UNIVERSITY OF CALGARY

The Association between Cigarette Smoking and Major Depression in the Canadian Population: a Longitudinal Investigation of Competing Non-causal and Causal Models

by

Salma M. Khaled

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSPHY

DEPARTMENT OF COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

DECEMBER, 2011

UNIVERSITY OF
CALGARY

Abstract

The comorbidity between cigarette smoking and major depression (MD) is consistently reported in clinical and community-based samples. However, there are no clear public health directives in relation to the achievement of reduction in the risks of these commonly co-occurring phenomena. This is important because cigarette smoking is the leading cause of disease and mortality in the world while MD is associated with smoking initiation and poor smoking cessation outcomes. In Canada, an undeveloped literature on this association may be an obstacle to public health action. We addressed this gap in knowledge by epidemiologic analyses using cross-sectional data from the Canadian Community Health Survey (CCHS) and longitudinal data from the National Population Health Survey (NPHS). In cross-sectional analyses, the 12-month prevalence of major depressive episodes (MDE) was lowest among never smokers (3.9%, 95% CIs: 3.4-4.4) and elevated among those who were current smokers especially among those who smoked daily (10.6%, 95% CIs: 9.5-11.7) and those who were classified as having high levels of ND (12.2%, 95% CIs: 5.8-18.6). Elevated prevalence was also found among those who attempted to quit unsuccessfully (12.5%), those who did not attempt to quit (10.7%), and those who quit in the past year (9.7%). Among long-term quitters (greater than one year), the prevalence of MDE was low (4.8%) and comparable to those of never smokers. Longitudinally, we assessed whether MDEs predicted transition to severe levels of nicotine dependence (ND) as assessed using time to first cigarette (TTFC) of the day. MDE emerged as a predictor for progression to severe levels of dependence (HR=1.7, 95% CIs: 1.1-2.5, $p<0.05$). Finally, we assessed the risk of first MDEs among persistent heavy smokers and persistent abstainers who were former heavy

smokers after controlling for a variety of potential confounders. Relative to twelve years of heavy smoking abstinence, persistent heavy smoking emerged as a significant predictor of MDE risk (HR=3.1, 95% CI: 1.9-5.2, $p<0.001$). Evidence for decrease in risk of MDE in a dose-response fashion as function of smoking cessation duration was also discerned. These findings suggest that unlike short-term abstinence, long-term smoking cessation maintenance in the general population may improve mental health. Smoking status may be an unappreciated risk determinant for MDE in the population.

Preface

In the course of this thesis, the following three manuscripts have been published or in press. For all three manuscripts, the first author undertook the analysis, interpreted the results, and wrote the manuscripts. This was done with the guidance of the senior author. All authors provided critical reviews of the manuscripts and contributed intellectual content. These articles were reproduced in their entirety and included as chapters within this thesis after written permission was obtained from the publishers.

Khaled SM, Bulloch AG, Exner DV, Patten SB. Cigarette smoking, stages of change, and major depression in the Canadian population. Canadian Journal of Psychiatry. 2009 March; 54 (3): 204-8.

Khaled SM, Bulloch AG, Williams JV, Lavorato DH, Patten SB. Major Depression Is a Risk Factor for Shorter Time to First Cigarette Irrespective of the Number of Cigarettes Smoked Per Day: Evidence From a National Population Health Survey. Nicotine & Tobacco Research. 2011 September 7; 13(11): 1059-67.

Khaled SM, Bulloch AG, Williams JV, Lavorato DH, Patten SB. Persistent Heavy Smoking as Risk Factor for Major Depression (MD) Incidence - Evidence from a Longitudinal Canadian Cohort of the National Population Health Survey. Journal of Psychiatric Research. 2011 (In press).

Acknowledgements

I would like to express my gratitude to all those who helped me on this inherently rewarding, but tough learning journey. Special thanks go to my supervisor for his intellectual support, constant encouragement, and guidance. Thanks to Jeanne Williams for her ingenuity, motherly care, and for being a valuable well of knowledge on all things related to this dissertation and beyond. Thanks to Dina Lavorato for taking the time to help out on many technical issues related to this dissertation and its contents. Thanks to all those who provided me with valuable feedback and supported me through the ups and downs of this journey including my committee members and the wonderful people at the prairie regional data center. Finally, very special thanks to my beloved husband, for his humour, patience, understanding, and valuable perspective.

Dedication

To my grandfather, who instilled in me courage, kindness, and an enduring love for life, you will forever be my inspiration! To my husband and best friend who is there for me day-in and day-out, who continues to believe in me, gives me so much love, and makes me laugh no matter what life has up its sleeves!

Table of Contents

List of Tables

List of Figures and Illustrations

List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
AD	Alcohol Dependence
CAI	Computer Assisted Interviewing
CCHS	Canadian Community Health Survey
CIDI-SFAD	Composite International Diagnostic Interview-Short Form for Alcohol Dependence
CIDI-SFMD	Composite International Diagnostic Interview-Short Form for Major Depression
CI	Confidence Interval
CV	Coefficient of Variation
CPD	Cigarettes Smoked per Day
DSM	Diagnostic and Statistical Manual
FTQ	Fagerstrom Test Questionnaire
FTND	Fagerstrom Test of Nicotine Dependence
HPA	Hypothalamic-Pituitary-Adrenal
HS	Heavy Smoking
HSI	Heavy Smoking Index
ICD	International Classification of Diseases
LFS	Labour Force Survey
MAO	Monoamine Oxidase
MD	Major Depression
MDD	Major Depressive Disorder
ND	Nicotine Dependence
NPHS	National Population Health Survey
PD	Prevalence Difference
PH	Proportional Hazard
PUMF	Public Use Microdata File
RDCs	Regional Data Centers
TMC	Transtheoretical Model of Change
TTFC	Time to First Cigarette

Epigraph

"Let the beauty of what you love be what you do"

Jalal Ad-Din Rumi

CHAPTER ONE: INTRODUCTION

Cigarette smoking is one of the most preventable causes of premature death and morbidity while *Major Depressive Disorder* ***(MDD)*** is now the leading cause of disability world-wide (1). The majority of studies (cross-sectional and longitudinal) have found a moderate to strong association between cigarette smoking and depression, though there are a few community-based studies that reported no associations (2, 3). MDD is characterized by *Major Depressive Episodes* ***(MDEs)*** in the absence of a past history of manic, hypomanic or mixed episodes. The more generic descriptor, *Major Depression* ***(MD)*** is sometimes found in the literature. In this dissertation, these three terms are all used depending on which best fits the particular context. Despite evidence supporting an association between smoking and depression across study designs and measurement methods, there are still no firm health policy directives in Canada to translate these findings into health service planning and prevention initiatives. One reason for the lack of public health action may be the undeveloped nature of the existing literature. Currently, population-level Canadian studies on the association between smoking and MD are scarce. Cross-sectional investigations on this topic are important in order to describe and quantify the prevalence patterns of these phenomena in the Canadian population. Longitudinal investigations are further needed to determine whether this comorbidity may reflect underlying etiology. An important unexplored area is whether modifying smoking patterns may lead to reduction in the risks of MD or vice versa. Another reason for the lack of public health action may be the mixed interpretations of findings from longitudinal studies conducted outside of Canada on this topic. While most epidemiological findings point towards a bidirectionality of effects, it remains controversial whether this bidirectionality reflects an underlying causal effect in both

directions or whether apparent bidirectional effects merely arise due to shared vulnerability factors that are predispositions to both conditions (see Figure 1.1). As such, we are faced with the following conundrum: observational studies cannot unequivocally provide evidence for causality and ethical considerations prohibit experimental studies on this topic.

1.1 Aims

The primary aim of this dissertation is to explore different aspects of the association between smoking and MDE at the population level. In order to address the lack of Canadian studies on this topic both cross-sectional and longitudinal Canadian data sets were used in the course of this dissertation.

1.2 Background

At the time of writing the first manuscript (Manuscript I), there were no descriptive studies that reported the 12-month prevalence of MD across different smoking categories and patterns in the Canadian population. An essential first step in filling the gaps in the Canadian literature involved: first, describing the pattern of the relationship between smoking and MD at the population level; second, shedding light on mental health needs of certain smoking-related categories in the Canadian population; and third generating hypotheses to set the stage for longitudinal exploration of this topic (including the next two manuscripts presented in this dissertation). The prevalence of MD was quantified in the general population across different categories of smoking status (former, current, never); different frequencies of use (daily smoker, occasional smoker); different levels or behavioural measures of nicotine dependency (high versus low, smoke when sick versus

those who do not smoke when sick); and different stages of change (no quit attempts, tried to quit unsuccessfully, quit less than a year ago, quit for a year or more).

Based on the findings from Manuscript I and previous studies (4-8), MD emerged as a potential barrier to smoking cessation as evident from its high prevalence among those who tried to quit unsuccessfully. MD was also found to be associated with high levels of nicotine dependency. *Nicotine dependence* ***(ND)*** is an important factor that is associated with greater risk of quitting failure or relapse even after long-term smoking cessation (9-11). One possible explanation is that MD may be a risk factor for the development of severe ND. In turn, this would make it more difficult for those with MD to quit or maintain smoking cessation. If MD is a risk factor for ND, then public health recognition of this finding may lead to improvement of smoking cessation outcomes since MD is potentially modifiable. This sparked our interest and led to the second manuscript (Manuscript II) that assessed whether MD is a determinant of progression to severe levels of ND.

While several prospective studies have reported that MD is a predictor of smoking initiation, progression to daily smoking, and decreased smoking cessation success (4, 12-14), there is a dearth of longitudinal studies in the literature investigating the role of MD as a predictor of ND onset and progression to severe levels of dependency. In fact, a literature search identified only one study by Breslau et al. (15) that investigated, over a period of 14 months, the role of lifetime history of MDD as a predictor of ND in adulthood. This study sampled young adults who were members of a health maintenance organization. The authors reported that MDD significantly doubled the odds of onset of ND. A variety of demographic variables (sex, education level, race), psychiatric disorders

(anxiety disorders), and substance use disorders (alcohol and illicit drugs) did not confer similar risk (15). Preliminary findings of this study raise the concern that MD may be an important predictor of ND. However, the generalizability of these results to the Canadian population is unclear as the sample was restricted to a narrow age range (21 to 30 years old) and was not drawn from the general population.

A limitation of the abovementioned study, which also constitutes a gap in the current literature, is the lack of assessment of potential mechanisms by which MD may predispose individuals to develop and progress to severe levels of ND. This was further addressed in Manuscript II. Comorbidity research has shown that depression is strongly associated with *heavy smoking **(HS)*** and severe levels of ND (16-19). Thus, HS is one conceivable mechanism through which MD may predispose individuals to ND. Depressed individuals may smoke heavily for purposes of self-medication, that is using nicotine to minimize negative affect and increase arousal (20, 21). Experimental studies show that under stress, smokers tend to smoke more and that their reported "need" to smoke increases (22, 23). While stress may cue increased smoking independent of depressed affect, further evidence suggests that individuals with MD may be more likely to engage in emotion-centered coping behaviours such as smoking more under stress (24). In Manuscript II we assessed the possible role of HS as a mediator in the association between MD and ND. In addition, we further assessed the role of the tendency to smoke more under stress, if any, in the MD to ND pathway.

A further question arising from the preliminary findings of Manuscript I was whether smoking cessation maintenance decreased the risk of MD. Evidence that former smokers had lower MD prevalence relative to current smokers who did not attempt to

quit deserved further exploration. Preliminary evidence was also discerned in support of the importance of smoking cessation maintenance duration to MD prevalence. Specifically, former smokers who quit within twelve months exhibited elevated prevalence of MD while those who quit for twelve months or more exhibited lower prevalence of MD, similar to that of non-smokers. As the data was cross-sectional, further exploration of these questions with longitudinal data was necessary, prompting a third manuscript (Manuscript III) to further explore these questions.

The literature review for Manuscript III found consistent evidence in support of the hypothesis that current smoking status is a risk factor of MD, despite the differences in terminology and methodology from various longitudinal studies (25-29). This finding has important clinical and public health implications. However, the potential for translating these findings into public health action has been downplayed due to the following observations. First, effects in the reverse direction have also been observed especially in the context of studies reporting bidirectional effects with smoking as a predictor of MD and vice versa (12, 15, 30-32). These findings have tended to be interpreted in ways that shed doubt on the causal nature of the association. Specifically, the issue of confounding by shared vulnerability factors (e.g. temperamental or genetic factors) has been put forward as a potential explanation since these would likely manifest as a bidirectional association. Second, evidence from short-term (6-12 months) smoking cessation research (primarily clinical trials) supports an increase in risk of MD following smoking cessation (5, 7, 33) as opposed to an expected decrease in the risk of MD that would follow if current smoking status constituted a true risk factor of MD. This suggests that a short-term increase in risk (a potential time for closer monitoring) may precede

reduction in risk upon long-term maintenance. Of relevance is the question of the duration of increased risk of MD after smoking cessation. This remains unanswered. Finally, the dynamic nature of smoking and its various stages and transitions between these stages (initiation, progression to daily smoking, heavy smoking, nicotine dependence, quitting, and relapse) makes it a relatively complex phenomenon to study. Due to these challenges, there is still little known about the long-term effects of smoking cessation maintenance on the risk of MD in the general population. Addressing this gap in the literature has great potential to clarify the clinical and public health implications of the relationship between smoking and MD in the general population. Longitudinal data provide us with an opportunity to explore these questions.

1.2.1 Biological Plausibility

The role of deficiencies in monoamine neurotransmitters such as dopamine and serotonin in the etiology of depression has long been recognized (34-36). Dopaminergic mesostriatal and mesocorticolimbic pathways are involved in the reward-seeking behaviours especially the processing of rewards in animals and humans (37). Evidence from pharmacological, MRI, and post-mortem studies (37-39) show that depressed individuals have reduced dopamine function in these motivational-reward pathways, which also explains symptoms such as anhedonia (inability to experience pleasure) commonly experienced by depressed individuals. In addition, several lines of evidence suggest that alterations in serotonergic pathways also occur in depression. Studies conducted among healthy volunteers, individuals at high risk of depression or among those in remission show that the result of low levels of serotonin is dysphoric mood and impaired cognitive processes (36, 40). Furthermore, genetic studies show that genetic

variations in serotonin receptor-transporter systems may impact individual vulnerability to mood disorders and response to antidepressant treatment (41-44).

Psychoactive effects of smoking are predominately due to the action of nicotine in cigarettes (45). There are nicotinic acetylcholine (nAchRs) receptors distributed throughout the human brain with high concentrations in the thalamus, striatum, hippocampus, cerebellum, basal ganglia, and cerebral cortex (45). One implication of the distribution of these receptors is that nicotine interacts with cognitive (attentional and sensory), emotional, and motivational-reward pathways of its users. In fact, smokers often report enhancement of cognitive processes and elevation of mood as well as a sense of euphoria that is indistinguishable from the euphoric effects of drugs like cocaine and morphine, which may explain its highly addictive nature (46). The predominant function of these receptors is the modulation of several neurotransmitter pathways. Both nicotine and acetylcholine are agonists of these receptors and the binding of either substance impacts the levels of various neurotransmitters in the nervous system including those that are implicated in depression such as serotonin, dopamine, norepinephrine, and acetylcholine. Several studies have shown that the transient mood elevation and the reinforcing qualities of nicotine stems from its ability to elevate levels of dopamine in the mesolimbic system, especially the nucleus accumbens, a pathway that is also shared by other addictive drugs such as cocaine, amphetamine, and morphine (46). The nucleus accumbens is involved in the expression of emotions and is an integral player in the reward pathways of addiction (37). Evidence from animal models of depression suggests that nicotine also appears to have long lasting antidepressant-like properties, which are also mediated by these same receptors (37). For example, several studies have shown that

chronic administration of nicotine improves learned helplessness in rats and such effects are reversed by the action of nicotine antagonist (47).

Other psychoactive substances in cigarettes include *monoamine-oxidase* ***(MAO)*** inhibitors, which inhibit MAO enzymes responsible for breaking down catecholamines such as dopamine, serotonin, and norepinephrine at the synapse (48). Consequently, the levels of these neurotransmitters may be elevated in the synapse, resulting in mood boost in smokers (48). This action of MAO inhibitors in cigarette smoke and by extension their effects on levels of neurotransmitters like serotonin in the brain seem to be long lasting because of the slow turnover rate (over 40 days) of MAO (48). This mechanism is also utilized by class of antidepressants (MAOIs), which were the first class of antidepressants to be used in the 1950s (48).

Depression is also marked by dysregulation of the *Hypothalamic-Pituitary-Adrenal* ***(HPA)*** axis, which is a neurochemical stress-response system that plays an important role in the regulation of stress. Studies show that depression is marked by hypersecretion of cortisol (stress-hormone) and that the disruption of the HPA system increases the risk for depression onset and recurrence (49, 50). It has also been shown that nicotine is closely involved in stress-response pathways of the HPA axis. Research suggests that nicotine stimulates cortisol release directly and indirectly (51). In fact, one of the acute effects of smoking is sustained cortisol hyperscerétion (52, 53). There is also evidence to suggest that cortisol hypersecretion either in response to stress or smoking in turn results in reduced sensitivity to nicotine and that the combination of stress and smoking may have additive effects on cortisol secretion in humans (54). The reduction in sensitivity to nicotine in turn results in greater nicotine consumption in order to elicit the

same desired response experienced previously (54). Meanwhile, chronic smoking may result in desensitized nicotine receptors that could inhibit the presynaptic release of neurotransmitters including dopamine and serotonin and may result in reduction in the release of cortisol in response to stress (55). Therefore, chronic stimulation with nicotine may alter responsiveness to stress and may precipitate depression among heavy smokers during smoking cessation (55).

In summary, depression and cigarette smoking involve common neurobiological systems. The neurotransmitter pathways that are affected by cigarette smoking are some of the same as systems implicated in depression. Depression has been suspected to arise from functional deficiencies in monoamine neurotransmitters such as dopamine, serotonin, and norepinephrine; cigarette smoking results in elevation of these neurotransmitter levels in the brain by promoting their release and inhibiting their breakdown at the synapse. However, long-term effects may differ from those seen with short-term exposure to nicotine.

1.3 Methods

1.3.1 Datasets

The data analyzed in this dissertation were collected by Statistics Canada. Specifically, two data sets were utilized. The first was cross-sectional data from the *Canadian Community Health Survey* ***(CCHS),*** cycle 2.1 (2003). The second dataset was longitudinal data from the *National Population Health Survey* ***(NPHS)***, cycles 1-7 (1994-2004). Both surveys had similar target populations: household residents in all Canadian provinces and territories with few exceptions. The same sampling frame, similar sample

selection designs, and similar interviewing strategies were employed. Similar smoking and depression modules were used. Similar objectives were also adopted in both surveys with the main focus being on the assessment of health status as well as the distribution of the determinants of health and health system utilization in the Canadian population. Both surveys also assessed a wide variety of psychosocial factors that may be associated with smoking or MD or both.

1.3.1.1 The Canadian Community Health Survey (CCHS)

Manuscript I is based on data from the Canadian Community Health Survey (CCHS). The CCHS is a cross-sectional survey that collected information related to health status, determinants of health, and health care utilization in the Canadian population. The CCHS operates on a two-year data collection cycle. The CCHS (cycle 2.1) was collected between January 2003 and December 2003. The surveyed population (approximately 134,000) consisted of household residents aged 12 and over (approximately 98% of the Canadian population) from 126 health regions and living in all provinces and territories with the exclusion of individuals living on Native Reserves, Crown Lands, institutional residents, full-time members of the Canadian Armed Forces, and residents of certain remote regions (56).

The *Canadian Labour Force Survey* ***(LFS)*** was the primary sampling frame used by the CCHS. The sample design of the LFS is a multistage stratified cluster design in which the dwelling is the final sampling unit. In the first stage, homogeneous strata were created and clusters were independently sampled from each stratum. In the second stage,

household lists were prepared for each cluster and households were then selected from the list. Within each household, a single respondent was then randomly selected (56).

The survey questions in the CCHS were arranged in modules and further organized into core and optional contents. The core questions were asked at the national level in all health regions. The optional questions were only asked in certain health regions based on specific interests of the provinces. The CCHS questions were designed for *computer-assisted interviewing* ***(CAI)*** with programmed questions, content flow, and allowable responses (ranges or answers) based on data collected during the interview (56).

For the purpose of data dissemination, Statistics Canada produces two types of CCHS data files. The *Public Use Microdata Files* ***(PUMF)*** and the Master files. These files were made in response to confidentiality guidelines under the Statistic Act that are enforced to protect the anonymity of survey respondents. A number of sensitive (e.g. detailed income) variables in the Master file were collapsed, capped or completely deleted from the PUMF file. Access to the Master file can be gained through the *Research Data Centres* ***(RDCs)*** program. The RDCs are facilities run by Statistic Canada employees and all results undergo a confidentiality screening process before being made available to users. In contrast, the PUMF file is made widely available to the public, often through University-based libraries. Manuscript I was based on the PUMF data file of the CCHS (cycle 2.1).

1.3.1.2 The National Population Health Survey (NPHS)

The analyses in Manuscripts II and III were conducted using data from the NPHS, a prospective longitudinal survey of health status of the Canadian population. The main objectives of the NPHS were to assist public policy makers in understanding the determinants of health by collecting data on the demographic, economic, social, occupational , and environmental correlates of health (57). By following panel members over time, the NPHS aimed to capture a dynamic picture of health and illness in the general population.

The NPHS had two components: household and institutional. Data obtained from the household component were used for all analyses presented hereafter. Data from the institutional component covered long-term residents of hospitals and residential care facilities and were not included in any of the analyses presented here. The household questionnaire was further composed of two components: a general component and health component (57). The general component collected basic information from an adult member knowledgeable about the sociodemographics and health information of all members of the household while in-depth health, behavioural, and psychological information was collected from a randomly selected member within each household in the health component. The randomly selected members from all sampled households (one member per household only) who filled out the health component of the questionnaire constituted the longitudinal panel of the NPHS (57). This panel provided the data that were analyzed over the course of this dissertation.

The NPHS target population was defined as household residents in all the provinces and territories, with the principle exclusion of residents on Native Reserves, Canadian Forces, and some remote areas (58). This was essentially the same target population as the CCHS. These exclusions preclude inferences being made in relation to this excluded portion of the general population. The NPHS used probability-based multistage sampling methods (including clustering and stratification) to randomly select a representative sample of household residents (n=17,276). In all provinces except Quebec, the NPHS used the Canadian LFS's sampling frame and sampling methodology (58). In general, each province was divided into three major areas: major urban centers, urban towns, and rural areas. Depending on each area type, homogenous strata were then formed based on geography and socioeconomic characteristics. Independent samples of clusters were then drawn from each stratum. Dwellings were then chosen from within these clusters. Panel respondents were then chosen by randomly selecting one person per surveyed household (58). Within the major urban centers, clusters containing approximately 150 to 250 dwellings were created, while for urban towns and geographical areas 6 clusters (typically Census Enumeration Areas) were constituted from each stratum using a randomized probability-proportional-to-size scheme, where size is determined by the number of households (58).

Data collection began in 1994-1995 and continued every two years for seven cycles: 1994-1995, 1996-1997, 1998-1999, 2000-2001, 2002-2003, 2004-2005 and 2006-2007. Initial contacts with the sampled households were face-to-face, while subsequent interviews were usually conducted by telephone during which all data was collected using CAI procedures (57). Different strategies were employed by Statistics Canada over

the course of data collection to enhance the overall quality of the data and to minimize loss to follow-up. Interviewers were provided with special training in handling refusals and "Don't know" responses, rescheduling interviews, and following extended call back rules to contact hard-to-reach respondents. In attempting to avoid loss-to-follow up, all initially sampled individuals were provided with "Change of Address" cards and asked to provide alternative contact information. Tracing strategies such as searching telephone directories and commercial databases for names, contacting relatives with the same last name, and matching mortality or institutional files were also employed when participants were not successfully located after several attempts (59)**.**

Between 1994 and 1995, 20,095 household residents were selected for the in-depth health interview and participation in the longitudinal panel. Of these, 17,276 residents agreed to participate, resulting in approximately 86% national response rate for cycle 1. For subsequent cycles, the national response rates were as follows: 92.8% in cycle 2, 88.3% in cycle 3, 84.9% in cycle 4, 80.8 % in cycle 5, 77.6% in cycle 6, and 77.0% in cycle 7. By the end of cycle 7, there were a total of 2,032 deaths, 148 institutionalizations, and 3,221 non-responses (refusals and unable to trace) (59).

