Epidemiology of Co-morbid Substance Use Disorders and Major Depression

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ABSTRACT

Background. Many patients with mental disorders receiving treatment in mental health centres are using illicit drugs while a large proportion of those in addiction care programs have significant mental health issues. Substance use disorder and major depression are highly prevalent in the general population. They frequently co-exist, share common biological, psychological and social risk factors and affect one another in clinically significant ways. Comorbid substance use disorder and major depression represent a major health problem globally. The primary goal of this thesis is to further our understanding of the relationship between substance use disorders and co-occurring major depressive disorder by applying different epidemiological methods.

Methods. The study designs used in this thesis were cross-sectional design (Chapters 3,4 and 5), population cohort design (Chapter 6) and systematic review with meta-analysis (Chapter7). Existing datasets from Statistics Canada were used for Chapters 3,4,5 and 6 while the systematic review collected data via a computerized search for original studies. Trend (Chapter 3), multilevel logistics regression (Chapter 4), Multinomial logistics regression (Chapter 5), Poisson regression (Chapter 6) and meta-analysis (Chapter 7) were done. Descriptive analysis was also done for all chapters.

Results. The pooled prevalence of substance use disorder comorbid with major depression is 3.2%. The prevalence of comorbid alcohol dependence and major depression increased from 1996 to 2012 in females, those 30 years and older, who had a household income of less than $50,000 and no post-secondary graduate level education. Individuals with substance dependence and cannabis dependence were about three times (pooled OR (95%CI): 3.62 (95%CI 2.82-4.63)) and five times (pooled OR (95%CI): 5.77 (95%CI 3.8-8.77)) more likely to have comorbid major depression. Alcohol dependence increased the risk of persistent or recurrent major depression by three-fold. Comorbid substance use disorder with major depression was significantly associated with increased disability and suicide ideation.

Conclusion. Given the significant overlap in comorbid substance use disorder and major depression, it is crucial that co-occurring disorders are managed proactively and concurrently. The consensus of research evidence and clinical expertise is that the treatment of comorbid

substance use and mental health disorders is insufficient if they are solely psychiatric focused or addiction focused. It is recommended that an integrated treatment approach should be adopted.

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LIST OF ABBREVIATIONS

Alcdep: ..... Alcohol Dependence
ALCMD: ..... Comorbid Alcohol Dependence and Major Depression
AUD: ..... Alcohol Use Disorders
BDI: ..... Becker Depression Inventory
BMI: ..... Body Mass Index
CCHS 1.1: ..... Canadian Community Health Survey 2001
CCHS 2012:MH ..... Canadian Community Health Survey, Mental Health Component
CCHS-1.2: ..... Canadian Community Health Survey, Mental Health and Wellbeing
CIDI-SF: ..... World Health Organization Composite International Diagnostic Interview Short Form
CIHI: ..... Canadian Institute for Health Information
CINAHL: ..... The Cummulative Index to Nursing and Allied Health Literature
COGA: ..... Collaborative Study on the Genetics of Alcoholism study
CPES: ..... Collaborative Psychiatric Epidemiology Studies
CUD: ..... Cannabis Use Disorders
DALYs: ..... Disability-Adjusted Life-Years
DSM-5: ..... Diagnostic Statistical Manual of Mental Disorders 5th Edition
DSM-III-R: ..... Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM-IV: ..... Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DUD: ..... Drug Use Disorders
ECA: ..... Epidemiological Catchment Area
ESEMed: ..... European Study of the Epidemiology of Mental disorders
GBD: ..... Global Burden of Disease
HIV: ..... Human Immunodeficiency Virus
ICD: ..... International Classification of Disease
ICF: ..... International Classification of Functioning
ICPE: ..... The Internatonal Consortium in Psychaitric Epidemiology
KECA: ..... Korean Epidemiologic Catchment Area study.
MCAR: ..... Missing Completely At Random
MDD: ..... Major Depressive Disorder
MDE: ..... Major Depressive Episode
MSU: ..... Mental Health and Substance
NCS: ..... The US National Comorbidity Survey
NCS-R: ..... National Comorbidity Survey Replication
ND: ..... no diagnosis
NEMESIS: ..... The Netherlands Mental Health Survey and Incidence Study
NESDA: ..... Netherlands Study of depression and Anxiety
NHSDA: ..... National Household Survey on Drug Abuse
NLAES: ..... The National Longitudinal Alcohol Epidemiologic Survey
NOS: ..... Newcastle-Ottawa Scale
NPHS, 1994/1995-2010/2011: ..... Longitudinal National Population Health Survey
NPHS: ..... National Population Health Survey
NSERC: ..... National Epidemiologic Survey on Alcohol and Related Conditions
NSMH&WB: ..... National Survey on Mental Health and WellBeing
OR: ..... odds ratio
PRISMA: ..... Preferred Reporting Items for Systematic Reviews and Meta-analysis
PUMF: ..... Public Use Microdata Files
QoL: ..... Quality of Life
ROC: ..... receiver operating curve
RR: ..... relative risk
SUD: ..... Substance Use Disorders

svy: ..... survey
TPMS: ..... Taiwan Psychiatric Morbidity Survey
WHO: ..... World Health Organization
WHO-CIDI: ..... World health Orgaization Composite International Diagnostic Interview
WHODAS 2.0: ..... World Health Organization Disability Assessment Schedule Score 2.0
WMH-CIDI: ..... World Mental health version of the Composite International Diagnostic Interview
YLD: ..... Years Lived with Disability

CHAPTER 1. INTRODUCTION

1.1 The nature and burden of substance use disorder and mental health disorders

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), defines Substance Use Disorders (SUD) as "a problematic pattern of using alcohol or another substance that results in impairment in daily life or noticeable distress" (American Psychiatric Association, 2013). It refers to a habitual pattern of illicit drug or alcohol use that results in substantial problems in various facets of one's life such as employment, family, financial, and physical well-being (Drake, Mueser, Clark, & Wallach, 1996; Substance Abuse and Mental Health Services Administration (US), 2016; United Nations Office on Drugs and Crime (UNODC), 2016). Substance use disorders may involve any number of substances such as alcohol, cannabis, hallucinogens, tobacco, inhalants, opioids (e. g. heroin), sedatives, hypnotics, or anxiolytics (e.g. valium) and stimulants (cocaine, methamphetamine) (American Psychiatric Association, 2013; United Nations Office on Drugs and Crime (UNODC), 2016; World Health Organization, 1992).

Mental health disorders are illnesses that result in significant distress, behavioral/ psychological dysfunction, pain, disability and premature mortality (American Psychiatric Association, 2013; Kennedy, Lin, & Schwab, 2002; Druss, Rosenheck, & Sledge, 2000). They also have an economic impact in terms of absenteeism, productivity loss, joblessness and health costs (Stewart, Ricci, Chee, Hahn, & Morganstein, 2003; Lim, Jacobs, Ohinmaa, Schopflocher, & Dewa, 2008; Canadian Substance Use Costs and Harms Scientific Working Group, 2018). Mental health disorders result in disproportionate disability, due in part to their early age of onset, their chronicity, and that a minority of individuals receive treatment for their conditions (Canadian Centre on Substance Abuse, 2009). The single largest group of major psychiatric disorders are mood disorders with about 10-25% of women and 5-12% of men globally, developing a major depressive disorder, a type of mood disorder at some point in their life (Canadian Centre on Substance Abuse, 2009).

Alcohol use was estimated to be the seventh-leading risk factor in terms of disability-adjusted life-years (DALYs) in 2016 with an attributable DALYs increase of more than 25% between 1990 and 2016 (GBD 2016 Risk Factors Collaborators, 2017). It is the leading risk

factor in DALYs between ages 15 years and 49 years globally (GBD 2016 Risk Factors Collaborators, 2017). In 2012, 5.1% of the global burden of disease and injury, as measured in DALYs and 5.9% of all global deaths were attributable to alcohol abuse (World Health Organization, 2014a). In Canada in that same year, the number of persons with substance use disorders (6 million) over the course of a lifespan was greater than the number with mood disorders (3.5million) (Pearson, Janz, & Ali, 2013). Approximately 18.1% of Canadians met the criteria for alcohol abuse or dependence while 6.8% of Canadians identified as cannabis consumers in 2012 (Pearson, Janz, & Ali, 2013).[1] Of all psychoactive substances under international control worldwide, cannabis, which is now legalized in Canada is the most commonly used (World Health Organization, 2016; United Nations Office on Drugs and Crime (UNODC), 2016). Recreational cannabis was used by approximately 181.8million individuals between the ages of 15 and 64 years globally in 2013 (World Health Organization, 2016; United Nations Office on Drugs and Crime (UNODC), 2015).

The nature and extent of the adverse health effects of cannabis use have been under debate and perceived to be relatively harmless or benign when compared with other substances of abuse (Volkow, Baler, Compton, & Weiss, 2014; Nutt, King, Saulsbury, & Blakemore, 2007; Lachenmeier, 2015; George & Vaccarino, 2015). However, evidence have demonstrated the adverse effects of cognitive impairment and psychiatric symptoms associated with cannabis use, especially high frequency usage and early initiation at a very young age (United Nations Office on Drugs and Crime (UNODC), 2016; Lubman, Cheetham, & Yucel, 2015; Meier, et al., 2012; Hall, 2015; Hall & Degenhardt, 2009; Hall, 2009). The lower risk found in studies compared to other psychoactive substances or alcohol and tobacco does not mean 'no risk' because, there is a worrying increase in the demand for healthcare services for cannabis use disorders and associated health conditions (World Health Organization, 2016; United Nations Office on Drugs and Crime (UNODC), 2016).

[1] "Substance abuse refers to the harmful or hazardous use of psychoactive substances (alcohol and illicit drugs) while substance dependence is a cluster of behavioural, cognitive, and psychological phenomena (difficulties controlling its use or the strong desire to use, persisting in its use despite harmful consequences, higher priority given to the drug use than other activities or obligations, increased tolerance, physical withdrawal) that develop secondary to repeated use of the substance" (World Health Organization, 2018). Substance use disorders (alcohol, illicit drugs) refers to substance abuse and /or dependence (American Psychiatric Association, 1994).

Individuals using substances are more likely to suffer from mood disorders and this association usually occurs with the more severe forms of substance use disorders and vice versa (Merikangas, et al., 1998; Brière, Rohde, Seeley, & Daniel Klein, 2014; Sullivan, Fiellin, & O'Connor, 2005; Clark, Cuthbert, Lewis-Fernandez, Narrow, & Reed, 2017; Canadian Centre on Substance Abuse, 2013). In other words, as the severity of either disorder increases, the likelihood of the other co-occurring also increases.

1.2 Comorbid substance use and mental health disorders

Mental health and substance use disorders occur on a continuum and when they occur together, they are called concurrent disorders, multimorbidity, comorbid disorders or dual diagnosis (Canadian Centre on Substance Abuse, 2013; Wittchen, Perkonnig, & Reed, 1996; Buckley & Brown, 2006). A concurrent disorder emerges when they intersect at any point on the continuum, resulting in a near-endless list of possible combinations which vary, depending on the type and severity of the mental health problem, the substance of abuse and severity of the abuse. The more severe the first disorder is, the more likely it is concurrent with another disorder (Canadian Centre on Substance Abuse, 2013; Clark, Cuthbert, Lewis-Fernandez, Narrow, & Reed, 2017; Bulloch, Lavorato, Williams, & Patten, 2012).

A large body of evidence has documented the interconnections and adverse interactions between mental disorders and substance use problems (Hasin, et al., 2016; Grant, et al., 2016; Compton, Thomas, Stinson, & Grant, 2007; Brière, Rohde, Seeley, & Daniel Klein, 2014; Brunette, Mueser, & Drake, 2004; George & Vaccarino, 2015; Buckley & Brown, 2006). It is widely recognized that addiction and mental health disorders frequently co-occur. The co-occurrence of substance use and mental health disorders affect the clinical course of both disorders with respect to treatment engagement, thoughts of suicide/attempts, homelessness, increased risk of victimization, life expectancy and treatment outcomes (Burns, Teesson, & O'Neill, 2005; Burcusa & Iacono, 2007; Canadian Centre on Substance Abuse, 2009; Drake, Mueser, Clark, & Wallach, 1996; Spijker, et al., 2004; Boschloo, et al., 2011; Hjorthoj, et al., 2015; Bottomley, et al., 2010; Buckley & Brown, 2006). Compared to patients diagnosed with single SUD or mental health disorder, patients with co-morbid disorders have a higher risk of delayed diagnosis, more severe symptoms, lower compliance with treatment, poorer treatment

outcomes, more impairment in social functioning, increased admissions to emergency departments, higher prevalence of physical co-morbidity, and suicidal tendencies (Langås, Malt, & Opjordsmoen, 2011; Britton, et al., 2015; Borges, Benjet, Orozco, Medina-Mora, & Menendez, 2017; Cornelius, et al., 1995; Garcia-Toro, et al., 2013; Bulloch, Lavorato, Williams, & Patten, 2012; Canadian Institute for Health Information, 2013; Buckley & Brown, 2006). They are more often unemployed, homeless, and involved in violent episodes, or criminal behavior (Langås, Malt, & Opjordsmoen, 2011; Willis, Willis, Male, Henderson, & Manderscheid, 1998).

Why is there a high overlap of substance use and mental health disorders? One theory, the "self-medication hypothesis", postulates that mental health disorders lead to substance use disorders due to the misuse of substances to alleviate mental health symptoms. For example, individuals with anxiety disorders will turn to substances with depressant or calming effects to self-medicate their anxiety (MacDonald, Baker, Stewart, & Skinner, 2000; Khantzian, 1985; Maremmani, Perugi, Pacini, & Akiskal, 2006). A second theory suggests that the use of substances leads to the development of mental health disorders (Kushner, Abrams, & Borchardt, 2000; American Psychiatric Association, 2000). In addition, repeated withdrawal from substances may trigger the development or worsening of a mental health disorder (Schuckit & Hesselbrock, 1994; Zvolensky, Bernstein, Yartz, McLeish, & Feldner, 2008). Another mechanism that might explain the overlap between substance use disorders and mental health disorders is the presence of an overlapping predisposition, that is, a common vulnerability involving genetic and /or environmental factors (Goldman, Orozi, & Ducci, 2005; Kendler, Prescott, Myers, & Neale, 2003; Li & Burmeister, 2009; Agrawal & Lynskey, 2014; Edvardsen, et al., 2008; Agrawal & Lynskey, 2008). Irrespective of the pathway that led to the comorbid state, once an individual has developed both, a vicious cycle may be at play where each disorder maintains or exacerbates the other (Canadian Centre on Substance Abuse, 2009; Stewart & Conrod, 2008; Stewart & Conrod, 2008b).

This co-morbidity represents a complex interaction of genetic, biochemical, cognitive-behavioural and environmental factors which while appearing homogenous in clinical presentations are often heterogeneous in etiology (Swendson & Merikangas, 2000).

1.3 The burden of comorbid substance use and mental health disorder

Evidence suggests that about 50% of individuals seeking help for addiction also have a mental illness while 15-20% of those seeking help for mental illness have a substance use disorder (Canadian Centre on Substance Abuse, 2009; RachBeisel, Scott, & Dixon, 1999; Canadian Institute for Health Information, 2012). Mental and Substance Use (MSU) disorders are primary causes of disability globally, associated with significant health, economic and social costs, and when left untreated these disorders can result in premature death (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; Hjorthoj, et al., 2015; Borges, Benjet, Orozco, Medina-Mora, & Menendez, 2017; Flensborg-Madsen, et al., 2009; Canadian Institute for Health Information, 2013). The Global Burden of Disease (GBD) study (2016) highlighted that the disability-adjusted life-years (DALYs) attributable to MSU disorders rose by about 47% between 1990 and 2016, and 12% between 2006 and 2016 (GBD 2016 DALYs and HALE Collaborators, 2017). The MSU were responsible for 7.4% of global DALYs and 22.9% of global years lived with disability (YLD) in 2010, making them the leading cause of YLDs and the fifth leading cause of DALYs at the time (Whiteford, et al., 2013). In 2016, across the lifespan and among both sexes, MSU disorders were consistently shown to be leading causes of YLDs worldwide (GBD 2016 DALYs and HALE Collaborators, 2017).

Comorbid substance use and mental health disorders represent a major health problem in Canada. In Canada, mental health disorders account for 43% of disability and 22% of the total burden of disease (sum of years lived with disability and premature death) and having more than one disorder results in greater disability (Canadian Centre on Substance Abuse, 2009). A study using the Canadian Community Health Survey on Mental Health and Well Being, found that individuals with major depression in the previous 12 months were more likely to report concurrent harmful alcohol use (12.3% compared to 7% in the general population), alcohol dependence (5.8% compared to 2.6% in the general population), and drug dependence (3.2% compared to 0.8% in the general population) (Gravel & Beland, 2005). Conversely, in another study, individuals with SUDs in the previous 12 months were more likely to report a concurrent major depression - 8.8% among alcohol-dependent individuals and 16.1% in persons dependent on an illegal substance compared to 4.0% in the general population (Adlaf, Begin, & Sawka, 2005).

In 2013, The Canadian Institute for Health Information (CIHI) found that Canadians 15years and older with comorbid SUD and mental illness required more in-patient mental health services, had longer length of stays in the hospital and more re-admissions than those with an isolated diagnosis of either SUD or psychiatric illness (Canadian Institute for Health Information, 2013). The longer length of stays and increased hospital readmissions resulted in higher costs for the healthcare system (Canadian Institute for Health Information, 2013; Book, McNeil, & Simpson, 2005; Odlaug, et al., 2016; Buckley & Brown, 2006). The high rates of comorbid SUD and mental illness and the entanglement with physical illness, homelessness and marginalization poses a major challenge to the health care and social welfare systems across the country (O'Toole, Pollini, Gray, Bigelow, & Ford, 2007; Kamal, et al., 2007; Boyd & Kerr, 2016). Inner-city populations, especially individuals injecting drugs, are at an increased risk of drug-related harm like HIV infection, Hepatitis C infection, severe bacterial infection and death from overdose (Kuyper, Hogg, Montaner, Schechter, & Wood, 2004; United Nations Office on Drugs and Crime (UNODC), 2018).

In British Columbia, an estimated 130,000 persons met the criteria for comorbid substance use and mental health disorders (Patterson, Somers, McIntosh, Shiell, & Frankish, 2008). The Vancouver's Downtown Eastside survey by the Vancouver Police Department showed that 50% of all emergency calls involved people with either mental illness or SUD demonstrating a marked increase in police interaction with mentally ill persons and the resultant draining of resources (Canadian Centre on Substance Abuse, 2009; Boyd & Kerr, 2016). The British Columbia Adolescent Health Survey of students in Grades 7-12 showed that the presence of comorbid mental health and substance use disorders increased the chances of self- harm compared to one disorder (McCreary Centre Society, 2012).

Recognizing the global burden, the World Health Organization's (WHO) World Health Report 2001 recommended the integration of the treatment of mental health and substance use in primary care (World Health Organization, 2001; Canadian Centre on Substance Abuse, 2009; Marel, et al., 2016; Torrens, Rossi, Martinez-Riera, Martinez-Sanvisens, & Balbuena, 2012; Canadian Centre on Substance Abuse, 2013b). Evidence suggests that this integration can enhance service delivery and offer support to clients with comorbid substance use and mental health disorders (Drake, Mercer-McFadden, Mueser, McHugo, & Bond, 1998; Mills, et al., 2012;

Marel, et al., 2016; Kelly & Daley, 2013; Torrens, Rossi, Martinez-Riera, Martinez-Sanvisens, & Balbuena, 2012).

