Past year prevalence of self-reported suicide-related thoughts            | M: 9.3%  
F: 15.1%  
M/F: 12.3% | |

---

**Outcome Definitions:**
- "Suicide-related thoughts" refers to thoughts of ending one's life.
- "Suicide attempts" refers to actions taken to bring about one's own death.
- "Self-harm" refers to deliberate self-injury without suicidal intent.

**Notes:**
- *Did not report sex-specific estimates.
- All estimates were significantly higher in females.
- *High heterogeneity between studies.
- *Irrespective of suicidal intent.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Age Range</th>
<th>Survey Source/Year</th>
<th>Prevalence of Suicide-Related Thoughts and Attempts</th>
<th>Sex Specific Estimates</th>
<th>Additional Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipari et al., 2017</td>
<td>USA</td>
<td>18-25</td>
<td>National Survey on Drug Use and Health</td>
<td>Past year prevalence of serious suicide-related thoughts (2013-2014)</td>
<td>M/F: 7.4% (national)</td>
<td>*Did not report sex specific estimates</td>
</tr>
<tr>
<td>Borges et al., 2016</td>
<td>Mexico</td>
<td>19-26</td>
<td>Mexican National Comorbidity Survey</td>
<td>Lifetime and past year prevalence’s of suicide-related thoughts and suicide attempts</td>
<td>Lifetime Suicide-related thoughts M/F: 15.9% Suicide attempts M/F: 6.7%</td>
<td>*Did not report sex specific estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Past year Suicide-related thoughts M/F: 4% Suicide attempts M/F: 1.5%</td>
<td></td>
</tr>
<tr>
<td>McKinnon et al., 2016</td>
<td>International</td>
<td>13-17</td>
<td>2003-2012 Global School-based Health Surveys</td>
<td>Past year prevalence of suicide-related thoughts</td>
<td>F: 16.2% M: 12.2% (pooled across WHO region countries)</td>
<td></td>
</tr>
<tr>
<td>Zubrick et al., 2016</td>
<td>Australia</td>
<td>12-17</td>
<td>National Survey (2013-2014)</td>
<td>Annual prevalence of suicide-related thoughts and suicide attempts</td>
<td>Suicide-related thoughts: F: 10.7% M: 4.5% M/F: 7.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suicide attempts: F: 3.4% M: 1.5% M/F: 2.4%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Age Range</td>
<td>Study Design/Methodology</td>
<td>Prevalence Measure</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>---------</td>
<td>-----------</td>
<td>--------------------------</td>
<td>--------------------</td>
<td>----------</td>
<td></td>
</tr>
</tbody>
</table>
| Kaess et al., 2011                         | Germany | 9th grade students (mean age=14.8) | School based study in Southern Germany | Lifetime prevalence self-reported suicide-related thoughts and suicide attempts | Suicide-related thoughts: F: 19.8%, M: 9.3%  
  Suicide attempts: F: 10.8%, M: 4.9% |
| Wolitzky-Taylor et al., 2010                | USA     | 12-17     | National Survey of Adolescents (NSA)-Replication (2005) | Lifetime prevalence of self-reported suicide-related thoughts and suicide attempts | Suicide-related thoughts: F: 14.3%, M: 7.6%  
  Suicide attempts: F: 4.5%, M: 1.5%  
  Measured suicide-related thoughts and attempts in the context of depression (depression module from the NSA) |
| Nock et al., 2013                           | USA     | 13-18     | National Comorbidity Survey Replication – Adolescent Supplement | Lifetime prevalence of CIDI confirmed suicide-related thoughts, plans and attempts | Suicide-related thoughts: M/F: 14.1%  
  Suicide-related plans: M/F: 4.0%  
  Suicide attempts: M/F: 4.1% |
| Fedorowicz et al., 2007                     | France  | 15-23     | community mail out survey | Lifetime and past year prevalence/100 of self-reported suicide-related thoughts | Lifetime  
  15-16: F: 54.8, M: 28.1  
  17-18: F: 49.6, M: 35.1  
  19-20: F: 64.0, M: 44.0  
  Past year  
  15-16: F: 31.4, M: 18.4  
  17-18: F: 29.9, M: 16.7  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th>21-22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F: 23.2, M: 18.6</td>
</tr>
</tbody>
</table>