Data from all seven cycles of the NPHS were accessed through the Prairie Regional Data Center at the University of Calgary. All results presented here underwent strict disclosure risk analysis by an on site analyst. It is important to note that while the analyses presented here are based on data provided by Statistics Canada, the interpretations of these results and conclusions arising from this body of research do not represent the views of Statistics Canada.

1.3.2 Major Depressive Episodes (MDEs) Assessment

In casual language, depression may refer to a lowering of mood that often arises in response to loss or some unpleasant event or circumstance. Most people experience lowered mood during their lifetimes. However, what distinguishes normal from abnormal lowering in mood is the severity of the symptom, its persistence, and whether it significantly interferes with the daily functioning of the individual. Depression can also be conceptualized as one or more depressive symptoms, a conceptualization that is still different from a diagnosis of mood disorder. In diagnostic classification, a mood disorder (MDD, Bipolar Disorder, and Dysthymia) is defined as an illness characterized by a constellation of co-occurring symptoms lasting for a specified period of time contributing to significant psychosocial impairment (60). These concepts of depressed mood and depressive symptoms are distinct from major depressive disorder (MDD), the concept of depression that was incorporated into this thesis.

The classifications for mental disorders that are currently in use are the *Diagnostic and Statistical Manual of Mental Disorders* ***(DSM)*** (60, 61) and the *International Statistical Classification of Diseases and Related Health Problems* ***(ICD)*** (62). According to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised (DSM-III-R), a diagnosis of MDE requires depressed mood or loss of interest for at least two weeks accompanied by any of the following symptoms: sleep disturbance (insomnia or hypersomnia), changes in weight and appetite, psychomotor retardation or agitation, concentration, thinking or decision-making problems, exhaustion or fatigue, feelings of worthlessness or extreme guilt, and frequent thoughts of death, suicide or

suicide attempts. These symptoms must not arise solely due to medical illness, substance use or bereavement (60). In contrast to the DSM-III-R definition, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and the ICD-10 stipulate that these symptoms must produce significant impairment in psychosocial functioning (61, 62).

In the NPHS, a MDE was assessed using the *Composite International Diagnostic Interview - Short Form for Major Depression* ***(CIDI-SFMD)*** (63). This was derived from the full version of the CIDI (64) and was validated by Kessler and colleagues (63). As a fully structured interview designed for use in the general population and requiring no clinical judgment for its administration, the CIDI-SFMD module was administered by lay interviewers trained by Statistics Canada as part of the NPHS interview (see Appendix A). Participants aged 12 years and over were asked questions about depressive symptoms in the preceding 12 months. A probability score for a MDE was then generated based on responses to these questions. A probability score of 0.9 or above was used to define the presence of a MDE. This cut-point corresponds to the presence of 5 out of a total of 9 symptoms (including loss of interest or depressed mood) approximating the symptom-based parts of the DSM-IV diagnostic criteria for MDE (63). Kessler and colleagues reported sensitivity and specificity values for the CIDI-SFMD of 0.9 and 0.94, respectively, when the five symptoms cut-point is applied (63). One limitation of the CIDI-SFMD is the absence of probe questions that rule out substance use, medical illness, or bereavement as potential cause of the MDE. However, this can also be viewed as an advantage of the analyses presented here rather than a limitation. This is because categories concerned with organic mood disorders are almost entirely based on clinical

judgement about etiology (61). Disease definitions with explicit reference to etiology go against the basic tenets of epidemiology as empirical science (65).

1.3.3 Cigarette Smoking Assessment

1.3.3.1 The Transtheoretical Model of Change (TMC)

The *Transtheoretical Model of Change* ***(TMC)*** (66) posits that there are a series of stages of change through which smokers transition as they succeed in smoking cessation. These stages include pre-contemplation (no motivation to attempt quitting); contemplation (motivation to quit in the next 6-months); preparation (motivation to quit in the next month with at least a single quit attempt in the past year); action (quit smoking within the past 6-months); and maintenance (quit smoking for 6-months or more). Rather than relying solely on dichotomies (smoker versus non-smoker) to study the effects of smoking on prevalence of depression, we adopted a broad version of the TMC for the purpose of Manuscript I with a main focus on three stages: "Tried to quit" *as* proxy measure of the preparation stage, "Quit < Year" as proxy measure of the action stage and "Quit >year" as proxy measure of the maintenance stage. Various studies in the literature have implicated these smoking transitions with changes in risk for MD. For example, various clinical studies have implicated quitting with increase in risk of MD (4, 5, 6, 8, 67). Although the cross-sectional nature of the dataset precludes speculation about risk, we set out to use the TMC as a conceptual framework to describe patterns of prevalence of MD as function of certain smoking transitions.

1.3.3.2 Assessment of Nicotine Dependence (ND)

The complexity of the ND construct, which can be measured using different instruments, may explain some of the difficulty in studying its etiology. For example, Breslau and colleagues (15) used criteria for assessment of ND based on the DSM-III-R. These criteria (presence of three or more out of nine defining symptoms) were criticized for being excessively generic in that they encompass most of the physiological, psychological, and behavioural features of substance dependence without adequate specificity to nicotine (68). Some of these criteria underwent revisions in the newer edition of the DSM, the (DSM-IV). In particular, the newer revisions do stipulate the presence of physiological symptoms (either tolerance or withdrawal) for diagnosis. Nevertheless, it is still unclear how well these substance dependence criteria conceptualize ND (68, 69).

Brief self-report measures of ND are more widely used in epidemiological settings than diagnostic measures of ND. The *Fagerstrom Test Questionnaire* ***(FTQ)*** and its derivatives such as *Fagerstrom Test of Nicotine Dependence* ***(FTND)*** and *Heaviness of Smoking Index* ***(HSI)*** (70-72) are examples of widely used brief measures of ND in research settings. Unlike the DSM criteria for ND, the FTQ was originally designed for the specific assessment of physiological dependence on nicotine or tolerance (70, 73). However, the literature is still ambiguous about how well some of these brief instruments predict important criteria of dependence relative to single-item measures of ND, which have also been widely used in large survey studies. These generally assess one of two

smoking dimensions: heaviness of smoking as measured by the number of *cigarettes smoked per day* ***(CPD)*** and minutes to smoking the first cigarette of the day also known as *Time to First Cigarette* ***(TTFC).*** The combination of these two items gave rise to the HSI scale (72). These items were also the two of the original eight items of the FTQ that have been consistently identified as the most powerful and efficient indicators of ND as they most closely corresponded to biochemical indices of ND (71, 72, 74, 75).

In Manuscript I, ND was assessed using items from the FTQ (Appendix B). Each item of the questionnaire was scored on 2 to 3 point scales and a total score on all items was computed for each respondent. A variable was then derived by Statistics Canada for levels of ND based on the FTQ scores of these respondents with the following ordinal categories made available to the PUMF users: very low dependence, low dependence, medium dependence, high dependence, and very high dependence. To avoid running into small cell counts, we initially looked at the crude prevalence of MD across all of these categories. We then dichotomized this variable by collapsing the following categories based on similarities of the point estimates and the extent of overlap of the corresponding 95% *Confidence Intervals* ***(CIs)*****:** very low dependence, low dependence, and medium dependence were collapsed into a single category indicating generally low levels of dependence while high and very high dependence were collapsed into one category designating higher levels of dependence.

In Manuscript II, we used TTFC as a measure of the severity of ND because of evidence to suggest that much of the predictive value of the FTND (a six-item instrument) is attributable to a single item: TTFC (72, 76-79). In fact, recent studies have identified TTFC as the best predictor of ND due to its ability to capture withdrawal

following overnight abstinence and relapse vulnerability (78, 80). Originally, TTFC was conceptualized as time in minutes to the first cigarette of the day upon awakening: less than or equal to 5, 6 to 30, 31 to 60 and greater than 60. Shorter or reduced TTFC indicate greater severity of dependence (72). Shorter TTFC has been associated with poorer smoking cessation outcomes (78, 81, 82).

1.3.3.3 Assessment of Heavy Smoking (HS) Status

For current daily smokers, the amount of CPD was assessed in the NPHS using the question: "how many cigarettes do you smoke each day now?" Former smokers, who used to be daily smokers, were asked the question "how many cigarettes did you usually smoke each day?" Both of these questions were only administered to individuals who reported smoking greater than or equal to 100 cigarettes in their lifetime and either currently or formerly smoking at least one CPD. This variable was further dichotomized into heavy smoking categories based on report of current or former daily consumption of greater than 20 CPD. In the literature, this is the standard cut-off for heavy smoking and is widely used in various smoking related instruments including the FTND (71) . The same definition of heavy smoking status was used in all manuscripts. Alternative data based approaches could have been taken to identify the best cut-off for denoting heavy smoking status in the context of depression. However, such approaches may have given rise to results that are too specific to the data limiting the comparability of our results to other previous studies.

In order to assess claims of confounding by shared vulnerability as the main explanation for the observed association between smoking and depression, we used

former-heavy smokers as the referent category in the main analysis in Manuscript III. This strategy was adopted because ever-heavy smokers (current and former) may share similar genetic, behavioural, and environmental vulnerabilities, at least for heavy smoking initiation. In turn, if these shared factors were dominant characteristics that also convey risks for MD, we would expect former-heavy smokers to continue to have elevated risks of MDEs similar to the elevated risks of MDEs among current-heavy smokers. However, if the persistence of the exposure (current as opposed to former) had the dominant effect on the risk for MD relative to shared vulnerability factors, then current-heavy smokers would be expected to have higher risks of MD relative to former-heavy smokers.

1.3.3.4 The Validity of Time to First Cigarette (TTFC) and Cigarettes Per Day (CPD)

The lack of a gold standard or universally agreed upon criteria to measure ND precludes comments on the sensitivity and specificity of its instruments or ideal cut-offs for identifying dependent smokers (83). However, both TTFC and CPD were found by a recent study to be considerably consistent between measurements as well as being independent predictors of quit attempts and cessation maintenance (84). In addition, the continuous scoring of TTFC and CPD was not found to be superior to their categorical versions in predicting smoking cessation outcomes (84). When cotinine was used as a proxy measure of nicotine uptake, TTFC was significantly correlated with CPD and continie levels (urinary and plasma) in another study (85).

1.3.4 Covariates Assessment

A variety of psychosocial variables were identified in the NPHS and assessed for their potential roles as confounders under the auspices of various theoretical underpinnings that may underlie both smoking and MD including social learning (156), cognitive (157), and behavioural theories (158). In Manuscript III, these variables included family history and personal history of depression; psychological factors such as rebelliousness (86), self-esteem (87), sense of mastery (88), Antonovsky's sense of coherence (89), and distress (90); behavioural factors such as ineffective coping styles (91) and binge drinking (92-94); psychosocial factors such as childhood trauma (95), stress (96, 97), and perceived social support (98); health-related factors such as the presence of one or more chronic health conditions and self-reported pain were also included (99).

Family history of depression was assessed based on a single survey question (introduced in 2004-2005) that asked respondents if any of their first-degree relatives (birth father, birth mother, birth sister, birth brother) had been diagnosed with depression by a health care professional. Respondents were classified as having a family history of MD if they reported at least one first-degree relative as having been diagnosed with depression as opposed to having no close relatives diagnosed with depression.

A proxy-measure for personal history of depression among respondents was created based on two variables directly assessed in the NPHS: a diagnosis of MD by a health professional and the age of diagnosis with MD. Respondents were classified as having a history of MD if their age of diagnosis was also the age in which they were

enrolled in the study or preceded it. The personal history variable was used to exclude participants with apparent history of MD at or prior to the baseline year for the NPHS in 1994. This was done to minimize the influence of recurrent MDEs among those with previous history of MD on estimates of the risk of new MDEs among individuals without a previous history of MD. In addition, individuals who were classified as having a MDE in 1994 according to the CIDI-SF were also removed from the sample in order to study incidence rather than prevalence of MDEs.

Early age of first experimentation with cigarettes was included in our analyses due to findings from previous studies that suggest that early experimentation may be a strong confounder of the association between smoking and depression in adolescents (86). Sense of mastery is the extent to which individuals believe their life-chances are under their control. This was assessed in the NPHS by a total of seven questions yielding scores ranging from 0 to 28 (88). Self-esteem refers to the extent of positive feelings an individual holds about his or herself and was measured using a subset of six items taken from Rosenberg's original 10-items self-esteem scale (87). Sense of coherence or psychological wellbeing is based on Antonovsky's sense of coherence scale and is a measure of the extent to which an individual views life as comprehensible, manageable, and meaningful (89). This variable was assessed based on 13 questions that were summarized into a scale with potential scores ranging from 0 to 78. Psychological distress is a state of generalized, non-specific anxiety, and depression symptoms assessed based on Kessler's six-item distress scale yielding scores ranging from 0 to 24 (90).

Behavioural variables such as ineffective coping styles that are not based on problem-solving such as self-reported "drinking more under stress" and "use drugs more

under stress" were also estimated using single items from a coping style questionnaire included in the 2002 survey (91). The tendency for binge drinking was also assessed based on reported consumption of five or more drinks on a single occasion at least once monthly in the past 12 months. We used a threshold of five or more drinks to dichotomize this variable because it has been used by various other studies to index problem drinking in the NPHS sample (92-94).

Various other psychosocial variables were also assessed in the NPHS. Exposure to childhood trauma was indicated through reporting the occurrence of at least one or more of the following adverse events in childhood or adolescence: parental divorce, a lengthy hospital stay, prolonged parental unemployment, traumatised for years, frequent parental alcohol or drug use, being sent away from home, and physical abuse by a parent or a relative. Stress was assessed using a 16-item scale based (96, 97). This scale captures the extent of exposure to daily stressors in various life domains including personal (activity overload and role expectations), financial, relationship, environmental (undesirable friends or neighbours), and family health problems. Social support was assessed using a 4-item index that measured the extent of perceived social support in terms of having someone to confide in, someone to count on, someone to give advice, someone that makes them feel loved, and cared for (98).

Finally, broad measures of physical health status were assessed. These included nominal categories indicating the presence of one or more chronic conditions (total of 18 long-term health conditions, diagnosed by a health professional). A dichotomous variable was derived from this series of items by identifying respondents reporting one or more of these conditions. The list included allergies, asthma, arthritis, back problems, high blood

pressure, chronic bronchitis or emphysema, diabetes, epilepsy, heart disease, cancer, stomach ulcers, cataracts, glaucoma, and thyroid conditions. A dichotomous variable indicating the presence of moderate to severe pain as opposed to no pain or mild pain was also created from a set of questions in the NPHS about the experience of pain or discomfort and its severity. Further details on these measures can be found in a publication by Statistics Canada (95).

In Manuscript II, *Alcohol dependence **(AD)*** and the tendency to smoke more under stress were among the covariates included at the modeling stage in addition to stress and non-specific psychological distress (described above). AD was assessed using a module of the World Health Organization's *Composite International Diagnostic Interview Short form for Alcohol Dependence **(CIDI-SFAD)*** (63). In 1996-1997, participants who reported the consumption of 5 or more drinks on single occasion at least once monthly were asked questions about AD. The CIDI-SFAD is composed of seven questions that assess symptoms of AD in the past 12 months. These include question probes about interference of alcohol use with daily roles and activities, use in hazardous situations, emotional or psychological problems arising from use, strong urge or desire to drink, spending an extended amount of time using or recovering from use, drinking more or longer than intended, and increase quantity of use to obtain the same effect. A "caseness" probability score of 0.85 or higher was used to designate AD. This cut-off score corresponds to three or more reported symptoms of AD based on the DSM-III-R criteria (60) . The tendency to smoke more under stress was assessed using a single item from a coping style questionnaire included in the 2002 survey (91). This variable was

used as a proxy measure of the tendency to self-medicate with cigarettes in response to stress.

Covariates based on "pseudo-continuous" scales, such as stress, self-esteem, and sense of coherence, were generally dichotomized based on the upper or lower quartile cut-off points (details are provided in the papers that follow). The decision to dichotomize these variables was based on various considerations. First, the inclusion of dichotomous variables in models often facilitates ease of interpretation of results especially when the units of measurements on these scales are not intuitively meaningful. Second, most of these covariates were highly skewed or not normally distributed. Higher or lower quartile cut-off scores were often used as a threshold as opposed to the median split because of the probable clinical relevance of high or low scores (high levels of stress or low levels of self-esteem) to MD etiology. Third, when most of these covariates were modeled as continuous predictors of MD risk, we found evidence of break-down of the linearity assumption especially at the extreme ends of the scales which necessitated their categorization (100).

1.3.5 Methodological Issues

In this section, only a few relevant methodological details will be covered. These details were not included in the main manuscripts because of journal specific space limitations. In Manuscript I, the unadjusted and adjusted (age and sex) prevalence estimates of MD were computed for each smoking category and smoking stages. Corresponding 95% CIs for these estimates were also calculated to quantify the extent of

precision in these estimates. These CIs were calculated based on tables of approximate *Coefficient of Variations* ***(CVs)*** made available by Statistics Canada. The CVs are based on variance formulae that take into account the survey design effects including clustering and stratification. The release guidelines for the PUMF file were based on the number of sampled respondents who contribute to the calculation of a CV estimate. According to Statistics Canada guidelines, if this number is less than 30, the weighted estimate should not be released regardless of the value of the coefficient of variation for this estimate (56). As such, there were a few estimates that were not released due to these guidelines.

As our main objective in Manuscript I was to compare the prevalence of MDE in each smoking category, we kept the measures of association in this analysis to a minimum to avoid inflating Type I error arising from multiple comparisons. The measures of association reported were as follows: the prevalence difference for occasional and daily current smokers; the difference in prevalence between those who tried to quit unsuccessfully and those who successfully quit for longer than one year; the prevalence difference between those who have high ND and those with low ND; and the prevalence difference between those who smoke even when sick compared to those who do not. For purposes of interpretation, these were considered the most important estimates to make.

For the purpose of Manuscript II, the baseline for the longitudinal analysis was taken to be in 1996 since this was the year that the NPHS included detailed questions in the smoking module. These were not asked in 1994 (including TTFC). Hence, data from 10 years of follow-up (1996-2006) was used. The NPHS longitudinal cohort included children, but the analysis was restricted to those who were 12 years or older in 1996 and

who responded to the CIDI-SF (N=12,907), as the instrument was not administered to children under the age of 12 years.

For the purpose of Manuscript III, the baseline year was 1994, which was the year when the initial interviews were conducted in the NPHS. At the time that data analysis was initiated, the entire available follow-up data were utilized - a total of 12 years of follow-up (1994-2006). The main restriction criteria were to exclude those who had missing responses on the smoking module at one or more times during the follow-up so that only those who were 12-years and older at baseline and who had complete data on smoking status and the amount smoked for the entire follow-up period were included (n=7,488). Further restriction was also applied so that those who changed their smoking status during the follow-up period from that reported at baseline were removed (3,059). Therefore, only persistent current, persistent former, and persistent never smokers constituted the sample analyzed in this study. The restriction was necessary to ensure that the results were specific to persistent smoking status and long-term smoking cessation maintenance and not to be mixed up with results from transitions such as short-term quitting and relapse. The remaining analytical sample was 3,824. To ensure that the analyzed sample obtained from these restriction criteria did not differ from the original sample in terms of distribution of variables related to smoking levels and MD, we carried out a sensitivity analysis that entailed re-running our analyses without the exclusion of individuals who had incomplete data on smoking during follow-up. Respondents with less than complete data on smoking variables were included in the sensitivity analysis and censored when they left the sampling frame due to death, institutionalization or if they had not experienced a MDE by the study end date. We also compared the

distribution of potential confounders before and after the exclusion criteria to examine the extent of change in the distribution of these variables.

All of the longitudinal analyses conducted in Manuscripts II and III were based on discrete-time *proportional hazard models* ***(PH)***. Data management included removal of individuals who had the outcome of interest at the outset. This was done because of the greater importance of incident as opposed to prevalent events in relation to the goals of both studies. It is important to note that the event of interest in each manuscript was non-repeated so that respondents who developed the outcome of interest during an interval were removed from the subsequent risk set. Individuals were also removed (or censored) from the original risk set if they were lost to follow-up, died or were institutionalized during each interval in accordance to customs of event history or survival analyses.

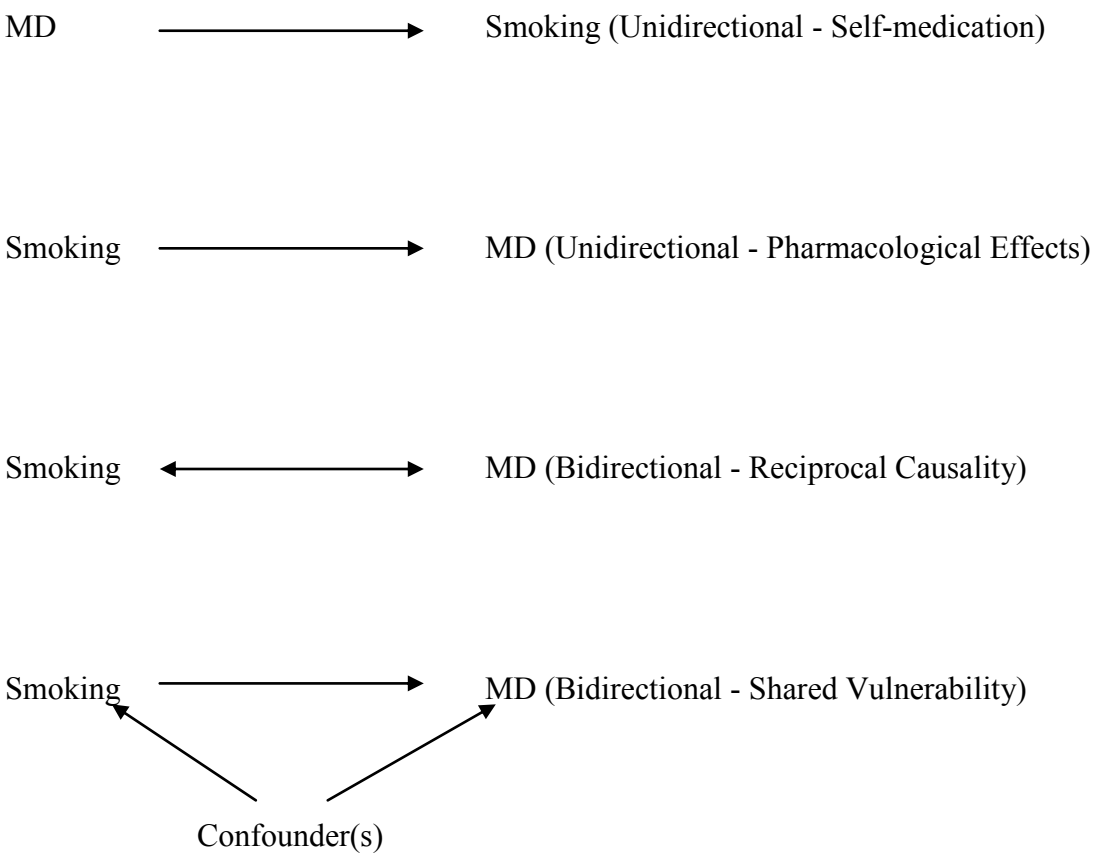
1.4 Thesis Outline

This thesis examines the relationship between smoking and depression in the general population. The body of research presented here draws upon valuable population-based Canadian data sets collected by Canada's national statistical agency – Statistics Canada. Data from the CCHS provided us with a cross-sectional picture of the associations between MD and smoking (status, frequency, and stages of change) in the Canadian population. The NPHS provided us with an opportunity to further investigate long-term outcomes of depression and smoking while controlling for a wide variety of covariates potentially implicated in the depression to smoking pathway and vice versa.