1.4 The context of this research

Comorbid SUDs and mental health disorders are particularly challenging to address in primary health care (Drake, Mueser, Clark, & Wallach, 1996; Britton, et al., 2015; Balkrishnan, Joish, Yang, Jayawant, & Mullins, 2008; Glasner-Edwards, et al., 2009; Stewart & O'Connor, 2009). Over the years, the rates of professional care for mental health disorders and SUDs have increased yet unmet needs for care remains and a significant public health concern (Canadian Centre on Substance Abuse, 2009; Boyd & Kerr, 2016).

Mainstream psychiatric and addiction research and scientific trials have largely excluded comorbid disorders to avoid "muddying the waters" – the uncertainty surrounding the cause of an effect if subjects with both disorders are included in a trial (Canadian Centre on Substance Abuse, 2009). Addiction research using animal models focus on a single condition or substance, therefore, making application to a more complex clinical condition like concurrent disorders difficult. Concurrent disorders are not well understood, and the management provided for them may be inappropriate and can be improved (Canadian Centre on Substance Abuse, 2009).

Co-morbidity research is important because comorbidity has an impact on clinical severity and outcome (Swendson & Merikangas, 2000; Buckley & Brown, 2006; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Ineffective management of mental health problems and co-occurring substance use disorders can lead to impaired self-care, increased morbidity and mortality, higher health care expenditure and decreased productivity (Drake, Mueser, Clark, & Wallach, 1996; Stewart & O'Connor, 2009; Canadian Institute for Health Information, 2013; Canadian Institute for Health Information, 2012). To develop effective interventions with possible changes to treatment systems, it is crucial we understand these disorders and their overlap (Canadian Centre on Substance Abuse, 2009; Hasin, et al., 2006).

The primary goal of this thesis research is to further our understanding of the relationship between substance use disorders and co-occurring major depression (one of the most prevalent mental health disorders) using nationally representative Canadian population samples and by

synthesizing existing nationally representative primary research. This research involves the application of a variety of epidemiological techniques informing three levels of evidence for prevention interventions, program planning, and policy-making.

This thesis aims to:

- Demonstrate current trends in comorbid alcohol dependence with major depression in the Canadian population
- Assess the risk of suicide ideation and disability associated with co-morbid substance use disorders with major depression in a nationally representative sample of Canadians.
- Determine the associations between substance use disorders, overweight/obesity and co-morbid major depressive disorder.
- Determine the 6-year and 16-year persistence or recurrence of major depression among those with concurrent alcohol dependence.
- Conduct a systematic review and meta-analysis of the existing literature assessing the prevalence and strength of association between co-morbid substance use disorders, cannabis use disorders with major depression in nationally representative population sample surveys.

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CHAPTER 2. STUDY DESIGNS AND METHODS

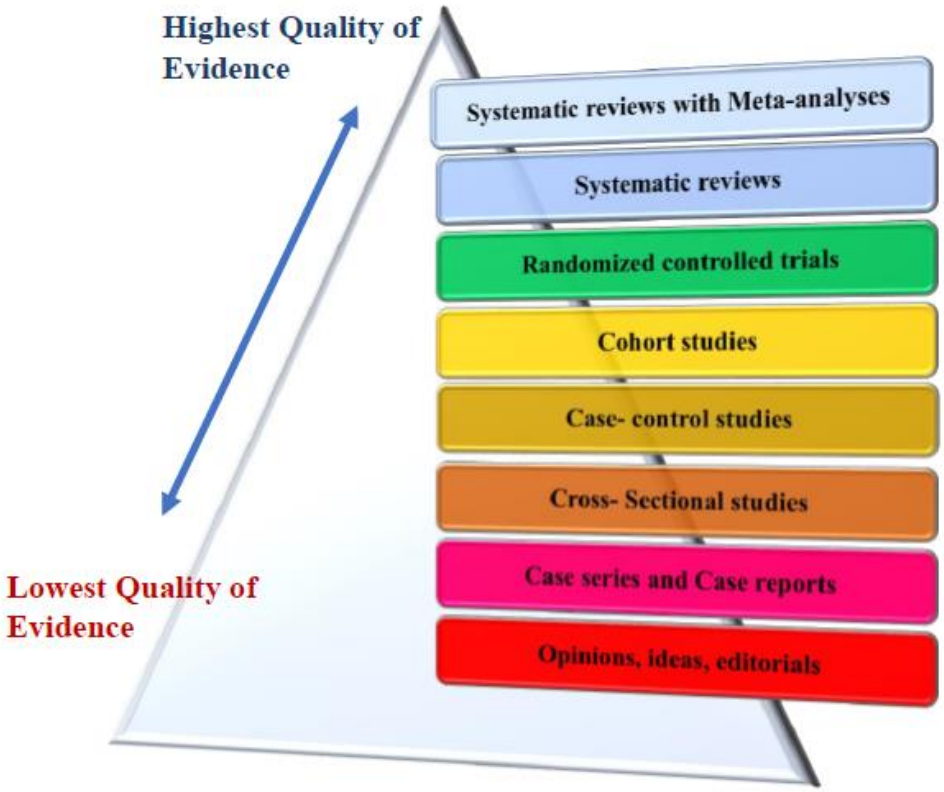
This thesis involves the secondary use of survey data and a review of existing literature. It consists of five major studies (see Table 2-1) and a concluding chapter on the overall implications for future research direction, program and policy development (Chapter 8).

2.1 Chapter 3: Time trends in the prevalence of alcohol dependence and comorbid major depression in the Canadian population (1996/97-2012)

Is the frequency of depression, alcohol dependence, and comorbid depression with alcohol dependence changing over time or have they remained static? The time trends in the prevalence of alcohol dependence, major depression and comorbid alcohol dependence with major depression were assessed in this chapter using data from four national Canadian cross-sectional surveys between 1996/97 to 2012. The National Population Health Survey (NPHS) 1996/97, The Canadian Community Health Survey, 2001 (CCHS 1.1), The Canadian Community Health Survey, Mental Health and Wellbeing, 2002 (CCHS 1.2) and The Canadian Community Health Survey, Mental Health component, 2012 (CCHS 2012:MH). As cross-sectional surveys, with different diagnostic criteria used over the years, the level of evidence generated is weak (Figure 2-1) but it is the best currently available. The surveys used are large nationally representative samples and of high quality.

The analyses involved age and gender standardization of prevalence estimates for alcohol dependence, major depression and comorbid alcohol dependence and major depression using the 2001 census data for standardization.

Figure 2-1. Hierarchy of evidence



Modified from (Griffin, Jordan, & El Gawad, 2016)

2.2 Chapter 4: Co-morbid substance use and major depression: disability and risk of suicide in a nationally representative sample

In this chapter, I assessed the risk of suicidal ideation and disability associated with the comorbid major depression with substance use disorder diagnosis compared to single diagnosis of either major depression or substance use disorder, or neither diagnosis. The data examined in this chapter was from the Canadian Community Health Survey, 2012: Mental Health Component (CCHS, 2012: MH).

This survey is a cross sectional study design. Although cross sectional study designs do not allow for causal inference, they are analytical designs that are representative of the Canadian population and thus can provide very useful information on prevalence and associated risk factors. This survey is of high quality and a large sample size (N=25 113).

Multilevel logistic regression models were used to assess two outcomes of interest, the risk of suicide and associated disability in comorbid substance use disorders and major depression.

2.3 Chapter 5: Substance use disorder, overweight/obesity and co-morbid major depression

The co-existence of obesity and substance use disorder is said to be highly prevalent and the relationship is inverse. Being obese or underweight are risk factors for a variety of physical health problems. In this chapter, I assessed the relationship between substance use and obesity with underlying comorbid major depression in a national sample of Canadians.

The Canadian Community Health Survey, 2012: Mental Health Component (CCHS, 2012: MH) was also used for this chapter and it has been described in the previous Section 2.2 The risk of overweight and obesity were assessed with underlying comorbid substance use disorders and major depression using multinomial regression models.

2.4 Chapter 6: Alcohol dependence and the persistence or recurrence of major depression

The National Population Health Survey was used for this chapter. This is a national longitudinal study of 17, 276 participants. This design is superior to cross sectional designs because it has temporal component to assess cause and effect. Its major drawback is the loss of participants due to follow-up.

In this chapter, the persistence or recurrence of major depression was the outcome of interest. The 6-year and 16-year persistence or recurrence were assessed in the presence of concurrent alcohol dependence and other risk factors.

In this longitudinal analysis, modified Poisson models were used to fit the data.

2.5 Chapter 7: A systematic review and meta-analysis of comorbid substance use disorders, cannabis use disorders with major depression.

This chapter is a systematic review of the associations between co-morbid substance use disorders, cannabis use disorders with major depression in nationally representative population-

based surveys. This review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati, et al., 2009). This study design, a systematic review with meta-analysis represents the strongest and most informative source of evidence (Figure 2-1) for clinicians to keep up-to-date and informed policy-making. The most notable limitations are potential publication bias and the pooling of evidence from studies of different quality.

In summary, Table 2-1 below summarizes the topics, study design and methods of analysis used in subsequent chapters of this thesis.

Table 2-1 Summary of studies in this thesis

Study design ***Level of evidence***	**Title of study**	**Method & analysis**
Meta-analysis ***High***	**Chapter 7** A systematic review and meta-analysis of comorbid substance use disorders, cannabis use disorders, with major depression	Systematic review; Meta-analysis;
Prospective cohort ***Moderate***	**Chapter 6** Alcohol dependence and the persistence or recurrence of major depression	Descriptive analysis; Modified Poisson regression
Cross-sectional ***Low to medium depending on the specifics of the survey design***	**Chapter 5** Substance use disorder, overweight/obesity and co-morbid major depression	Descriptive Multinomial regression
	Chapter 4 Co-morbid substance use with major depression: disability and risk of suicide in a nationally representative sample	Descriptive Multilevel logistics regression
Time series ***Low to medium***	**Chapter 3** Time trends in the prevalence of comorbid alcohol dependence and major depression in the Canadian population (1996/97-2012)	Descriptive

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CHAPTER 3. TIME TRENDS IN THE PREVALENCE OF ALCOHOL DEPENDENCE AND COMORBID MAJOR DEPRESSION IN THE CANADIAN POPULATION (1996/97-2012)

3.1 Introduction

Major depression and alcohol use disorders (AUD) are among the most prevalent mental disorders in Canada (Pearson, Janz, & Ali, 2013) and are significant causes of disability burden in most regions of the world (World Health Organization, 2001). In 2016, the disability-adjusted live years (DALYs) and death attributed to alcohol were 4.2% and 5.2% respectively, making alcohol the seventh-leading cause of DALYs and death (GBD 2016 Risk Factors Collaborators, 2017; GBD 2016 Alcohol Collaborators, 2018).

The concurrent existence of major depression and alcohol dependence is common (Deykin, Levy, & Wells, 1987; Regier, et al., 1990; Grant & Harford, 1995; Grant, et al., 2015; Grant B. F., et al., 2004). Compared to the general population, the risk of becoming alcohol dependent is significantly higher in individuals diagnosed with depression and vice versa (Kessler, et al., 1996; Kessler, et al., 1997; Brière, Rohde, Seeley, & Daniel Klein, 2014; Britton, et al., 2015). Evidence from five US Epidemiological Catchment Area community surveys suggests that the odds of developing Major Depressive Episode (MDE) after 1 year has a dose-dependent relationship with the baseline severity of alcohol dependence and vice versa (Gilman & Abraham, 2001). In their systematic review, Sullivan et al concluded that lifetime alcohol use disorder occurs in 30% (range 10-60%) of individuals with depression compared to 16-24% of the general population (Sullivan, Fiellin, & O'Connor, 2005).

The comorbidity of alcohol dependence and depression is likely to remain a significant public health concern because the prevalence of both disorders has always been high in the younger age groups (Klerman & Weissman, 1989; Helzer, et al., 1990; Burke, Burke, Rae, & Regier, 1991; Blazer, Kessler, McGonagle, & Swartz, 1994; Wittchen, Nelson, & Lachner, 1998; Cross-National Collaborative Group, 1992; Grant, et al., 2015; Grant, et al., 2009). With the early onset, comes the increased risk of secondary psychiatric conditions (Christie, et al., 1988; Rohde, Lewinsohn, & Seeley, 1991; Giaconia, et al., 1994; Kasch & Klein, 1996; Brière, Rohde, Seeley, & Daniel Klein, 2014). Comorbidity also presents as a more severe disease with lower

levels of functioning, more suicidal behaviours, violence and polysubstance use (Swanson, Holzer, Ganju, & Jono, 1991; Cornelius, et al., 1995; Britton, et al., 2015; Brière, Rohde, Seeley, & Daniel Klein, 2014; Hjorthoj, et al., 2015; Borges, Benjet, Orozco, Medina-Mora, & Menendez, 2017) leading to increased health and social service utilization. Studies on the relationship of alcohol dependence and major depression have focused on several areas such as, prevalence, strength of the association, causation (Merikangas, Leckman, Prusoof, Pauls, & Weissman, 1985; Schuckit, 1986; Coryell, Winokur, Keller, Scheftner, & Endicott, 1992; Grant, et al., 2015), and chronicity (Coryell, Winokur, Keller, Scheftner, & Endicott, 1992; Burcusa & Iacono, 2007). Very few studies have assessed the time trends of these conditions and most time trends look at these conditions independently, not the comorbidity (Grant B. F., et al., 2004; Patten, et al., 2015; Wiens, et al., 2017). For example, in their study on the trend of major depression in the Canadian population, Patten et al (2015) found that the prevalence of major depression is not increasing.

Important research and public health implications come with changes in the prevalence of comorbid alcohol dependence and major depression. Understanding true changes in the prevalence of a complex disorder with both genetic and environmental influences over time may be crucial in interpreting research on etiology (Rice, et al., 2003). Changing prevalence would suggest changes in the level of environmental risk since the distribution of risk or protective genetic factors do not vary within a period as short as a decade (Grant B. F., et al., 2004). The need for focused planning in policy and prevention efforts is dependent on accurate information on changes in potentially vulnerable groups (Grant B. F., et al., 2004). It is important for projecting future services, treatment needs and understanding the impact of shifting demographics. The paucity of studies on time trends in the prevalence of comorbid alcohol dependence and major depression reflects a major gap in public health information. This present study is in part, designed to bridge the gap and provide some information.

3.2 Objectives

This study was aimed to assess the time trends in the lifetime prevalence of alcohol dependence, major depression and comorbid alcohol dependence with major depression in Canada from 1996/1997 to 2012.

3.3 Methods

3.3.1 Data Sources

Data were from four Canadian national surveys. These surveys were selected because the variables major depression and alcohol dependence were both assessed to allow for comorbidity estimates.

- **The National Population Health Survey (NPHS)1996/97: Household Component**

The National Population Health Survey, the NPHS was conducted between June 1, 1996 and June 30, 1997 and had a total number of respondents of 81,804. It included household residents across all age groups in all provinces and excluded populations on Indian Reserves, Canadian Forces Bases and some remote areas in Ontario and Quebec and northern territories. The survey captured questions related to health status, use of health services, determinants of health and a range of demographic and economic information (Statistics Canada, 2015).

- **The Canadian Community Health Survey, 2001: Cycle 1.1** (CCHS 1.1**)**

The Canadian Community Health Survey, 2001 (CCHS 1.1) is a cross-sectional survey and the first cycle in a series designed to collect information related to health status, health care utilization and health determinants for the Canadian population. The sampling frame included persons aged 12 years or older, living in private occupied dwellings and excluded individuals living on Indian Reserves and on Crown Lands, Institutional residents, full-time members of the Canadian Armed Forces and residents of certain remote regions. Data was collected between September 5, 2000 and November 30, 2001. The total sample was 130,880 (Statistics Canada, 2005).

- **Canadian Community Health Survey, 2002: Cycle 1.2, Mental Health and Well-being** (CCHS 1.2**)**

The CCHS 1.2 assessed characteristics associated with the mental health of Canadians such as the status, determinants, and utilization. Data was collected between May 2002 and December 2002, with a total sample of 36,984 Canadians who were 15 years or older and resident in one of the ten provinces. Individuals that were full-time members of the Canadian Forces were not

sampled. In addition, individuals who were resident in remote areas, Indian reserves, Crown Lands, or institutions were excluded (Statistics Canada, 2007).

- **The Canadian Community Health Survey 2012 – Mental Health Component (CCHS 2012:MH)**

The CCHS 2012: MH is a comprehensive look at mental health with respect to who is affected by specific mental health disorders, positive mental health, access to and utilization of formal and informal mental health services and support; as well as individual functionality, regardless of the presence of a mental health problem (Statistics Canada, 2014). Data collection was between January 01, 2012 and December 31, 2012. The survey included persons aged 15 years or more and resident in one of the ten Canadian provinces. Criteria for exclusion from the survey were living in certain remote areas, institutions, and reserves. In addition, full-time members of the Canadian Forces were not surveyed. These excluded populations make an estimated 3% of the target national population (Statistics Canada, 2014). The total number of respondents were 25,113 (Statistics Canada, 2014).

3.3.2 Diagnostic Criteria

The diagnosis of lifetime major depression and alcohol dependence in NPHS 96/97 and CCHS 2001 were derived from the World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF) based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R criteria (Statistics Canada, 2005; Statistics Canada, 2015).

The World Mental Health version of the Composite International Diagnostic Interview (WMH-CIDI) was used to derive the diagnosis of lifetime major depression and alcohol dependence in CCHS 1.2 and CCHS 2012: MH. However, in CCHS 1.2, the WMH-CIDI was based on both DSM-III-R and DSM-IV criteria while in CCHS 2012: MH it was based on DSM-IV criteria (Statistics Canada, 2007; Statistics Canada, 2014). The CIDI-SF and WMH-CIDI are structured diagnostic tools made for comparative and easier administration of epidemiological surveys across populations (Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998; Kessler & Ustun, 2004).

3.3.3 Statistical Analyses

Analysis was done using Stata version 14. First, age and gender standardization of all four datasets to get standard proportions for each age-gender strata were done using the 2001 census data for ages 15years and older. Since age and gender are related to the outcomes, the standardization ensures the removal of their confounding effects and allows for comparison of prevalence estimates across surveys with different age structures over time. Second, a new variable *standard weight* was generated for each dataset. Next, the census proportions of each corresponding age-gender strata were assigned using the standard weight variable. The outcome variables, major depression and alcohol dependence were coded dichotomous, where the absence of the outcome is '0' and presence is '100' to give prevalence in percentages. Comorbid alcohol dependence with major depression was derived as a new variable by combining alcohol dependence and major depression and coded dichotomous (comorbid versus no diagnosis of either alcohol dependence or major depression, isolated major depression and isolated alcohol dependence). Variables for age, gender, marital status, highest level of education and total household income were recoded to have the same categorization and labels in all datasets.