Appendix Ci: Additional results

The differential effect of timing of first exposure to maternal depressive symptoms on suicide-related thought and attempts risk

The purpose of this supplementary analysis was to determine if associations between maternal depressive symptoms and offspring SRT and SA differ by timing of first exposure in childhood (zero to two years of age, three to five years of age, and six to ten years of age) given the evidence of potential sensitive periods during these time periods.\textsuperscript{49, 50}

The NLSCY cohort was reduced to offspring who were age zero at baseline (i.e., birth cohort). This was necessary to ensure all individuals had the chance to be first exposed starting at zero as the NLSCY included offspring from zero to 11 years at the baseline cycle. After restricting the sample to zero-year-olds at baseline, this reduced the age at last cycle from 26 to 14 years, therefore the outcome time-period was shortened to when respondents were between 11 to 14 years of age. This reduced sample included 1167 respondents (unweighted), and 2013 observations.

We estimated the hazard of incident SRT and SA between 11 to 14 years of age among offspring first exposed from zero to two years of age, three to five years of age, and six to ten years of age. Dichotomous variables were coded reflecting whether offspring were first exposed during each of these three sensitive periods compared to a referent of not exposed or exposed during a later time-period. In light of the aging cohort, there was a higher number of older exposed children compared to younger exposed children, contributing to smaller numbers of young exposed offspring compared older offspring.

Exposure to maternal depressive symptoms was most strongly related to offspring incident SRT and SA between 11 to 14 years of age if first exposure was from three to five years of age, relative to non-exposed offspring, or those exposed at a later period, although this was only significant for SRT (HR: 4.44, 95% CI: 1.20, 2.27), and not SA (HR: 3.55, 95% CI: 0.54, 7.35) (Appendix C Table i). First exposure to maternal depressive symptoms from zero to two years of age was
paradoxically protective of SRT and SA, yet the number of exposed in this time-period was extremely low. Therefore, these findings should be interpreted cautiously
Appendix C Table i. Timing of first exposure to maternal depressive symptoms and hazard of suicide-related thoughts and suicide attempts from 11-14 years of age, weighted\textsuperscript{a} to reflect the Canadian general population

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposure time period (years)</th>
<th>Unadjusted</th>
<th>Adj usted\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95%CI\textsuperscript{c}</td>
</tr>
<tr>
<td>Suicide - related</td>
<td>0 to 2</td>
<td>0.44</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>3 to 5</td>
<td>4.04</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>6 to 10</td>
<td>1.17</td>
<td>0.46</td>
</tr>
<tr>
<td>Suicide attempts</td>
<td>0 to 2</td>
<td>0.71</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>3 to 5</td>
<td>4.36</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>6 to 10</td>
<td>2.06</td>
<td>0.68</td>
</tr>
</tbody>
</table>

CI: confident intervals; HR: hazard ratio/rate; obs: observations
\textsuperscript{a}Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.
\textsuperscript{b}Adjusted for sex, socio-economic status, respondent participation in religious activities (time varying), maternal and spouse binge drinking (0-10 years), offspring stressful life events (4-10 years).
\textsuperscript{c}Estimated using Statistics Canada Bootstrap weights.
Appendix Cii. Additional results

**The association between maternal depressive symptoms in childhood and offspring suicide attempts from 11 to 25 years of age, additionally adjusting for offspring prior suicide-related thoughts**

The purpose of this supplementary analysis was to determine how hazard ratios and relative rates of the association between maternal depressive symptoms in childhood and offspring SA change after adjusting for offspring prior suicide-related thoughts.

The same methods employed in Chapter 4 were conducted for this additional analysis. A dichotomous measure reflecting presence of suicide-related thoughts occurring prior to the first reported suicide attempt, compared to no prior suicide-related thoughts was included in the final multivariable model (Appendix C Table iii).