In this chapter, we have provided background information on these data sets as well as a general introduction to instruments used in the assessment of smoking,

depression, and covariates. We also highlight some of the questions that arise from the body of research conducted on this topic thus far and some of the issues that still remain to be addressed. Each of the next three chapters of this document constitutes a unique component of this thesis in the form of an independent publication formatted as part of a paper-based thesis. Nevertheless, all components are linked by the unifying theme of improving current knowledge of the smoking and depression association in the general population. The reporting of p-values across the manuscripts reflects the way in which these values were reported in the published papers. In the last chapter, we present a general discussion of the findings from all three manuscripts and their potential implications for clinical and public health services.

Figure 1.1 - Mixed Interpretations for Findings in Relation to the Directionality of Effects between Smoking and Major Depression (MD)



CHAPTER TWO: CIGARETTE SMOKING, STAGES OF CHANGE, AND MAJOR DEPRESSION IN THE CANADIAN POPULATION

2.1 Abstract

Objective To describe the 12-month prevalence of Major Depression in relation to smoking status, nicotine dependence levels, commitment to quit, attempts to quit, and maintenance of smoking cessation in the Canadian general population.

Methods Data from Public Use Microdata File (PUMF) of the Canadian Community Health Survey (CCHS) cycle 2.1 were used. The Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SF) was used to assess depressive disorder status. The survey also included a smoking module. There were 49,249 respondents who completed the smoking module and the CIDI-SF. Analyses used appropriate measures to deal with survey design effects.

Results The prevalence of Major Depression was highest in current smokers, followed by former smokers, and was lowest in the never smokers. This pattern persisted after stratification for age and gender. With respect to quitting, the prevalence of major depression was highest among those who tried to quit, followed by those who considered quitting, those who quit in the past year, and lowest among those who maintained their smoking cessation status for longer than one year. The prevalence of depression among those with a high nicotine dependence level, as assessed by the Fagerstrom Tolerance scale, was approximately twice that of those with a low nicotine dependence level.

Conclusions The strikingly high prevalence of major depression among current smokers who are young, those who are trying to quit, and those with high nicotine dependence levels in the general population indicates that further longitudinal exploration of this topic is urgently needed.

Clinical Implications

People wanting to quit or attempting to quit smoking have an elevated prevalence of major depression.

Poor smoking cessation outcomes may be related to elevated prevalence of major depression within the first year of smoking cessation

Smokers with high levels of nicotine dependence have an increased prevalence of major depression.

Limitations

Due to cross-sectional nature of the survey causal inferences cannot be made.

Due to the small number of observations in some of the cells (< 30 observations), age- and sex- specific estimates could not be evaluated for all strata.

Further research will be required to fully determine the implications of these findings for smoking cessation treatment.

2.2 Background

The role of major depression as an impediment to smoking cessation has received attention since the late 1980s (101). Numerous studies have explored the association of depression with smoking cessation (4, 5, 102), and many hypotheses have been put forward with respect to the influence of depression on smoking cessation, abstinence, and relapse (8, 103-105). Few population-based studies (4, 5, 8, 102, 103-106) and no Canadian studies have been reported.

Cigarette smoking has long been found to be more prevalent in the psychiatric population than the general population (107). However, cigarette smoking may be related to major depression in the general population in important ways. The current study provides descriptive data about the relationship between smoking, nicotine-dependence, stages of change (contemplation of quitting, attempting to quit, maintenance of quitting), and major depression prevalence in the Canadian general population.

2.3 Methods

The CCHS is a cross-sectional household survey conducted by Statistics Canada. Its methods are fully described elsewhere (56) Cycle 2.1 of the CCHS interviewed a representative sample of Canadian household residents between January 2002 and December 2003. The CCHS incorporates the CIDI-SF for assessing major depression prevalence. This is a brief adaptation of the major depression module of the full CIDI (63), which is currently the standard structured diagnostic interview in psychiatric epidemiologic studies (108). The CIDI-SF identifies respondents with a high probability

of past year episodes of major depression according to diagnostic criteria from the DSM-IIIR, which closely resemble those of DSM-IV (61). The CCHS 2.1 also included a smoking module that assessed smoking status, stages of change questionnaire (based on the Transtheoretical Model of Change) (66), and the Fagerstrom Tolerance scale (71, 109). Both the CIDI-SF and smoking modules were optional contents that could be selected by individual provinces and health regions. These items and instruments were administered to a sizable subset (see below), but not all, of the (n=134,072) sample members.

A total of 49,249 respondents were administered the smoking module and the CIDI-SF (n=46,271 non-depressed and n=2,978 depressed). The Fagerstrom Tolerance scale is only relevant to those who were current smokers and was administered to a subset of 2,306 of these respondents. There were 2,481 responses to the item about smoking when sick. All estimates were weighted to adjust for unequal selection probabilities, multi-stage, clustered sampling, and non-response. Confidence intervals were calculated using coefficients of variation from tables provided by Statistics Canada for this purpose. All estimates adhere to release cut-offs and guidelines provided by Statistics Canada (110).

2.4 Results

As shown in Table 2.1, elevated prevalence rates of major depression were observed in current smokers (10.6%) with former smokers (5.3%) having a prevalence that fell between this value and that of never smokers (3.9%). The results were similar after stratification for age and sex. However, within the current and former smoking

categories, the estimates tended to be higher in a younger age group (12 to 44 years) than an older group (45 years or older). The prevalence of major depression among current smokers was higher in the younger age category than in the older one: Prevalence difference (PD) = 4.7% (95% CI 2.7 to 6.7). Since the 95% confidence interval does not extend into the negative range, the difference is unlikely to be due to sampling variability. Among the current smokers, the PD between those who smoked daily and those who smoked occasionally was 3.4% (95% CI 1.2 to 5.5). Again, the confidence interval indicates that the difference is unlikely to be due to sampling variability. Among ever-smokers, prevalence of major depression was lowest among those who had successfully quit smoking for longer than one year (4.8%), a prevalence that closely resembles that of the general population. In contrast, it was higher among those who reported that they were trying to quit (12.5%), had quit in the past year (9.7%), or had not considered quitting (10.7%). The PD between those who tried to quit unsuccessfully and those who successfully quit for a period longer than a year was 7.7% (95% CI 5.5 to 9.9).

As shown in Table 2.1, the PD for major depression among smokers with a high nicotine dependence level, compared to those with a low nicotine dependence level, was 7.8% (95% CI 0.8 to 14.9). This is a large prevalence difference, but the confidence intervals approach the null value of zero, indicating that the actual difference in the population may be small. Owing to the small number of observations in some of the cells, age- and sex- specific estimates could not be further evaluated. The prevalence of major depression was higher among those who reported smoking even when sick (21.9%), than for those who reported that they would not smoke smoking when sick (9.7%), for a PD of 12.2% (95% CI 5.8 to 18.6).

2.5 Discussion

We observed a high prevalence of major depression among current-smokers in the general Canadian population. This prevalence was especially elevated among smokers in the younger age groups. This may have important public health implications. Specifically, identification of adolescents at risk for smoking may allow more efficient targeting of intensive education resources. Further, effective management of depression in these individuals may contribute to reduced rates of smoking, a possibility that deserves exploration in future longitudinal studies.

This analysis also provides important data on the relationship of depression to smoking cessation patterns and nicotine dependency. On the stages of change questionnaire, the highest prevalence of major depression was found among those who tried to quit unsuccessfully in the last year. These results run contrary to the common belief among health care providers that depressed smokers are less interested or less willing to quit smoking. However, the high prevalence of major depression among unsuccessful quitters suggests that they may be less able to successfully quit. This finding is in agreement with other studies in the literature, which showed that depressive symptoms tend to be exacerbated after smoking cessation (5, 67). For those who successfully quit in the last year, the prevalence of major depression was surprisingly high compared to the prevalence among those who had quit successfully for more than a year, which have prevalence levels that resemble those among the never smokers.

Individuals having evidence of nicotine dependence had an elevated prevalence of major depression. This is in agreement with findings in the literature that reported stronger association between major depression and nicotine dependence than cigarette smoking (17) and with studies suggesting that nicotine dependence may be related to the etiology of major depression through shared genetic or environmental factors (15, 31).

One limitation of this study is the potential lack of specificity of the CIDI-SF, which could result in the overestimation of the prevalence of major depression (111). This may arise from an inability to distinguish major depression from dysthymia, adjustment disorder, organically-induced depressive syndromes, and bereavement. For example, the CIDI-SF does not distinguish between major depressive disorder, major depressive episodes that occur as part of a bipolar disorder, or those that occur as part of substance use disorder or those that occur in the course of psychotic disorders (108). Therefore, the issue of comorbidity of major depression with other mental disorders in cigarette smokers was not accounted for in this analysis and deserves further investigation.

Existing literature suggests that causal mechanisms are likely to go in both directions: long-term smoking may contribute to the etiology of major depression by altering brain neurochemistry (112). Additionally, major depression can influence the course of cigarette smoking (12). The cross-sectional nature of the data represents another limitation of this analysis, as directional causation cannot be addressed. The extent to which smoking may influence the development or persistence of depression, as opposed to an effect of depression on smoking initiation or persistence cannot be fully

determined, nor can an effect of non-specific psychiatric symptoms, such as distress be excluded as a causal mechanism. We also had limited data on other factors that may influence the initiation or maintenance of smoking such as educational or socio-economic factors.

2.6 Conclusions

As an appreciable number of people in the general population who are trying to quit are depressed, smoking cessation programs should have the capacity to deal with this clinical reality. This is further reinforced by the possibility that attempts to quit may increase the risk of major depressive episodes. Smoking cessation services need to coordinate their activities with suitable mental health services. Elucidation of the directionality of these associations by longitudinal studies deserves further attention.

Table 2.1 - Unadjusted, Age-specific and Sex-specific Estimates of the Frequency of Major Depression in Relation to Smoking Category, Attempting to Quit Smoking, Nicotine Dependence Levels and Smoking Even When Sick[b]

Category	Unadjusted 12-month Prevalence		Age[c] Group (12-44)		Age[c] Group (45+)		Women[c]		Men[c]	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Never smoked n = 18 117 Not depressed n = 17 416 Depressed n = 701	3.9	3.4-4.4	4.3	3.7-4.9	3.1	2.4-3.8	4.6	3.9-5.3	2.8	2.2-3.4
Current smoker n = 11 787 Not depressed n = 10 522 Depressed n = 1 265	10.6	9.5-11.7	12.2	10.8-13.6	7.5	6.0-9.0	14.8	13.1-16.5	7.2	6.1-8.3
Daily smoker n = 9 478 Not depressed n = 8 425 Depressed n = 1 053	11.4	10.3-12.5	13.4	11.9-14.9	7.9	6.3-9.5	15.5	13.4-17.6	8.0	6.7-9.3
Occasional smoker n = 2 309 Not depressed n = 2 097 Depressed n = 212	8.0	6.4-10.2	8.9	6.7-11.1	5.1[d]	2.1-8.1	12.4	9.2-15.6	4.5[d]	2.7-6.3
Former smoker n = 19 345 Not depressed n = 18 333 Depressed n = 1 012	5.3	4.8-5.9	6.9	5.9-7.9	4.0	3.3-4.7	7.4	6.4-8.4	3.6	3.0-4.2

Category	Unadjusted 12-month Prevalence		Age[c] Group (12-44)		Age[c] Group (45+)		Women[c]		Men[c]	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Did not try to quit n = 2 132 Not Depressed n = 1 917 Depressed n = 215	10.7	8.75-12.6	12.6	9.8-15.4	7.7[d]	4.9-10.5	15.5	11.9-19.1	6.8	4.7-8.9
Tried to quit n = 2 731 Not depressed n = 2 363 Depressed n = 368	12.5	10.5-14.5	14.0	11.6-16.4	8.8[d]	5.7-11.8	17.8	14.3-21.2	8.5	6.3-10.8
Quit last year n = 535 Not depressed n = 474 Depressed n = 61	9.7[d]	5.6-13.7	10.8[d]	6.0-15.6	----[e]	----	17.4[d]	9.9-25.0	----[e]	----
Quit > 1 year n = 4 838 Not depressed n = 4 589 Depressed n = 249	4.8	3.8-5.6	6.8	4.9-9.0	3.7	2.6-4.8	6.4	4.7-8.0	3.6	2.5-4.7
Low dependence[a] n = 1 354 Not depressed n = 1 209 Depressed n = 145	11.6	8.3-14.9	14.8	10.6-18.9	----[e]	----	----[f]	----	----[f]	----
High dependence n = 624 Not depressed n = 509 Depressed n = 115	19.4	13.1-29.6	23.9	14.8-33.0	----[f]	----	27.8	17.1-38.5	----[f]	----

Category	Unadjusted 12-month Prevalence		Age[c] Group (12-44)		Age[c] Group (45+)		Women[c]		Men[c]	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Smokes when sick[b] n = 648 Not depressed n = 516 Depressed n = 132	21.9	15.9-27.8	25.8	17.9-33.5	14.8[d]	5.5-24.0	30.6	21.4-39.8	12.6	5.3-19.8
Do not smoke when sick n = 1 833 Not depressed n = 1 655 Depressed n = 178	9.7	7.1-12.3	13.0	9.3-16.6	----[e]	----	12.1	7.7-16.3	7.9	4.8-10.9

[a] Nicotine dependence levels were measured using the Fagerstrom Tolerance Questionnaire (71, 109).
[b] Smoking even when sick is another measure of high nicotine dependence.
[c] Calculated directly from the Approximate Sampling Variability Table provided by Statistic Canada.
[d] CV of the estimate was found to be marginally acceptable according to Statistics Canada release guidelines owing to high sampling variability (CV = 16.6 to 33.3).
[e] The CV of the estimate was found to be unacceptable according to Statistics Canada release guidelines owing to CV > 33% and does not meet the quality standards set forth by Statistics Canada.
[f] The number of people on which an estimate is based is less than 30. Hence the weighted estimate was not released.

CHAPTER THREE: MAJOR DEPRESSION IS A RISK FACTOR FOR SHORTER TIME TO FIRST CIGARETTE IRRESPECTIVE OF THE NUMBER OF CIGARETTES SMOKED PER DAY: EVIDENCE FROM A NATIONAL POPULATION HEALTH SURVEY

3.1 Abstract

Introduction We assessed whether Major Depression (MD) predicts progression of Nicotine Dependence (ND) as measured by reduction in the Time to First Cigarette (TTFC) after waking and the roles of the number of cigarettes smoked per day (CPD) and stress as explanatory variables of this association.

Methods 10-years of follow-up data from the National Population Health Survey (NPHS) were used. The analyses were based on this nationally representative sample of the Canadian population who were over the age of 12 years in 1996 (n=13,298). The NPHS included measures of MD and TTFC. Shorter TTFC was defined as TTFC within 5 minutes of waking. Heavy smoking (HS) was defined by smoking 20 or more CPD. Using proportional hazard (PH) models, unadjusted and adjusted hazard ratios (HRs) for shorter TTFC were estimated for those with and without MD.

Results The unadjusted HR for shorter TTFC among those with MD versus those without MD was 3.7 (95% CI: 2.6-5.3, $p<0.001$). MD predicted onset of shorter TTFC even after adjustment for HS and tendency to smoke more under stress (HR: 1.7; 95% CI: 1.1-2.5, $p=0.02$). When TTFC was defined using longer cut-offs (30 minutes and 60 minutes), HS completely accounted for the effect of MD on TTFC onset.

Conclusions MD appears to be a risk factor for transition to shorter TTFC independent of effects of HS and the tendency to smoke more under stress. As MD is often modifiable, the above association points towards a preventive opportunity in relation to worsening of ND.

3.2 Introduction

Despite public health efforts to raise awareness about the dangers of smoking on health and to encourage smoking cessation among members of the general population, the prevalence of smoking is still quite high. Approximately 25% of the population in developed countries are current smokers (113, 114). This impasse in smoking cessation efforts is often attributed to a multitude of factors; one commonly implicated is Nicotine Dependence (ND). Severe ND is associated with greater risk of quitting failure and relapse after long-term smoking cessation (9-11). The identification of potentially modifiable risk factors for progression to severe ND may lead to improvement of smoking cessation outcomes. Major depression (MD), a condition with a general lifetime population prevalence of 10-20% (115-117), may be an important modifiable determinant of severe ND, although it should be pointed out that MD itself can be recalcitrant to clinical management.

The majority of prospective studies report strong associations between depression and smoking initiation, progression to daily smoking, and decreased smoking cessation success (4, 6, 12-14). Several studies, however, have reported null associations between depression and various smoking stages (27, 118). Nevertheless, there is a dearth of population-based longitudinal studies reporting the role of MD as a predictor of ND onset and transition to severe dependency. This might be largely due to ND's multifaceted nature as a physiological, cognitive, and behavioural construct and its reliance on other smoking milestones. One study (15) investigated the role of lifetime history of Major Depressive Disorder (MDD) as a predictor of ND onset and progression to severe levels

of dependence. The sample consisted of young members of a health maintenance organization and was followed over 14 months. The authors reported that MDD doubled the odds of onset of ND (odds ratio: 2.1, 95% CI: 1.2-3.5) (15). These findings raise the concern that MD may be an important predictor of ND, but the public health implications are unclear as the sample was restricted to a narrow age range (21 to 30 years old) and was not necessarily representative of the general population. Furthermore, this study did not assess specific mechanisms potentially linking MD to ND.

One challenge in this area of research is the lack of consensus as to the best measure of ND and severe dependency. Some of the widely used instruments in epidemiological studies are the Fagerstrom Test of Nicotine Dependence (FTND) and the Heaviness of Smoking Index (HSI) (70-72). Despite their popularity, ambiguity still persists around the ability of these instruments to predict dependence and severity relative to simpler measures. For example, much of the predictive value of the FTND (a six-item instrument) is attributable to a single item: time to first cigarette (TTFC) after waking (76, 78, 79). In fact, recent studies have identified TTFC as the best predictor of ND due to its capability of capturing withdrawal and relapse vulnerability, hence its implication in smoking cessation outcomes (78, 80). Therefore, we used TTFC as an indicator of ND and shorter TTFC to index progression to severe levels of ND.

Originally, TTFC was conceptualized as a categorical variable with the following levels in minutes: ≤ 5, 6-30, 31-60, and >60 with reduced TTFC indicating greater severity of dependence (72). Reduced TTFC has also been associated with higher expiratory carbon monoxide, wider variability in amount of cigarettes smoked per day (CPD), higher cotinine levels (a major metabolite of nicotine) (71, 72, 85), and poor

cessation outcomes (78, 81, 82). Although there is no consensus as to the ideal cut-off denoting shorter versus longer TTFC and contradictory results regarding the association between CPD and TTFC in different ethnic groups have been reported (119, 120). These discrepancies have been attributed to the cut-off used to define reduced TTFC (121). Whether the effect of MD on TTFC depends on a particular TTFC cut-off remains unexplored. For the purpose of this study, TTFC ≤ 5 minutes is referred to as shorter TTFC hereafter.

Other explanatory variables that may influence the relationship between MD and TTFC are heavy smoking (HS) and stress since both are strongly associated with MD and severe levels of ND (16, 20, 22, 23, 122, 123). In addition, there are various smoking transitions that may lead to severe ND, which makes smoking status at baseline an important covariate, specially, in light of evidence suggesting that MD maybe more strongly associated with some smoking milestones than others. For example, MD has been inconsistently associated with smoking cessation success, with conflicting results arising from different studies (6, 118). However, MD has been consistently associated with smoking persistence, transition to daily smoking, and dependence (4, 13, 15, 124) such that there may be differential effects of MD within various categories of smoking status at baseline.

The objective of the current study was to assess whether MD predicts progression to severe levels of ND, as measured by reduction in TTFC, after accounting for HS, stress, and baseline smoking status (current versus never or former smokers). We also assessed whether our results were sensitive to the definition of TTFC and whether shorter TTFC predicted MD incidence.

3.3 Methods

3.3.1 Study Design

The current study is based on data from the National Population Health Survey (NPHS). The NPHS used probability-based multistage sampling methods to select a representative community sample of Canadian household residents of all ages initially interviewed in 1994 by Statistics Canada. The longitudinal cohort has been prospectively followed and re-interviewed every second year in subsequent cycles for 7 cycles to date. Detailed information on this sample and sampling methods are described elsewhere (57, 58).

3.3.2 Measures

3.3.2.1 Major Depression Assessment

The NPHS interview included a brief fully structured diagnostic interview for MD, the Composite International Diagnostic Interview Short Form (CIDI-SF) (63). This interview assesses the presence of past-year major depressive episodes (MDEs). The CIDI-SF algorithm is scored using a 90% predictive probability cut-point validated against DSM-III-R diagnostic criteria (60). These criteria closely resemble those of the DSM-IV-TR (61): an endorsement of minimum of 5 out of 9 symptom-based criteria for MDE, at least one of which must be either depressed mood or loss of interest or pleasure. The CIDI-SF was validated for assessment of MDEs in adolescents as young as 15 years of age (63). In the current sample, there were some subjects between the ages of 12 to 14 years. No validation data is currently available for this group. A decision was made not

to exclude these subjects in view of the face-validity of the instrument and because the longitudinal nature of the study meant that these respondents moved into the 15 years and over age group within one or two data collection cycles.

3.3.2.2 Heavy smoking & Nicotine Dependence Assessment

HS was assessed asking the question: "how many cigarettes do you usually smoke each day?" The question "how soon after you wake up do you smoke your first cigarette?" assessed TTFC. Both of these were only administered to current daily smokers (smoked ≥100 cigarettes in their lifetime and currently smoking at least 1 CPD). The HS question was open-ended while the TTFC question was categorical. HS was modeled both as a continuous variable and as a dichotomous variable with 20 CPD as the cut-off (71). TTFC was dichotomized in the primary analysis using smoking within 5 minutes to distinguish those who were highly dependent from those with low to moderate levels of dependence. This cut-off was chosen as it is usually the most heavily weighted in instruments such as the FTND (71). We carried out sensitivity analysis with other cut-offs for TTFC: within 30 and within 60 minutes.

3.3.2.3 Other Covariates Assessment

Alcohol dependence was assessed using a module of the CIDI-SFAD (63). A predictive cut-point of 0.85 was used to define probable alcohol dependence status. Stress was assessed using a 16-items scale based on the work of Pearlin and Schooler (97) and Wheaton (96). This scale was an abbreviated version adapted by Statistics Canada for use in surveys (Cronbach's α, 0.9) and has not been independently validated. The scale captures the extent of exposure to daily stressors in different life domains (personal,

financial, relationship, environmental, and family). This variable was modeled as a dichotomous variable with the median score as a cut-point designating higher levels of stress. A decision to dichotomize this variable was made to alleviate a breakdown of the linearity assumption at the upper end of the stress scale when stress was modeled as predictor of shorter TTFC, as recommended by Streiner (100). The tendency to smoke more under stress was assessed using a single item from a coping style questionnaire included in the survey in 2002 (91)**.** The Kessler 6-item (K6) non-specific psychological distress scale (range 0-24) (90) as a non-specific indicator of severe mental illness. This variable was modeled on a continuum and categorically with scores of 13 or more indicating severe levels of distress.

3.3.3 Study Population

The initial longitudinal cohort included 17,276 participants. The current study was restricted to those who, in 1996, were: either (1) current smokers who did not smoke their first cigarette within 5 minutes after waking or (2) were non-smokers (never or former). To be eligible, a respondent must also have responded to CIDI-SF (n=12,907). Non-smokers were not excluded because the duration between cycles was long enough for non-smokers at baseline to initiate daily smoking between follow-up interviews, potentially transitioning to shorter TTFC in the same interval. From the original sample of 12,907 followed to 2006, 7,525 (58.3%) subjects had complete data compared to 3,666 (28.4%) non-respondents at one or more time points on key survey questions (Appendix C).

The balance had partial response, were institutionalized or deceased during follow-up (Appendix C). Whenever possible, respondents were included in the analysis and censored when they left the sampling frame.