Age-gender-adjusted prevalence estimates and 95% confidence intervals (95% CI) for alcohol dependence, major depression, and comorbid alcohol dependence with major depression were generated using the *svy: mean* command with the standard weight variable on Stata. Prevalence estimates were calculated by age, gender, marital status, highest level of education, and total household income. Complex sampling methods of the surveys were accounted for with the survey weights provided in the datasets by Statistics Canada. Graphical display of results was done in Microsoft Excel.

3.4 Results

3.4.1 Prevalence of alcohol dependence, major depression and comorbid alcohol dependence and major depression

The survey characteristics of all datasets in this analysis and the accuracy of diagnostic instruments used (Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998; Kessler, et al., 2004) are shown in table 3-1. Table 3-2 and figure 3-1 show the time trends in the prevalence of alcohol dependence, major depression and comorbid alcohol dependence with major depression

between 1996 and 2012. There was a steady rise in the prevalence between 1996 and 2002 and a decrease between 2002 and 2012. Major depression was seen to have two-fold increase in prevalence from 1996 to 2012. The prevalence of major depression is about twice that of alcohol dependence for each year between 1996 and 2012.

Table 3 -1. Characteristics of surveys included in the study

Survey	Age range	Total Sample Size	Diagnostic Criteria	
			Diagnostic instrument	AUC for MDE
NPHS 96/97	All age groups	81,804	CIDI-SF	[a]0.91
CCHS 2001	12 years and older	130,880	CIDI-SF	[a]0.91
CCHS 1.2 (2002)	15 years and older	36,984	WMH-CIDI	[b]0.86
CCHS MH 2012	15 years and older	25,113	WMH-CIDI	[b]0.86

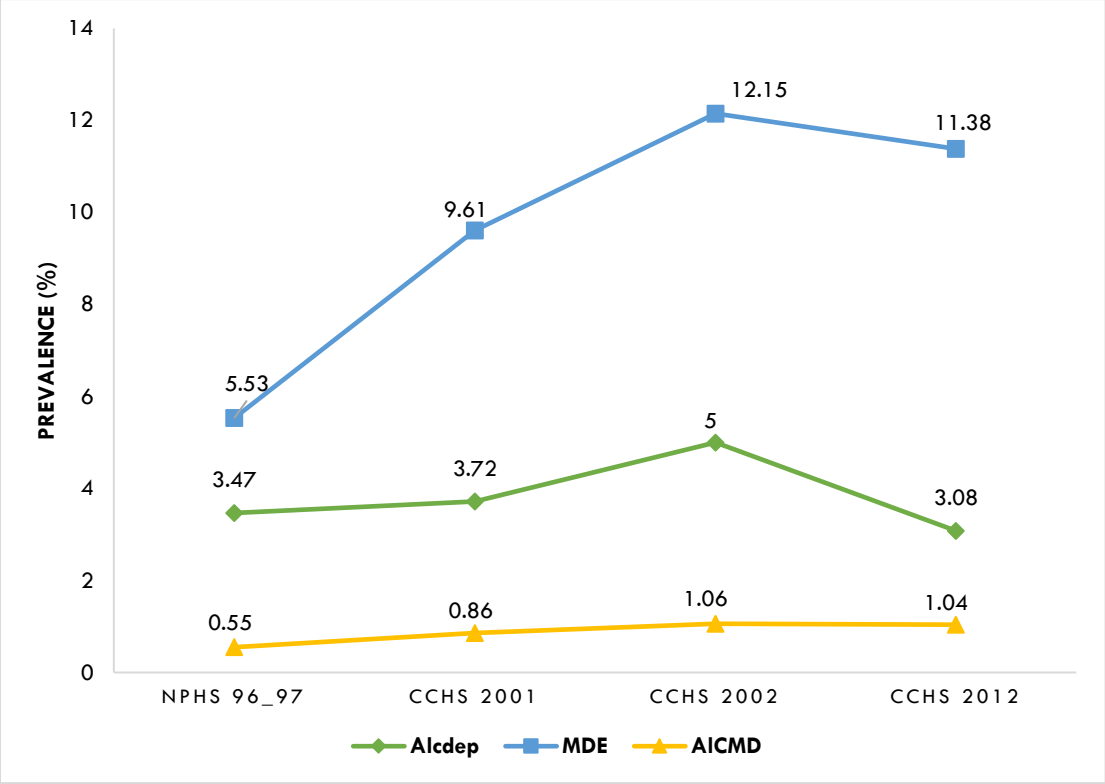
a – diagnostic instrument compared with gold standard DSM-III-R
b – diagnostic instrument compared with the gold standard DSM-IV
NPHS- National Population Health Survey: Household Component; CCHS- Canadian Community Health Survey; CCHS 1.2 – Canadian Community Health Survey, Mental Health and Wellbeing; CCHS MH- Canadian Community Health Survey, Mental Health Component; CIDI-SF- World Health Organization Composite International Diagnostic Interview Short Form; WMH-CIDI - World Mental Health version of the Composite International Diagnostic Interview

Table 3-2. Time trends in the lifetime prevalence of alcohol dependence, major depression and comorbid alcohol dependence with major depression

Survey/year	Alcohol dependence	Alcohol dependence 95% CI	Major depression	Major depression 95% CI	Alcohol dependence & major depression	Alcohol dependence & major depression 95% CI
NPHS 96_97	**3.50**	3.21-3.78	**5.51**	5.16-5.87	**0.56**	0.44-0.68
CCHS 2001	**3.73**	3.58-3.88	**9.60**	9.36-9.83	**0.86**	0.79-0.93
CCHS 1.2 (2002)	**5.40**	4.73-5.35	**12.13**	11.63-12.62	**1.06**	0.89-1.22
CCHS MH 2012	**3.10**	2.79-3.41	**11.38**	10.73-12.03	**1.04**	0.86-1.22

NPHS- National Population Health Survey: Household Component; CCHS- Canadian Community Health Survey; CCHS 1.2 – Canadian Community Health Survey, Mental Health and Wellbeing; CCHS MH - Canadian Community Health Survey, Mental Health Component

Figure 3-1. Time trends in the lifetime prevalence of alcohol dependence, major depression, and comorbid alcohol dependence with major depression 1996/97-2012

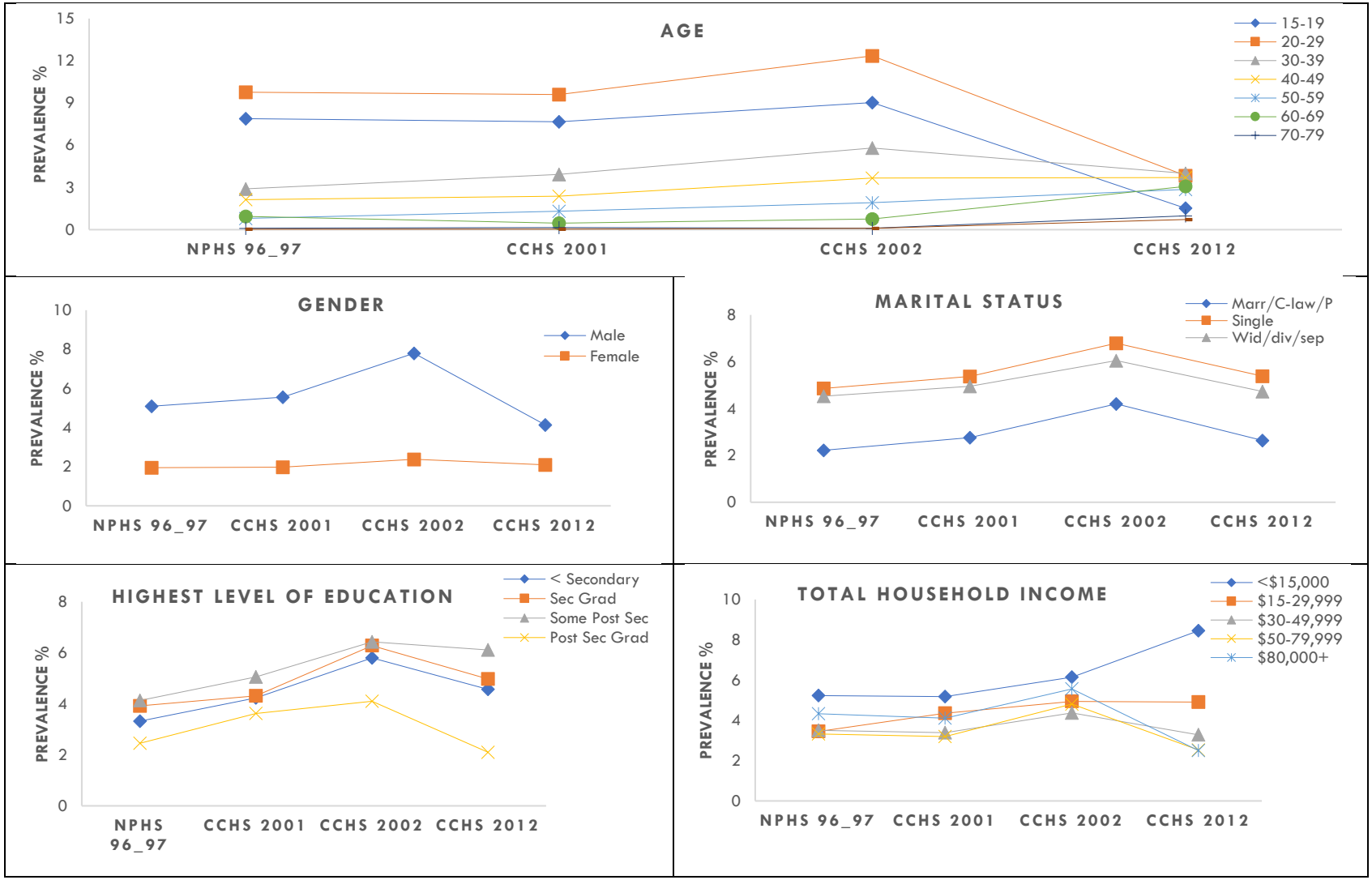


Alcdep – Alcohol Dependence; MDE – Major depression; ALCMD – comorbid alcohol dependence and major depression

3.4.2 Prevalence of alcohol dependence

From 1996 to 2012, alcohol dependence was most prevalent amongst the younger age groups, males, singles, those with some post-secondary education and lowest income level (Figure 3-2). The younger age groups had an increasing trend in the prevalence of alcohol dependence between 1996 and 2002 and a decrease between 2002 and 2012. The older age group and those with income less than $15,000 had a steady increase between 1996 and 2012. The prevalence of alcohol dependence in males was twice that of females for each year between 1996 to 2012.

Figure 3-2. Time trends in the lifetime prevalence of alcohol dependence 1996/97 – 2012 by age, gender, marital status, education and household income

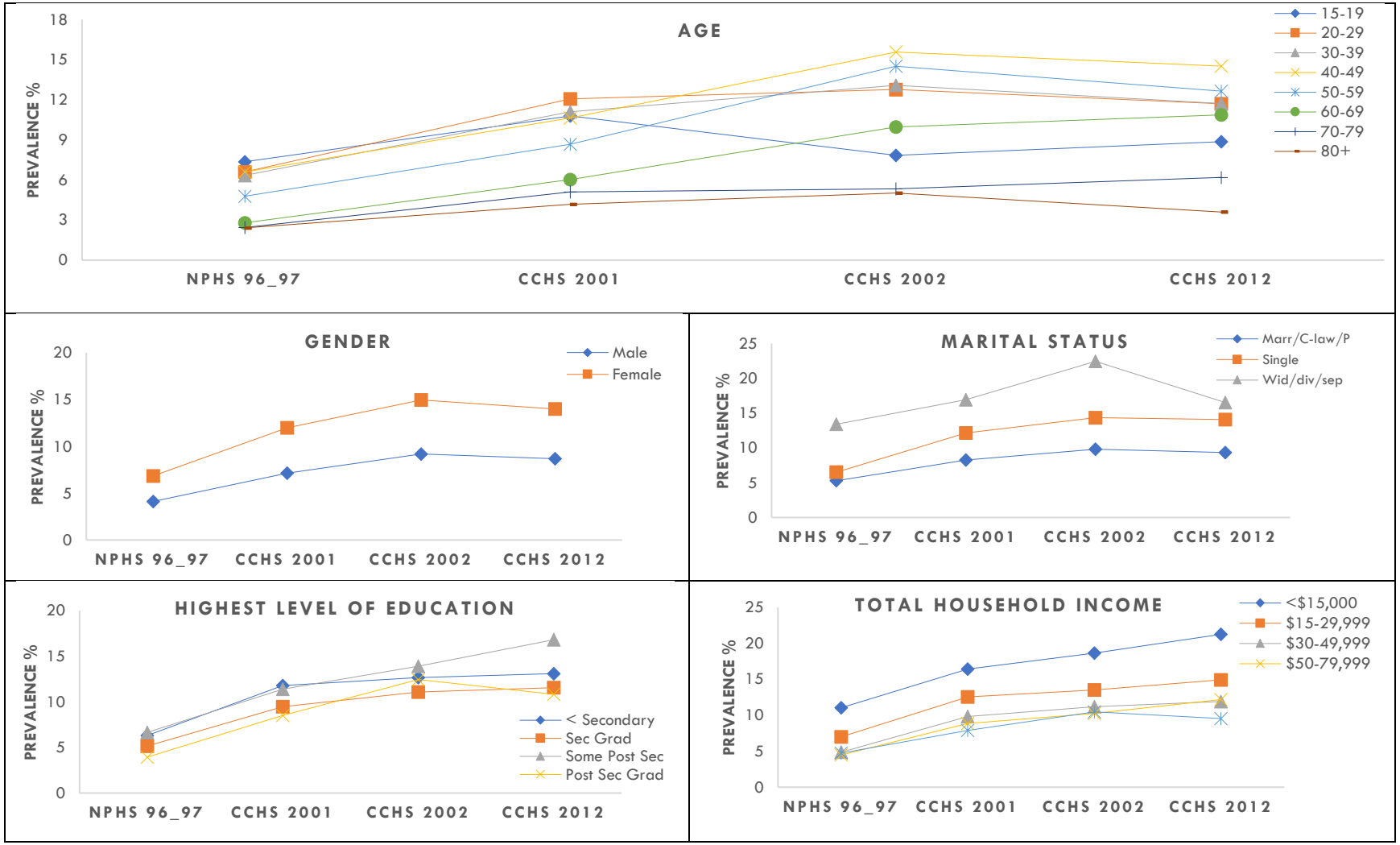


Marr/C-law/P – married/common-law/partner; wid/div/sep – widowed/divorced/separated; < secondary- less than secondary education; sec grad- secondary graduate; some post sec – some post secondary education; post sec grad- post secondary graduate

3.4.3 Prevalence of major depression

From 1996 to 2012, major depression was most prevalent in individuals aged 20-59years, females, widowed/divorced/separated, those with some post-secondary education and lowest income level (Figure 3-3). Individuals with less than $80,000 annual household income and who were not post-secondary graduates had an increasing trend in the prevalence of major depression between 1996 and 2012.

Figure 3-3. Time trends in the lifetime prevalence of major depression 1996/97-2012 by age, gender, marital status, education and household income

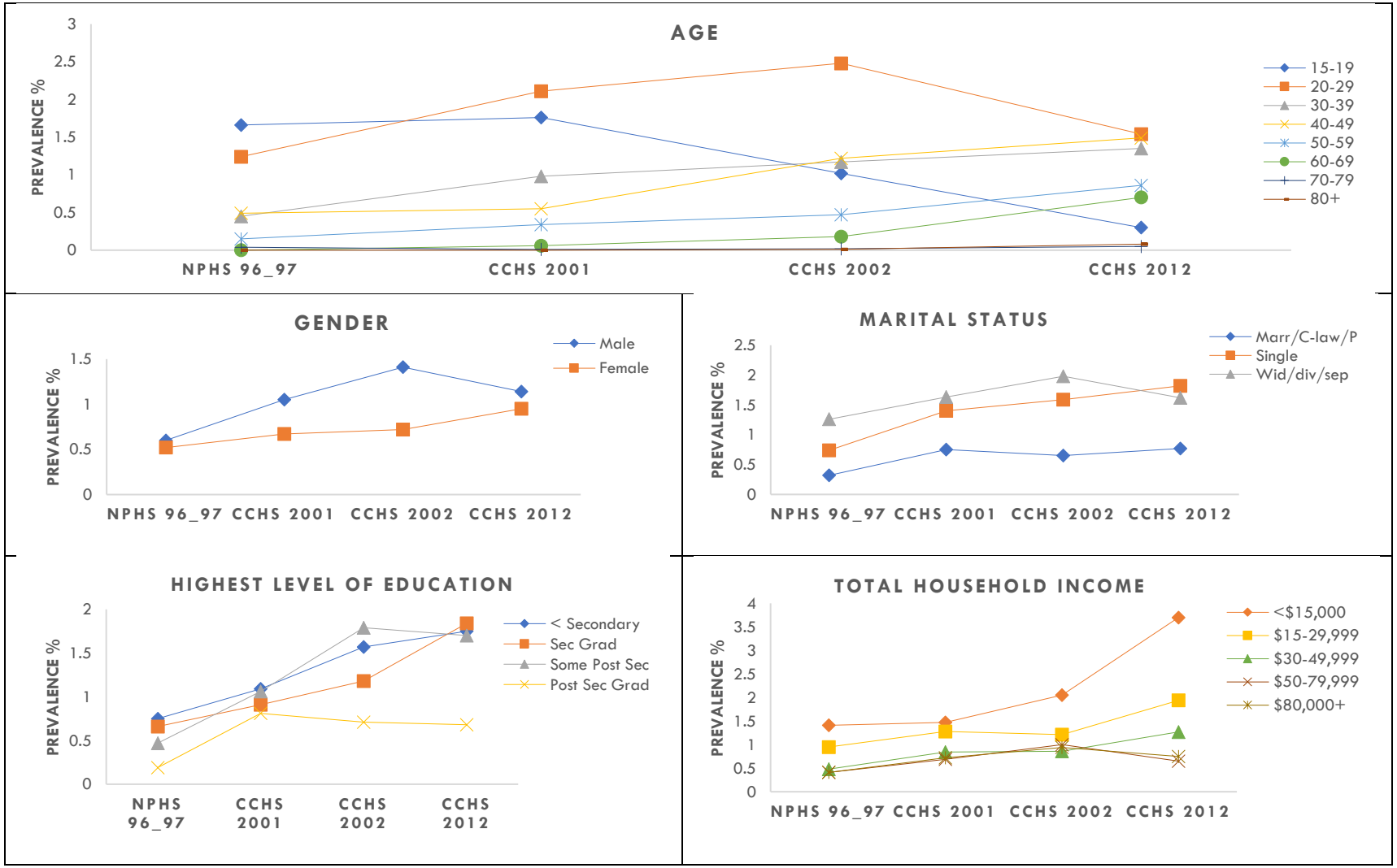


Marr/C-law/P – married/common-law/partner; wid/div/sep – widowed/divorced/separated; < secondary- less than secondary education; sec grad- secondary graduate; some post sec – some post secondary education; post sec grad- post secondary graduate

3.4.4 Prevalence of comorbid alcohol dependence and major depression

From 1996 to 2012, comorbid alcohol dependence and major depression was most prevalent in the younger age groups, males, widowed/divorced/separated, those who had less than secondary education, and earn less than $15,000 household income (Figure 3-4). The rates were found to increase from 1996 to 2012 in those that were aged 30-69years, single, earned <$50,000 household income, had less that secondary education and were females.