The adjusted rates of suicide attempts in offspring exposed compared to non-exposed to maternal depressive symptoms in childhood remained similar after including prior suicide-related thoughts, relative to no prior suicide-related thoughts to the multivariable model (Appendix C Table ii).
Appendix C Table ii. Hazard ratios, rates and 95% confidence intervals of suicide-related thoughts and suicide attempts in 11 to 25-year-olds among those exposed and non-exposed to maternal depressive symptoms, weighted\(^d\) to reflect the Canadian general population with additional adjustment for prior suicide-related thoughts

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted(^a)</th>
<th>Adjusted(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95%CI(^e)</td>
<td>#obs (unweighted)</td>
</tr>
<tr>
<td>SRT incident</td>
<td>1.67 1.37 2.08</td>
<td>17973</td>
</tr>
<tr>
<td>SA incident</td>
<td>1.93 1.43 2.50</td>
<td>22693</td>
</tr>
<tr>
<td>SRT recurrent</td>
<td>1.61 1.33 1.96</td>
<td>18478</td>
</tr>
<tr>
<td>SA recurrent</td>
<td>1.87 1.33 1.96</td>
<td>22945</td>
</tr>
</tbody>
</table>

CI: confident intervals; HR: hazard ratio/rate; obs: observations; SA: suicide attempt; SRT: suicide-related thoughts

\(^a\) Adjusted for sex, socio-economic status, respondent participation in religious activities (time varying), person most knowledgeable and spouse binge drinking from 0 to 10 years, child stress (4-10 years), and respondent age at cycle 1

\(^b\) Model additionally adjusted for prior suicide-related thoughts

\(^c\) Estimated using Statistics Canada Bootstrap weights

\(^d\) Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves
Appendix Ciii. Additional results

**Mean behaviours subscale scores from six to ten years of age**

The purpose of this supplementary analysis was to determine if the behaviours scale subscales, reflecting psychiatric symptoms examined as mediators varied from six to ten years of age. These were examined to determine if it was necessary to conduct sensitivity analyses examining the mediation models from Chapter 5 by different mediator age.

The unadjusted mean and standard deviations of each Behaviours subscale were estimated for each age ranging from six to ten. This descriptive analysis was analyzed using the study sample used in analyses pertaining to Chapter 5, which reflects 3,123 offspring with a weighted total of 816,140.

Mean behaviour subscale scores were similar from six to ten years of age (Appendix C Tableiii). Therefore, mediating pathways by different age of psychiatric symptom was not expected to change the findings from mediation models appreciably.
Appendix C Table iii: Means and standard deviations of child psychiatric subscale scores from six to ten years of age, weighted\textsuperscript{a} to reflect the Canadian population

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Standard deviation\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactivity at age 6</td>
<td>4.64</td>
<td>56.75</td>
</tr>
<tr>
<td>Hyperactivity at age 7</td>
<td>4.51</td>
<td>58.73</td>
</tr>
<tr>
<td>Hyperactivity at age 8</td>
<td>4.52</td>
<td>60.69</td>
</tr>
<tr>
<td>Hyperactivity at age 9</td>
<td>4.28</td>
<td>62.25</td>
</tr>
<tr>
<td>Hyperactivity at age 10</td>
<td>4.04</td>
<td>62.97</td>
</tr>
<tr>
<td>Conduct at age 6</td>
<td>1.47</td>
<td>30.91</td>
</tr>
<tr>
<td>Conduct at age 7</td>
<td>1.45</td>
<td>31.20</td>
</tr>
<tr>
<td>Conduct at age 8</td>
<td>1.32</td>
<td>31.17</td>
</tr>
<tr>
<td>Conduct at age 9</td>
<td>1.30</td>
<td>31.21</td>
</tr>
<tr>
<td>Conduct at age 10</td>
<td>1.21</td>
<td>31.58</td>
</tr>
<tr>
<td>Indirect aggression at age 6</td>
<td>1.00</td>
<td>26.24</td>
</tr>
<tr>
<td>Indirect aggression at age 7</td>
<td>1.21</td>
<td>28.16</td>
</tr>
<tr>
<td>Indirect aggression at age 8</td>
<td>1.23</td>
<td>28.94</td>
</tr>
<tr>
<td>Indirect aggression at age 9</td>
<td>1.32</td>
<td>31.45</td>
</tr>
<tr>
<td>Indirect aggression at age 10</td>
<td>1.25</td>
<td>30.77</td>
</tr>
<tr>
<td>Internalizing at age 6</td>
<td>2.39</td>
<td>39.87</td>
</tr>
<tr>
<td>Internalizing at age 7</td>
<td>2.64</td>
<td>41.65</td>
</tr>
<tr>
<td>Internalizing at age 8</td>
<td>2.64</td>
<td>44.66</td>
</tr>
<tr>
<td>Internalizing at age 9</td>
<td>2.81</td>
<td>46.90</td>
</tr>
<tr>
<td>Internalizing at age 10</td>
<td>2.73</td>
<td>47.98</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves

\textsuperscript{b}Estimated using Statistics Canada Bootstrap weights
Appendix Civ – Additional results

Sensitivity analysis: Estimating primary associations excluding parent respondents not reflecting the mother

The purpose of this sensitivity analysis was to determine if primary analyses change appreciable when omitting the parent respondent who was not the mother.

Approximately 8% of the entire cohort reflected parent respondents who were not the mother. This sensitivity analysis was conducted using the sample used in analyses in paper two, reflecting a study sample of 13,169 unweighted respondents (Appendix C Table iv/v), as well as the sample used in analyses in paper three, reflecting a study sample of 3123 unweighted respondents (Appendix C Table vi). The unadjusted proportion of offspring exposed and non-exposed to maternal depressive symptoms in childhood (0-10 years) with and without SRT and SA between 11 to 25 years of age were almost identical after excluding parent respondents who were not the mother (Appendix C Table iv). Further, the adjusted hazard of first reported SRT and SA between 11 to 25 years of age was very similar in the entire cohort compared to the cohort after excluding parent respondents not the mother (Appendix C Table v). Similarly, the adjusted odds of first reported SRT and SA between 11 to 19 years of age among offspring exposed to maternal depressive symptoms between 0 to 5 years of age compared to those non-exposed was very similar to initial estimates after excluding parent respondents not reflecting the mother (Appendix C Table vi). Adjusted associations between exposure to maternal depressive symptoms between 0 to 5 years of age and different psychiatric symptoms were also similar after excluding the parent respondents who were not the mother (Appendix C Table vi).

The decision to not exclude parent respondents who were not the mother was to increase precision of analyses and ensure adequate unweighted numbers owing to the rarity of the outcomes examined, particularly for analyses pertaining to effect measure modification and mediation. These results reflect that excluding these cases do not change the findings, and that these results can be appropriately extended to mothers.
Appendix C. Table iv: Unadjusted weighted proportions of those exposed and non-exposed to maternal depressive symptoms in childhood with and without suicide-related thoughts and attempts in the entire sample, and excluding parent respondents not reflecting the mother, weighted\(^a\) to reflect the Canadian general population

<table>
<thead>
<tr>
<th>Suicide attempts</th>
<th>Entire sample used in analyses for paper two</th>
<th>Entire sample used in analyses in paper two excluding parent respondents who were not the mother</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed</td>
<td>Non-exposed</td>
</tr>
<tr>
<td>YES</td>
<td>62716</td>
<td>13.20</td>
</tr>
<tr>
<td>NO</td>
<td>418987</td>
<td>86.98</td>
</tr>
<tr>
<td>YES</td>
<td>99393</td>
<td>20.63</td>
</tr>
<tr>
<td>NO</td>
<td>382310</td>
<td>79.37</td>
</tr>
</tbody>
</table>

\(^a\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.
Appendix C. Table v: Adjusted hazard ratios and 95% confidence intervals of associations between exposure to maternal depressive symptoms in childhood when offspring were between 0-10 years of age and offspring suicide-related thoughts and attempts from 11-25 years of age, and excluding parent respondents not reflecting the mother, weighted to reflect the Canadian general population.