3.3.4 Analytical Procedures

The 2-year prevalence of different TTFC categories stratified by baseline MD and HS status were calculated. Next, the 10-year cumulative incidence or risk of shorter TTFC stratified by baseline MD and HS status was estimated. Based on previous findings from the literature, a list of other covariates (see above) including the tendency to smoke more under stress were prepared and the 10-year risk of shorter TTFC was then stratified by these variables. In these preliminary stratified analyses, any factor that substantially changed the MD-shorter TTFC association was subsequently added to proportional hazard (PH) models estimating the HR for the entire follow-up period and making simultaneous covariate adjustments.

At the modeling stage, discrete PH models were used for covariate adjustments because the interviews were conducted two years apart (125). We initially modeled the 10-year risk of shorter TTFC as the primary outcome. Discrete-time models using the complementary log-log link function (125) were fit using STATA version 11.0 (148). We tested the PH assumption by comparing models with and without MD by time interactions using the likelihood ratio test. Time-invariant and time-varying predictors were then added to these models. MD effects on the risk of shorter TTFC were modeled as a lagged time-varying variable with MDE ascertainment 2 to 3 years prior to TTFC assessment. Similarly, CPD was modeled as lagged (two years prior to TTFC assessment)

time-varying variable. However, to ensure that our results were robust regardless of the assessment duration, we also modeled CPD as non-lagged variable (assessment of CPD assessment at the same cycle as TTFC). We modeled the effects of CPD and MD as time-varying rather than fixed in order to minimize the potential of misclassification bias.

As a secondary endpoint, we also modeled the 10-year risk of MD and delineated the effect of shorter TTFC on the risk of MD. The same modeling strategies and covariate-adjustments were used as those employed in modeling the TTFC to MD pathway.

In all our analyses, estimates were weighted to adjust for survey design effects: variation in the probability of selection and non-response. Replicate bootstrap weights accounted for clustering and stratification in variance estimation.

3.4 Results

3.4.1 Sample Characteristics

The sample consisted of slightly higher proportions of females (51.3%) than males (48.7%). Respondents aged 12-25 years comprised 22.9% of the sample compared to 37.9% of those aged 26-45 years, and 39.2 % of those 46 years and over. Table 3.1 compares those with and without MD at baseline on various potential risk factors for shorter TTFC. MD was positively associated with current smoking status, alcohol dependence, low income, separated or divorced marital status, and chronic stress. MD was negatively associated with never smoking status. The corresponding confidence intervals did not overlap suggesting that these associations are unlikely due to sampling

variability**.** The current sample (n=12,907) was slightly older, less likely to be current smokers, and more likely to report higher levels of stress at baseline than the original sample (n=17,276).

3.4.2 Prevalence and Incidence of TTFC by MD

Table 3.2 shows the prevalence of TTFC at baseline (1996) by MD status and the amount smoked in 1996. Irrespective of their HS status, individuals with MD compared to those without MD had significantly higher frequencies of shorter TTFC (58.3% versus 34.7%, $p<0.001$; 24.6% versus 11.0%, $p<0.001$). This pattern was not evident for other TTFC cut-offs.

Figure 3.1 shows the 10-year risk of shorter TTFC by MD and HS status in 1996. Among those with MD who were heavy smokers, the risk of shorter TTFC was approximately 3 times higher at each follow-up point when compared to those without MD who were not HS. [1996-1998: 17.0% versus 5.9%, ($p<0.05$); 1998-2000: 26.9% versus 9.8%, ($p<0.05$); 2000-2002: 30.9% versus 11.5% ($p<0.05$); 2002-2004: 34.0% versus 12.8% ($p<0.05$); and 2004-2006: 35.5% versus 13.5% ($p<0.05$)] .

Only 1.2% of all incident cases of shorter TTFC were respondents who were 12-14 years of age at baseline and who reported having MDEs between 1996 and 1998. Therefore, their contribution to the risk of shorter TTFC was negligible, which alleviates concern that the CIDI-SF has not been formally validated in this group.

In preliminary stratified analyses (not shown), there was no evidence of effect modification by any covariate. However, a number of covariates were found to account for some of the MD to TTFC association, which necessitated adjustment in multivariate

modeling (see below). No evidence against the PH assumption was found. Similarly, the likelihood ratio test with and without MD by time interactions was not significant (p=0.08)**.**

3.4.3 Statistical Models

Controlling for age, sex, marital status, education, alcohol dependence, and chronic stress did not substantially alter our results. Only controlling for HS and "smoke more under stress" reduced the hazard ratio (HR) compared to the unadjusted HR. Therefore, we report results on models including these two covariates.

3.4.3.1 Models for Shorter TTFC (within 5 minutes)

In a model with HS and MD alone (not shown), the HR for heavy versus non-heavy smokers independent of MD was 2.6 (95% CI: 2.1-3.3; p<0.001), while the adjusted HR for MD was 1.9 (95% CI: 1.3-2.7; p<0.001) compared to the unadjusted HR of 3.7 (95% CI: 2.6-5.3). Similarly, in a model with "smoke more under stress" and MD alone (not shown), the adjusted HR for "smoke more under stress" was 7.5 (95% CI: 5.5-10.2; p<0.001) while the HR for MD was reduced to 2.3 (95% CI: 1.5-3.6; p<0.001). In a model with all three variables, the effect of MD independent of HS and "smoke more under stress" was further reduced to 1.7 (95% CI: 1.1-2.5), but remained statistically significant (p=0.02) (Table 3.3).

3.4.3.2 Models for Longer TTFC (within 30 and 60 minutes)

In a model predicting TTFC within 30 minutes with HS and MD alone (not shown), the HR for heavy versus non-heavy smokers was 2.1 (95% CI: 1.6-2.7; p<0.001),

but the adjusted HR for MD was reduced to 1.0 (95% CI: 0.6-1.5) and was no longer significant (p=0.9) compared to unadjusted HR for MD of 2.1 (95% CI: 1.4-3.1; p<0.001). When controlling for both HS and "smoke more under stress" simultaneously, the HR for MD did not change in value and did not predict TTFC (HR=1.0, 95% CI: 0.5-1.7; p=0.9). Additionally, both variables remained significant predictors of TTFC. Similar results were obtained for MD (HR=0.7, 95% CI: 0.4-1.3; p=0.6) when modeling TTFC within 60 minutes with the exception that after adjustment for HS status (HR=1.7, 95% CI: 1.2-2.8; p=0.04) the HR for "smoke more under stress" was greatly reduced to a value of 1.1 (95% CI: 0.8-1.6). This variable was no longer a significant predictor of TTFC (p=0.4), and was removed from the model shown in Table 3.3.

Similar results were obtained when number of CPD was modeled as continuous variable rather than dichotomous HS status; when CPD was modeled as non-lagged variable relative to TTFC ascertainment; and when distress was added to these models. These results are available upon request.

To assess the effects of MD on risk of shorter TTFC as a function of baseline smoking status, an interaction term between MD and smoking status was added to a model (not shown) with main effects of MD, HS, and smoking status. There was no evidence of effect modification (p=0.8). We also re-ran separate analyses restricted to baseline current smokers at risk for shorter TTFC and baseline never or former smokers (Appendix D). Our main results were found to be robust when the analysis was approached in these differing ways.

3.4.3.3 Models for Shorter TTFC to MD pathway

We also modeled the effect of shorter TTFC on the risk of MD onset. The same modeling strategies and covariate-adjustments were used. Unlike previous analyses, controlling for age and sex in shorter TTFC-MD analyses substantially changed our results. Therefore, all reported models for these analyses were adjusted for age and sex accordingly. In a model with HS and shorter TTFC (not shown), the HR relating heavy versus non-heavy smokers was 1.4 (95% CI: 1.2-1.7; $p<0.001$), while the adjusted HR for shorter TTFC was 1.3 (95% CI: 1.1-1.6; $p<0.05$) compared to unadjusted HR of 1.6 (95% CI: 1.2-2.1). Similarly, in a model with "smoke more under stress" and shorter TTFC (not shown), the adjusted HR for "smoke more under stress" was 1.8 (95% CI: 1.4-2.3; $p<0.001$) while the HR for shorter TTFC was reduced to 1.2 (95% CI: 0.9-1.5) and was no longer statistically significant ($p=0.2$). In a model with all three covariates, only the effect of "smoke more under stress" remaining a predictor of MD onset (1.7, 95% CI: 1.2-2.4; $p<0.01$), neither the effect of shorter TTFC (HR=1.0, 95% CI: 0.7-1.5; $p=0.9$) nor HS status was statistically significant (HR=1.4, 95% CI: 1.0-2.0; $p=0.05$).

3.5 Discussion

To our knowledge, this is the first population-based prospective investigation reporting associations between MD and TTFC. Our results show that MD is a significant risk factor for progression to severe levels of dependence as characterized by transition to shorter TTFC after controlling for HS and tendency to smoke more under stress. However, when defining TTFC using longer cut-offs, HS completely accounted for the effect of MD on TTFC.

There are substantial pharmacologic effects (126) as well as reported reduction in craving, withdrawal, negative affect, and increase in positive affect after smoking the first cigarette of the day (127). Our findings implicate MD in shorter TTFC etiology and consequently to neurochemical processes that presumably result in these subjective changes in response to the first cigarette of the day. Although the underlying biological mechanisms that link MD to shorter TTFC are currently unknown, the biological plausibility of this association has been previously reported (20, 105, 112). Our findings with respect to MD-shorter TTFC may have important implications for smoking cessation interventions.

Recent research has found TTFC to be the single best predictor of ND (80). Further, reduction in TTFC is closely implicated in poor smoking cessation outcomes (78). Our findings point to MD as a risk factor for transitions to shorter TTFC especially among daily smokers. A clinical implication of this finding is that early detection and treatment of MD may help prevent worsening of ND, which may in turn lead to improvement in smoking cessation outcomes in this subset of the general population. In addition, TTFC appears to be an effective determinant of dosage strength in ND treatment allocation and may provide better dosing for some smokers than CPD (128). Given TTFC can be easily assessed during a brief clinical encounter in primary care compared to other instruments, its use to approximate ND and index its severity in patients with MD for purpose of ND treatment allocation may be warranted in clinical practice and deserves further exploration.

Previous studies have reported the lack of one-to-one concordance between CPD and different measures of ND in both adults and adolescents (85, 129, 130). Our results

replicate these findings for shorter TTFC, but not for longer TTFC. In addition, our results contribute to the current literature as MD may be a potential source for some of the discrepant findings. In particular, MD may account for some of the idiosyncrasies in sensitivity to nicotine at comparable levels of CPD.

Our results also point to the importance of the role of an ineffective coping style (tendency to smoke more under stress) as an independent predictor of transition to shorter TTFC. Although we have adjusted for this covariate in our models, its role as mediator in the MD-shorter TTFC pathway should not be ruled out especially with evidence from the literature pointing to its role in MD etiology (105, 123). If so, adjustment for this variable may result in underestimation of the association of interest. As a mediating factor, the self-medication of depressive symptoms is an emotion-focused coping strategy potentially amenable to psychosocial interventions that facilitate problem-focused coping strategies. This may potentially have valuable clinical or public health implications in prevention of escalation to severe dependence.

As for the influence of baseline smoking status on findings from this study, MD appears to be implicated in the transition from longer to shorter TTFC while the effects of MD on shorter TTFC among never and former smokers are more equivocal. However, since less than 2% of individuals transitioned from non-smoking to shorter TTFC, the lack of statistical significance of the association may be the result of Type II error.

While our data is non-experimental and causal inferences cannot be drawn, it is still valuable to assess the plausibility of other unmeasured variable(s) accounting for our findings. To this end, the latter half of our analyses focused on the reverse direction vis-à-vis shorter TTFC to MD pathway. Breslau and colleagues (15) reported the bidirectional

association between lifetime MDD and ND (defined by DSM-III) while our findings only support a unidirectional association: MD as predictor of shorter TTFC. Different covariate adjustments as well as different ND assessment methods may have contributed to this discrepancy. With respect to the latter, there is a lack of consensus on how well some ND criteria in the DSM predict smoking cessation outcomes. In contrast, the predictive validity of TTFC has recently been confirmed against both traditional and newer measures of dependence (78). Nevertheless, our results are preliminary and need further replication by future studies.

There are various limitations to our findings. One limitation is the self-report nature of the data and narrow scope of ND assessment**.** Second, the brief nature of CIDI-SF makes it susceptible to misclassification of MD status among respondents. Nevertheless, this type of bias is likely to be non-differential with an expected direction of bias is towards the null (131). This form of bias cannot account for the significant associations reported in this study. Third, the relatively long assessment duration between antecedent CPD and consequent development of TTFC may contribute to some misclassification with regards to CPD status. However, a similar pattern of results was observed with and without CPD as lagged time-varying variable. Hence, it is unlikely that such bias would invalidate our findings. Finally, the lack of direct assessment of psychiatric comorbidity (except alcohol dependence) is another potential limitation of this study. Our results do not rule out the possibility that other mental disorders accounted for the presented results.

In conclusion, the current study provides evidence in support of MD as a strong predictor of developing shorter TTFC independent of the amount of CPD and the tendency to smoke more under stress. TTFC provides a convenient way of assessing severity of ND in clinical practice and since MD is treatable, the association of MD with shorter TTFC may possibly point towards a promising preventive opportunity. People with MD may deserve closer monitoring and support in clinical settings as they are at risk of transitioning to severe ND.

Table 3.1 - Baseline Characteristics of Respondents at Risk for Shorter (≤ 5 Minutes) Time to First Cigarette (TTFC) by Major Depression (MD) in 1996

Baseline Characteristics	No MD [n=12,391] % (95% CI)	MD [n=516] % (95% CI)
Male, % (95% CI)	49.1 (48.6-49.7)	32.8 (27.3-38.3)
Age (years), M (SE)	41.9 (0.1)	37.4 (0.9)
Age categories (years)		
12-25 years	22.4 (21.7-23.0)	29.2 (24.1-34.3)
26-45 years	38.5 (37.8-39.1)	41.2 (36.3-46.1)
> 45 years	39.2 (38.6-39.8)	29.6 (24.8-34.4)
White	89.5 (88.7-90.3)	89.9 (85.6-94.2)
< Post-secondary education	44.5 (43.2-45.7)	46.8 (41.2-52.5)
Lowest income[a]	14.2 (13.3-15.1)	27.2 (22.4-32.1)
Marital Status		
Single	29.5 (28.6-30.4)	36.1 (30.6-41.6)
Widowed, separated, divorced	12.2 (11.6-12.9)	19.0 (15.2-22.9)
Married, common-law	58.3 (57.3-59.2)	44.8 (39.3-50.4)
Smoke more under stress	35.8 (33.4-38.2)	44.2 (33.7-54.8)

Baseline Characteristics	No MD [n=12,391] % (95% CI)	MD [n=516] % (95% CI)
Stress[b], M (SE)	2.3 (0.03)	4.3 (0.2)
Higher levels of stress	51.1 (50.0-52.3)	75.5 (71.0-80.0)
Distress[c], M (SE)	2.5 (0.03)	8.2 (0.3)
Higher levels of distress	0.8 (0.6-1.0)	18.5 (14.3-22.7)
Alcohol dependence[d]	1.5 (1.2-1.8)	9.8 (6.2-13.4)
Smoking Status		
Current	23.3 (22.4-24.2)	37.9 (32.9-42.9)
Former	32.7 (31.7-33.8)	30.0 (25.0-35.1)
Never	43.9 (42.8-45.1)	32.0 (27.3-36.8)
CPD, M (SE)	15.7 (0.2)	15.9 (0.7)
Heavy smoking status[e]	39.9 (37.3-45.3)	38.8 (29.5-48.2)

Note. CPD = Cigarette Smoked per Day; CI = Confidence Interval

[a] Lowest income is based on total household income in Canadian dollars and number of individuals within household: <$15,000 for 1-2 persons, <$20,000 for 3-4 persons, and <$30,000 for 5 or more persons.

[b] Stress index (min.=0, max.=16) is derived by Statistics Canada. A dichotomous variable is created using the median score as cut-off.

[c] Distress index (min.=0, max.=24) is based on the work of Kessler et al. (90). A dichotomous variable is created using score of 13 as cut-off.

[d] Alcohol dependence is assessed using CIDI-SF with dependence probability of 0.85 as cut-off.

[e] Heavy smoking status is based on smoking 20 or more cigarettes per day.

Table 3.2 - Prevalence of Different Definitions of Time to First Cigarette (TTFC) by Major Depression (MD) and Heavy Smoking Status (HS) in 1996

TTFC definitions (minutes)	Not MD, Not HS % (95% CI)	Not MD, HS % (95% CI)	MD, Not HS % (95% CI)	MD, HS % (95% CI)
≤ 5	11.0 (8.9-13.0)	34.7 (31.3-38.1)	24.6 (15.9-33.2)	58.3 (45.0-71.6)
6-30	31.0 (28.0-34.1)	42.8 (39.5-46.1)	27.9 (18.1-37.7)	31.2 (20.0-42.4)
31-60	21.5 (19.2-23.8)	16.4 (13.9-18.9)	20.7 (12.6-28.8)	6.9 (1.4-12.3)
> 60	36.5 (33.4-39.5)	6.0 (4.4-7.7)	26.9 (17.6-36.1)	3.6 (2.7-6.9)

Note: Heavy smoking status is based on smoking 20 or more cigarettes per day; HS=heavy smoking; MD=major depression; TTFC=time to first cigarette.

Figure 3.1 - The 10 Year Cumulative Incidence of Shorter (≤ 5 Minutes) Time to First Cigarette by Baseline Major Depression and Heavy Smoking Status in 1996.

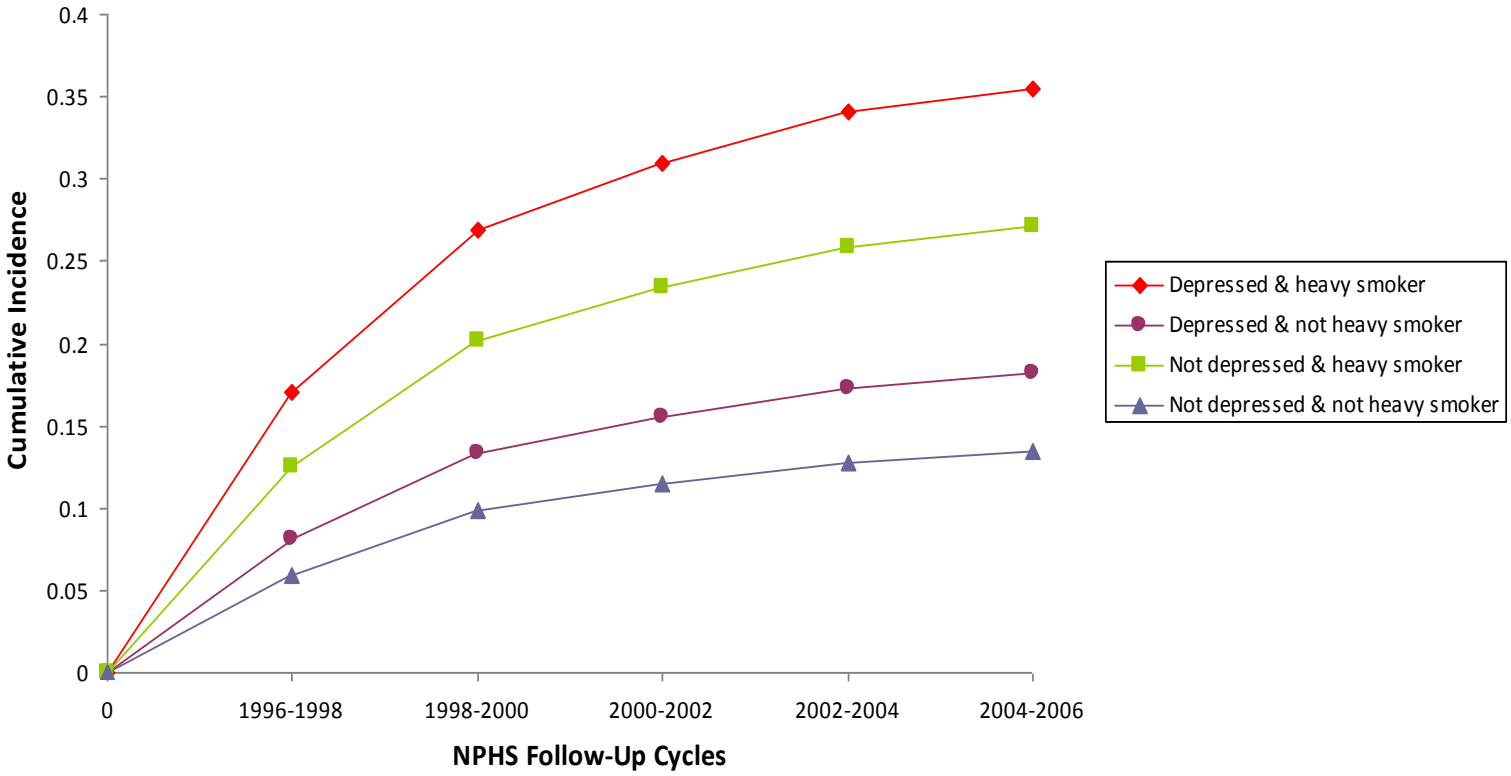


Table 3.3 - Crude and Adjusted Models for Risk of Time to First Cigarette (TTFC) Defined with Different Cut-offs among Smokers and Non-smokers at Baseline (n=11,705)

Definitions of TTFC (minutes)	Unadjusted HR	95% CI	Adjusted HR	95% CI
≤5	3.7***	2.6-5.3	1.7[a]*	1.1-2.5
≤30	2.1***	1.4-3.1	1.0[a]	0.5-1.7
≤60	2.0***	1.3-3.1	0.7[b]	0.4-1.3

Note. HR = Hazard Ratio relating MD status to TTFC; CI = Confidence Interval. Heavy smoking status was assessed as a time-varying variable.
[a]Adjusted for heavy smoking and smoke more under stress.
[b]Adjusted for heavy smoking only.
* $p < .05$. *** $p < .001$.

CHAPTER FOUR: PERSISTENT HEAVY SMOKING AS RISK FACTOR FOR MAJOR DEPRESSION (MD) INCIDENCE - EVIDENCE FROM A LONGITUDINAL CANADIAN COHORT OF THE NATIONAL POPULATION HEALTH SURVEY

4.1 Abstract

Background Reports of bidirectional associations between smoking and major depression (MD) have been interpreted as providing evidence for confounding by shared vulnerability factors that predispose individuals to both conditions. If this is true, then smoking cessation may not reduce the risk of MD. From clinical practice and public health perspectives, the long-term outcomes associated with smoking persistence and cessation are potentially important and deserve exploration. To this end, the 12-year risk of MD in persistent heavy smokers and abstainers who were former heavy smokers with and without adjustment for potential confounders were compared.

Methods Follow-up data from the National Population Health Survey (NPHS) was used. Multinomial logistic (ML) models were fit to identify potential confounders. Using proportional hazard (PH) models, unadjusted and adjusted hazard ratios (HRs) for MD outcome were estimated for different smoking patterns.

Results The unadjusted HR relating the risk of MD among current-heavy versus former-heavy smokers was 4.3 (95% CI: 2.6-6.9, $p<0.001$). Current-heavy smoking predicted onset of MD (HR=3.1, 95% CI: 1.9-5.2, $p<0.001$) even after adjustment for age, sex and stress – the main confounders. However, this was not the case for the never, former-light, and current-light categories. Evidence of decreased risk of MD among former-heavy relative to current-heavy smokers as function of smoking cessation maintenance time was also found.

Conclusions Contrary to common beliefs about the benefits of smoking for mental health, our results suggest that current-heavy rather than ever-heavy smoking is a major determinant of MD risk and point towards the benefits of smoking cessation maintenance.

4.2 Introduction

The association between smoking and depression is a well-documented phenomenon that is consistently reported among studies with different populations, study designs, analytical methods, definitions of smoking, and definitions of depression (4-6, 12, 18, 27, 29, 32, 132-136). Several cause and effect hypotheses have been proposed in response to these findings: a) unidirectional self-medication effects of pre-morbid depression on the risk of smoking and nicotine dependence (15, 17, 20, 21); b) unidirectional effects of chronic exposure to psychoactive substances in tobacco smoke including the proposed pharmacological effects of nicotine and monoamine oxidase (MAO) inhibitors on the neurobiological processes that are implicated in the etiology of a Major Depressive Episode (MDE) (21, 34, 48, 112, 137-139); and c) reciprocal or bidirectional effects with MDE increasing the risk for smoking and vice versa (12, 140).