Figure 3-4. Time trends in the lifetime prevalence of comorbid alcohol dependence with major depression 1996/97-2012 by age, gender, marital status, education and household income



Marr/C-law/P – married/common-law/partner; wid/div/sep – widowed/divorced/separated; < secondary- less than secondary education; sec grad- secondary graduate; some post sec – some post secondary education; post sec grad- post secondary graduate

3.5 Discussion and Conclusion

The overall prevalence of lifetime alcohol dependence in 1996 was 3.5%. In 2002, the prevalence rose to 5.4% and declined in 2012 to 3.1%. With regard to specific groups, alcohol dependence was most prevalent in males, younger age group (less than 40years), single, widowed/divorced/separated, or have a total household income of less than $15,000. These factors have been established in past studies. Men have higher rates of alcohol use disorder than women, those who are not married or younger age groups take more risks and have drinking patterns that lead to more problems (Dawson, Grant, & Chou, 1995; Grant B. F., 1997; Hasin, Stinson, Ogburn, & Grant, 2007; Caetano, Baruah, & Chartier, 2011; Grant B. F., et al., 2004). This trend analysis identified an emerging high-risk group for alcohol dependence. Individuals 40years and older experienced an increase in the prevalence from 1996 to 2012 approaching the rates of the stable high-risk group (younger) in 2012.

Lifetime prevalence of major depression increased markedly from 5.51% in 1996 to 12.13% in 2002 and remained stable at 11.38% in 2012. This trend in major depression is consistent with previous studies on the same population that did not find a change in the prevalence between 2000 and 2012 (Patten, et al., 2015; Wiens, et al., 2017). Our analysis showed the age groups 60-69years and 70-79years experienced an increase in depression from 1996/97 to 2012. This is consistent with a study that found an increase in the prevalence across age groups (Compton, Conway, Stinson, & Grant, 2006) and inconsistent with some studies that found increase in prevalence specific to a particular age-cohort at a particular point in time (Klerman & Weissman, 1989; Lewinsohn, Rhode, Seeley, & Fischer, 1993; Hagnell, Lanke, Rorsman, & Ojesjo, 1982; Cross-National Collaborative Group, 1992). Subgroup analysis also showed a consistent increase in major depression from 1996-2012 amongst those with total household income less than $80,000 and less than a graduate level education.

Comorbid alcohol dependence with major depression had a prevalence of 0.56% in 1996/97 and 1.06% in 2002 plateauing off at 1.04% in 2012. This trend mirrors the trend in major depression, unlike alcohol dependence that declined between 2002 and 2012. Comorbid alcohol dependence with major depression was most prevalent in males, younger age groups, low income, and low educational status as was the case for alcohol dependence. Despite the overall trend that plateaued between 2002 and 2012, the prevalence of this comorbidity had a

consistent increase from 1996 to 2012 in females, those 30 years and older, household income less than $50,000, and had no post-secondary graduate level education. It is thought that the elevated prevalence may result from the effect of alcohol dependence on major depression risk and vice versa (Bulloch, Lavorato, Williams, & Patten, 2012). Given its negative implications on the individuals, families, and society at large, comorbid alcohol dependence with major depression continue to pose a significant public health concern (Grant, et al., 2004) and have profound health care and economic implications. These findings underscore the need for prevention strategies through the life course - more prevalent in the younger age groups, emerging risks in the older age groups.

Since rapid changes in the prevalence of alcohol dependence, major depression and comorbid alcohol dependence with major depression over such a relatively short time cannot be explained by genetic factors, attention should be on environmental factors that have occurred in that time. Exploration of changes in historical and cultural factors, marital stability, household composition, and labour force dynamics, psychiatric and medical comorbidity, genetic vulnerability, health care utilization and economic indices are necessary to begin to understand the increasing rates of comorbid alcohol dependence with major depression.

Several factors may have contributed to the significant jump that occurred between 2001 and 2002 in the prevalence of alcohol dependence, major depression and comorbid alcohol dependence with major depression. First, there was a change in the structured diagnostic instrument from CIDI-SF in 2001 to WMH-CIDI in 2002. The WMH-CIDI addressed some of the shortcomings of the CIDI-SF including and but not limited to subthreshold diagnosis of mental health disorders where array of symptoms not meeting the criteria for a diagnosis are included to capture individuals that would have been missed otherwise (Kessler, et al., 2004). This may have increased the prevalence in 2002 compared to 2001 and explains the plateau found between 2002 and 2012. Second, the CIDI-SF diagnostic criteria was based on DSM-III-R while the WMH-CIDI was derived from both DSM-III-R and DSM-IV in 2002 (CCHS 1.2) and DSM-IV in 2012 (CCHS 2012: MH). Despite some similarities between DSM-III-R and DSM-IV, the *kappa* levels on both criteria are low partly due to the reclassification of some criteria and identification of undiagnosed DSM-III-R cases by DSM-IV (Schuckit, et al., 1994). In addition,

the CCHS 2002 and 2012 were mental health specific surveys with more details on mental health disorders compared to the 2001 survey which was a general population health survey.

One of the strengths of this study is that the NPHS, CCHS, and CCHS Mental Health Component are large household population surveys with good response rates, and therefore, are generalizable to the Canadian population (Statistics Canada, 2014; Statistics Canada, 2005; Statistics Canada, 2015; Statistics Canada, 2007). The complex data structures of the surveys were accounted for using the survey weights provided. Age and gender standardization of prevalence using census data is another strength of this study. This analysis has some limitations. The diagnostic criteria for major depression and alcohol dependence differed in the surveys, hence, resulting in the inability to pool effects in a trend analysis. Thus, chance occurrence cannot be ruled out. The surveys excluded the homeless individuals and those institutionalized, which are population groups with a higher prevalence of substance use disorders and at a higher risk for comorbidity (Canadian Centre on Substance Abuse, 2009). Other populations excluded were individuals on reserves and other Aboriginal settlements and full-time members of the Canadian Forces. This study was also based on self-reported data, which could be compromised by recall bias and under-reporting.

This study is among the first to examine the trends in the lifetime prevalence of comorbid alcohol dependence with major depression and demographic changes among individuals 15years and older in Canada. Our findings demonstrate that comorbid alcohol dependence with major depression has a high prevalence in the younger age group and continues to increase in adults particularly those with low income and educational status. A life course perspective is recommended as a prevention strategy.

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Appendix A. Time Trend Tables

Table A.1 Time trends in the prevalence of Alcohol dependence 1996/97-2012

	NPHS 96/97 (95%CI)	**CCHS 2001** (95%CI)	**CCHS 2002**(95%CI)	**CCHS 2012**(95%CI)
Age				
15-19 years	**7.89** (6.37-9.40)	**7.67** (7.06-8.28)	**9.03** (7.71-10.35)	**1.52** (0.92-2.11)
20-29years	**9.76** (8.56-10.96)	**9.6** (8.96-10.25)	**12.35** (11.19-13.52)	**3.84** (2.97-4.71)
30-39years	**2.9** (2.44-3.37)	**3.93** (3.59-4.28)	**5.8** (5.07-6.52)	**3.99** (3.10-4.87)
40-49years	**2.13** (1.59-2.67)	**2.37** (2.12-2.64)	**3.67** (3.01-4.34)	**3.7** (2.87-4.53)
50-59years	**0.8** (0.47-1.14)	**1.31** (1.1-1.52)	**1.91** (1.33-2.49)	**2.86** (2.27-3.45)
60-69years	**0.94** (0.33-1.55)	**0.46** (0.33-0.58)	**0.75** (0.41-1.09)	**3.07** (2.25-3.88)
70-79years	**0.1** (0.03-0.24)	**0.14** (0.06-0.22)	**0.1** (0.01-0.19)	**0.98** (0.57-1.40)
80 and above	**0.03** (0.02-0.08)	**0.04** (0.02-0.09)	**0.09** (0.02-0.20)	**0.72** (0.19-1.63)
Sex				
Male	**5.09** (4.61-5.58)	**5.55** (5.28-5.81)	**7.8** (7.23-8.37)	**4.14** (3.61-4.66)
Female	**1.95** (1.64-2.26)	**1.98** (1.83-2.12)	**2.38** (2.11-2.64)	**2.10** (1.76-2.44)
Marital status				
Mar/C-law/partner	**2.22** (1.47-2.98)	**2.76** (1.99-3.53)	**4.20** (2.9-5.51)	**2.64** (2.08-3.20)
Single	**4.86** (4.17-5.55)	**5.37** (5.01-5.74)	**6.79** (6.11-7.47)	**5.38** (4.46-6.29)
Wid/Div/Sep	**4.53** (3.16-5.9)	**4.95** (4.02-5.88)	**6.05** (4.82-7.28)	**4.73** (2.92-6.54)
Highest level of education				
<Secondary	**3.32** (2.63-4.02)	**4.23** (3.85-4.60)	**5.80** (5.00-6.60)	**4.57** (3.54-5.6)
Sec Grad	**3.92** (3.20-4.64)	**4.31** (3.96-4.66)	**6.28** (5.48-7.08)	**4.97** (3.80-6.15)
Some Post Sec	**4.13** (3.60-4.66)	**5.05** (4.49-5.61)	**6.43** (5.50-7.36)	**6.11** (3.95-8.27)
Post Sec Grad	**2.45** (1.25-3.66)	**3.62** (3.17-4.07)	**4.10** (3.44-4.77)	**2.10** (1.80-2.40)
Total Household Income				
<$15,000	**5.23** (4.06-6.4)	**5.18** (4.56-5.79)	**6.14** (5.02-7.26)	**8.45** (6.32-10.58)
$15,000-29,999	**3.45** (2.72-4.19)	**4.36** (3.89-4.82)	**4.94** (4.15-5.72)	**4.91** (3.74-6.08)
$30,000-49,999	**3.50** (2.85-4.16)	**3.39** (.09-3.68)	**4.37** (3.73-5.00)	**3.28** (2.61-3.95)
$50,000-79,999	**3.32** (2.73-3.90)	**3.19** (2.93-3.45)	**4.81** (4.24-5.38)	**2.53** (1.80-3.26)
$80,000 or more	**4.33** (3.25-5.41)	**4.11** (3.75-4.47)	**5.56** (4.85-6.28)	**2.50** (2.07-2.93)

Marr/C-law/P – married/common-law/partner; wid/div/sep – widowed/divorced/separated; < secondary- less than secondary education; sec grad- secondary graduate; some post sec – some post secondary education; post sec grad- post secondary graduate

Table A.2 Time trends in the prevalence of Major depression 1996/97-2012

	NPHS 96/97(95%CI)	**CCHS 2001**(95%CI)	**CCHS 2002**(95%CI)	**CCHS 2012**(95%CI)
Age				
15-19 years	**7.36** (5.88-8.85)	**10.79** (10.0-11.58)	**7.85** (6.56-9.14)	**8.86** (7.08-10.64)
20-29years	**6.6** (5.62-7.57)	**12.07** (11.38-12.76)	**12.77** (11.55-14.00)	**11.69** (10.19-10.64)
30-39years	**6.34** (5.51-7.17)	**11.11** (10.55-11.67)	**13.08** (11.93-14.23)	**11.72** (10.18-13.26)
40-49years	**6.6** (5.71-7.49)	**10.64** (10.10-11.19)	**15.57** (14.17-16.98)	**14.51** (12.47-16.54)
50-59years	**4.78** (3.92-5.65)	**8.67** (8.09-9.25)	**14.51** (13.15-15.87)	**12.65** (11.12-14.19)
60-69years	**2.79** (2.06-3.52)	**6.03** (5.44-5.77)	**9.96** (8.69-11.22)	**10.87** (9.50-12.24)
70-79years	**2.44** (1.61-3.27)	**5.10** (4.43-5.77)	**5.33** (4.38-6.29)	**6.19** (4.74-7.64)
80 and above	**2.41** (1.06-3.76)	**4.17** (3.26-5.10)	**5.02** (3.34-6.69)	**3.60** (2.47-4.73)
Sex				
Male	**4.12** (3.63-4.62)	**7.13** (6.82-7.43)	**9.19** (8.52-9.86)	**8.67** (7.85-9.48)
Female	**6.85** (6.34-7.36)	**11.98** (11.62-12.34)	**14.96** (14.23-15.7)	**13.99** (12.98-14.99)
Marital status				
Mar/C-law/partner	**5.28** (3.94-6.61)	**8.25** (7.42-9.09)	**9.81** (9.17-10.44)	**9.35** (8.54-10.17)
Single	**6.5** (5.59-7.42)	**12.16** (11.44-12.88)	**14.35** (12.89-15.81)	**14.06** (12.66-15.46)
Wid/Div/Sep	**13.4** (9.31-17.48)	**16.94** (15.78-18.10)	**22.44** (19.77-25.11)	**16.52** (13.42-19.63)
Highest level of education				
<Secondary	**6.31** (5.41-7.20)	**11.77** (11.11-12.43)	**12.65** (11.29-14.0)	**13.09** (10.73-15.45)
Sec Grad	**5.15** (4.41-5.89)	**9.47** (8.93-10.01)	**11.08** (9.97-12.19)	**11.55** (9.80-13.31)
Some Post Sec	**6.65** (5.05-6.25)	**11.37** (10.48-12.26)	**13.91** (12.20-15.61)	**16.80** (13.33-20.27)
Post Sec Grad	**3.94** (3.24-4.65)	**8.50** (8.05-8.96)	**12.44** (11.62-13.26)	**10.81** (9.91-11.71)
Total Household Income				
<$15,000	**11.03** (9.68-12.94)	**16.41** (15.42-17.40)	**18.63** (16.81-20.45)	**21.23** (17.99-24.47)
$15,000-29,999	**6.99** (6.02-7.97)	**12.53** (11.82-13.24)	**13.49** (13.49-17.01)	**14.91** (12.82-17.00)
$30,000-49,999	**4.86** (4.21-5.50)	**9.81** (9.29-10.33)	**11.19** (11.19-13.32)	**11.90** (10.21-13.58)
$50,000-79,999	**4.47** (3.67-5.28)	**8.86** (8.34-9.38)	**10.26** (10.26-12.14)	**12.17** (10.51-13.83)
$80,000 or more	**4.73** (3.52-5.94)	**7.89** (7.39-8.57)	**10.46** (9.33-11.60)	**9.52** (8.64-10.39)

Marr/C-law/P – married/common-law/partner; wid/div/sep – widowed/divorced/separated; < secondary- less than secondary education; sec grad- secondary graduate; some post sec – some post secondary education; post sec grad- post secondary graduate

Table A.3 Time trends in the prevalence of comorbid Alcohol dependence and major depression 1996/97-2012

	NPHS 96/97(95%CI)	**CCHS 2001**(95%CI)	**CCHS 2002**(95%CI)	**CCHS 2012**(95%CI)
Age				
15-19 years	**1.66** (0.82-2.51)	**1.76** (1.45-2.07)	**1.02** (0.54-1.50)	**0.30** (0.08-0.52)
20-29years	**1.24** (0.86-1.62)	**2.11** (1.82-2.40)	**2.48** (1.88-3.09)	**1.54** (0.97-2.12)
30-39years	**0.45** (0.27-0.63)	**0.98** (0.81-1.45)	**1.17** (0.84-1.50)	**1.35** (0.89-1.81)
40-49years	**0.49** (0.19-0.79)	**0.55** (0.43-0.66)	**1.22** (0.71-1.73)	**1.49** (0.95-2.03)
50-59years	**0.15** (0.01-0.3)	**0.34** (0.22-0.46)	**0.47** (0.28-0.67)	**0.86** (0.54-1.17)
60-69years	-	**0.06** (0.02-0.11)	**0.18** (0.05-0.31)	**0.70** (0.41-0.99)
70-79years	**0.04** (0.03-010)	**0.01** (0.01-0.02)	**0.02** (0.02-0.06)	**0.05** (0.01-0.11)
80 and above	-	-	**0.01** (0.01-0.12)	**0.08** (0.03-0.19)
Sex				
Male	**0.6** (0.42-0.77)	**1.05** (0.93-1.16)	**1.41** (1.19-1.71)	**1.14** (0.87-1.41)
Female	**0.52** (0.35-0.68)	**0.67** (0.58-0.75)	**0.72** (0.56-0.87)	**0.95** (0.71-1.19)
Marital status				
Mar/C-law/partner	**0.32** (0.04-0.67)	**0.75** (0.04-1.47)	**0.65** (0.46-0.84)	**0.77** (0.54-1.01)
Single	**0.74** (0.57-0.91)	**1.40** (1.18-1.61)	**1.59** (1.24-1.93)	**1.82** (1.33-2.31)
Wid/Div/Sep	**1.26** (0.66-1.86)	**1.63** (1.18-2.08)	**1.98** (1.35-2.60)	**1.62** (1.00-2.23)
Highest level of education				
<Secondary	**0.75** (0.37-1.14)	**1.09** (0.89-1.29)	**1.57** (1.15-1.99)	**1.75** (1.07-2.43)
Sec Grad	**0.66** (0.33-0.99)	**0.91** (0.75-1.06)	**1.18** (0.81-1.54)	**1.84** (1.05-2.64)
Some Post Sec	**0.47** (0.34-0.60)	**1.06** (0.82-1.30)	**1.79** (1.21-2.37)	**1.70** (0.89-2.51)
Post Sec Grad	**0.19** (0.09-0.30)	**0.81** (0.52-1.20)	**0.71** (0.50-0.92)	**0.68** (0.52-0.84)
Total Household Income				
<$15,000	**1.41** (0.78-2.04)	**1.47** (1.16-1.79)	**2.05** (1.38-2.73)	**3.70** (2.48-4.92)
$15,000-29,999	**0.95** (0.56-1.34)	**1.28** (1.05-1.51)	**1.21** (0.85-1.57)	**1.94** (1.09-2.8)
$30,000-49,999	**0.48** (0.25-0.72)	**0.84** (0.69-0.99)	**0.86** (0.55-1.16)	**1.27** (0.8-1.75)
$50,000-79,999	**0.41** (0.14-0.67)	**0.69** (0.56-0.82)	**1.00** (0.72-1.28)	**0.65** (0.30-1.0)
$80,000 or more	**0.41** (0.17-0.64)	**0.72** (0.57-0.87)	**0.94** (0.54-1.34)	**0.75** (0.52-0.98)

Marr/C-law/P – married/common-law/partner; wid/div/sep – widowed/divorced/separated; < secondary- less than secondary education; sec grad- secondary graduate; some post sec – some post secondary education; post sec grad- post secondary graduate

CHAPTER 4. CO-MORBID SUBSTANCE USE WITH MAJOR DEPRESSION: DISABILITY AND RISK OF SUICIDE IDEATION IN A NATIONALLY REPRESENTATIVE SAMPLE

4.1 Introduction

4.1.1 Prevalence of substance use disorders and major depression

Substance Use Disorders (SUDs) and major depression are the two most common mental health disorders in North America; and they often co-exist; especially in treatment-seeking patients (Grant, et al., 2004; Galbaud du Fort, Newman, Boothroyd, & Bland, 1999; RachBeisel, Scott, & Dixon, 1999). A total of 2.8 million Canadians (10.1%) in 2012, reported symptoms consistent with at least one of the following mental health or substance use disorders: mood disorders (depression or bipolar), generalized anxiety disorders, abuse and/or dependence of alcohol, cannabis or other drugs (Pearson, Janz, & Ali, 2013).