<table>
<thead>
<tr>
<th>Incident</th>
<th>HR</th>
<th>95% CI</th>
<th>#obs(unw)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident suicide-related thoughts</td>
<td>1.68</td>
<td>1.36</td>
<td>2.08</td>
</tr>
<tr>
<td>Incident suicide attempts</td>
<td>2.01</td>
<td>1.50</td>
<td>2.64</td>
</tr>
</tbody>
</table>

CI: confident intervals; HR: hazard ratio; obs: observations; unw: unweighted

*Adjusted for sex, socio-economic status, respondent participation in religious activities (time varying), person most knowledgeable and spouse binge drinking from 0 to 10 years, child stress (4-10 years), and respondent age at cycle 1

*Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves

*Estimated using Statistics Canada bootstrap weights
Appendix C. Table vi: Adjusted\(^a\) hazard ratios and 95\%!CI of associations between exposure to maternal depressive symptoms in childhood and offspring psychiatric symptoms from 6-10 years of age and suicide-related thoughts and attempts from 11-19 years of age, and excluding parent respondents not reflecting the mother weighted\(^b\) to reflect the Canadian general population

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Odds ratio (beta)</th>
<th>95%CI (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood exposure to maternal</td>
<td>Suicide-related thoughts</td>
<td>1.46 (beta=0.38)</td>
<td>0.82, 2.59 (p=0.1956)</td>
</tr>
<tr>
<td>depressive symptoms (0-5 years)</td>
<td>Suicide attempts</td>
<td>1.87 (beta=0.63)</td>
<td>0.87, 4.02 (p=0.1097)</td>
</tr>
<tr>
<td></td>
<td>Hyperactivity</td>
<td>3.02 (beta=1.10)</td>
<td>1.70, 5.37 (p=0.0002)</td>
</tr>
<tr>
<td></td>
<td>Internalizing</td>
<td>3.32 (beta=1.19)</td>
<td>1.91, 5.75 (p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>Conduct</td>
<td>2.09 (beta=0.73)</td>
<td>1.21, 3.60 (p=0.0087)</td>
</tr>
<tr>
<td></td>
<td>Indirect aggression</td>
<td>1.90 (beta=0.64)</td>
<td>1.09, 3.31 (p=0.0228)</td>
</tr>
</tbody>
</table>

\(^a\)sex, interaction of sex and exposure, socio-economic status, age at baseline, stress (4-10 years), person most knowledgeable and spouse binge drinking

\(^b\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves

\(^c\)Estimated using Statistics Canada bootstrap weights
Appendix D: Percent exposed to maternal depressive symptoms in childhood and the proportion of exposure measurements available by age, weighted\(^a\) to reflect the Canadian general population

\(^a\)Inverse probability weights were used to produce estimates that accurately reflect the characteristics of the Canadian population in 1994/1995 (the baseline of the longitudinal cohort from the NLSCY), excluding full-time members of the Canadian Armed Forces, inmates of institutions, and those residing (during the time of the survey) in Yukon, Nunavut, Northwest Territories and Indian reserves.
Appendix E: National Longitudinal Survey of Children and Youth cycle non-response rates and sample sizes

<table>
<thead>
<tr>
<th>Cycle</th>
<th>N</th>
<th>Cumulative child level response rate</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1 – 1994/1995</td>
<td>22,831</td>
<td>86.5%</td>
<td></td>
</tr>
<tr>
<td>Cycle 2 – 1996/1997</td>
<td>15,056</td>
<td>79.1%</td>
<td>5928 omitted for budget reasons</td>
</tr>
<tr>
<td>Cycle 3 – 1998/1999</td>
<td>13,763</td>
<td>76.0%</td>
<td></td>
</tr>
<tr>
<td>Cycle 4 – 2000/2001</td>
<td>11,655</td>
<td>67.8%</td>
<td></td>
</tr>
<tr>
<td>Cycle 5 – 2002/2003</td>
<td>11,006</td>
<td>63.1%</td>
<td></td>
</tr>
<tr>
<td>Cycle 6 – 2004/2005</td>
<td>10,098</td>
<td>57.6%</td>
<td></td>
</tr>
<tr>
<td>Cycle 7 – 2006/2007</td>
<td>9938</td>
<td>56.5%</td>
<td></td>
</tr>
<tr>
<td>Cycle 8 – 2008/2009</td>
<td>9366</td>
<td>52.7%</td>
<td></td>
</tr>
<tr>
<td>Total out of scope(^a)</td>
<td>828</td>
<td>---</td>
<td>&lt;3.6% of the original sample died</td>
</tr>
<tr>
<td>Total sample surveyed at cycle 2</td>
<td>16,903</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Died, moved out of Province/to Indian Reserve, age out range