Alternatively, a non-causal explanation (133), that the association results from shared genetic, behavioural, and environmental factors that predispose individuals to both conditions (33), has also been proposed. This is often referred to as the shared vulnerability hypothesis. A number of mechanisms have been proposed under this hypothesis. An example is a biopsychosocial model in which smoking and depression share certain personality phenotypes (neuroticism, extraversion and impulsive-unsocialized sensation-seeking) (141). Another possibility is common neurobiology that may influence the probability of both conditions (142-144).

The main approach in epidemiology has been to determine whether the effects are unidirectional or bidirectional, under the assumption that common etiologic factors as

outlined by the shared vulnerability hypothesis would likely to manifest as bidirectional associations. Although many prospective epidemiological studies have reported bidirectional associations between smoking and depression (12, 15, 30-32), only a few of these studies have actually assessed specific comorbidity hypotheses beyond the directionality of effects (30, 32). Furthermore, other epidemiological studies have also reported a unidirectional association; the majority of which reported smoking as predictor of depression onset (25-29).

Several twin and family studies have evaluated the possibility of shared genetic vulnerability between smoking and depression. Conflicting results have emerged with some studies supporting shared genetic liability (18, 136, 145), while others have failed to replicate these findings (132, 146, 147). This discrepancy may be due to different assessment methods of depression and smoking transitions as well as different analytical procedures (136).

Based on findings from the abovementioned literature, it is very likely that shared vulnerability factors account for some of the observed association between antecedent smoking and consequent MD. Whether these factors account for all of this association remains controversial. In particular, if the latter proposition is true, then smoking cessation may not reduce the risk of MDE. By explicating the long-term consequences of persistent heavy smoking as opposed to smoking cessation maintenance, the current study aims to clarify the clinical and public health implications, if any, of the smoking to MD association.

The current analysis has the following specific objectives: (1) to estimate the effect of antecedent heavy smoking persistence on the risk of MDE while adjusting for

potential confounders of this association (2) to assess any dose-response effects of heavy smoking persistence on risk of MDE, and (3) to assess the potential impact of heavy smoking cessation maintenance on risk of MDE.

4.3 Methods

4.3.1 Study Design

The current analyses are based on data from the National Population Health Survey (NPHS), a population-based cohort study of a representative community sample of the Canadian population. The initial interviews were conducted in 1994-1995. The respondents have been prospectively followed and re-interviewed every second year in subsequent cycles for up to 7 cycles to date (2006-2007). Detailed information on the characteristics and sampling methods of the NPHS are described elsewhere (57, 58).

4.3.2 Study Sample

In light of previous findings implicating short-term quitting and relapse in MDE etiology (5-8) and to avoid the potential of intermixing of the effects of other smoking transitions with the effects of heavy smoking persistence and continued heavy smoking cessation on the risk of MDEs, subjects who changed their smoking status during the follow-up period from that reported at baseline (3,059) were excluded from the current analyses (Figure 4.1). Therefore, the present sample is composed of 3,824 respondents who did not change their smoking status throughout the follow-up duration (i.e. only those who stayed current, former, and never smokers). This criterion for selection and other restriction rules are shown in Figure 4.1. Both death and the inability to trace

subjects (Appendix E) constituted a large proportion of the missing data in the original cohort and were consequently removed from the sample. A comparison between the original and the present analytical sample on various biopsychosocial variables associated with heavy smoking status and depression is available online (Appendix F).

4.3.3 Long-term MDE Risk Assessments among Ever-Heavy Smokers

Ever-heavy smokers (current and former) may share similar genetic, behavioural, and environmental vulnerabilities, at least for heavy smoking initiation. In turn, if these shared vulnerability factors were dominant characteristics that also convey risk for MDE, then we would expect former-heavy smokers to continue to have elevated risks of MDE similar to those predicted of current-heavy smokers. However, if the persistence of the exposure (current as opposed to former) had the dominant effect on the risk for MDE, then current-heavy smokers would be expected to have higher risks of MDE relative to former-heavy smokers.

4.3.4 Measures

4.3.4.1 Smoking Status (exposure)

The number of cigarettes smoked per day (CPD) was dichotomized based on reporting current or former daily consumption of 20 or more CPD (70). Current or former smokers were considered ever-heavy smokers if they reported smoking greater than 20 CPD at any time-point during the study. Only individuals consistently reporting smoking 20 CPD or less throughout follow-up were considered light smokers (past or current). We carried out dose-response assessments. Among current smokers, we assessed any dose-

response effects of smoking amount on the risk of MDE over the 12-years of follow-up. Among former-heavy smokers, we assessed the risk of MDE as a function of the number of years since smoking cessation.

4.3.4.2 Major Depression Episode (outcome)

The NPHS included a brief fully structured diagnostic interview for MDE, the Composite International Diagnostic Interview Short Form (CIDI-SF) (63), which assesses the presence of depressive symptoms lasting a minimum of 2 weeks in the 12 months prior to the interview. The CIDI-SF algorithm is scored using a 90% predictive probability cut-point that has been validated against DSM-III-R diagnostic criteria for MDE (60). These criteria closely resemble those used by the DSM-IV-TR (61) that is an endorsement of a minimum of 5 (out of 9) symptoms for MDE, at least one of which must be either depressed mood or loss of interest or pleasure. To estimate the 12-year cumulative incidence (or risk) of first MDE (the outcome of interest in this study), we excluded individuals who at baseline were depressed (n=242), had missing depression values (n=158) or reported a history of depression (n=205) (Figure 4.1). A personal history of MD at or prior to the baseline year in 1994 was used to exclude participants with a previous history of MD to minimize the influence of recurrent MDEs on our estimates of the risk for first MDEs.

4.3.4.3 Potential Confounders

Based on previous findings, a number of biopsychosocial variables were selected and assessed (Appendix G). These covariates included family history of depression; psychological variables such as rebelliousness (86), self-esteem (87), sense of mastery

(88), Antonovsky's sense of coherence (89), and psychological distress (90); behavioural variables such as ineffective coping styles (91) and binge drinking (92-94); environmental variables such as childhood trauma (96), stress (97), and perceived social support (98); and finally health-related variables such as the presence of one or more chronic health conditions, and self-reported pain were also included (99). For any of these covariates to act as a confounder, it has to be associated with the exposure (heavy smoking status) and be independent risk factor of MDE.

4.3.4.4 Analytical Procedures

Multinomial logistic (ML) regression models were fit to assess differences, if any, in the baseline distribution of various sociodemographics (age, sex, income, marital status, and education) and biopsychosocial variables among the three main categories of heavy-smoking exposure: never, former-heavy, and current-heavy. At baseline, any factor that appeared to be strongly associated with either one or both of the ever-heavy smoking categories versus the never smoking category was subsequently added to proportional hazard (PH) model for the longitudinal component of the analysis.

Discrete-time PH models as generalized linear models with the complementary log-log link were fit to the data because the time intervals were discrete (follow-up interviews conducted two years apart) (125). We assessed the PH assumption by using the likelihood ratio test to compare models with and without heavy smoking status by time interactions. All analyses were conducted in STATA (Version 11) (148).

At the PH modeling stage, we estimated the hazard ratio (HR) for MDE over the 12 years of follow-up. Smoking status was the main study factor defined as five levels

(never, former-light, current-light, current-heavy, and former-heavy). MDE was the main outcome of interest. The reference category in most of the fitted PH models was the former-heavy smokers group. This choice for the reference category was established a priori to provide HRs that directly compared the effects of other heavy smoking categories relative to heavy smoking cessation maintenance on the risk of MD.

The PH modeling was carried out in three stages. The first stage involved single-covariate adjustment with each potential confounder identified from the ML models. At the second stage, only variables that were independent risk factors of MDE and appeared to substantially alter the magnitude of one or more HRs (relating heavy smoking status to MDE) underwent simultaneous adjustments in PH models. At the third stage, we used only covariates that appeared to have confounding effects beyond those predicted by other covariates to obtain final adjusted HR estimates (see below). We also fit models that included all of the measured covariates.

To ensure the analyzed sample obtained from restriction rules (Figure 4.1) did not differ from the original sample in terms of baseline distribution of characteristics in relation to heavy smoking status and MDE, we carried out a sensitivity analysis that included individuals who had incomplete data on the smoking module during follow-up. Respondents with a minimum of one cycle of response to smoking-module questions were included in the sensitivity analysis and censored when they left the sampling frame due to death, institutionalization or if they have not experienced a MDE by the end of cycle 7 (study end date).

In all the analyses (including the models), estimates were weighted to adjust for survey design effects including variation in the probability of selection and non-response.

Replicate bootstrap weights (500 replicates as recommended by Statistics Canada) were applied to account for clustering and stratification in variance estimation.

4.4 Results

In terms of missing data, potentially problematic non-responses on smoking status ("not stated", "refusals", "do not know") constituted the smallest percentage of total missing data ranging from 0.1% to 2.5% across all survey cycles with the exception of cycle 7 (Appendix E). Conversely, loss-to-follow-up was the largest source for missing data and was highest in cycle 7 (22.5%). The current sample is slightly older, less likely to be single, with more females than males, higher education and income, lower distress, less likely to report ineffective coping styles, and higher prevalence of chronic conditions than the original NPHS cohort (Appendix F).

The baseline distribution of various variables among the three main smoking categories all at risk for MDE is shown in Table 4.1. In comparison to the never-smokers (the reference category throughout Table 4.1), ever-heavy smokers share the following common factors, respectively: less likely to be female, more likely to have had one or more childhood traumas, more likely to report increased drinking frequency in response to stress, and more likely to report low levels of social support (Table 4.1)

Only two factors were comparable across all three groups: low self-esteem and family history of depression. Meanwhile, relative to the never smokers, the following factors were disproportionately distributed among the current-heavy as opposed to former-heavy smokers: younger age (age $\leq$ 45), lower household income, less than post-secondary education, earlier experimentation with cigarettes (age $\leq$ 12 years), lower

mastery, lower sense of coherence, and higher levels of non-specific psychological distress (Table 4.1). The current-heavy smokers were also more likely than the former-heavy smokers to experience higher levels of stress and to use drugs under stress. In contrast, the former-heavy smokers were more likely than the current-heavy smokers to report having one or more chronic conditions and moderate to higher levels of pain (Table 4.1).

In the PH models, the likelihood ratio test comparing a model with all smoking levels by time interactions to a model without any of these interactions was not significant ($p=0.6$). Hence, no evidence against the proportional hazards assumption was found.

The 12-year risk of MDE for the entire sample was 13.2% (95% CI: 11.8-14.6). The risk of MDE among current-heavy, former-heavy, and never smokers was 26.7% (95% CI: 19.9-23.4), 7.1% (95% CI: 4.8-9.4), and 12.2% (95% CI: 10.2-14.1), respectively.

At the PH modeling stage, we found no evidence for effect modification by any of the covariates shown in Table 4.1 including no interaction between sex and heavy smoking status categories (current-heavy, current-light, former-light and never smokers) on the risk of MDE ($p=0.8$, $p=0.1$, $p=0.3$, $p=0.4$).

The unadjusted HRs (Table 4.2) for the effect of each category of heavy smoking status (current-heavy, current-light, former-light and never smokers) relative to the former-heavy smokers on the risk of MDE were HR=4.3 ($p<0.001$), HR=2.0 ($p<0.05$), HR=1.5 ($p=0.07$), and HR=1.75 ($p<0.01$), respectively. The risk for MDE among the current-heavy smokers was approximately 3 times the risk for MDE among the former-

heavy smokers (HR=3.1, p<0.001) even after adjustment for age, sex, and stress (Table 4.2). Similar results were also obtained when a model was fit with continuous age centered at 45 years and with the inclusion of main effects for all the covariates presented in Table 4.1 as opposed to only few selected variables (Table 4.2). In this all-inclusive model, the following terms remained significant predictors of MD: family history of MD (HR=1.8, p<0.001), "use drugs under stress" (HR=3.1, p<0.001), childhood trauma (HR=1.5, p<0.01), lower sense of coherence (HR=2.5, p<0.001), stress (HR=1.7, p<0.01), pain (HR=1.6, p<0.01), sex (HR=1.5, p<0.05), and continuous age (HR=1.0, p<0.001). Furthermore, we explored the potential for non-linear effects in age (not shown), but no evidence of departure from linearity was discerned (p=0.09).

Results from the sensitivity analysis (not shown) were similar to those presented here with the exception of the adjusted HR relating current-light smokers to MDE relative to former-heavy smokers ($HR_{Current\text{-}Light}$=2.0, p<0.001).

The HRs relating former heavy-smoking to MDE relative to those who persisted heavy smoking for the entire 12 years of follow-up decreased incrementally from a value of 0.5 (p<0.05) for those who quit heavy smoking for 1-5 years to a value of 0.2 (p<0.001) for those who quit for 21 years or more (Table 4.3). Evidence of dose-response effects for different levels of CPD on risks for MDE was also found (Appendix H).

4.5 Discussion

Under the shared vulnerability hypothesis, ever-heavy smokers may be expected to have similar elevated risk for MDE irrespective of their smoking status during follow-up. However, our results point to the contrary. After adjustment for confounding by

various variables, the HR relating current-heavy smoking to MDE, as opposed to former-heavy smoking, was still associated with a three-fold increase in the risk of MD. These results were specific to current-heavy smokers as a group. In addition, there appears to be protective effects in relation to increasing duration of heavy smoking abstinence. Therefore, our findings are consistent with the view that the heavy smoking to MD pathway is causal in nature, rather than mainly due to confounding by shared vulnerability factors.

Although the specific underlying mechanisms that link heavy smoking to depression are still unknown, several pertinent findings from our study are noteworthy. Traits such as having experienced a childhood trauma and the tendency to use drugs to cope with stress were significant predictors of MD, but were more strongly associated with the ever-heavy as opposed to never smoking status at baseline. These traits are likely to act as antecedent risk factors to both heavy smoking initiation and subsequent developments of MDE and deserve further exploration by future studies. In contrast, the absence of somatic pain and having a low sense of coherence were disproportionately expressed in current-heavy smokers as opposed to former-heavy smokers and were also significant predictors of MDE during follow-up. Of particular interest is the extent to which low sense of coherence may play a role in both heavy smoking and MD comorbidities. Moreover, whether traits such as low coherence and tendency to use maladaptive stress coping strategies are modifiable through psychological or behavioural interventions remain an important issue for future studies to explore as both appear implicated in the heavy smoking to MD pathway.

Although we did not assess whether depression predicts heavy smoking, it is important to acknowledge that bidirectional findings do not necessarily negate causal explanations in one or both directions of an association. Similarly, bidirectional findings are not sufficiently unequivocal to infer causality due to potential confounding by variables that may increase risk for both conditions. In this respect, our results should not be viewed in disagreement with studies that reported such findings (12, 30-32).

Our results run contrary to findings from some cross-sectional genetic studies (13, 18, 145). While valuable for generating hypotheses, these studies remain limited by their reliance on lifetime data for depression and smoking ascertainment. In contrast to findings from these studies, evidence from a Finnish study of adult twins followed within a prospective cohort design found that persistent smoking relative to never smoking status predicted depression even after controlling for family and genetic liabilities (146). Furthermore, evidence was found by the same authors that, in comparison to never smokers, depression risk was elevated among short-term former smokers, but not among long-term former smokers (146). In a recent study Korhonen et al. (139) found that if compared to persistent smokers, long-term abstainers had significantly lower risk of several depression dimensions. This difference between short-term and long-term cessation may have substantial clinical and public health implications because it strongly suggests that successful smoking cessation leads to a lowering of risk, but also clarifies that this occurs in the long-term rather than short-term.

Our results are in agreement with various findings from previous longitudinal studies that do not utilize twin or family data (26-29). In particular, a recent prospective study (25) with 26 years of follow-up data reported increased risk for MD among women

and men with dose-response pattern for increasing CPD levels. This study also reported that female former smokers had lower risk of MD relative to the never smokers (25). A similar pattern was also observed in our study, irrespective of sex. In addition, we observed a statistically significant pattern of decreased risk of MD as a function of the number of years of smoking cessation among former-heavy smokers relative to persistent heavy-smokers. A similar pattern was observed previously by a Norwegian population-based study (28) in which those who quit for greater than 5 years appeared to have a lower risk of first depressive episode than those who quit within 5 years. However, these findings failed to achieve statistical significance (28). Replication by future studies of our findings with respect to the importance of the duration of smoking maintenance while controlling for CPD among former smokers (not only current smokers) is still needed.

Although short-term smoking cessation research shows that there is an increased risk for post-smoking cessation MD (5, 6, 8, 101), there is little population-based research into the long-term effects of smoking cessation on the risk of MDE. Our findings shed light on this important question by showing that the hazard of MDE among former-heavy smokers decreases as function of smoking-cessation maintenance time. This may mean that monitoring for increased risk of MD may be unnecessary following the first year post-smoking cessation. Another important implication is that investing in public health interventions aimed at maintenance of smoking cessation efforts among former-heavy smokers may result in reduction in risk of MDEs. For patients who persist with smoking heavily, it seems reasonable that they should be advised that long-term benefits might follow if they quit and maintain their smoking cessation, even if the short term effects seem negative (139, 146, 149).

Findings from this study need to be interpreted in context of the following limitations. First, some strong assumptions were made in the course of this study. One assumption is that former-heavy and current-heavy smokers are similar on some unmeasured shared vulnerability factors that lead to their heavy smoking in the first place. However, it is important to acknowledge that shared vulnerability factors including genetic vulnerability in the context of smoking and depression may not be limited to smoking initiation and heavy smoking onset (150), but may also influence the ability to quit smoking and maintain smoking cessation (151). Second, our findings cannot be used to definitively support or refute any particular hypothesis with regards to etiology due to the non-experimental nature of this study. However, experimental studies are not feasible for ethical reasons making observational studies on this topic of additional importance. A third limitation is the self-report nature of the data especially with respect to heavy smoking assessment. A fourth limitation stems from a lack of direct assessment of psychiatric comorbidity. Hence, our results do not rule out the potential role of other mental disorders in accounting for the results presented here. Fifth, various precautionary measures were taken to minimize the effects of MD to heavy smoking pathway on our results. These measures entailed excluding participants with prior history of MD and those who changed their smoking status during follow-up as well the use of non-repeated event history analysis to analyze the data. Despite these efforts, the issue of "reverse-causality" is still a possibility, as two years passed between NPHS interviews, hence, this comprises a limitation of the current study. Finally, although the sensitivity analysis showed that the exclusion of incomplete data do not change the main findings from this study, it is conceivable that those who were not traced were more likely to be heavy

smokers and depressed than never smoker and not depressed, in which case bias may have been introduced.

Despite these limitations, our study has several strengths. First, the large population-based sample and longitudinal study design. Second, it addresses some unanswered issues arising from previous studies with respect to the extent of the contribution of some of the shared-vulnerability factors underlying the heavy smoking to depression association. Finally, it sheds light on the long-term impact of smoking cessation on the risk of MD – an important question to clinical and public health practice.

The shared vulnerability hypothesis may have diminished recognition of the importance of heavy smoking as a determinant of depression risk. In this respect, our results challenge the shared vulnerability hypothesis. In fact, in light of the strength of the association, the dose-response effects, the temporality, the biological plausibility, and the consistency of evidence discussed thus far, there is sufficient ground to suggest that antecedent heavy smoking is an independent risk factor for MD. Contrary to the beliefs held by some smokers that smoking improves their mental health, our results suggest the opposite and point towards mental health benefits of quitting maintenance. Future efforts aimed at maintenance of smoking cessation among former-heavy smokers as well targeting smoking cessation among current-heavy smokers may provide a valuable opportunity to reduce risk of MDEs in the ever-heavy smoking subset of the general population.

Table 4.1 - Baseline Characteristics among Respondents at Risk for Major Depression (MD) by Main Categories of Heavy Smoking Status: Current-Heavy, Former-Heavy and Never Smokers

Characteristics	Current-Heavy (n=479) % (n)	Former-Heavy (n=1,184) % (n)	Never (n=1,785) % (n)	$OR_{Current\text{-}heavy/Never}$ (95% CI)	$OR_{Former\text{-}heavy/Never}$ (95% CI)
Sociodemographics					
Mean Age (SE)	38.6 (0.7)	49.5 (0.6)	40.6 (0.5)	1.0*** (0.9-1.1)	1.0*** (0.9-1.1)
Age ≤ 45	74.8 (349)	40.4 (432)	64.2 (1,065)	1.8*** (1.45-2.3)	0.4*** (0.3-0.5)
Female	44.8 (220)	36.4 (454)	63.5 (1,202)	0.4*** (0.3-0.5)	0.3*** (0.2-0.5)
Marital Status[a]					
Married	67.2 (286)	81.7 (875)	66.0 (1,075)	1.0	1.0
Single	20.6 (107)	6.7 (112)	25.1 (448)	0.9 (0.7-1.1)	0.3*** (0.2-0.4)
Other	12.3 (86)	11.6 (197)	8.9 (262)	1.2 (0.9-1.6)	0.9 (0.7-1.2)
< Post-secondary Education	53.3 (250)	43.3 (512)	39.5 (703)	1.7*** (1.4-2.1)	1.2 (1.0-1.4)
Lowest Income[b]	23.2 (139)	11.0 (155)	10.2 (242)	2.6*** (2.0-3.2)	1.0 (0.7-1.3)

Characteristics	Current-Heavy (n=479) % (n)	Former-Heavy (n=1,184) % (n)	Never (n=1,785) % (n)	$OR_{Current\text{-}heavy/Never}$ (95% CI)	$OR_{Former\text{-}heavy/Never}$ (95% CI)
Genetics					
Family History of Depression	20.8 (80)	14.1 (168)	17.1 (298)	1.0 (0.8-1.3)	0.8 (0.6-1.1)
Psychological Factors					
Age 1st Cigarette[c]	20.4 (83)	14.9 (201)	---	2.0[ß***] (1.4-2.9)	---
Low Mastery[d]	24.4 (133)	21.8 (274)	23.0 (407)	1.3[*] (1.1-1.6)	1.0 (0.8-1.2)
Low Self-esteem[e]	28.0 (197)	30.0 (326)	30.6 (626)	1.0 (0.8-1.2)	0.9 (0.7-1.1)
Low sense of coherence[f]	33.9 (169)	20.6 (245)	20.9 (351)	2.1[***] (1.7-2.6)	1.0 (0.8-1.2)
High Distress Levels[g]	12.5 (66)	6.1 (77)	9.0 (148)	1.8[***] (1.3-2.4)	0.8 (0.5-1.1)
Behavioural Factors					
Use Drugs under Stress,	5.2 (23)	2.0 (31)	1.8 (39)	2.2[**] (1.2-4.0)	0.7 (0.4-1.6)

Characteristics	Current-Heavy (n=479) % (n)	Former-Heavy (n=1,184) % (n)	Never (n=1,785) % (n)	$OR_{Current\text{-}heavy/Never}$ (95% CI)	$OR_{Former\text{-}heavy/Never}$ (95% CI)
Drink under Stress,	17.1 (75)	10.1 (99)	4.9 (86)	3.6*** (2.7-4.9)	1.8** (1.3-2.5)
Binge Drinking[h]	74.8 (356)	51.4 (621)	51.2 (939)	2.7*** (2.1-3.4)	1.2 (1.0-1.6)
Environmental Factors					
Childhood Trauma[i]	62.7 (278)	51.5 (591)	38.4 (656)	2.2*** (1.8-2.7)	1.5*** (1.3-1.8)
Higher Levels of Stress[j]	20.9 (118)	10.3 (127)	11.4 (193)	2.5*** (2.0-3.3)	0.9 (0.7-1.2)
Low Social Support[k]	18.3 (97)	17.1 (176)	12.6 (91)	1.8*** (1.4-2.3)	1.4** (1.1-1.9)
Health-related factors					
Pain[l]	8.4 (47)	11.6 (133)	8.2 (146)	1.2 (0.9-1.7)	1.4* (1.1-1.9)
Chronic Conditions[m]	50.9 (241)	60.3 (761)	49.6 (967)	0.9 (0.7-1.0)	1.5*** (1.2-1.9)

Note. Current-heavy smokers (n=479), former-heavy smokers (n=1,184), and never smokers (n=1,785). Only respondents who did not change their smoking status during follow-up were considered. Odds ratios (ORs) were obtained by entering each variable one at time into multinomial logistic regression models with smoking status as dependent variable. All estimates in this table including percentages (%) and means (M) are weighted and bootstrapped. All variables were measured at baseline (1994-1995). "Other" in marital status refers to those who are divorced, widowed, or separated.