Alcohol and cannabis are among the most commonly used substances in Canada (Statistics Canada, 2017a; Pearson, Janz, & Ali, 2013). Correspondingly, alcohol and cannabis use disorders are fairly common. Globally, the harmful use of alcohol ranks among the top seven risk factors for disease, disability, and death (World Health Organization, 2011; Lim, et al., 2012; World Health Organization, 2014a; GBD 2016 Risk Factors Collaborators, 2017; GBD 2016 Alcohol Collaborators, 2018). Cannabis use has also been associated with a wide range of mental illness, including depression (Kessler, et al., 1996; Lev-Ran, Le Foll, McKenzie, George, & Rehm, 2013; Mathews, Hall, & Gartner, 2011; Volkow, Baler, Compton, & Weiss, 2014; Wright & Metts, 2016). Evidence from the 1990 United States (U.S.) National Comorbidity Survey suggests that 90% of respondents with marijuana dependence had lifetime DSM-III psychiatric disorders (Kessler, et al., 1996). Among people at high risk of SUDs, those with mental health problems are some of the most vulnerable (Shi, 2014).

Comorbid substance use disorder (SUD) with major depression tend to occur more commonly among young people (de Graaf, Bijl, Smit, Vollebergh, & Spijker, 2002), is higher in people with drug use disorders compared to alcohol use disorders (Jane-LIopis & Matytsina, 2006; Regier, et al., 1990) and among those with substance use dependence (the cluster of behavioural, cognitive, and psychological phenomena that develop secondary to repeated use of

substances) as opposed to abuse (the harmful or hazardous use of psychoactive substances) (Jane-LIopis & Matytsina, 2006; Merikangas, et al., 1998; World Health Organization, 2018). In patient samples, comorbid Major Depressive Disorder (MDD) in individuals with SUDs have been found to be associated with poorer quality of life (Saatcioglu, Yapici, & Cakmak, 2008), elevated rates of disability (Olfson, et al., 1997), elevated suicide risk (Glasner-Edwards, et al., 2008; Berglund & Ojehagen, 1998; Grant & Hasin, 1999; Waller, Lyons, & Costantini-Ferrando, 1999) and, negative treatment outcomes whether considered as comorbid diagnosis (Burns, Teesson, & O'Neill, 2005; Glasner-Edwards, et al., 2009) or a continuous measure of depressive symptoms (Dodge, Sindelar, & Sinha, 2005).

4.1.2 Disability and comorbid substance use disorders with major depression

In the U.S. employers lose an excess of 31 billion dollars of productive time from workers with depression compared to those without depression per year (Stewart, Ricci, Chee, Hahn, & Morganstein, 2003). High levels of disability in several domains of functioning have been associated with mental illness (Druss, Rosenheck, & Sledge, 2000). A study by Kennedy et al. (2002) found significantly higher functional impairments in work, family and social domains in patients with depression compared to those without depression (Kennedy, Lin, & Schwab, 2002). Evidence from the 1998 US National Health Interview Survey showed that 35.4% of individuals with a mental disorder had trouble finding or keeping a job, 33.3% were unable to perform major activities and 5.2% were unable to work or were limited in their work due to mental health problems (Willis, Willis, Male, Henderson, & Manderscheid, 1998). Similar to other mental illnesses, SUDs also have high levels of disability. Previous studies suggest considerable disability associated with major life activities and keeping or finding a job (Willis, Willis, Male, Henderson, & Manderscheid, 1998; Holder & Blose, 1991; Aldaf, Smart, & Walsh, 1992). The cost of substance use (SU) in 2014 categorized as healthcare costs, lost productivity costs, criminal justice costs and other direct costs were $38.4 billion in Canada with 40.8% related to the cost of lost productivity (Canadian Substance Use Costs and Harms Scientific Working Group, 2018). Four substances with the largest costs were alcohol, tobacco, opioids, and cannabis. Seventy percent of these costs were due to alcohol and tobacco (Canadian Substance Use Costs and Harms Scientific Working Group, 2018).

While functional disabilities associated with single mental disorders or SUDs can be severe, comorbidity in patients has been associated with significantly worse disabilities and to have a considerable impact on the Quality of Life (QoL) (Saatcioglu, Yapici, & Cakmak, 2008). For example, evidence from the National Comorbidity Survey showed that individuals with comorbidities of two or more disorders had on average four times more work days lost and three times more work cutback days than those with one disorder (Kessler, Foster, Saunders, & Stagg, 1995). Individuals with comorbid disorders are more likely to be unemployed, divorced, socially isolated (Olfson, et al., 1997; Kessler R. C., 1995) and frequent users of health services in comparison to individuals diagnosed with single disorders (Burns & Tesson, 2002).

4.1.3 Suicide risk and comorbid substance use disorders with major depression

In 2012, approximately 804,000 completed suicides were reported worldwide. This translates to a yearly age-standardized rate of 11.4 suicides per 100,000 persons (World Health Organization, 2014b). An estimated 50% and 71% of brutal deaths in males and females respectively are attributed to suicides worldwide. In adolescents and young adults aged 15-25 years old, suicide was ranked the second leading cause of mortality worldwide (World Health Organization, 2014b).

SUDs increase the risk of suicide (Schneider, 2009; Beautrias, et al., 1996; Borges, Walters, & Kessler, 2000; Miller, et al., 2011; Petronis, Samuel, Mosckicki, & Anthony, 1990; Wong, Zhou, Goebert, & Hishinuma, 2013; Westman, et al., 2015; Hjorthoj, et al., 2015) with 25 – 50% of all suicides associated SUDs and 22% attributable to AUD, meaning that every fifth suicide could have been prevented if alcohol was not consumed (Cavanagh, Carson, Sharpe, & Lawrie, 2003). Emerging evidence suggest a role of cannabis on suicidal behavior (Agrawal & Lynskey, 2014; Borges, et al., 2017b; Borges, Benjet, Orozco, Medina-Mora, & Menendez, 2017a; Shalit, Shoval, Shlosberg, Feingold, & Lev-Ran, 2016), a matter of great relevance and considerable debate due to its high prevalence (United Nations Office on Drugs and Crime, 2015) and actual and proposed changes in legislation covering its use in several countries including Canada (Statistics Canada, 2017a; Borges, Benjet, Orozco, Medina-Mora, & Menendez, 2017a).

While the lifetime risk of suicide is estimated to be 4% in patients with mood disorders (Bostwick & Pankraz, 2000), and 7% in people with alcohol dependence (Schneider, 2009), it

increases considerably with comorbidity (Cavanagh, Carson, Sharpe, & Lawrie, 2003). In high-income countries like Canada, mental disorders were present in up to 90% of completed suicides (Cavanagh, Carson, Sharpe, & Lawrie, 2003). Suicidal behaviour is most commonly associated with depression and alcohol use disorders (World Health Organization, 2014b) and the combination of alcohol dependence and depression is considered the leading risk factor for completed suicides (Gliatto & Rai, 1999). Major depression and alcohol dependence were responsible for the first and second largest proportion of the suicide disability-adjusted life-years (DALY) that were attributable to mental and substance use disorders in 2010, respectively (Ferrari, et al., 2014).

Since suicide is a sensitive and complex issue, a rare outcome and illegal in some countries, analytical studies on suicides are complicated and suicides are very likely to be under-reported and misclassified (World Health Organization, 2014b; Borges, Benjet, Orozco, Medina-Mora, & Menendez, 2017a). Key risk factors for suicides are suicide attempts and suicide ideation (World Health Organization, 2014b; Nock, et al., 2008). Suicide attempts and suicide ideation, therefore, represent surrogates for studies on suicides and associated factors (Borges et al., 2009).

Several studies on comorbid SUD with psychiatric disorders have focused on prevalence and risk factors with very few on the impact of the comorbidity such as associated disability and the risk of suicide. In addition, most of the studies that have assessed the impact of comorbid SUD with psychiatric disorders used patient samples (Gliatto & Rai, 1999; Glasner-Edwards, et al., 2008; Saatcioglu, Yapici, & Cakmak, 2008). This study aims the bridge the gaps in the literature using a national representative sample of Canadians to assess the impact of comorbid SUD with major depression on disability and risk of suicide.

4.2 Objectives

This study aimed to first, determine the disability associated with comorbid substance use disorders (SUD) with depression and second, the associated risk of suicide ideation in comorbid SUD with depression in a nationally representative sample.

4.3 Methods

4.3.1 Subjects

Subjects were participants of the Canadian Community Health Survey (CCHS), 2012: Mental Health Component (CCHS 2012: MH), N= 25,113, response rate = 86.3%. The CCHS 2012: MH provides a comprehensive look at mental health with respect to who is affected by specific mental health disorders, positive mental health, access to and utilization of formal and informal mental health services and support; as well as individual functionality, regardless of the presence of a mental health problem (Statistics Canada, 2014). The survey included persons aged 15 years or more and resident in one of the ten Canadian provinces. Criteria for exclusion from the survey were living in certain remote areas, institutions, and reserves. In addition, full-time members of the Canadian Forces were not surveyed. These excluded populations make an estimated 3% of the target national population (Statistics Canada, 2014).

This secondary analysis of the CCHS, MH 2012 dataset was done using the Public Use Microdata Files (PUMF). Unlike the confidential microdata files (Master data files) which are accessible through Research Data Centres only, PUMFs are available through University Libraries across Canada. PUMFs are manipulated files done to make data widely available while still maintaining confidentiality. Such manipulations include aggregating, capping or completely erasing identifying variables (Statistics Canada, 2017b).

4.3.2 Measures

Major Depression

The World Mental Health version of the Composite International Diagnostic Interview (WMH-CIDI) is a structured diagnostic interview based on symptoms and symptom severity associated with specific psychiatric disorders. The WMH-CIDI algorithm derived from the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) was applied to the symptom data to define specific psychiatric diagnosis, in this case, Unipolar Major Depressive Episode (MDE) - lifetime and 12-month (Statistics Canada, 2014).

Substance Use Disorder

The WMH-CIDI algorithms derived from DSM IV were applied to the symptom data to define substance use disorders (SUD), that is, substance abuse and/or dependence for alcohol (alcohol use disorder -AUD), cannabis (Cannabis use disorder – CUD) and other drugs excluding cannabis (drugs use disorder- DUD) in the data. Lifetime and 12-month SUDs were defined (Statistics Canada, 2014).

World Health Organization Disability Assessment Schedule Score 2.0

The World Health Organization Disability Assessment Schedule Score 2.0 (WHODAS 2.0) is a "generic assessment instrument for health and disability in adult populations. It produces standardized disability levels and profiles across cultures and it is constructed on the conceptual framework of the International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2016). It assesses functioning based on six main domains- *cognition, mobility, self-care, getting along, life activities and participation"* (World Health Organization, 2016). In this data, the score for total disability was derived by Statistics Canada and individuals were classified into two groups < 40 (lowest recordable degree of disability) versus 40 or more (high degree of disability) (Statistics Canada, 2014).

Suicidal Ideation

The risk of suicide was assessed using the proxy, suicidal thoughts (ideation). Statistics Canada used the WHM CIDI symptom data to develop algorithms for lifetime and 12-months suicidal thoughts (ideation) in the data. These algorithms classified respondents based on whether they ever (lifetime) thought of committing suicide or taking their own life and whether or not those thoughts occurred in the past 12 months (Statistics Canada, 2014).

Other Measures

Other variables that were included in these analyses were: sociodemographic factors - age, sex, marital status (married**,** common-law**,** widowed**,** divorced or separated**,** single), highest level of education (less than secondary education, secondary education graduate, some post secondary education, post secondary education graduate), total household income in Canadian dollars (no income or <20,000, 20,000-39,999, 40,000-59,999, 60,000-79,999, 80,000 or more), race (white, non-white), smoking status, personal and family history of mental health disorder, history of a chronic disease and childhood traumatic events.

4.3.3 Statistical Analysis

All statistical analyses were carried out using STATA version 14.0. First, a new variable, comorbid SUD with MDE was created by merging each SUD (alcohol, cannabis, other drugs) variable and MDE. For each SUD, the new variable created had four levels – no diagnosis (neither SUD nor MDE), single diagnosis of SUD (AUD or CUD or DUD), single diagnosis of MDE and comorbid diagnosis of SUD with MDE. Then, participants were described by sociodemographic characteristics and DSM IV diagnosis. For each outcome variable (disability and suicide ideation), a Chi-Square test was done to depict the relationship between the DSM-IV diagnoses (isolated and comorbid) and the probability of having disability or suicide ideation in the population.

The MCAR test on Stata version 14 was used to determine if data was missing completely at random (MCAR) and a justification for a complete case analysis. Data was not MCAR (Appendix 1). Then, Multiple imputations using chained equations was carried out following significant Chi Square associations between the independent variables and the missingness in the outcome variables (disability and risk of suicide ideation) (Appendix 1). Prior to imputation, the area under the receiver operating curve (ROC) was used to assess the discriminatory accuracy of the models to correctly classify respondents based on the outcomes. Generalized Hosmer–Lemeshow goodness of fit was used to fit the imputation models prior to imputation. After estimation with the imputed data, the models were tested for equal fraction-missing-information to check that the between-imputation and within-imputation variances were proportional. The complex sampling method of the data was accounted for by using the sampling weights provided by Statistics Canada on the survey (svy) command in Stata.

Multilevel logistic regression models with province of residence as the group variable were used to assess the two outcomes – disability and risk of suicide. Four models were constructed for each outcome using stepwise multivariate analyses with backward elimination of covariates. In step one, the first model for each outcome was constructed using the sociodemographic factors (age, sex, marital status, education, income, race, smoking), personal and family history of mental illness, history of childhood maltreatment and history of chronic disease. In step two, three other models were constructed for each outcome by adding the comorbid substance use

disorder with major depression variable (alcohol & depression- model 2, cannabis & depression – model 3 and other drugs except cannabis & depression – model 4) to the covariates listed in step one. Since the multilevel models did not allow pairwise comparison post hoc analyses for the variable 'comorbid substance use disorder with major depression' in the three comorbid models, comparisons were generated by changing the reference category. The odds ratio (OR) of all covariates in step 1 final models and step 2 final models were reported for each outcome. Confounding was assessed for variables eliminated from the multivariate models and re-entered into the models if present. Since the focus of the analysis was to understand the main effects and the differences between isolated substance use disorders, major depression and the comorbidities on the risk of suicide ideation and disability, biologically plausible interaction terms were not assessed.

4.4 Results

4.4.1 Participants characteristics

Table 4-1 shows weighted percentages of the sociodemographic characteristics and distribution of DSM-IV diagnoses for the target population. A third of the population were residents of Ontario and aged 25-44 years. About half of the population were married, female, were post secondary graduates with total household income of $80,000 or more. Major depressive episode (MDE), Alcohol use disorders (AUD), Cannabis use disorders (CUD), other drugs excluding cannabis use disorder (DUD) had lifetime prevalence rates of 11.4%, 19%, 6.8% and 4.0% respectively while the lifetime comorbid diagnoses of MDE with AUD, MDE with CUD, MDE with DUD had prevalence rates of 3.23%, 1.73% and 1.29% respectively. About 2% of the population had high degree of disability (disability scroe of 40 or more).

Table 4-1. CCHS 2012:MH participants socio-demographic characteristics, distribution of DSM-IV diagnoses and WHO disability score

	Weighted percentages	95% CI
Province of residence		
Newfoundland and Labrador	1.55	1.45 - 1.65
Prince Edward	0.40	0.38 - 0.43
Nova Scotia	2.77	2.65 - 2.90
New Brunswick	2.15	2.05 - 2.26
Quebec	23.81	23.0 - 24.65
Ontario	38.95	38.03 - 39.89
Manitoba	3.43	3.20 - 3.68
Saskatchewan	2.82	2.67 - 2.97
Alberta	10.95	10.44 -11.48
British Columbia	13.16	12.60 - 13.75
Age		
15 to 24 years	8.52	7.97 - 9.10
25 to 44 years	36.14	34.97 - 37.32
45 to 64 years	37.22	36.03 -38.43
65 years and above	18.13	17.41 - 18.87
Sex		
Male	49.09	47.89 - 50.28
Female	50.91	49.72 - 52.11
Marital status		
Married	53.76	52.58 – 54.94
Common-law	11.89	11.14 – 12.69
Widowed	5.07	4.71 – 5.45
Divorced or Separated	8.67	7.96 – 9.43
Single	20.61	19.70 – 21.55
Highest level of education		
<Secondary	14.22	13.44 – 15.03
Secondary grad	15.70	14.09 – 16.55
Some post-secondary	5.96	5.40 – 6.57
Post-secondary grad	64.12	62.99 – 65.24
Race		
White	77.63	76.53 – 78.69
Non-white	22.37	21.31 – 23.47
Total household income (CDN$)		
No income or <20,000	4.16	3.77 – 4.59
20,000-39,999	11.84	11.22 – 12.48
40,000-59,999	18.15	17.29 – 19.04
60,000-79,999	17.75	16.85 – 18.68
80,000 or more	48.10	46.91 – 49.30
No of types of childhood maltreatment		
No child abuses	52.37	51.17 – 53.56
1-3 types of child abuses	40.28	39.11 – 41.47
4-6 types of child abuses	7.35	6.76 – 7.99
Type of smoker		
Daily	16.28	15.42 – 17.18
Occasionally	5.37	4.76 – 6.05
Not at all	78.35	77.31 – 79.36
Family history of mental health disorder		
Yes	39.19	38.04 – 40.35
No	59.85	58.69 – 61.00
Personal history of mental health disorder		
Yes	33.46	32.38 – 34.56
No	66.54	65.44 – 67.62
12-month major depressive episode	4.54	4.10 – 4.97
Lifetime major depressive episode	11.42	10.75 – 12.13

12-month alcohol use disorder[1]	2.85	2.49 – 3.25
Lifetime alcohol use disorder	18.96	18.11 – 19.86
12-month alcohol use disorder and major depression	0.42	0.31 – 0.58
Lifetime alcohol use disorder and major depression	3.23	2.91 - 3.58
12-month cannabis use disorder[2]	0.97	0.80 – 1.18
Lifetime cannabis use disorder	6.80	6.26 – 7.39
12-month cannabis use disorder and major depression	0.23	0.14 – 0.38
Lifetime cannabis use disorder and major depression	1.73	1.48 – 2.01
12-month drug use disorder[3]	0.59	0.47 – 0.76
Lifetime drug use disorder (other)	4.03	3.64 – 4.47
12-month drug use disorder and major depression	0.25	0.17 – 0.38
Lifetime drug use disorder (other) and major depression	1.29	1.10 – 1.51
12-month suicide ideation	3.00	2.65 – 3.40
Lifetime suicide ideation	11.61	10.95 – 12.31
WHO Disability Assessment Score (WHODAS)		
0 (lowest recordable degree)	97.95	97.61 - 98.24
1 (40 or more – high degree)	2.05	1.76 - 2.39

CCHS 2012: MH - Canadian Community Health Survey (CCHS), 2012: Mental Health Component
< Secondary- less than secondary education; Secondary grad- secondary education graduate; Some post sec – some post secondary education; Post-secondary grad – post secondary education graduate
[1]Alcohol abuse or dependence; [2]Cannabis abuse or dependence; [3]Drugs (excluding cannabis) abuse or dependence

4.4.2 Comorbid diagnosis and disability

The prevalence of disability using the WHO disability assessment score for the general Canadian population was 2.05% (Table 4-1). Notable factors associated with an increased risk for disability were older age, being widowed, history of a chronic condition, and personal history of a mental illness (Table 4-2). Higher income and educational status were protective from disability (Table 4-2).

Table 4-2. Participants sociodemographic factors associated with disability

	Crude OR (95% CI)	[a]Adjusted	
		OR (95% CI)	Statistic (p-value)
Age			0.004
15 to 24 years	1	1	
25 to 44 years	1.44 (0.67-3.06)	1.32 (0.75-2.32)	
45 to 64 years	**3.72** (1.79-7.74)**	**2.47** (1.34-4.53)*	
65 years and above	**4.80** (1.67-13.77)**	**2.26** (1.22-4.21)*	
Sex			
Male	1	1	
Female	**1.35** (1.09-1.67)*	1.12 (0.89-1.41)	
Marital Status			0.0005
Single	1	1	
Married	**1.34** (1.02-1.76)*	1.14 (0.86 -1.53)	
Common-law	0.88 (0.58-1.33)	0.76 (0.53-1.09)	
Widowed	**4.14** (2.27-7.52)**	**1.69** (1.22-2.35)**	
Divorced or Separated	**3.19** (2.38-4.27)**	1.46 (0.93-2.28)	
Educational status			0.005
<secondary	1	1	
Secondary grad	**0.60** (0.41-0.89)*	0.81 (0.56-1.17)	
Some post sec	0.83 (0.46-1.53)	1.27 (0.79-2.02)	
Post-secondary grad	**0.51** (0.42-0.63)**	**0.76** (0.66-0.88)**	
Race			
White	1	1	
Non-white	0.83 (0.63-1.07)	**1.30** (1.02-1.65)*	
Total Household Income ($)			<0.0001
No income or <20,000	1	1	
20,000-39,999	**0.68** (0.54-0.87)**	**0.77** (0.59-0.99)*	
40,000-59,999	**0.27** (0.17-0.44)**	**0.36** (0.21-0.63)**	
60,000-79,999	**0.24** (0.11-0.54)**	**0.35** (0.13-0.95)*	
80,000 or more	**0.15** (0.10-0.21)**	**0.25** (0.16-0.42)**	
Type of smoker			<0.0001
Not at all	1	1	
Daily	**2.10** (1.62-2.72)**	1.37 (0.94-1.98)	
Occasionally	**0.42** (0.27-0.66)**	**0.48** (0.32-0.73)**	
Types of childhood maltreatment			
None	1	x	
1-3 types	**1.49** (1.04-2.13)*		
4-6 types	**4.86** (2.89-8.19)**		
History of chronic disease			
Yes	**24.49** (15.18-39.52)**	**13.80** (8.61-22.13)**	
No	1	1	
Family history of mental health disorder			
Yes	**1.70** (1.16-2.48)*	**1.45** (1.04-2.03)*	
No	1	1	
Personal history of mental illness			
Yes	**2.96** (2.47-3.57)**	**2.35** (1.86-2.97)**	
No	1	1	

a - adjusted in a multivariate model
x – lost in multivariate analysis
Significant values are marked in bold print
* p-value < =0.05
** p-value <0.01
0.3% of variation explained by the province of residence (p-value=0.07)
< Secondary- less than secondary education; Secondary grad- secondary education graduate; Some post sec – some post secondary education; Post-secondary grad – post secondary education graduate

Individuals with single diagnosis of MDE only were 4 times (OR, 95%CI – **4.68,** 3.46-6.33) more likely to have disability while the risk was 2-fold (OR, 95%CI – **2.92,** 1.65-5.18) in single diagnosis of DUD only (Table 4.3). Compared to no diagnosis (ND), individuals with comorbid AUD with MDE, CUD with MDE and DUD with MDE had 4-, 6- and 9-times higher risk of disability respectively. Individuals with single MDE, comorbid AUD with MDE and DUD with MDE had significantly higher risk of disability compared to those with single SUD only (AUD, and DUD).

Table 4-3. Lifetime comorbid SUD with major depression and associated disability

	OR (95%CI)		
	Ref= ND	***Ref = SUD***	***Ref = MD***
Alcohol and major depression (model 1)			
ND	1	0.95 (0.60-1.50)	**0.21** (0.16-0.29)**
AUD only	1.05 (0.67-1.67)	1	**0.23** (0.14-0.37)**
MDE only	**4.68** (3.46-6.33)**	**4.44** (2.73-7.24)**	1
AUD & MDE	**3.97** (2.51-6.27)**	**3.77** (1.87-7.60)**	0.85 (0.45-1.61)
Cannabis and major depression (model 2)			
ND	1	0.58 (0.20-1.65)	**0.22** (0.18-0.25)**
CUD only	1.72 (0.61-4.91)	1	**0.37** (0.14-0.99)*
MDE only	**4.64** (3.94-5.46)**	**2.69** (1.00-7.20)*	1
CUD & MDE	**5.97** (3.08-11.61)**	3.46 (0.88-13.93)	1.29 (0.68-2.43)
Other drugs (excluding cannabis) and major depression (model 3)			
ND	1	**0.34** (0.19-0.61)**	**0.21** (0.19-0.24)**
DUD only	**2.92** (1.65-5.18)**	1	0.61 (0.34-1.10)
MDE only	**4.79** (4.24-5.40)**	1.64 (0.90-2.98)	1
DUD & MDE	**8.54** (3.89-18.76)**	**2.92** (1.00-8.50)*	1.78 (0.82-3.40)

Significant values are marked in bold print
* p-value < =0.05
** p-value <0.01
1 – reference category
Models were adjusted for age, gender, marital status, highest level of education, race, smoking status, history of any mental health disorder, family history of mental health disorder in multivariate analyses
Variation explained by the province of residence: model 1 = 0.5% (p-value=0.08); model 2 = 0.4% (p-value=0.1); model 3 = 0.5% 9 (p-value=0.1)
ND – no diagnosis; AUD - Alcohol use disorders is defined DSM-IV Alcohol Abuse /or Dependence diagnoses.; CUD - Cannabis use disorders is defined DSM-IV Cannabis Abuse /or Dependence diagnoses.; DUD - Drug use disorders is defined as DSM-IV diagnoses of drug abuse/or dependence diagnoses on opiates, sedatives, tranquilizers, amphetamines hallucinogens, heroin, cocaine, inhalants, and/or other drug except cannabis.; MDE - Major Depression is defined DSM-IV diagnosis of major depressive episode. SUD – AUD (model 1), CUD (model 2) and DUD (model 3)
Disability was assessed with the World Health Organization Disability Assessment Schedule (WHODAS) 2.0 score (40 or more versus <40)

4.4.3 Comorbid diagnosis and suicide ideation

The lifetime and 12-month prevalence of suicide ideation were 11.61% and 3.0% respectively (Table 4-1). Table 4-4 shows factors associated with suicidal ideation. The risk of suicidal thoughts is increased in those with a history of chronic health condition, childhood maltreatment, family and personal history of mental illness. Older age and being married or common-law, being a graduate (secondary or post secondary) were protective from suicidal ideation.

Table 4-4. Participants sociodemographic factors associated with 12-month suicide ideation

	Crude OR (95% CI)	[a]Adjusted	
		OR (95% CI)	Statistic (p-value)
Age			<0.0001
15 to 24 years	1	1	
25 to 44 years	**0.63** (0.50-0.80)**	**0.61** (0.50-0.75)**	
45 to 64 years	**0.47** (0.42-0.53)**	**0.39** (0.32-0.49)**	
65 years and above	**0.22** (0.18-0.27)**	**0.21** (0.16-0.27)**	
Sex			
Male	1	1	
Female	1.08 (0.96-1.22)	1.08 (0.92-1.27)	
Marital Status			0.0003
Single	1	1	
Married	**0.37** (0.33-0.41)**	**0.72** (0.64-0.81)**	
Common-law	0.51 (0.26-1.00)	**0.56** (0.35-0.89)*	
Widowed	**0.36** (0.22-0.60)**	0.96 (0.56-1.64)	
Divorced or Separated	0.89 (0.73-1.08)	1.02 (0.82-1.28)	
Educational status			0.05
<secondary	1	1	
Secondary grad	**0.67** (0.52-0.87)**	**0.64** (0.46-0.90)*	
Some post sec	0.95 (0.65-1.39)	0.60 (0.34-1.04)	
Post-secondary grad	**0.58** (0.50-0.68)**	**0.69** (0.52-0.91)*	
Race			
White	1	1	
Non-white	1.13 (0.88-1.45)	**1.34** (1.12-1.61)**	
Total Household Income ($)			<0.0001
No income or <20,000	1	1	
20,000-39,999	0.69 (0.44-1.10)	0.95 (0.64-1.42)	
40,000-59,999	**0.48** (0.29-0.80)*	0.81 (0.52-1.27)	
60,000-79,999	**0.44** (0.29-0.65)**	0.72 (0.46-1.13)	
80,000 or more	**0.30** (0.22-0.40)**	**0.51** (0.40-0.67)**	
Type of smoker			0.04
Not at all	1	1	
Daily	**2.38** (2.09-2.72)**	**1.19** (1.01-1.40)*	
Occasionally	**2.36** (1.48-3.76)**	1.43 (0.96-2.13)	
Types of childhood maltreatment			<0.0001
None	1	1	
1-3 types	**2.66** (1.94-3.64)**	**1.80** (1.21-2.68)*	
4-6 types	**8.08** (6.08-10.77)**	**3.05** (2.29-4.06)**	

History of chronic disease		
Yes	**3.05** (2.60-3.58)**	**2.47** (2.02-3.03)**
No	1	1
Family history of mental health disorder		
Yes	**2.70** (2.50-2.91)**	**1.62** (1.38-1.89)**
No	1	1
Personal history of mental illness		
Yes	**7.06** (5.61-8.88)**	**4.41** (3.42-5.69)**
No	1	1

a – adjusted in a multivariate model
Significant values are marked in bold print
* p-value < =0.05
** p-value <0.01
Variation explained by the Province of residence is 0.001% (p-value=0.7)
< Secondary- less than secondary education; Secondary grad- secondary education graduate; Some post sec – some post secondary education; Post-secondary grad – post secondary education graduate

Compared to those with no diagnosis (Table 4-5), individuals with comorbid diagnosis of AUD with MDE, CUD with MDE, DUD with MDE were 9 to 16 times more likely to have suicide ideation (OR 95% CI - **9.02,** 5.61-14.49**; 11.27,** 7.57-16.78**; 16.19,** 11.10-23.63 respectively). Individuals with comorbid diagnosis of AUD with MDE, CUD with MDE and DUD with MDE had about six to eight-fold increase in the risk of suicide when compared with individuals with single SUD only (OR 95% CI - **5.58,** 4.28-7.27**; 8.11,** 5.01-13.12**; 6.63,** 5.10-8.64 respectively). A single diagnosis of MDE gave about 7-fold increase in the risk of suicide ideation when compared with no diagnosis, and three to five-fold increase when compared with a single diagnosis of DUD, AUD and CUD (OR 95% CI - **2.92,** 2.18-3.91**; 4.08,** 2.10-7.93**; 5.16,** 3.75-7.09) respectively. A single diagnosis of DUD only gave a 2-fold increase in the risk of suicide ideation compared to individuals with no diagnosis.

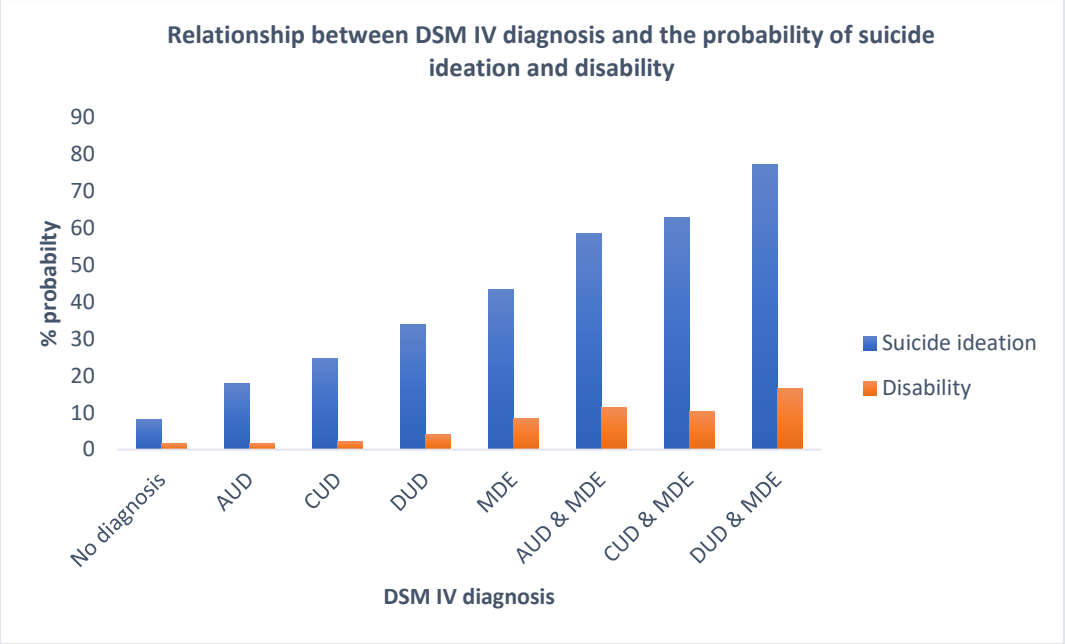
Table 4-5. DSM-IV diagnoses and the risk of 12-month suicide ideation

	OR (95%CI)		
	Ref= ND	***Ref = SUD***	***Ref = MD***
Alcohol and major depression (model 1)			
ND	1	0.62 (0.38-1.02)	**0.15** (0.11-0.22)**
AUD only	1.62 (0.98-2.66)	1	**0.25** (0.13-0.48)**
MDE only	**6.59** (4.58-9.47)**	**4.08** (2.10-7.93)**	1
AUD & MDE	**9.02** (5.61-14.49)**	**5.58** (4.28-7.27)**	1.37 (0.80-2.35)
Cannabis and major depression (model 2)			
ND	1	0.72 (0.51-1.01)	**0.14** (0.09-0.22)**
CUD only	1.39 (0.99-1.96)	1	**0.19** (0.14-0.27)**
MDE only	**7.17** (4.49-11.46)**	**5.16** (3.75-7.09)**	1
CUD &MDE	**11.27** (7.57-16.78)**	**8.11** (5.01-13.12)**	1.57 (0.86-2.88)
Other drugs (excluding cannabis) and major depression (model 3)			
ND	1	**0.41** (0.28-0.60)**	**0.14** (0.09-0.21)**
DUD only	**2.44** (1.66-3.59)**	1	**0.34** (0.26-0.46)**
MDE only	**7.13** (4.76-10.68)**	**2.92** (2.18-3.91)**	1
DUD &MDE	**16.19** (11.10-23.63)**	**6.63** (5.10-8.64)**	**2.28** (1.47-3.53)**

Significant values are marked in bold print
* p-value < =0.05
** p-value <0.01
1 – reference category
Models were adjusted for age, gender, marital status, highest level of education, race, smoking status, history of any mental health disorder, family history of mental health disorder in multivariate analyses
Variation explained by the Province of residence: model 1=0.01% (p-value=0.6); model 2=0.01% (p-value=0.4); model 3=0.01% (p-value=0.4)
ND – no diagnosis; AUD - Alcohol use disorders is defined DSM-IV Alcohol Abuse /or Dependence diagnoses.; CUD - Cannabis use disorders is defined DSM-IV Cannabis Abuse /or Dependence diagnoses.; DUD - Drug use disorders is defined as DSM-IV diagnoses of drug abuse/or dependence diagnoses on opiates, sedatives, tranquilizers, amphetamines hallucinogens, heroin, cocaine, inhalants, and/or other drug except cannabis.; MDE - Major Depression is defined DSM-IV diagnosis of major depressive episode. SUD – AUD (model 1), CUD (model 2) and DUD (model 3)

The relationship between DSM-IV diagnosis and the probability of suicide ideation and disability in the population is shown in figure 4-1. The probability of suicide ideation and disability is <10% and <2% respectively in individuals with no diagnosis of either SUD (AUD, CUD or DUD) or MDE. There is 18-34% and 2-4% probability of suicide ideation and disability respectively with isolated diagnosis of a SUD. With a diagnosis of comorbid SUD with MDE, the probability of the suicide ideation and disability range from 60-80% and 11-17% respectively.

Figure 4-1. Relationship between DSM-IV diagnosis and the probability of suicide ideation and disability



AUD - Alcohol use disorder, defined DSM-IV Alcohol Abuse /or Dependence diagnoses.; CUD - Cannabis use disorder, defined DSM-IV Cannabis Abuse /or Dependence diagnoses; DUD - Drug use disorder, defined as DSM-IV diagnoses of drug abuse/or dependence diagnoses on opiates, sedatives, tranquilizers, amphetamines hallucinogens, heroin, cocaine, inhalants, and/or other drug except cannabis.; MDE - Major depressive episode, defined DSM-IV diagnosis of major depressive episode.

4.5 Discussion

4.5.1 Prevalence and associations of comorbid diagnosis

The past 12-month prevalence of AUD, CUD, DUD, and MDE were 2.9%, 0.97%, 0.6% and 4.5% respectively. This prevalence of MDE, which is about twice that of AUD, is consistent with the findings from a previous Canadian survey on the same population (Currie, et al., 2005). A much higher prevalence was found for depression (Hasin, Goodwin, Stinson, & Grant, 2005), alcohol use disorder (Grant, et al., 2015; Grant, et al., 2004), cannabis and drugs use disorder (Grant, et al., 2004) in the US compared to our study. Prevalence of comorbid diagnosis of SUD with MDE in our study was much lower than those found in the US (Grant, et al., 2004). These variations in the prevalence of SUDs, MDE and comorbid SUD with MDE could be due to different population characteristics, research methodologies, and diagnostic criteria.

4.5.2 Comorbid SUD with MDE and disability

Our study showed a gradual increase in the probability of disability in the population as one moves from 'no diagnosis' to single diagnosis of a SUD, a single diagnosis of MDE through comorbid diagnosis of SUD with MDE. The risk of disability was high in individuals with single diagnosis of DUD or MDE and comorbid diagnosis of SUD with MDE in our study. Our study showed a significantly higher odds of disability in comorbid AUD with MDE (OR, 95%CI - **3.77**, 1.87-7.60) and comorbid DUD with MDE (OR, 95%CI - **2.92**, 1.00-8.50) compared to single diagnosis of AUD and DUD respectively. This was consistent with other studies that found increased social, occupational and functional disability as well as healthcare utilization amongst individuals with comorbid substance use and psychiatric disorders (Wilk, West, Rae, & Regier, 2006; Olfson, et al., 1997; Kessler, et al., 1996; Kessler, Foster, Saunders, & Stagg, 1995; Kessler R. , 2004; Burns, Teesson, & O'Neill, 2005). This finding could be explained by the synergistic interaction of the pathological effects of comorbid conditions.