[a]Married is the reference category.

[b]Lowest Income is based on household income in Canadian dollars of <$15,000 for 1-2 persons, <$20,000 for 3-4 persons, and <$30,000 for 5 or more persons.

[c]Dichotomous variable based on reported age of ≤12 years as the age when respondent smoked 1st whole cigarette.

[d]Based on mastery scale (88). The score range is 0-28. Low mastery was defined at the lower quartile.

[e]Based on Rosenberg's self-esteem scale (87). The score range is 0-24. Low self-esteem was defined at the lower quartile.

[f] Based on Antonovsky's sense of coherence scale (89). The score range is 0-78. Low sense of coherence was defined at the lower quartile.

[g]Based on Kessler's 6-item (K6) non-specific psychological distress scale (90). The score range is 0-24. Higher levels of distress were defined at the upper quartile.

[h]Binge drinking is defined as drinking 5 or more drinks on any one occasion in the past 12 months.

[i]Childhood trauma was based on reporting at least one or more of the following traumatic experiences in childhood or adolescence: parental divorce, a lengthy hospital stay, prolonged parental unemployment, traumatised for years, and frequent parental alcohol or drug use, being sent away from home and physical abuse by a parent or a relative .

[J]Stress was assessed using a 16-item scale based on work by Wheaton (96) and Pearlin and Schooler (88).The upper quartile was used as the cut-point to designate high levels of stress

[k]Perceived social support has a range of 0-4. Low social support was defined by affirming the presence of 1 of 4 dimensions of social support.

[l]Presence of pain was based on reporting moderate to high levels of pain as opposed to absence or low-levels of pain.

[m]Chronic conditions are defined as having one or more conditions diagnosed by a health professional.

[ß]Odds ratio comparing current-heavy versus former-heavy smokers.

$^{*}p<.05.$ $^{**}p<.01.$ $^{***}p<.001$

Table 4.2 - Unadjusted and Adjusted Hazard Ratios (HRs) for Onset of Major Depression (MD)

	N (cases)	Unadjusted HR[a] (95% CI)	Adjusted HR[b] (95% CI)	Adjusted HR[c] (95% CI)
Former Heavy	1,184 (103)	1.0	1.0	1.0
Former Light	206 (25)	1.5 (1.0-2.4)	1.3 (0.8-2.1)	1.2 (0.7-2.1)
Never	1,785 (265)	1.75 (1.2-2.6)	1.3 (0.9-2.0)	1.7* (1.1-2.8)
Current Light	170 (30)	2.0* (1.1-3.5)	1.1 (0.6-2.2)	1.6 (0.9-3.1)
Current Heavy	479 (158)	4.3*** (2.6-6.9)	3.1*** (1.9-5.2)	3.3*** (1.8-6.2)

Note. CI = Confidence Interval. Heavy smoking is based on smoking 20 or more cigarettes per day.
[a]Hazard ratios based on former-heavy smokers as reference category.
[b]Hazard ratios based on former-heavy smokers as reference category adjusted for age (≤45 years), sex, and stress.
[c]Hazard ratios based on former-heavy smokers as reference category adjusted for continuous age (centered at 45 years), sex, marital status, education, income, stress, family history of depression, tendency to drink more and/or use drugs under stress, mastery, self-esteem, sense of coherence, social support, unspecified psychological distress, chronic conditions, pain, and childhood trauma.
*$p<.05$ ***$p<.001$

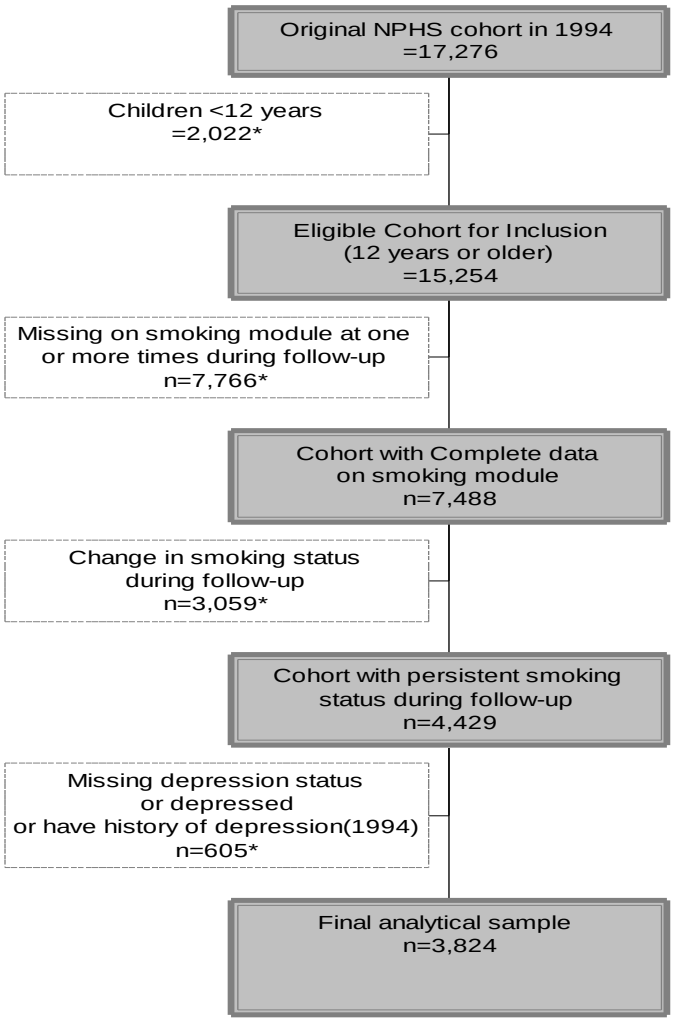
Table 4.3 - Effects of Duration of Smoking Cessation Maintenance on the Risk of Major Depression (MD)

Variables	N (cases)	Hazard Ratio	95% Confidence Interval
Smoking cessation (years)			
Current-heavy	479 (158)	1.0	-
Former-heavy 1-5 years	231 (26)	0.5[a*]	0.3-0.9
Former-heavy 6-10 years	277 (24)	0.45[a*]	0.25-0.8
Former-heavy 11-15 years	220 (20)	0.4[a**]	0.2-0.8
Former-heavy 16-20 years	196 (16)	0.3[a**]	0.2-0.6
Former-heavy 21+ years	260 (17)	0.2[a***]	0.1-0.5

Note. Duration of smoking cessation was based on the difference in years between reported age at baseline and age at which respondent reported having stopped smoking daily.

[a]Hazard ratios based on current-heavy smokers who persisted smoking for 12 years as reference category adjusted for age, sex, and stress.

Figure 4.1 - Restriction Criteria Applied to National Population Health Survey (NPHS) Cohort to Obtain Final Analytical Sample Used in this Study.



* Excluded from current analysis

CHAPTER FIVE: DISCUSSION

5.1 Summary of Main Findings

In this dissertation, we have addressed several inter-related questions with respect to the association between smoking and depression using two national surveys - the cross-sectional CCHS (cycle 2.1) and the longitudinal NPHS (cycles 1-7).

In Manuscript I, we estimated the 12-month prevalence of MDE across different smoking categories in the Canadian population. We found that the highest prevalence of MD was among current-daily smokers at 10.6 %, followed by former smokers at 5.3%, and lowest among the never smokers at 3.9%. The estimate of the annual prevalence of MDE among the never smokers reported here resembles the 12-month prevalence estimates for depression (4%-5%) that have been consistently reported across different Canadian studies (152-154). As for the stages of change, the 12-month prevalence of MDE among the ever-smokers was lowest among those who had successfully quit smoking for longer than one year (4.8%), a prevalence that closely resembles the never-smokers' prevalence proportion in the general population. In contrast, it was noticeably higher among those who reported unsuccessful attempts to quit smoking in the past year (12.5%), those who had successfully quit in the past year (9.7%) or had not considered quitting (10.7%). The PD between those who tried to quit unsuccessfully and those who successfully quit for a period longer than a year was 7.7% (95% CI 5.5-9.9). The CIs indicated that the difference in MDE prevalence between these two groups was unlikely due to chance. Irrespective of the smoking status or stage, these annual estimates of MDE

were higher in females than males (approximately 2:1) and elevated among younger respondents (12 to 45 years) than older respondents (older than 45 years) consistent with most findings from epidemiological literature with respect to MD.

A similar trend to that observed of the prevalence estimates described above has also been reported for MD risk especially in relation to smoking cessation. In particular, there have been consistent reports of an elevation in the risk of MD in response to attempts to quit and short-term cessation (12 months) (5, 7, 33). There is little known in the general population about long-term cessation maintenance (past 12 months) though the emerging evidence suggests that long-term smoking cessation may have protective effects against MD (139, 146).

This paradoxical trend may be explained by bidirectional "causal" effects whereby depression may cause people to smoke as predicted by the self-medication hypothesis, this may lead to short-term improvement in depression symptoms and negative affect that maybe exacerbated once again following quitting attempts or short-term cessation. Meanwhile, long-term smoking persistence may cause increased risk of depression via alterations in neurotransmitter pathways following chronic exposure such that long-term smoking cessation may decrease risk of MDE through a long-term process of neurobiological normalization.

There has been much speculation in the literature that bidirectional associations identified in longitudinal data may arise from shared vulnerability factors so that these effects are not causal at all. In particular, shared genetic liability has been suspected. This is an important consideration since in this case long-term smoking cessation maintenance would not necessarily be expected to decrease the risk of MDE. This was the question

that was addressed in Manuscript III. Irrespective of shared vulnerability claims, we compared the long-term MDE risk among persistent heavy smokers relative to that of persistent abstainers who used to be former-heavy smokers. We found that persistent heavy smokers were approximately three times more likely to report experiencing a MDE over 12-years of follow-up relative to former-heavy smokers who abstained from smoking. The effect was evident even after adjustment for wide-variety of potential confounders of the HS to MD association. Evidence of dose-response effects of increasing CPD on the risk of MDE was also discerned. These dose-response effects were similar to those reported by previous studies. Finally, evidence that the risk for a MDE among former-heavy smokers relative to persistent current-heavy smokers decreases with increasing duration of smoking cessation was also observed. While our results also supported an increase in risk of MD among the never smokers relative to the former-heavy smokers, this finding may be either due to type I error or due to real gains in mental health benefits in response to heavy smoking cessation maintenance. Future studies should explore these findings in greater detail.

While Manuscript III explains the finding of Manuscript I that long-term former smokers do not have an elevated prevalence of MDE, the high frequency observed among smokers that had recently or unsuccessfully attempted to quit was not explained. In Manuscript II, we assessed whether MDE predicted progression to severe levels of ND after controlling for two potential mechanisms linking a MDE to ND: 1) HS status and 2) the tendency to smoke under stress (self-medicating with nicotine). Our results confirmed that MD predicted progression to severe levels of ND as irrespective of these potential explanatory variables. These results highlighted the specificity of MD's effects on ND by

implicating MD in progression to severe levels of ND as measured by TTFC (within 5 minutes), but not when ND was defined using longer cut-offs for TTFC (30 minutes and 60 minutes). Consistent with the Manuscript I, these results suggest that heavy smoking and MDE are associated with progression to what appears to be a severe form of ND.

5.2 Challenges in Studying the Association between Smoking and Depression

Past research consistently reported a strong association between smoking and depression with robust findings irrespective of the study design and measurement methods. Longitudinal studies on this topic have largely focused on the directionality of effects in attempt to address questions of causality. This approach is somewhat limited because, while the majority of these studies (25-29, 146) reported on smoking being a unidirectional risk factor of depression, there remains evidence of bidirectionality of effects (12, 15, 30-32). Bidirectionality of effects were largely interpreted in favour of the shared vulnerability hypothesis although it was equally plausible that these associations may manifest due to underlying reciprocal causality between smoking and depression. The tendency to assume that the effects were due to shared vulnerability factors (non-causal) may have discouraged attempts to deal with the impact of smoking on mental health in both clinical practice as well as in the public health domain.

Bidirectionality of effects has proven to be a complex issue for epidemiological studies. Acknowledging bidirectionality poses the question: how do researchers account for the potential of reversibility of effects in their unidirectional studies? In Manuscripts II and III, we addressed this issue with the use of the discrete event-history approach

while treating the outcome of interest as a non-repeatable event. In Manuscript III, we applied further strategies, such as exclusion of individuals that changed their smoking status during follow-up and those with pre-existing history of MD. Other studies employed alternative analytical strategies to deal with this issue including the use of structural equation modelling to permit reciprocal associations between smoking and depression, hence accounting for probable causal pathways. A recent study using data from a longitudinal birth cohort with repeated measurements on smoking and depression (ages 18, 21,and 25 years) supported a unidirectional pathway from smoking to MD (26). In fact, this model was found to be superior to a bidirectional model or a model in which MD predicted onset of smoking (26).

The lack of information concerning the roles of various potential determinants in the relationship between smoking and depression presents a further challenge in this area of research. One common approach that may lead to erroneous conclusions is the over-adjustment for variables as potential confounders. However, these variables may be links in the causal chain and act as mediators. The majority of epidemiological studies on this topic (including the analyses presented here) treat stress as a confounder although there is evidence to suggest that it may be implicated in the etiology of depression and smoking (105, 123). This may not be a suitable approach and deserves further exploration. Specifically, smoking may contribute to increased levels of stress, in turn contributing to the etiology of depression. Research into specific mechanisms is needed to help elucidate some of the potential pathways leading from smoking to depression and vice versa. This alternative approach may potentially clarify the role of specific variables in these associations rather than providing a blanket treatment of these variables that assumes they

act as confounders. Furthermore, it would be reasonable to explore the value of smoking cessation as a preventive intervention for depression. The results of this project lead to a firm hypothesis that smoking cessation will be a beneficial intervention for depression in the long-term. One may envision an intervention organized around the principle of supporting participants through expected short-term difficulties but with the expectation of long-term gains. While there are many reasons for encouraging patients to quit smoking, smoking cessation efforts do not seem to be well integrated into mental health services.

A further limitation of epidemiological data is the inability of research in this field to account for the effects of non-observed confounders on the smoking and depression associations. However, various researchers have devised novel ways to address this challenge including the use of discordant twin design in which monozygotic twins who are discordant for the exposure variable, but otherwise comparable on genetic and certain environmental factors, are compared on the outcome measure. One such study that employed prospective follow-up design in a genetic sample of monozygotic twins (146) found that persistent smoking especially among men (OR=1.4, 95% CI 1.1-1.9) remained associated with an increase in the risk of depression after controlling for family and genetic background. Another example in non-genetic samples is the use of fixed-effects regression models to control for unmeasured confounding variables (26, 155). The results of these analyses supported a unidirectional "causal" relationship between smoking and depression, also consistent with the results reported here. In Manuscript III, we accounted for some of the potential confounding by non-observed shared vulnerability factors by the choice of the reference category – the former-heavy smokers. This referent group was

chosen over the never-smokers, which may have been a more traditional choice, because both former-heavy and current-heavy smokers may be similar with respect to unmeasured confounding factors related to their heavy smoking initiation. Although not an ideal approach, our findings were still consistent with investigations that employed genetic or non-genetic approaches to the issue of potential confounding by unmeasured variables.

5.3 Clinical and Public Health Implications

Prevention is commonly divided into three levels: primary, secondary, and tertiary interventions (131). Primary prevention often involves intervention at the population level to reduce incidence of the disease or outcome of interest (131). Secondary prevention involves early detection and treatment of existing disease even if prevention at the primary level is not possible (131). Tertiary prevention entails intervention to improve functioning, reduce additional disability or morbidity, and precipitate recovery or remission among those diagnosed with the disease (131).

There are several potential clinical and public health implications arising from the findings reported here. Under the assumption of a causal pathway leading persistent heavy smokers to MD, it can be concluded that some cases of MD may be prevented upon quitting and maintenance of heavy smoking cessation. Indeed, emerging evidence from studies with long-term follow-up durations (including analyses conducted in the course of this dissertation) support this proposition. It is important to note that the above statement is qualified by the word "some" as it is unlikely that heavy smoking is a

sufficient and necessary cause of MD, but rather constitutes a component cause as evident from the observation that never smokers may also develop depression though at relatively lower rate than predicted for current-heavy smokers. Also, the results presented here are consistent with the idea that, in the short-term, at the time of smoking discontinuation an elevated prevalence and incidence of MDE may be expected, but benefits are likely to accrue in the longer term. The results of the second study reinforce the idea that people with MDE (who may be tempted to smoke in an effort to self-medicate) are at risk for progress to severe levels of ND. Awareness of this may provide a basis for designing interventions for primary prevention of ND. At the very least, it seems important that long-term diminution of depression risk be emphasized to smokers engaged in cessation efforts. Intuition suggests that this would foster their persistence with cessation efforts, particularly by confronting what appear to be common perceptions that smoking improves mental health.

Irrespective of causal assumptions, it is the clinical reality that the comorbidity between smoking (persistent heavy or nicotine dependent smokers, those who attempt to quit unsuccessfully or quit for less than a year) and depression is considerable. This means that identifying heavy or nicotine dependent smokers in clinical settings as a target group for secondary prevention activities for depression may be a reasonable intervention strategy that deserves further exploration. Moreover, in light of our findings with respect to MD to TTFC pathway, it may also be important clinical practice to warn patients against smoking during a depressive episode, as this is a time of high risk for development of severe dependency. Among those who do initiate smoking during MDE, there may be clinical value in using TTFC to assess ND for planning early and effective

intervention. One may speculate that it may be valuable for patients to be aware that reduced TTFC is a sign of dependence, as this may help motivate them to quit through highlighting the danger of ND. For example, clinicians managing MD routinely warn their patients against the risks associated with alcohol consumption and often incorporate clinical interventions that will prevent entrenchment of lasting comorbidities during a depressive episode. Similar clinical management guidelines may be incorporated for cigarette smoking among people being monitored during depression treatment and urgent resources should be made available to these patients in the event of smoking initiation. Among those who report tendency to smoke more under stress, special monitoring may also be warranted as this trait may also facilitate progression to severe dependence. Furthermore, psychological and behavioural interventions to modify such maladaptive coping strategies may also help prevent worsening of smoking outcomes among depressed patients. For patients who persist with smoking heavily, it seems reasonable that they should be advised that long-term benefits may follow if they quit and maintain their smoking cessation, even if the short term effects seem negative. Clinicians should be encouraged to facilitate smoking cessation among these patients with established treatments such as nicotine replacement therapy as well as psychological or behavioural interventions. These results also suggest that monitoring and support may be particularly essential during at least the first year of smoking cessation.

5.4 Directions for Future Research

The majority of the current research remains focused on the question of causality, especially the directionality of effects in the relationship between smoking and depression. Although questions with regards to causality are useful for the purpose of primary prevention efforts and may be better answered with prospective investigations involving more frequent and detailed follow-up, many questions remain unanswered with regards to secondary and tertiary prevention efforts. These questions should be further researched. Such studies would lay a foundation for future intervention trials. It is our hope that findings from the presented analyses will direct the current literature towards more tangible clinical and public health implications. Future studies should build upon these findings and clarify further prevention strategies at these levels. Although our results strongly suggest the value of certain types of clinical and public health interventions, their efficacy should be confirmed by randomized controlled trials.

Datasets such as the NPHS, although a valuable resource for addressing primary prevention questions, remain limited by their non-clinical focus. For example, the extent of the effects of smoking persistence relative to quitting maintenance on the course of MD including symptom severity, episode duration, and episode frequency remain largely unknown. Future research should explore these avenues as well as questions with regards to smoking cessation and depression treatment outcomes.

It is only in recent years that smoking has begun to be regarded as an important determinant of mental health. Alternative non-causal explanations under the shared vulnerability and self-medication hypotheses may have detracted from the level of

interest that normally would have been triggered by this consistent epidemiologic association. This lack of interest may have stemmed from a tacit acceptance among researchers that smoking produces mental health benefits. The results presented here, together with those of other studies, strongly challenge this assumption and point towards the necessity of developing new clinical and public health strategies to address this comorbidity.

REFERENCES

1. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet. 1997 May 24;349(9064):1498-504.

2. Frerichs RR, Aneshensel CS, Clark VA, Yokopenic P. Smoking and depression: a community survey. Am J Public Health. 1981 Jun;71(6):637-40.

3. Haines AP, Imeson JD, Meade TW. Psychoneurotic profiles of smokers and non-smokers. Br Med J. 1980 Jun 14;280(6229):1422.

4. Anda RF, Williamson DF, Escobedo LG, Mast EE, Giovino GA, Remington PL. Depression and the dynamics of smoking. A national perspective. JAMA. 1990 Sep 26;264(12):1541-5.

5. Glassman AH, Covey LS, Stetner F, Rivelli S. Smoking cessation and the course of major depression: a follow-up study. Lancet. 2001 Jun 16;357(9272):1929-32.

6. Glassman AH, Helzer JE, Covey LS, Cottler LB, Stetner F, Tipp JE, Johnson J. Smoking, smoking cessation, and major depression. JAMA. 1990 Sep 26;264(12):1546-9.

7. Tsoh JY, Humfleet GL, Muñoz RF, Reus VI, Hartz DT, Hall SM. Development of Major Depression After Treatment for Smoking Cessation. Am J Psychiatry 2000;157:368-74.

8. Covey LS, Glassman AH, Stetner F. Depression and depressive symptoms in smoking cessation Comprehensive Psychiatry. 1990;31:350-4.

9. Killen JD, Fortmann SP. Role of nicotine dependence in smoking relapse: results from a prospective study using population-based recruitment methodology. Int J Behav Med. 1994;1(4):320-34.

10. Perkins KA, Gerlach D, Broge M, Sanders M, Grobe J, Fonte C, Cherry C, Wilson A, Jacob R. Quitting cigarette smoking produces minimal loss of chronic tolerance to nicotine. Psychopharmacology (Berl). 2001 Oct;158(1):7-17.

11. Zhoua X, Nonnemakera J, Sherrilla B, Gilsenana AW, Costeb F, West R. Attempts to quit smoking and relapse: Factors associated with success or failure from the ATTEMPT cohort study. 2009;34(4):365-73.

12. Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and stages of smoking. A longitudinal investigation. Arch Gen Psychiatry. 1998 Feb;55(2):161-6.

13. Patton GC, Carlin JB, Coffey C, Wolfe R, Hibbert M, Bowes G. Depression, anxiety, and smoking initiation: a prospective study over 3 years. Am J Public Health. 1998 Oct;88(10):1518-22.

14. Rohde P, Kahler CW, Lewinsohn PM, Brown RA. Psychiatric disorders, familial factors, and cigarette smoking: II. Associations with progression to daily smoking. Nicotine Tob Res. 2004 Feb;6(1):119-32.

15. Breslau N, Kilbey MM, Andreski P. Nicotine dependence and major depression. New evidence from a prospective investigation. Arch Gen Psychiatry. 1993 Jan;50(1):31-5.

16. Breslau N. Psychiatric comorbidity of smoking and nicotine dependence. Behav Genet. 1995 Mar;25(2):95-101.

17. Breslau N, Kilbey M, Andreski P. Nicotine dependence, major depression, and anxiety in young adults. Arch Gen Psychiatry. 1991 Dec;48(12):1069-74.

18. Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC. Smoking and major depression. A causal analysis. Arch Gen Psychiatry. 1993 Jan;50(1):36-43.

19. Breslau N, Johnson EO, Hiripi E, Kessler R. Nicotine dependence in the United States: prevalence, trends, and smoking persistence. Arch Gen Psychiatry. 2001 Sep;58(9):810-6.

20. Carmody TP. Affect regulation, nicotine addiction, and smoking cessation. J Psychoactive Drugs. 1989 Jul-Sep;21(3):331-42.

21. Pomerleau OF, Pomerleau CS. Neuroregulators and the reinforcement of smoking: Towards a biobehavioral explanation. Neuroscience and Biobehavioral Reviews. 1984;8:503-13.

22. Perkins KA, Grobe JE. Increased desire to smoke during acute stress. Br J Addict. 1992 Jul;87(7):1037-40.

23. Pomerleau C, Pomerleau O. The effects of a psychological stressor on cigarette smoking and subsequent behavioral and physiological responses. Psychophysiology. 1987; 24(3):278-85.

24. Wang J, Patten SB. The moderating effects of coping strategies on major depression in the general population. Can J Psychiatry. 2002;47(2):167-73.

25. Flensborg-Madsen T, von Scholten MB, Flachs EM, Mortensen EL, Prescott E, Tolstrup JS. Tobacco smoking as a risk factor for depression. A 26-year population-based follow-up study. J Psychiatr Res. 2011 Feb;45(2):143-9.

26. Boden JM, Fergusson DM, Horwood LJ. Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. Br J Psychiatry. 2010 Jun;196(6):440-6.

27. Goodman E, Capitman J. Depressive symptoms and cigarette smoking among teens. Pediatrics. 2000 Oct;106(4):748-55.

28. Klungsoyr O, Nygard JF, Sorensen T, Sandanger I. Cigarette smoking and incidence of first depressive episode: an 11-year, population-based follow-up study. Am J Epidemiol. 2006 Mar 1;163(5):421-32.

29. Wu LT, Anthony JC. Tobacco smoking and depressed mood in late childhood and early adolescence. Am J Public Health. 1999 Dec;89(12):1837-40.

30. Audrain-McGovern J, Rodriguez D, Kassel JD. Adolescent smoking and depression: evidence for self-medication and peer smoking mediation. Addiction. 2009 Jun 22.

31. Brown RA, Lewinsohn PM, Seeley JR, Wagner EF. Cigarette smoking, major depression, and other psychiatric disorders among adolescents. J of Acad of Child and Adol Psychiatry. 1996;35:1602-10. .

32. Windle M, Windle RC. Depressive symptoms and cigarette smoking among middle adolescents: prospective associations and intrapersonal and interpersonal influences. J Consult Clin Psychol. 2001 Apr;69(2):215-26.

33. Hughes JR. Clonidine, depression, and smoking cessation. JAMA. 1988 May 20;259(19):2901-2.

34. Schildkraut JJ, Kety SS. Biogenic amines and emotion. Science. 1967 Apr 7;156(771):21-37.

35. Neumeister A. Tryptophan depletion, serotonin, and depression: where do we stand? Psychopharmacol Bull. 2003;37(4):99-115.

36. Delgado PL, Price LH, Miller HL, Salomon RM, Aghajanian GK, Heninger GR, Charney DS. Serotonin and the neurobiology of depression. Effects of tryptophan depletion in drug-free depressed patients. Arch Gen Psychiatry. 1994 Nov;51(11):865-74.

37. Quattrocki E, Baird A, Yurgelun-Todd D. Biological aspects of the link between smoking and depression. Harv Rev Psychiatry. 2000 Sep;8(3):99-110

38. Drevets WC. Neuroimaging and neurobiological studies of depression: implications for cognitive-emotional features of mood disorders. Curr Opin Neurobiol. 2001;11(2):240-9.

39. Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based alogarithms for diagnosis and optimized treatment. Br Med Bull. 2003;65:193-207.

40. Riedel WJ, Sobczak S, Schmitt JA. Tryptophan modulation and cognition. Adv Exp Med Biol. 2003;527:207-13.

41. Peters EJ, Slager SL, McGrath PJ, Knowles JA, Hamilton SP. Investigation of serotonin-related genes in antidepressant response. Mol Psychiatry. 2004 Sep;9(9):879-89.

42. Collier DA, Stober G, Li T, Heils A, Catalano M, Di Bella D, Arranz MJ, Murray RM, Vallada HP, Bengel D, Muller CR, Roberts GW, Smeraldi E, Kirov G, Sham P, Lesch KP. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Mol Psychiatry. 1996 Dec;1(6):453-60.

43. Firk C, Markus CR. Review: Serotonin by stress interaction: a susceptibility factor for the development of depression? J Psychopharmacol. 2007 Jul;21(5):538-44.

44. Serretti A, Artioli P. The pharmacogenomics of selective serotonin reuptake inhibitors. Pharmacogenomics J. 2004;4(4):233-44.

45. Court JA, Martin-Ruiz C, Graham A, Perry E. Nicotinic receptors in human brain: topography and pathology. J Chem Neuroanat. 2000 Dec;20(3-4):281-98.

46. Henningfield JE, Miyasato K, Jasinski DR. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. J Pharmacol Exp Ther. 1985 Jul;234(1):1-12.

47. Semba J, Mataki C, Yamada S, Nankai M, Toru M. Antidepressantlike effects of chronic nicotine on learned helplessness paradigm in rats. Biol Psychiatry. 1998 Mar 1;43(5):389-91.

48. Fowler JS, Logan J, Wang GJ, Volkow ND. Monoamine oxidase and cigarette smoking. Neurotoxicology. 2003 Jan;24(1):75-82.

49. Goodyer IM, Herbert J, Tamplin A, Altham PM. Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. Br J Psychiatry. 2000 Dec;177:499-504.

50 Harris TO, Borsanyi S, Messari S, Stanford K, Cleary SE, Shiers HM, Brown GW, Herbert J. Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. Br J Psychiatry. 2000 Dec;177:505-10.

51. Seyler LE, Jr., Fertig J, Pomerleau O, Hunt D, Parker K. The effects of smoking on ACTH and cortisol secretion. Life Sci. 1984 Jan 2;34(1):57-65.

52. Friedman AJ, Ravnikar VA, Barbieri RL. Serum steroid hormone profiles in postmenopausal smokers and nonsmokers. Fertil Steril. 1987 Mar;47(3):398-401.

53. Wilkins JN, Carlson HE, Van Vunakis H, Hill MA, Gritz E, Jarvik ME. Nicotine from cigarette smoking increases circulating levels of cortisol, growth hormone, and prolactin in male chronic smokers. Psychopharmacology (Berl). 1982;78(4):305-8.

54. Pomerleau OF, Pomerleau CS. Behavioural studies in humans: anxiety, stress and smoking. Ciba Found Symp. 1990;152:225-35; discussion 35-9.

55. Semba J, Wakuta M, Maeda J, Suhara T. Nicotine withdrawal induces subsensitivity of hypothalamic-pituitary-adrenal axis to stress in rats: implications for precipitation of depression during smoking cessation. Psychoneuroendocrinology. 2004 Feb;29(2):215-26.

56. Statistics Canada, Health Statistics Division. Canadian Community Health Survey 2003 User Guide for the Public Use Microdata File. Ottawa; January 2005. p. 1-65.

57. Swain L, Catlin G, Beaudet MP. The National Population Health Survey--its longitudinal nature. Health Rep. 1999 Spring;10(4):69-82(ENG); 73-89(FRE).

58. Tambay JL, Catlin G. Sample design of the national population health survey. Health Rep. 1995;7(1):29-38, 1-42.

59. Statistics Canada National Population Health Survey Household Component Cycles 1 to 7 (1994/1995 to 2006/2007) Longitudinal Documentation. In: Division HS, editor. Ottawa; July 2008. p. 1-67.

60. Diagnostic and Statistical Manual of Mental Disorders Revised Version (DSM-III-R). Third ed. Washington DC: American Psychiatric Association (APA); 1987.

61. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Fourth ed. Washington DC: American Psychiatric Association (APA); 1994.

62. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Orgarnization (WHO); 1992.

63. Kessler RC, Andrews G, Mroczek D, Ustun B, Wittchen HU. The World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF). . International Journal of Methods in Psychiatric Research 1998;7(171–85).

64. Composite International Diagnostic Interview (CIDI), Version 1.0. Geneva: World Health Organization (WHO); 1990.

65. Rothman KJ. Epidemiology. An introduction. Epidemiology in clinical settings. Oxford: Oxford University Press; 2002. p. 198-217.

66. Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: Toward an integrative model of change. Journal of Consulting and Clinical Psychology. 1993;51:390-5.

67. Covey LS, Glassman AH, Stetner F. Major depression following smoking cessation. Am J Psychiatry. 1997 Feb; 154(2):263-5

68. Hughes JR. Should criteria for drug dependence differ across drugs? Addiction. 2006 Sep;101 Suppl 1:134-41.

69. Hughes JR, Baker T, Breslau N, Covey L, Shilffman S. Applicability of DSM criteria to nicotine dependence. Addiction. 2011 May; 106(5): 894-5; discussion 5-7.

70. Fagerstrom KO. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict Behav. 1978;3(3-4):235-41.

71. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 1991 Sep;86(9):1119-27.

72. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. Br J Addict. 1989 Jul;84(7):791-9.

73. Moolchan ET, Radzius A, Epstein DH, Uhl G, Gorelick DA, Cadet JL, Henningfield JE. The Fagerstrom Test for Nicotine Dependence and the Diagnostic Interview Schedule: do they diagnose the same smokers? Addict Behav. 2002 Jan-Feb;27(1):101-13.

74. Kozlowski LT, Porter CQ, Orleans CT, Pope MA, Heatherton T. Predicting smoking cessation with self-reported measures of nicotine dependence: FTQ, FTND, and HSI. Drug Alcohol Depend. 1994 Feb;34(3):211-6.

75. Prokhorov AV, De Moor C, Pallonen UE, Hudmon KS, Koehly L, Hu S. Validation of the modified Fagerstrom tolerance questionnaire with salivary cotinine among adolescents. Addict Behav. 2000 May-Jun;25(3):429-33.

76. Dale LC, Glover ED, Sachs DP, Schroeder DR, Offord KP, Croghan IT, Hurt RD. Bupropion for smoking cessation : predictors of successful outcome. Chest. 2001 May;119(5):1357-64.

77. Razavi D, Vandecasteele H, Primo C, Bodo M, Debrier F, Verbist H, Pethica D, Eerdekens M, Kaufman L. Maintaining abstinence from cigarette smoking: effectiveness of group counselling and factors predicting outcome. Eur J Cancer. 1999 Aug;35(8):1238-47.

78. Baker TB, Piper ME, McCarthy DE, Bolt DM, Smith SS, Kim SY, Colby S, Conti D, Giovino GA, Hatsukami D, Hyland A, Krishnan-Sarin S, Niaura R, Perkins KA, Toll BA. Time to first cigarette in the morning as an index of ability to quit smoking: implications for nicotine dependence. Nicotine Tob Res. 2007 Nov;9 Suppl 4:S555-70.

79. Haberstick BC, Timberlake D, Ehringer MA, Lessem JM, Hopfer CJ, Smolen A, Hewitt JK. Genes, time to first cigarette and nicotine dependence in a general population sample of young adults. Addiction. 2007 Apr;102(4):655-65.

80. Fagerstrom K. Time to first cigarette; the best single indicator of tobacco dependence? . Monaldi Archives for Chest Disease 2003;59:91-4.

81. Foulds J, Gandhi KK, Steinberg MB, Richardson DL, Williams JM, Burke MV, Rhoads GG. Factors associated with quitting smoking at a tobacco dependence treatment clinic. Am J Health Behav. 2006 Jul-Aug;30(4):400-12.

82. Hymowitz N, Cummings KM, Hyland A, Lynn WR, Pechacek TF, Hartwell TD. Predictors of smoking cessation in a cohort of adult smokers followed for five years. Tob Control. 1997;6 Suppl 2:S57-62.

83. Hughes JR, Oliveto AH, Riggs R, Kenny M, Liguori A, Pillitteri JL, MacLaughlin MA. Concordance of different measures of nicotine dependence: two pilot studies. Addict Behav. 2004 Nov; 29 (8): 1527-39.

84. Borland R, Yong HH, O'Connor RJ, Hyland A, Thomspon ME. The reliability and predictive validity of the Heaviness of Smoking Index and its two components: findings from the International Tobacco Control Four Country Study. Nicotine Tob Res. 2010 Oct; Suppl: S45-50.

85. Muscat JE, Stellman SD, Caraballo RS, Richie JP, Jr. Time to first cigarette after waking predicts cotinine levels. Cancer Epidemiol Biomarkers Prev. 2009 Dec;18(12):3415-20.

86. Albers AB, Biener L. The role of smoking and rebelliousness in the development of depressive symptoms among a cohort of Massachusetts adolescents. Prev Med. 2002 Jun;34(6):625-31.

87. Rosenberg M. Conceiving the Self. New York: Basic Books; 1979. p. 291-5.

88. Pearlin LI, Lieberman MA, Menaghan EG, Mullan JT. The stress process. J Health Soc Behav. 1981 Dec;22(4):337-56.

89. Antonovsky A. The structure and properties of the sense of coherence scale. Soc Sci Med. 1993 Mar;36(6):725-33.

90. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, Walters EE, Zaslavsky AM. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med. 2002 Aug;32(6):959-76.

91. Lazarus RS, Folkman S. Stress, Appraisal and Coping. New York: Springer; 1984

92. Wang JL, Patten SB. Prospective Study of Frequent Heavy Alcohol Use and the Risk of Major Depression in the Canadian General Population. Depression and Anxiety. 2002;15:42-5.

93. Moscato BS, Russell M, Zielezny M, Bromet E, Egri G, Mudar P, Marshall JR. Gender differences in the relation between depressive symptoms and alcohol problems: a longitudinal perspective. Am J Epidemiol. 1997 Dec 1;146(11):966-74.

94. Patten SB, Charney DA. Alcohol consumption and major depression in the Canadian population. Can J Psychiatry. 1998 Jun;43(5):502-6.

95. Statistics Canada National Population Health Survey Household Component Documentation for the Derived Variables and the Constant Longitudinal Variables (Specifications) Cycles 1 to 7 (1994/1995 to 2006/2007). In: Statistics Canada HSD, editor. Ottawa; September 2009.

96. Wheaton B. Stress, personal coping resources, and psychiatric symptoms: an investigation of interactive models. J Health Soc Behav. 1983 Sep;24(3):208-29.

97. Pearlin LI, Schooler C. The structure of coping. J Health Soc Behav. 1978 Mar;19(1):2-21.

98. Berkman L, Glass T. Social Epidemiology. Social integration, social networks, social support, and health. In: Berkman LF, Kawachi I, ed. New York, NY: Oxford University Press; 2000. p. 137-73.

99. Patten SB, Williams JVA, Lavorato DH, Modgill G, Jetté N, Eliasziw M. Major depression as a risk factor for chronic disease incidence: longitudinal analyses in a general population cohort. Gen Hosp Psychiatry. 2008;30(5):407-13 Sep/Oct

100. Streiner DL. Breaking up is hard to do: the heartbreak of dichotomizing continuous data. Can J Psychiatry. 2002 Apr;47(3):262-6.

101. Glassman AH, Stetner F, Walsh BT, Raizman PS, Fleiss JL, Cooper TB, Covey LS. Heavy smokers, smoking cessation, and clonidine. Results of a double-blind, randomized trial. JAMA. 1988 May 20;259(19):2863-6.

102. Glassman AH. Cigarette smoking: implications for psychiatric illness. Am J Psychiatry. 1993 Apr;150(4):546-53.

103. Borrelli B, Niaura R, Keuthen NJ, Goldstein MG, DePue JD, Murphy C, Abrams DB. Development of major depressive disorder during smoking-cessation treatment. J Clin Psychiatry. 1996 Nov;57(11):534-8.

104. Ginsberg D, Hall SM, Reus VI, Muñoz RF. Mood and depression diagnosis in smoking cessation. Exp Clin Psychopharmacol. 1995;3(4):389-95.

105. Lerman C, Audrain J, Orleans CT, Boyd R, Gold K, Main D, Caporaso N. Investigation of mechanisms linking depressed mood to nicotine dependence. Addict Behav. 1996 Jan-Feb;21(1):9-19.

106. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-based prevalence study. JAMA. 2000 Nov 22-29;284(20):2606-10.

107. Leonard S, Adler LE, Benhammou K, Berger R, Breese CR, Drebing C, Gault J, Lee MJ, Logel J, Olincy A, Ross RG, Stevens K, Sullivan B, Vianzon R, Virnich DE, Waldo M, Walton K, Freedman R. Smoking and mental illness. Pharmacol Biochem Behav. 2001 Dec;70(4):561-70.

108. Patten SB, Brandon-Christie J, Devji J, Sedmak B. Performance of the composite international diagnostic interview short form for major depression in a community sample. Chronic Dis Can. 2000;21(2):68-72.

109. Fagerström KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. J Behav Med. 1989;12(2):159-82.

110. Statistics Canada. Canadian Community Health Survey Guide: Public Use Microdata File. Appendix E: approximate sampling variability tables (cycle 2.1). Ottawa; 2003.

111. Beaudet MP. Depression. Health Rep. 1996 Spring;7(4):11-24, 11-25.

112. Balfour DJ, Ridley DL. The effects of nicotine on neural pathways implicated in depression: a factor in nicotine addiction? Pharmacol Biochem Behav. 2000 May;66(1):79-85.

113. Rock V, Malarcher A, Kahende J, Asman K, Husten C, Caraballo R. Cigarette Smoking Among Adults --- United States, 2006. Morbidity and Mortality Weekly Report 2007;56(44):1157-61.

114. General Household Survey:Smoking and drinking among adults 2007. Office for National Statistics. 2008.

115. Patten SB, Wang JL, Williams JV, Currie S, Beck CA, Maxwell CJ, El-Guebaly N. Descriptive epidemiology of major depression in Canada. Can J Psychiatry. 2006 Feb;51(2):84-90.

116. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003 Jun 18;289(23):3095-105.

117. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro JM, Katz SJ, Kessler RC, Kovess V, Lepine JP, Ormel J, Polidori G, Russo LJ, Vilagut G, Almansa J, Arbabzadeh-Bouchez S, Autonell J, Bernal M, Buist-Bouwman MA, Codony M, Domingo-Salvany A, Ferrer M, Joo SS, Martinez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacin C, Romera B, Taub N, Vollebergh WA. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl. 2004(420):21-7.

118. Hitsman B, Borrelli B, McChargue DE, Spring B, Niaura R. History of depression and smoking cessation outcome: a meta-analysis. J Consult Clin Psychol. 2003 Aug;71(4):657-63.

119. Royce JM, Hymowitz N, Corbett K, Hartwell TD, Orlandi MA. Smoking cessation factors among African Americans and whites. COMMIT Research Group. Am J Public Health. 1993 Feb;83(2):220-6.

120. Ahijevych K, Weed H, Clarke J. Levels of cigarette availability and exposure in black and white women and efficient smokers. Pharmacol Biochem Behav. 2004 Apr;77(4):685-93.

121. Luo Z, Alvarado GF, Hatsukami DK, Johnson EO, Beirut LJ, Breslau N. Race differences in nicotine dependence in the Collaborative Genetic Study of Nicotine Dependence (COGEND). Nicotine Tob Res. 2008 July; 10 (7): 1223-30.

122. Pomerleau OF, Pomerleau CS, Mehringer AM, Snedecor SM, Ninowski R, Sen A. Nicotine dependence, depression, and gender: characterizing phenotypes based on withdrawal discomfort, response to smoking, and ability to abstain. Nicotine Tob Res. 2005 Feb;7(1):91-102.

123. Kassel JD, Stroud LR, Paronis CA. Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. Psychol Bull. 2003 Mar;129(2):270-304.

124. Dierker LC, Avenevoli S, Merikangas, KR, Flaherty BP & Stolar, M. Association between psychiatric disorders and the progression to tobacco use behaviours. Journal of the American Academy of Child and Adolescent Psychiatry. 2001 40: 1159-1167.

125. Singer JD, Willett JB. Fitting Basic Discrete-Time Hazard Models. Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. New York Oxford University Press; 2003. p. 357-406.

126. Benowitz NL. Nicotine addiction. N Engl J Med. 2010 Jun 17;362(24): 2295-303.

127. Toll BA, Schepis TS, O'Malley SS, McKee SA, Krishnan-Sarin S. Subjective reactivity to the first cigarette of the day as a predictor of smoking relapse: a preliminary study. Drug Alcohol Depend. 2007 Jul 10;89(2-3):302-5.

128. Shiffman S, Dresler CM, Hajek P, Gilburt SJ, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. Arch Intern Med. 2002 Jun 10;162(11):1267-76.

129. Colby SM, Tiffany ST, Shiffman S, Niaura RS. Are adolescent smokers dependent on nicotine? A review of the evidence. Drug Alcohol Depend. 2000 May 1;59 Suppl 1:S83-95.

130. Dierker LC, Donny E, Tiffany S, Colby SM, Perrine N, Clayton RR. The association between cigarette smoking and DSM-IV nicotine dependence among first year college students. Drug Alcohol Depend. 2007 Jan 12;86(2-3):106-14.

131. Kleinbaum DG, Kupper LL, Morgenstern H. Information Bias. Epidemiologic Research. New York: Van Nostrand Reinhold; 1982. p. 220-41.

132. Dierker LC, Avenevoli S, Stolar M, Merikangas KR. Smoking and depression: an examination of mechanisms of comorbidity. Am J Psychiatry. 2002 Jun;159(6):947-53.

133. Fergusson DM, Goodwin RD, Horwood LJ. Major Depression and cigarette smoking: results of a 21- year Longitudinal study. Psychological Medicine. 2003;33:1357-67.

134. Fergusson DM, Lynskey MT, Horwood LJ. Comorbidity between depressive disorders and nicotine dependence in a cohort of 16-year-olds. Arch Gen Psychiatry. 1996 Nov;53(11):1043-7.

135. Hall SM, Munoz R, Reus V. Smoking cessation, depression and dysphoria. NIDA Res Monogr. 1991;705:312-3.

136. Johnson EO, Rhee SH, Chase GA, Breslau N. Comorbidity of depression with levels of smoking: an exploration of the shared familial risk hypothesis. Nicotine Tob Res. 2004 Dec;6(6):1029-38.

137. Benwell ME, Balfour DJ, Anderson JM. Smoking-associated changes in the serotonergic systems of discrete regions of human brain. Psychopharmacology (Berl). 1990;102(1):68-72.

138. Breese CR, Marks MJ, Logel J, Adams CE, Sullivan B, Collins AC, Leonard S. Effect of smoking history on [3H]nicotine binding in human postmortem brain. J Pharmacol Exp Ther. 1997 Jul;282(1):7-13.

139. Korhonen T, Koivumaa-Honkanen H, Varjonen J, Broms U, Koskenvuo M, Kaprio J. Cigarette smoking and dimensions of depressive symptoms: longitudinal analysis among Finnish male and female twins. Nicotine Tob Res. 2011 Apr;13(4):261-72.

140. Mueser KT, Drake RE, Wallach MA. Dual diagnosis: a review of etiological theories. Addict Behav. 1998 Nov-Dec;23(6):717-34.

141. Gilbert DG, Gilbert BO. Personality, psychopathology, and nicotine response as mediators of the genetics of smoking. Behav Genet. 1995 Mar;25(2):133-47.

142. Greene JG. Gene expression profiles of brain dopamine neurons and relevance to neuropsychiatric disease. J Physiol. 2006 Sep 1;575(Pt 2):411-6.

143. Levinson DF. The genetics of depression: a review. Biol Psychiatry. 2006 Jul 15;60(2):84-92.

144. Munafo MR, Zetteler JI, Clark TG. Personality and smoking status: a meta-analysis. Nicotine Tob Res. 2007 Mar;9(3):405-13.

145. Lyons M, Hitsman B, Xian H, Panizzon MS, Jerskey BA, Santangelo S, Grant MD, Rende R, Eisen S, Eaves L, Tsuang MT. A twin study of smoking, nicotine dependence, and major depression in men. Nicotine Tob Res. 2008 Jan;10(1):97-108.