Major depression was found to have an associated increased risk of disability compared to isolated AUD or CUD. However, comorbid SUD (AUD, CUD, DUD) with MDE were not significantly associated with disability when compared with isolated MDE. Two possible explanations could be responsible for these findings. Firstly, it could be that the substance use by individuals with comorbid diagnosis was seen secondary to self-medication for the mood disorder, hence, the substance use disorders are less severe with less effect on functioning (Wilk, West, Rae, & Regier, 2006). Secondly, since pharmacological therapy is an integral part of the treatment of mood disorders, those with comorbid diagnosis are more likely to be on pharmacological agents that may lessen the effect of substance use disorders on patient functioning (Wilk, West, Rae, & Regier, 2006).

Disability is known to be significantly associated with poorer quality of life (Üstün, et al., 2010; Thomas, Nisha, & Varghese, 2016; Tharoor, NarasimhanaSharma, & Chauhan, 2007). Therefore, the increased disability associated with comorbid SUD with MDE found in our study provides further evidence of a lower quality of life by individuals with the comorbidity (Saatcioglu, Yapici, & Cakmak, 2008).

4.5.3 Comorbid SUD with MDE and risk of suicide ideation

Findings from our study showed a gradual increase from 'no diagnosis' to comorbid diagnosis of SUD with MDE in the probability of having suicidal thoughts in the population. Our study also showed an increased risk of suicidal thoughts in individuals with comorbid SUD with MDE and sole diagnosis of MDE or DUD, consistent with previous studies (Currie, et al., 2005; Sher, et al., 2008; Cornelius, et al., 1995). This also supports other studies that demonstrated AUDs and major depression as the most commonly diagnosed major pathological disorders in persons who commit suicide (Fawcett, Clark, & Busch, 1993; Rudd, Dahm, & Rajab, 1993; Henriksson, et al., 1993).

When compared with individuals with no diagnosis, the risk of suicide ideation associated with comorbid SUD with MDE (OR, 95%CI: AUD/MDE - **9.02** , 5.61-14.49; CUD/MDE- **11.27,** 7.57-16.78; DUD/MDE -**16.19**, 11.10-23.63) was much higher than the risk associated with single diagnosis of MDE (OR, 95%CI - **7.13**, 4.76-10.68). Comorbid SUD with MDE significantly increased the odds of suicide ideation when compared with the sole diagnosis of AUD (OR, 95%CI -**5.58**, 4.28-7.27), CUD (OR, 95%CI - **8.11**, 5.01-13.12), DUD (OR, 95%CI- **6.63**, 5.10-8.64) and MDE (OR, 95%CI - **2.28**, 1.47-3.53). These findings were consistent with previous findings of a disproportionate increase in suicide ideation with comorbid AUD with MDE (Barraclough, Bunch, Nelson, & Sainsbury, 1974; Cornelius J. R., et al., 1995; Britton, et al., 2015; Brière, Rohde, Seeley, & Daniel Klein, 2014). In addition, when compared with the single diagnosis of SUD, a single diagnosis of MDE had a two to five-fold increase in the risk of suicide ideation, also consistent with previous findings where primary major depression without secondary AUD conferred a prospective risk of suicide attempts on the population (Britton, et al., 2015).

This associated increased risk of suicide ideation in comorbid SUD with MDE can be explained by depression mediating the effect of SUD on suicide or SUD being the consequence of MDE. Studies suggest that suicidal behaviour, aggression, and alcoholism have been linked to abnormal serotonergic function (Mann & Malone, 1997; Mann, Brent, & Arango, 2001); and this has been proposed to mediate an individual's genetic and developmental predispositions (Mann, Waternaux, Haas, & Malone, 1999). In addition, studies on humans and animals alike have shown that increased uninhibited psychopathology, substance abuse, and impulsive aggression

were secondary to serotonin abnormalities (Crabbe, et al., 1996; Saudou, et al., 1994; Mann, Brent, & Arango, 2001).

Consistent with previous studies, drug use disorders had significant association with suicide ideation (Schneider, 2009; Borges, Walters, & Kessler, 2000; Miller, et al., 2011; Petronis, Samuel, Mosckicki, & Anthony, 1990; Borges, Benjet, Orozco, Medina-Mora, & Menendez, 2017a). Inconsistent with previous reports, our study did not find an increased risk of suicide ideation in AUD and CUD only (Sher, et al., 2008; Flensborg-Madsen, et al., 2009; Borges, Benjet, Orozco, Medina-Mora, & Menendez, 2017a; Shalit, Shoval, Shlosberg, Feingold, & Lev-Ran, 2016) after controlling for sociodemographic factors and family history of mental illness. This we attributed to the DSM IV substance use disorder criteria, that is the presence of DSM IV substance abuse or DSM IV substance dependence without an indication of severity as seen in DSM V. This finding was however, consistent with a previous finding of no association in low to moderate severity of cannabis use (Shalit, Shoval, Shlosberg, Feingold, & Lev-Ran, 2016).

4.5.4 Strengths and limitations

A strength of this analysis is that it was based on a nationally representative sample of the Canadian population which provides insight into these comorbidities among individuals irrespective of their health-seeking behaviors. Another strength was that the diagnoses of substance use disorders and major depressive episodes were derived from DSM IV criteria using a structured diagnostic interview and algorithm (WMH-CIDI). This study included different comparison groups of SUD and MDE highlighting the actual effects of comorbid associations. Missing values were accounted for using multiple imputations and the complex data structure was accounted for with multilevel random effects models and survey weights, enabling generalizability. Limitations of this study include the cross-sectional study design which does not allow for causal inference. Further studies would be required to assess causality. Individuals living on reserves and other Aboriginal settlements, in institutions and full-time members of the Canadian Forces which make up about 3% of the total population were excluded from the data. Therefore, our analysis may have underestimated the true strength of associations of interest. This study was based on self-reported data, thus could be compromised by recall bias and under-reporting.

4.6 Conclusion

In conclusion, this study does provide further evidence of associated risk of disability and the risk of suicide ideation among persons who have comorbid alcohol use disorders, cannabis use disorders, drug use disorders with major depression. Effective integration of mental health and addictions services may contribute to better treatment outcomes.

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Appendix A. Missing values analysis

Table A.1 Summary of missing values

Variables	Observed	Missing	Imputed	Total
Marital status	25,045	68	68	25113
Educational status	25,002	111	111	25113
Race	25,012	101	101	25113
Income	25,099	14	14	25113
12-month CUD	24,910	203	203	25113
Lifetime CUD	24,905	208	208	25113
12-month DUD	24,833	280	280	25113
Lifetime DUD	24,828	285	285	25113
12-month AUD	24,737	376	376	25113
Lifetime AUD	24,719	394	394	25113
12-month MDE	24,954	159	159	25113
Lifetime MDE	24,951	162	162	25113
12-month suicide ideation	25038	75	75	25113
Lifetime suicide ideation	25040	73	73	25113
WHO disability assessment score	24974	319	319	25113
Childhood maltreatment	22562	2551	2551	25113
Smoking status	25,097	16	16	25113
Family history of mental illness	24,832	281	281	25113
Personal history of mental illness	24,373	740	740	25113
History chronic condition	25086	27	27	25113

CUD- cannabis us disorder; AUD- alcohol use disorder; DUD – other drugs (excluding cannabis) use disorder; MDE – major depressive episode; WHO – World health Organization

Test for Missing Completely At Random (MCAR)

Little's MCAR test: Prob > chi-square = 0.0000

Data is not MCAR.

Table A.2 Association of predictor variables and missingness in 12-month suicide ideation

Variables	Chi square p-value
Province of residence	0.10
Age	0.55
Sex	0.46
Marital status	0.36
Educational status	0.05
Race	0.58
Income	0.003
12-month CUD	0.33
Lifetime CUD	0.08
12-month DUD	0.48
Lifetime DUD	0.27
12-month AUD	0.15
Lifetime AUD	0.001
12-month MDE	0.96
Lifetime MDE	0.67
Smoking status	0.47
Childhood maltreatment	0.31
Family history of mental illness	<0.0001
Personal history of mental illness	0.95
History of a chronic condition	0.07

CUD- cannabis us disorder; AUD- alcohol use disorder; DUD – other drugs (excluding cannabis) use disorder; MDE – major depressive episode

Table A.3 Association of predictor variables and missingness in WHO disability assessment score

Variables	Chi square p-value
Province of residence	0.20
Age	<0.0001
Sex	<0.0001
Marital status	<0.0001
Educational status	<0.0001
Race	0.82
Income	<0.0001
Body mass index	0.76
12-month CUD	0.04
Lifetime CUD	0.52
12-month DUD	0.43
Lifetime DUD	0.41
12-month AUD	0.09
Lifetime AUD	0.05
12-month MDE	<0.0001
Lifetime MDE	0.04
Smoking status	0.08
Childhood maltreatment	0.16
Family history of mental illness	<0.0001
Personal history of mental illness	0.63
Has a chronic condition	<0.0001

WHO- World Health Organization; CUD- cannabis us disorder; AUD- alcohol use disorder; DUD – other drugs (excluding cannabis) use disorder; MDE – major depressive episode

CHAPTER 5. SUBSTANCE USE DISORDER, OVERWEIGHT/OBESITY AND CO-MORBID MAJOR DEPRESSION

5.1 Introduction

Obesity/overweight and substance use disorders (SUDs) are major risk factors in the global burden of disease (Pasch, Velazquez, Cance, Moe, & Lytle, 2012). They are significant public health problems associated with increased health risks, morbidity, mortality, medical costs and reduced life expectancy (Bertakis & Azari, 2005; McGinnis & Foege, 1999; Must, et al., 1999; N'Goran, et al., 2015). Psychiatric disorders also contribute immensely to global disease burden (Kessler, Chiu, Delmer, Merikangas, & Walters, 2005; Greenberg, et al., 1999), and frequently co-occur with both obesity (Simon, et al., 2006) and substance use disorders (Kessler, Chiu, Delmer, Merikangas, & Walters, 2005; Grant, et al., 2004; Hasin, Goodwin, Stinson, & Grant, 2005) with major depression having an increased likelihood for this association. Despite this comorbidity with psychiatric disorders, an inverse relationship is said to exist between obesity and SUD (Gruchow, Sobocinski, Barboriak, & Scheller, 1985; Lahti-Koski, Pietinen, Heliovaara, & Vartiainen, 2002; Liu, Serdula, Williamson, Mokdad, & Byers, 1994; Kleiner, et al., 2004; Gearhardt & Corbin, 2009; Warren, Frost-Pineda, & Gold, 2005; Pickering, et al., 2011).

Several mechanisms have been suggested to explain the association between body mass index (BMI) and substance use. One mechanism is the 'coping model'. Here, it is suggested that to cope with the negative social and emotional consequences of their excess weight, individuals problematically use substances (Pasch, Velazquez, Cance, Moe, & Lytle, 2012). Those who are overweight/obese may also use substances as a weight control strategy in the 'weight control model' (Pasch, Velazquez, Cance, Moe, & Lytle, 2012). In another mechanism, some substances may increase the risk of future weight gain especially alcohol and cannabis, in the 'weight gain model' (Pasch, Velazquez, Cance, Moe, & Lytle, 2012). Alcohol may affect the energy balance and cannabis has been linked to increased appetite and decreased inhibitions. This can lead to increased calorie intake and dulling of the incentive to physical activity (Pasch, Velazquez, Cance, Moe, & Lytle, 2012). Finally, it is suggested that food intake and substance use both

compete for the same neural reward sites in the brain and as such, a higher BMI is most likely to be associated with lower substance use (Blüml, et al., 2012).

Some literature support the hypothesis that common neural substrates underlie both food and illicit drug consumption (Kalivas & Volkow, 2005; Trinko, Sears, Guarnieri, & DiLeone, 2007; Volkow, Wang, Fowler, & Telang, 2008; Volkow & Wise, 2005). The hypothesized neurobiological pathways responsible for the regulation of food intake and substance use are the mesolimbic and mesocortical dopaminergic reward-motivation circuits and endogenous opioid systems (Volkow & Wise, 2005; Trinko, Sears, Guarnieri, & DiLeone, 2007; Wang, Volkow, Thanos, & Fowler, 2004; Di Chiara & Imperato, 1988; MacDonald, Billington, & Levine, 2004). A disorder in the reward homeostasis and/or a deficit in the neural reward circuits are thought to be the mechanisms through which obesity and substance use disorder occur (Johnson & Kenny, 2010). Evidence from neuro-functional imaging studies showed low levels of dopamine D2 in drug-addicted subjects (Volkow, Fowler, & Wang, 2004) and in obese patients with an inverse relationship between BMI and dopamine D2 receptor levels (Wang, et al., 2001). In addition, genome scan studies reported that different consumption phenotypes, that is food or drug abuse, have common genetic determinants (Ehlers & Wilhelmsen, 2007).

Several large epidemiological studies show the inverse relationship between substance use and BMI (Gearhardt & Corbin, 2009; Kleiner, et al., 2004; Duncan, et al., 2009; Breslow & Smothers, 2005; Blüml, et al., 2012) but these results are not unanimous as other studies could not find this inverse association (Arif & Rohrer, 2005; Barry & Petry, 2009; Pickering, Grant, Chou, & Compton, 2007; Petry, Barry, & Pietrzak, 2008; McLaren, Beck, Patten, Fick, & Adair, 2008). However, most of these studies were cross-sectional and lack the ability to determine causality since cross-sectional study designs do not have the temporality criterion; an important determinant of causality (Hill A. B., 1965). Even though some studies found no association (Mather, Cox, Enns, & Sareen, 2009; Petry, Barry, & Pietrzak, 2008) or a positive relationship (McLaren, Beck, Patten, Fick, & Adair, 2008) between obesity and SUD, in their longitudinal study, Pickering et al., (2011) found that persons who were overweight or obese had a reduced likelihood of having alcohol or SUDs after 3 years. Thus, with the excess consumption of one substance (e.g., drug abuse), the reward system is activated and the desire for and use of the other substance (e.g., food) may be blocked or reduced (Gearhardt, Harrison, & McKee, 2012).

Few studies have been done to examine the association between obesity and substance use with underlying major depression and none in Canada. Studying the association between obesity and SUD with depression is important since depression may encourage the excessive consumption of food and addictive substances (Gearhardt, Harrison, & McKee, 2012). Major depression may increase the likelihood of either obesity or SUDs, but does it alter the relationship between obesity and SUDs? This forms the basis for the hypothesis, that major depression could alter the inverse relationship between obesity and SUDs.

5.2 Objective

This study was aimed to examine the associations between substance use disorders and overweight/obesity, and the effect major depression has on this relationship.

5.3 Methods

5.3.1 Subjects

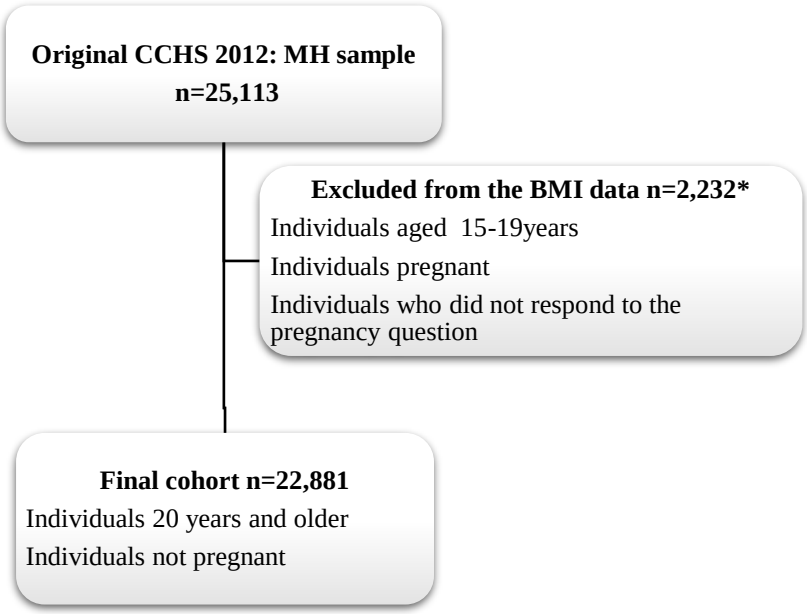
Data for these analyses came from the Canadian Community Health Survey (CCHS), 2012: Mental Health Component (CCHS 2012: MH) (Statistics Canada, 2014). Briefly, it is a cross sectional survey of persons aged 15 years or more and resident in one of the ten Canadian provinces. Criteria for exclusion from the survey were living in certain remote areas, institutions, and reserves. In addition, full-time members of the Canadian Forces were not surveyed. These excluded populations make an estimated 3% of the target national population (Statistics Canada, 2014). The CCHS 2012: MH is a comprehensive look at mental health with respect to who is affected by specific mental health disorders, positive mental health, access to and utilization of formal and informal mental health services and support; as well as individual functionality, regardless of the presence of a mental health problem (Statistics Canada, 2014). The data was collected by Statistics Canada between January and December of 2012, (N = 25,113) with a response rate of 86.3%.

The current analysis was conducted for the cohort of individuals who met the inclusion criteria for deriving Body Mass Index (BMI) in the data, N= 22,881 (Figure 5-1). Inclusion criteria for BMI in the data was adult respondents aged 20 and over and not pregnant. Female respondents who were between ages 18 to 49 years and were pregnant or did not respond to the

pregnancy question were excluded from the BMI data. In addition, the BMI data was suppressed for individuals 15-19year old since BMI classification for less than 18 is different from adults (Statistics Canada, 2014).

This secondary analysis of the CCHS 2012: MH dataset was done using the Public Use Microdata Files (PUMF). Unlike the confidential microdata files (Master data files) which are accessible through Research Data Centres only, the PUMF is manipulated by aggregating, capping, or completely erasing variables that are considered personal identifiers to allow for accessibility through University libraries while maintaining confidentiality (Statistics Canada, 2017).

Figure 5-1. Cohort sample derivation



Excluded from the analysis

5.3.2 Major Depression

Unipolar Major Depressive Episode (MDE) was defined using the World Mental Health version of the Composite International Diagnostic Interview (WMH-CIDI) algorithm derived from the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV). This analysis was based on both the 12-month and lifetime MDE (Statistics Canada, 2014).

5.3.3 Substance Use Disorder (SUD)

The WMH-CIDI algorithms derived from DSM IV were used to define substance abuse or dependence for alcohol (alcohol use disorder -AUD), cannabis (cannabis use disorder – CUD) and other drugs excluding cannabis (drugs use disorder- DUD) in the data (Statistics Canada 2014). This analysis was based on symptoms of abuse or dependence reported in the last 12-months and lifetime (Statistics Canada, 2014).

5.3.4 Body Mass Index (BMI)

Body Mass Index was derived from self-reported weight and height in the survey data and was classified as: underweight (<18.5), normal weight (18.5 – 24.9), over-weight (25.0 – 29.9) and obese (>= 30.0) for adults 20years and over using the international standard (Statistics Canada, 2014). Female respondents aged 18 to 49 who were pregnant or did not answer the pregnancy question were excluded from the BMI data (Statistics Canada, 2014).