146. Korhonen T, Broms U, Varjonen J, Romanov K, Koskenvuo M, Kinnunen T, Kaprio J. Smoking behaviour as a predictor of depression among Finnish men and women: a prospective cohort study of adult twins. Psychol Med. 2007 May;37(5):705-15.

147. McCaffery JM, Niaura R, Todaro JF, Swan GE, Carmelli D. Depressive symptoms and metabolic risk in adult male twins enrolled in the National Heart, Lung, and Blood Institute twin study. Psychosom Med. 2003 May-Jun;65(3):490-7.

148. StataCorp. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP; 2009.

149. Khaled SM, Bulloch A, Exner DV, Patten SB. Cigarette smoking, stages of change, and major depression in the Canadian population. Can J Psychiatry. 2009 Mar;54(3):204-8.

150. Madden PA, Pedersen NL, Kaprio J, Koskenvuo MJ, Martin NG. The epidemiology and genetics of smoking initiation and persistence: crosscultural comparisons of twin study results. Twin Res. 2004 Feb;7(1):82-97.

151. Xian H, Scherrer JF, Madden PA, Lyons MJ, Tsuang M, True WR, Eisen SA. The heritability of failed smoking cessation and nicotine withdrawal in twins who smoked and attempted to quit. Nicotine Tob Res. 2003 Apr;5(2):245-54.

152. Offord DR, Boyle MH, Campbell D, Goering P, Lin E, Wong M, Racine YA. One-year prevalence of psychiatric disorder in Ontarians 15 to 64 years of age. Can J Psychiatry. 1996 Nov;41(9):559-63.

153. Patten SB, Wang J, Williams JV, Currie S, Beck CA, Maxwell CJ, El-Guebaly N. Descriptive epidemiology of major depression in Canada. Can J Psychiatry. 2006 Feb;51(2):84-90.

154. Spaner D, Bland RC, Newman SC. Epidemiology of psychiatric disorders in Edmonton. Major depressive disorder. Acta Psychiatr Scand Suppl. 1994;376:7-15.

155. Fergusson DM, Boden JM, Horwood LJ. Tests of causal links between alcohol abuse or dependence and major depression. Arch Gen Psychiatry. 2009 Mar;66(3):260-6.

156. Bandura A, Walters RH. Social learning and personality development. Holt, Rinehart, Winston, editors. New York; 1963.

157. Beck AT, Rush AJ, Shaw, BF, Emery G. Cognitive Therapy of Depression. The Guildford Press, 1979.

158. Miller WR, Sleigman ME, Kurlander HM. Learned helplessness, depression, and anxiety. J Nerv Ment Dis. 1975 Nov; 161(5): 347-57.

APPENDIX A: COMPOSITE INTERNATIONAL DIAGNOSTIC INTERVIEW - SHORT FORM FOR MAJOR DEPRESSION (CIDI-SFMD) IN THE NPHS

The following description and questions were taken from the NPHS, Household Component, Cycle 7 (2006-2007) documentation and questionnaire (Statistics Canada, 2008)

Depression Scale - Predicted Probability (MHCnDPP)
This variable calculates the probability (expressed as a proportion) that the respondent would have been diagnosed as having experienced a major depressive episode in the past 12 months, if they had completed the Long-Form Composite International Diagnostic Interview (CIDI)

MH_Q02 **During the past 12 months, was there ever a time when you felt sad, blue, or depressed for 2 weeks or more in a row?**
1 Yes
2 No (Go to MH_Q16)
DK, R (Go to next section)

MH_Q03 **For the next few questions, please think of the 2-week period during the past 12 months when these feelings were the worst. During that time, how long did these feelings usually last?**
INTERVIEWER: Read categories to respondent.
1 All day long
2 Most of the day
3 About half of the day (Go to MH_Q16)
4 Less than half of a day (Go to MH_Q16)
DK, R (Go to next section)

MH_Q04 **How often did you feel this way during those 2 weeks?**
INTERVIEWER: Read categories to respondent.
1 Every day
2 Almost every day
3 Less often (Go to MH_Q16)
DK, R (Go to next section)

MH_Q05 **During those 2 weeks did you lose interest in most things?**
1 Yes (KEY PHRASE = Losing interest)
2 No
DK, R (Go to next section)

MH_Q06 **Did you feel tired out or low on energy all of the time?**
1 Yes (KEY PHRASE = Feeling tired)
2 No
DK, R (Go to next section)

MH_Q07 **Did you gain weight, lose weight or stay about the same?**
1 Gained weight (KEY PHRASE = Gaining weight)
2 Lost weight (KEY PHRASE = Losing weight)
3 Stayed about the same (Go to MH_Q09)
4 Was on a diet (Go to MH_Q09)

MH_Q08A **About how much did you [gain/lose]?**
INTERVIEWER: Enter amount only.
|_|_| Weight
(MIN: 1) (MAX: 99; warning after 20 pounds / 9 kilograms)
DK, R (Go to MH_Q09)

MH_Q08B INTERVIEWER: Was that in pounds or in kilograms?
1 Pounds *MHC0_8LB*
2 Kilograms *MHC0_8KG*
(DK, R are not allowed)

MH_Q09 **Did you have more trouble falling asleep than you usually do?**
1 Yes (KEY PHRASE = Trouble falling asleep)
2 No (Go to MH_Q11)
DK, R (Go to next section)

MH_Q10 **How often did that happen?**
INTERVIEWER: Read categories to respondent.
1 Every night
2 Nearly every night
3 Less often
DK, R

MH_Q11 **Did you have a lot more trouble concentrating than usual?**
1 Yes (KEY PHRASE = Trouble concentrating)
2 No
DK, R (Go to next section)

MH_Q12 **At these times, people sometimes feel down on themselves, no good or worthless. Did you feel this way?**
1 Yes (KEY PHRASE = Feeling down on yourself)
2 No
DK, R (Go to next section)

MH_Q13 **Did you think a lot about death - either your own, someone else's or death in general?**
1 Yes (KEY PHRASE =Thoughts about death)
2 No
DK, R (Go to next section)

MH_C14 If "Yes" in MH_Q5, MH_Q6, MH_Q9, MH_Q11, MH_Q12 or MH_Q13, or MH_Q7 is "gain" or "lose", go to MH_Q14C. Otherwise, go to next section.

MH_Q14C **Reviewing what you just told me, you had 2 weeks in a row during the past 12 months when you were sad, blue or depressed and also had some other things like (KEY PHRASES).**

MH_Q15 **Think about the last time you felt this way for 2 weeks or more in a row. In what month was that?**
1 January 7 July
2 February 8 August
3 March 9 September
4 April 10 October
5 May 11 November
6 June 12 December

MH_Q16 **During the past 12 months, was there ever a time lasting 2 weeks or more when you lost interest in most things like hobbies, work or activities that usually give you pleasure?**
1 Yes
2 No (Go to next section)
DK, R (Go to next section)

MH_Q17 **For the next few questions, please think of the 2-week period during the past 12 months when you had the most complete loss of interest in things. During that 2-week period, how long did the loss of interest usually last?**
INTERVIEWER: Read categories to respondent.
1 All day long
2 Most of the day
3 About half of the day (Go to next section)
4 Less than half of a day (Go to next section)
DK, R (Go to next section)

MH_Q18 **How often did you feel this way during those 2 weeks?**
INTERVIEWER: Read categories to respondent.
1 Every day
2 Almost every day
3 Less often (Go to next section)
DK, R (Go to next section)

MH_Q19 **During those 2 weeks did you feel tired out or low on energy all the time?**
1 Yes (KEY PHRASE = Feeling tired)
2 No
DK, R (Go to next section)

MH_Q20 **Did you gain weight, lose weight, or stay about the same?**
1 Gained weight (KEY PHRASE = Gaining weight)
2 Lost weight (KEY PHRASE = Losing weight)
3 Stayed about the same (Go to MH_Q22)
4 Was on a diet (Go to MH_Q22)
DK, R (Go to next section)

APPENDIX B: FAGERSTROM TOLERANCE SCORE

The following description and questions were taken from the Canadian Community Health Survey (CCHS) Questionnaire for Cycle 2.1 (Statistics Canada, 2003).

This variable classifies current daily smokers into categories, according to level of nicotine dependency. The measure combines an index of consumption (cigarettes per day) with difficulty tolerating reduced nicotine levels. **Note:** Occasional smokers and non-smokers are excluded from the population.

NDE_Q1 **How soon after you wake up do you smoke your first cigarette?**
1 Within 5 minutes
2 6 - 30 minutes after waking
3 31 - 60 minutes after waking
4 More than 60 minutes after waking
DK, R (Go to NDE_END)

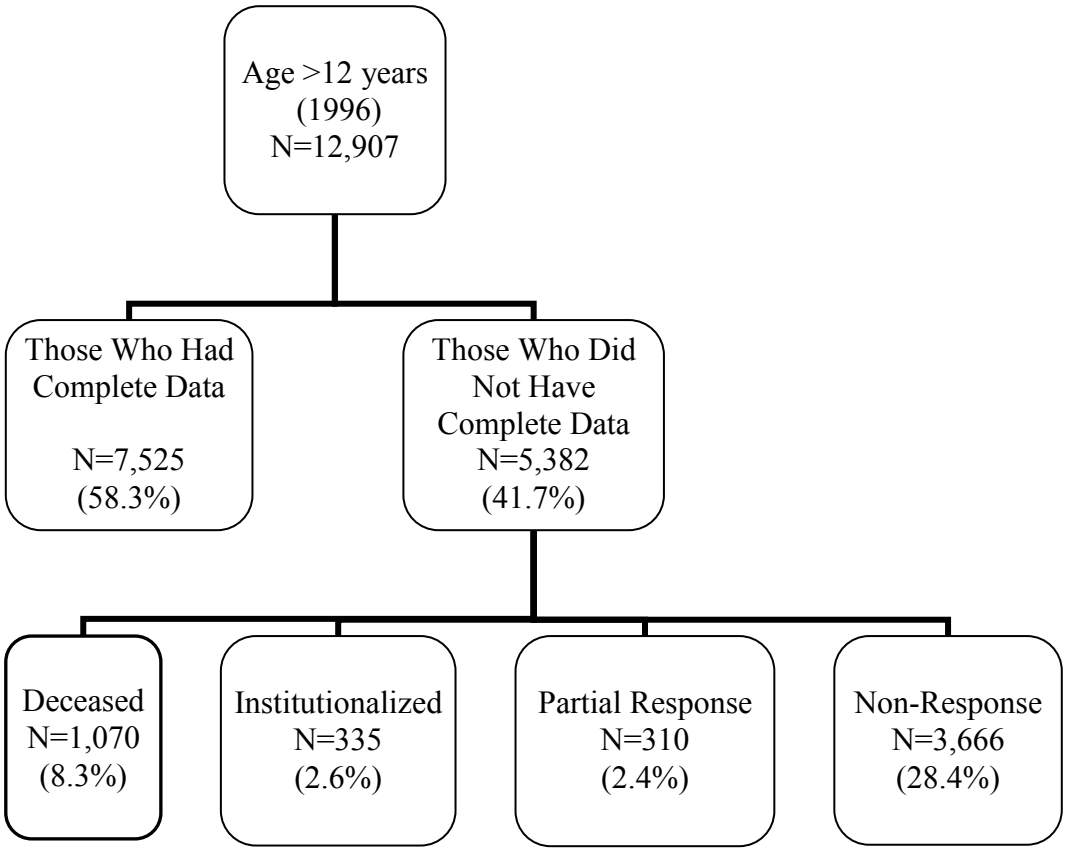
NDE_Q2 **Do you find it difficult to refrain from smoking in places where it is forbidden?**
1 Yes
2 No
DK, R

NDE_Q3 **Which cigarette would you most hate to give up?**
INTERVIEWER: Read categories to respondent. DK, R
1 The first one of the day
2 Another one

NDE_Q4 **Do you smoke more frequently during the first hours after waking, compared with the rest of the day?**
1 Yes
2 No
DK, R

DNDE_Q5 **Do you smoke even if you are so ill that you are in bed most of the day?**
1 Yes
2 No
DK, R

APPENDIX C: LOSS TO FOLLOW-UP IN THE NATIONAL POPULATION HEALTH SURVEY (NPHS) AMONG THOSE WHO WERE AT RISK FOR DEVELOPING SHORTER (≤ 5 MINUTES) TIME TO FIRST CIGARETTE



APPENDIX D: EFFECTS OF MAJOR DEPRESSION (MD) ON THE RISK OF SHORTER (≤ 5 MINUTES) TIME TO FIRST CIGARETTE (TTFC) BY BASELINE SMOKING STATUS

	Current smokers [n=3,215]		**Former/Never smokers [n=7,637]**	
	HR	95% CI	HR	95% CI
Model 1[a]	2.1***	1.5-3.1	7.6**	2.3-24.8
Model 2[b]	1.9**	1.3-2.8	1.9	0.5-7.1
Model 3[c]	1.7*	1.1-2.7	1.5	0.3-6.6

Note. HR = Hazard Ratio relating MD status to shorter TTFC; CI = Confidence Interval.
[a] Crude model with HR relating MD to risk of shorter TTFC.
[b] Model with HR relating MD to risk of shorter TTFC adjusted for heavy smoking only.
[c] Model with HR relating MD to risk of shorter TTFC adjusted for heavy smoking and tendency to smoker more under stress.
*$p < .05$. **$p < .01$. ***$p < .001$.

APPENDIX E: DETAILED INFORMATION ON MISSING STATUS IN THE NPHS BY CYCLE AND RESPONSE TO SMOKING MODULE

Missing status	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7
Completed[a]	14,856	13,836	12,745	11,734	10,606	9,854	9,199
Not stated[b]	18	21	27	81	177	126	388
Dead	0	276	599	957	1,285	1,652	2,002
Institutionalized[c]	0	62	114	133	161	144	148
Partial response[d]	380	121	102	77	120	76	82
Not able to trace	0	938	1,667	2,272	2,905	3,402	3,435
Total	15,254	15,254	15,254	15,254	15,254	15,254	15,254

[a]Completed survey including smoking questions.
[b]Completed survey, but did not complete smoking module.
[c]Institutionalized and did not complete smoking module.
[d]Partial response on survey and not stated on smoking variables.

APPENDIX F: COMPARISON BETWEEN FINAL ANALYTICAL SAMPLE AND ORIGINAL NATIONAL POPULATION HEALTH SURVEY (NPHS) COHORT ON VARIOUS BASELINE VARIABLES ASSOCIATED WITH HEAVY SMOKING AND DEPRESSION

Characteristics	Original NPHS cohort (n=17,276)	Final analytical sample (n=3,824)
Sociodemographics		
Age (years), M (SE)	35.1 (0.05)	42.6 (0.3)
Age ≤ 45, % (95% CI)	69.0 (68.8-69.3)	59.7 (58.0-61.3)
Female, % (95% CI)	50.5 (50.0-51.0)	56.2 (54.3-58.2)
Marital status, % (95% CI)		
Married	49.3 (48.6-49.9)	70.8 (68.8-72.8)
Single	40.6 (40.0-41.2)	19.0 (17.3-20.6)
Other	10.1 (9.7-10.6)	10.2 (9.1-11.4)
< Post-secondary, % (95% CI)	48.2 (47.2-49.3)	40.9 (38.6-43.1)
Lowest income[a], % (95% CI)	18.4 (17.6-19.2)	12.0 (10.4-13.5)
Genetics		
Family history of depression, % (95% CI)	20.0 (18.9-21.0)	17.7 (16.1-19.4)
Psychological		
Age1st cigarette[b], M(SE)	15.9 (0.1)	16.1 (0.1)
Age 1st cigarette, % (95% CI)	14.7 (13.5-15.9)	13.4 (11.6-15.3)
Mastery[c], M (SE)	19.6 (0.05)	20.3 (0.1)

Characteristics	Original NPHS cohort (n=17,276)	Final analytical sample (n=3,824)
Low mastery, % (95% CI)	28.1 (27.2-29.1)	23.1 (21.4-24.8)
Self-esteem[d], M (SE)	20.1 (0.04)	20.6 (0.06)
Low self-esteem, % (95% CI)	36.1 (35.1-37.2)	30.9 (28.8-32.9)
Sense of coherence[e], M (SE)	58.9 (0.1)	61.0 (0.3)
Low sense of coherence, % (95% CI)	29.7 (28.6-30.7)	22.9 (21.1-24.7)
Distress[f], M (SE)	3.5 (0.04)	2.8 (0.06)
High distress levels, % (95% CI)	15.6 (14.7-16.4)	9.2 (8.0-10.3)
Behavioural factors		
Use drugs under stress, % (95% CI)	4.6 (4.0-5.1)	2.8 (2.2-3.5)
Drink under stress, % (95% CI)	11.5 (10.7-12.4)	8.6 (7.3-10.0)
Binge drinking[g], % (95% CI)	67.3 (66.5-68.1)	54.5 (52.2-56.7)
Environmental factors		
Childhood trauma[h], % (95% CI)	49.0 (47.8-50.1)	46.3 (44.1-48.5)
Stress[i], M (SE)	3.0 (0.03)	2.7 (0.05)
Higher levels of stress, % (95% CI)	19.0 (18.0-20.0)	13.0 (11.6-14.4)
Social support[j], M (SE)	3.7 (0.01)	3.8 (0.01)
Low social support, % (95% CI)	16.8 (15.9-17.7)	14.7 (13.0-16.3)
Health-related factors		
Pain[k], % (95% CI)	10.4 (9.8-11.0)	9.4 (8.3-10.5)
Chronic conditions, % (95% CI)	49.4 (48.4-50.4)	53.1 (50.9-55.3)

Notes. All estimates including percentages (%) and means (M) are weighted and bootstrapped. All variables were measured at baseline (1994-1995). "Other" in marital status refers to those who are divorced, widowed, or separated.

[a]Lowest Income is based on household income in Canadian dollars of <$15,000 for 1-2 persons, <$20,000 for 3-4 persons, and <$30,000 for 5 or more persons.

[b]Dichotomous variable based on reported age of ≤12 years as the age when respondent smoked 1st whole cigarette.

[c]Based on mastery scale (Pearlin et al., 1981). The score range is: 0-28. Low mastery was defined at the lower quartile.

[d]Based on Rosenberg's self-esteem scale (Rosenberg, 1979). The score range is 0-24. Low self-esteem was defined at the lower quartile.

[e]Based on Antonovsky's sense of coherence scale (Antonovsky, 1993). The score range is: 0-78. Low sense of coherence was defined at the lower quartile.

[f]Based on Kessler's 6-item (K6) non-specific psychological distress scale (Kessler et al., 2002).The score range is :0-24. Higher levels of distress were defined at the upper-quartile.

[g]Binge drinking is defined as drinking 5 or more drinks on any one occasion in the past 12 months.

[h]Childhood trauma was based on reporting of at least one or more of the following traumatic events in childhood or adolescence: parental divorce, a lengthy hospital stay, prolonged parental unemployment, traumatised for years, frequent parental alcohol or drug use, being sent away from home and physical abuse by a parent or a relative (Wheaton, 1983).

[i]Stress was assessed using a 16-item scale based on work by Pearlin and Schooler (Pearlin et al., 1978). The upper quartile was used as the cut-point to designate high levels of stress.

[j]Perceived social support has a range of 0-4. Low social support was defined by affirming the presence of one out of 4 dimensions of social support.

[k]Presence of pain was based on reporting moderate to high levels of pain as opposed to absence or low-levels of pain.

[l]Chronic conditions are defined as having one or more conditions diagnosed by a health professional.

APPENDIX G: DETAILED ASSESSMENT METHODS OF THE BIOPSYCHOSOCIAL VARIABLES MEASURED IN THE STUDY

Variables	Description
Genetic	
Family History of Depression	Defined as having at least one first-degree relative who has been diagnosed with depression by a professional, as reported by the respondent.
Personal History of Depression	This variable was created based on two questions: having a diagnosis of MD by health professional and the age at diagnosis with MD. Respondents were classified as having a history of MD if their age of diagnosis was also the age in which they were enrolled in the study or preceded it. This variable was used to exclude participants with history of MD as part of the restriction criteria for Manuscript III.
Psychological	
Early experimentation with Cigarettes	Based on the age at which respondents reported smoking their first whole cigarette and was dichotomized using a cut-off of 12 years of age or earlier.
Self-esteem	Brief index based on Rosenberg's Self-Esteem scale (Rosenberg, 1979). The score range is 0-24. Low self-esteem was defined based on lower quartile cut-off score.
Mastery	Based on an index measuring a sense of the extent to which individuals believe that their life-chances are under their control (Pearlin et al., 1981). This score range is 0-28. Low mastery was defined based on lower quartile cut-off score
Sense of coherence	Based on Antonovsky's sense of coherence scale (Antonovsky, 1993) assessing the extent to which individuals perceive events as comprehensible, manageable, and meaningful. The score range is 0-78. Low self-coherence was defined based on lower quartile cut-off.

Variables	Description
Distress	Based on Kessler 6-item (K6) non-specific psychological distress scale (Kessler et al., 2002). The score range is 0-24. High levels of distress were defined based on upper-quartile cut-off score.
Behavioural	
Tendency to drink or use drugs more under stress	Based on self-reported coping style of drinking more under stress or using drugs more under stress assessed using a single item from a coping style questionnaire included in the survey in 2002 (Wang et al., 2002).
Binge drinking	Based on reported consumption of 5 or more drinks on a single occasion at least once monthly in the past 12 months. The threshold of 5 or more drinks has been used by previous studies as an indicator for problem drinking (Moscato et al., 1997; Patten et al., 1998; Wang et al., 2002).
Environmental	
Childhood trauma	Based on reporting of at least one or more of the following traumatic events in childhood or adolescence: parental divorce, a lengthy hospital stay, prolonged parental unemployment, frequent parental alcohol or drug use, being sent away from home.
Stress	Assessed using a 16-items scale based on work by Pearlin and Schooler (Pearlin et al., 1978) and Wheaton (1983). This scale captures the extent of exposure to daily stressors in different life domains including personal (activity overload and role expectations), financial, relationship, environmental (undesirable friends and neighbours) and family health problems. Adjustment by the number of applicable items for each respondent was made. A dichotomous stress variable was derived from this scale using the upper quartile as a cut-point.
Social Support	Based on a 4-items index that measures the extent of perceived social support in terms of having someone to confide in, someone to count on, someone to give advice, and someone that makes them feel loved (Berkman et al., 2000). Low social support was defined by affirming only presence of one out of 4 dimensions of social support.

Variables	Description
Health-related	
Pain	Based on self-reported severity levels of pain. Presence of pain was indicated by reporting moderate to high levels of pain as opposed to absence or low-levels of pain.
Chronic conditions	Defined as health conditions that had been diagnosed by a health professional and had lasted or were expected to last six months or more. The interviewer read a list of over 30 chronic conditions (diabetes, heart disease, asthma, migraine etc.). Respondents who reported having one or more conditions were classified as having a chronic condition. Two conditions including "multiple chemical sensitivity" and "chronic fatigue syndrome" were excluded from this list because of concerns about their validity.

Note. For exact wordings of these questions, please refer to the NPHS questionnaire available at: http://www.statcan.gc.ca/concepts/nphs-ensp/nphs-ensp1-eng.htm.

APPENDIX H: TESTS OF POSSIBLE DOSE-RESPONSE EFFECTS FOR REPORTED AMOUNT OF CIGARETTES SMOKED PER DAY (CPD) ON THE RISK OF MAJOR DEPRESSION (MD)

Variables	HRs	95% CI
Cigarettes Smoked Per Day (CPD)		
Former > 20	1.0	-
Former 11-20	1.1[a]	0.7-2.0
Former 1-10	1.4 [a]	0.8-2.5
Never	1.4[a]	0.9-2.3
Current 1-10	1.4[a]	0.6-3.3
Current 11-20	2.4[a**]	1.3-4.3
Current > 20	3.7[a***]	1.8-7.3

Note. HRs =Hazard Ratios; CI = Confidence Interval. CPD is modeled as time-varying variable over 12 years of follow-up. The actual amount of CPD was based on each respondent's reported amount of cigarettes smoked per day (former or current) averaged over 6 intervals (7 cycles).
[a]Hazard ratios based on former-heavy smokers as reference category adjusted for age, sex, and stress.