5.3.5 Other measures

Demographic information was obtained for: age, sex, gender, marital status, (married**,** common-law**,** widowed**,** divorced or separated**,** single), highest level of education (less than secondary education, secondary education graduate, some post secondary education, post secondary education graduate), total household income in Canadian dollars (no income or <20,000, 20,000-39,999, 40,000-59,999, 60,000-79,999, 80,000 or more), race (white, non-white), smoking status, personal and family history of mental health disorder.

5.3.6 Statistical Analyses

First, by merging each SUD (alcohol, cannabis, other drugs) variable and MDE, a new variable, comorbid SUD with MDE was created. For each SUD, the new variable created had four levels – no diagnosis (neither SUD nor MDE), single diagnosis of SUD (AUD or CUD or DUD), single diagnosis of MDE and comorbid diagnosis of SUD with MDE. Second, participants were described according to the BMI category. Third, analyses to examine the sociodemographic and other risk factors of BMI was done. The main associations between major depression, SUDs (alcohol, cannabis only and other drugs excluding cannabis) on BMI category were also done. Then, the comorbid associations, that is, SUDs with MDE on BMI category

were assessed. These associations were assessed using multinomial logistic regression models in STATA version 14 after a failed proportional odds assumption test (the Brant test). In these analyses, individuals with normal weight BMI category were the reference category.

Missing values were assessed using MCAR test on Stata 14 to determine if data was missing completely at random (MCAR) and a justification for a complete case analysis. Data was not MCAR (Appendix 1). Multiple imputations using chained equations was then carried out following significant Chi Square associations between the independent variables and the missingness in the outcome variable (BMI) (Appendix 1). Generalized Hosmer–Lemeshow goodness of fit was used to fit the outcome models and imputation models prior to imputation. After estimation with the imputed data, the models were tested for equal fraction-missing-information to check that the between-imputation and within-imputation variances were proportional. The complex sampling method of the data was accounted for by using the sampling weights provided by Statistics Canada on the survey (svy) command in Stata.

Four models (AUD, CUD, DUD and MDE) were assessed for the main associations with BMI while three models (alcohol and depression, cannabis and depression, other drugs excluding cannabis and depression) were examined for the comorbid associations between SUD and MDE on BMI. Using a stepwise multinomial logistic regression analysis with backward elimination of covariates, multivariate models were built with the addition of sociodemographic factors and other risk factors as covariates. Since the multinomial models of multiply data did not allow pairwise comparison post hoc analyses, comparisons of different levels of the comorbid variable were generated by changing the reference category. The relative risk ratios (RRR) of the risk factors of BMI , the main associations and comorbid models were reported. Confounding was assessed for variables eliminated from the multivariate models and re-entered into the models if present. Since the focus of the analysis was to understand the main effects and the differences between isolated substance use disorders, major depression and the comorbidities on the risk of overweight/obesity, biologically plausible interaction terms were not assessed.

5.4 Results

5.4.1 Participant characteristics

Table 5-1 below shows the participants sociodemographic distributions in relation to their BMI status. About a fifth of the population was obese while a third was overweight. Obese participants were more likely to be middle-aged, more likely to be married, more likely to be a post-secondary graduate and white.

Table 5-1. CCHS 2012: MH participants characteristics by BMI

	Underweight % (95%CI)	Normal weight % (95%CI)	Overweight % (95%CI)	Obese % (95%CI)	Total % (95%CI)
Age					
20 to 24 years	0.5 (0.3-0.6)	5.3 (4.8-5.7)	1.6 (1.4-1.9)	1.0 (0.8-1.1)	8.3 (7.8-8.9)
25 to 44 years	0.9 (0.7-1.1)	17.1 (16.1-18.0)	11.2 (10.4-12.0)	6.3 (5.8-6.9)	35.5 (34.3-36.6)
45 to 64 years	0.5 (0.4-0.6)	14.7 (13.8-15.7)	13.8 (13.0-14.6)	8.6 (7.9-9.3)	37.5 (36.4-38.7)
65 years and above	0.4 (0.3-0.6)	7.6 (7.1-8.0)	7.0 (6.6-7.5)	3.7 (3.3-4.0)	18.7 (18.0-19.4)
Sex					
Male	0.7 (0.5-0.8)	19.5 (18.5-20.5)	19.9 (19.1-20.9)	10.1 (9.4-10.8)	50.2 (49.0-51.4)
Female	1.6 (1.4-1.9)	25.1 (24.1-26.2)	13.6 (12.4-14.4)	9.4 (8.7-10.1)	49.8 (48.6-51.0)
Marital status					
Married	0.8 (0.6-0.9)	22.2 (21.2-23.2)	19.4 (18.5-20.3)	11.3 (10.6-12.1)	53.7 (52.5-54.8)
Common law	0.3 (0.2-0.5)	5.4 (5.0-6.0)	3.7 (3.2-4.2)	2.2 (1.9-2.5)	11.6 (10.9-12.4)
Widowed	0.2 (0.1-0.4)	2.2 (2.0-2.4)	1.6 (1.5-1.8)	1.2 (1.0-1.4)	5.2 (4.9-5.6)
Divorced/Separated	0.2 (0.1-0.3)	3.9 (3.4-4.5)	3.3 (2.9-3.8)	1.4 (1.2-1.6)	8.8 (8.1-9.6)
Single	0.8 (0.6-1.0)	10.9-10.2-11.7)	5.4 (5.1-6.1)	3.5 (3.1-3.9)	20.7 (19.8-21.7)
Highest level of education					
< secondary	0.4 (0.3-0.5)	5.5 (5.0-6.1)	5.1 (4.7-5.6)	3.6 (3.3-4.1)	14.6 (13.8-15.4)
Secondary grad	0.4 (0.3-0.6)	6.3 (5.8-6.8)	5.6 (5.1-6.1)	3.3 (2.9-3.8)	15.6 (14.8-16.4)
Some post sec	0.2 (0.1-0.3)	2.8 (2.4-3.2)	1.8 (1.5-2.2)	1.2 (1.0-1.5)	6.0 (5.5-6.6)
Post-secondary grad	1.3 (1.1-1.5)	30.1 (29.0-31.2)	21.1 (20.2-22.1)	11.4 (10.7-12.1)	63.9 (62.7-65.0)
Race					
White	1.5 (1.3-1.7)	32.7 (31.6-33.8)	26.6 (25.7-27.7)	17.0 (16.2-17.9)	77.8 (76.7-78.8)
Non-white	0.8 (0.6-1.0)	11.9 (11.0-12.8)	7.0 (6.3-7.7)	2.6 (2.3-3.0)	22.2 (21.2-23.3)
Total household income					
<$20,000 or no income	0.2 (0.1-0.3)	2.1 (1.8-2.5)	1.3 (1.1-1.5)	0.8 (0.7-1.0)	4.5 (4.1-4.9)
$20,000-39,999	0.4 (0.3-0.5)	5.4 (5.0-5.9)	4.1 (3.7-4.5)	2.5 (2.2-2.8)	12.3 (11.7-13.0)
$40,000-59,999	0.6 (0.5-0.8)	8.3 (7.7-9.0)	5.9 (5.4-6.5)	3.6 (3.3-4.0)	18.4 (17.6-19.3)
$60,000-79,999	0.4 (0.3-0.5)	7.8 (7.2-8.5)	5.9 (5.4-6.4)	3.5 (3.1-4.0)	17.6 (16.7-18.5)
$80,000 or more	0.7 (0.6-0.9)	21.0 (20.0-22.1)	16.4 (15.6-17.4)	9.0 (8.4-9.8)	47.2 (46.0-48.4)

Type of smoker					
Daily	0.6 (0.5-0.8)	7.4 (6.9-8.0)	5.4 (4.8-6.0)	3.1 (2.7-3.5)	16.4 (15.6-17.3)
Occasionally	0.1 (0.06-0.2)	2.8 (2.3-3.3)	1.8 (1.5-2.2)	0.8 (0.7-1.0)	5.5 (4.9-6.2)
Not at all	0.6 (1.4-1.9)	34.4 (33.3-35.6)	26.4 (25.4-27.4)	15.7 (14.9-16.5)	78.1 (77.1-79.1)
History of mental health disorder					
Yes	0.7 (0.6-0.9)	14.2 (13.4-15.0)	12.0 (11.3-12.7)	7.4 (6.9-8.0)	34.2 (33.2-35.3)
No	1.5 (1.3-1.8)	30.4 (29.2-31.5)	21.7 (20.7-22.7)	12.2 (11.4-13.0)	65.8 (64.7-66.8)
Family history of mental health disorder					
Yes	0.8 (0.7-0.9)	17.1 (16.2-18.1)	12.7 (12.0-13.4)	8.4 (7.8-9.0)	39.0 (37.8-40.1)
No	1.5 (1.3-1.8)	27.4 (26.3-28.5)	21.0 (20.0-22.0)	11.2 (10.5-11.9)	61.0 (60.0-62.2)
All participants	**2.3 (2.0-2.6)**	**44.6 (43.4-45.8)**	**33.6 (32.5-34.7)**	**19.5 (18.6-20.4)**	**1**

CCHS 2012:MH - Canadian Community Health Survey (CCHS), 2012: Mental Health Component

< Secondary- less than secondary education; Secondary grad- secondary education graduate; Some post sec – some post secondary education; Post-secondary grad – post seconadary education graduate

Table 5-2. CCHS 2012: MH participants distribution of DSM-IV diagnoses by BMI categories

	Underweight (95% CI)	Normal weight % (95% CI)	Overweight % (95% CI)	Obesity % (95% CI)	Total % (95% CI)
[a]Alcohol use disorders					
12month	0.05 (0.03-0.1)	1.3 (1.1-1.6)	1.0 (0.8-1.3)	0.5 (0.3-0.8)	**2.9 (2.5-3.3)**
Lifetime	0.3 (0.25-0.5)	7.4 (6.9-7.9)	7.3 (6.7-7.9)	4.1 (3.7-4.5)	**19.1 (18.3-20.0)**
[b]Cannabis use disorders					
12month	0.06 (0.03-0.1)	0.5 (0.4-0.7)	0.3 (0.2-0.4)	0.1 (0.07-0.2)	**1.0 (0.8-1.2)**
Lifetime	0.2 (0.1-0.3)	3.1 (2.7-3.6)	2.2 (1.9-2.5)	1.3 (1.1-1.6)	**6.8 (6.3-7.4)**
[c]Other drugs (excluding cannabis) use disorders					
12month	0.001 (0.0005-0.0011)	0.4 (0.3-0.5)	0.1 (0.07-0.2)	0.2 (0.1-0.3)	**0.6 (0.5-0.8)**
Lifetime	0.1 (0.06-0.2)	1.7 (1.5-2.0)	1.4 (1.2-1.7)	0.9 (0.7-1.2)	**4.1 (3.7-4.6)**
[d]Major depression					
12month	0.14 (0.1-0.2)	2.2 (1.9-2.5)	1.3 (1.1-1.5)	1.0 (0.9-1.2)	**4.6 (4.2-5.1)**
Lifetime	0.3 (0.2-0.4)	5.0 (4.5-5.5)	3.7 (3.3-4.1)	2.6 (2.3-3.0)	**11.6 (10.9-12.3)**
Alcohol use disorder and major depression					
12month	0.009 (0.003-0.02)	0.2 (0.17-0.4)	0.1 (0.05-0.2)	0.1 (0.05-0.2)	**0.5 (0.3-0.6)**
Lifetime	0.1 (0.05-0.2)	1.4 (1.2-1.6)	1.2 (1.0-1.4)	0.7 (0.6-0.9)	**3.4 (3.1-3.8)**
Cannabis use disorder and major depression					
12month	0.002 (0.0003-0.003)	0.2 (0.09-0.3)	0.01 (0.004-0.03)	0.05 (0.02-0.2)	**0.2 (0.1-0.4)**
Lifetime	0.04 (0.008-0.2)	0.7 (0.5-0.8)	0.5 (0.4-0.7)	0.4 (0.3-0.6)	**1.7 (1.4-2.0)**
Other drugs use disorder & major depression					
12month	0.003 (0.0001-0.004)	0.1 (0.09-0.2)	0.03 (0.01-0.06)	0.1 (0.05-0.2)	**0.3 (0.2-0.4)**
Lifetime	0.02 (0.006-0.04)	0.5 (0.4-0.7)	0.4 (0.3-0.5)	0.4 (0.3-0.5)	**1.3 (1.1-1.6)**

[a]Alcohol use disorders is defined DSM-IV Alcohol Abuse /or Dependence diagnoses (past 12months and lifetime).
[b]Cannabis use disorders is defined DSM-IV Cannabis Abuse /or Dependence diagnoses (past 12months and lifetime).
[c]Drug use disorders is defined as DSM-IV diagnoses of drug abuse/or dependence diagnoses on opiates, sedatives, tranquilizers, amphetamines hallucinogens, heroin, cocaine, inhalants, and/or other drugs except cannabis (past 12months and lifetime)
[d]Major Depression is defined DSM-IV diagnosis of major depressive episode (past 12 months or lifetime).

Table 5-2 shows the distribution of DSM-IV diagnoses by BMI categories. Participants were more likely to have major depression and alcohol use disorders. Lifetime AUD and MDE were found in 19.1% and 11.5% of individuals respectively while lifetime concurrent AUD and MDE was found in 3.4% of the population.

The associated risk of being overweight and obese was significantly higher across the age groups compared to the youngest age group (Table 5-3). Compared to single participants, individuals that were married, divorced or separated had increased risk of being overweight. A history of mental health disorder was shown to increase the risk of overweight and obesity. Participants had reduced risk of overweight or obesity if they were females, had higher level of education and were daily smokers. In contrast, being female or a daily smoker increased the risk of being underweight among the participants.

Table 5-3. Participants sociodemographic factors and the risk of overweight/obesity

	Crude RRR (95%CI)			[a]Adjusted RRR (95%CI)			
	Underweight vs normal weight	**Overweight vs normal weight**	**Obese vs normal weight**	**Underweight vs normal weight**	**Overweight vs normal weight**	**Obese vs normal weight**	**Statistic (p-value)**
Age							<0.0001
20 to 24 years	1	1	1	1	1	1	
25 to 44 years	**0.62** (0.43– 0.89)*	**2.09** (1.73-2.58)**	**2.01** (1.61-2.53)**	0.81 (0.51-1.28)	**1.99** (1.61-2.47)**	**2.18** (1.68-2.83)**	
45 to 64 years	**0.39** (0.25-0.60)**	**2.96** (2.45-3.58)**	**3.13** (2.50-3.92)**	**0.57** (0.33-0.97)*	**2.58** (2.06-3.23)**	**2.92** (2.24-3.80)**	
65 years and above	0.69 (0.46-1.01)	**2.95** (2.45-3.54)**	**2.62** (2.09-3.29)**	0.88 (0.53-1.49)	**2.46** (1.94-3.13)**	**1.96** (1.47-2.30)**	
Sex							
Male	1	1	1	1	1	1	
Female	**1.91**(1.40-2.61)**	**0.53** (0.48-0.60)**	**0.73** (0.64-0.82)**	**2.00** (1.46-2.73)**	**0.51** (0.46-0.58)**	**0.71** (0.62-0.81)**	
Marital status							<0.0001
Married	**0.48** (0.35-0.67)**	**1.71** (1.49-1.95)**	**1.58** (1.35-1.86)**	**0.60** (0.39-0.91)*	**1.31** (1.11-1.55)**	1.19 (0.99-1.44)	
Common law	0.86 (0.56-1.33)	**1.32** (1.08-1.62)**	1.24 **(**1.00-1.55)	1.00 (0.62-1.61)	1.09 (0.88-1.34)	0.93 (0.73-1.17)	
Widowed	1.42 (0.88-2.29)	**1.41** (1.17-1.71)**	**1.60**(1.26-2.04)**	1.33 (0.74-2.38)	1.12 (0.89-1.42)	1.19 (0.90-1.58)	
Divorced/Separated	0.66 (0.37-1.16)	**1.67** (1.33-2.11)**	1.12 (0.89-1.41)	0.75 (0.41-1.37)	**1.38** (1.07-1.78)*	0.84 (0.66-1.07)	
Single	1	1	1	1	1	1	
Highest level of education							<0.0001
< Secondary	1	1	1	1	1	1	
Secondary grad	1.05 (0.66-1.67)	0.94 (0.78-1.13)	0.80 (0.64-0.99)	1.17 (0.71-1.93)	1.04 (0.85-1.27)	0.80 (0.64-1.01)	
Some post sec	1.19 (0.72-1.97)	**0.70** (0.53-0.92)*	**0.67** (0.49-0.90)**	1.17 (0.67-2.04)	0.86 (0.64-1.17)	0.75 (0.55-1.02)	
Post-secondary grad	**0.67** (0.46-0.95)*	**0.75** (0.64-0.88)**	**0.57** (0.48-0.68)**	0.82 (0.57-1.19)	**0.77** (0.65-0.92)**	**0.54** (0.45-0.66)**	
Total Houshold income							
Less than $20,000	1	1	1	x	x	x	x
$20,000 – 39,999	0.71 (0.41-1.24)	1.25 (0.98-1.60)	1.18 (0.88-1.58)				
$40,000 – 59,999	0.74 (0.43-1.30)	1.18 (0.93-1.50)	1.13 (0.85-1.50)				
$60,000 – 79,999	0.54 (0.30-0.97)*	1.24 (0.98-1.58)	1.17 (0.87-1.58)				
$80,000 or more	0.37 (0.22-0.65)**	1.29 (1.03-1.60)*	1.11 (0.84-1.45)				
Race							
Non-white	1	**1**	**1**	1	1	1	
White	**0.70** (0.50-0.98)*	**1.39 (1.21-1.60)****	**2.37** (1.99-2.82)**	**0.63** (0.45-0.89)**	**1.29** (1.11-1.50)**	**2.24** (1.86-2.70)**	
Type of smoker							<0.0001
Daily	**1.70** (1.25-2.33)**	0.95 (0.81-1.10)	0.90 (0.77-1.06)	**1.77** (1.29-2.43)**	**0.84** (0.72-0.99)*	**0.75** (0.63-0.89)**	
Occasionally	0.78 (0.45-1.33)	0.86 (0.65-1.13)	**0.65** (0.48-0.88)**	0.69 (0.40-1.19)	0.93 (0.69-1.26)	0.73 (0.52-1.01)	
Not at all	1	1	1	1	1	1	
History of mental health disorder							
Yes	1.03 (0.78-1.36)	**1.19** (1.06-1.33)**	**1.31** (1.15-1.48)**	1.01 (0.75-1.36)	**1.15** (1.02-1.29)*	**1.23** (1.07-1.41)**	

No	1	1	1	1	1		
Family history of mental health disorder							
Yes	0.81 (0.62-1.05)	0.97 (0.87-1.09)	**1.20** (1.06-1.36)**	x	x	x	x
No	1	1	1				

a – adjusted in a multivariate model

Significant values are marked in bold print

* p-value < =0.05

** p-value <0.01

x – lost in multivariate model

< Secondary- less than secondary education; Secondary grad- secondary education graduate; Some post sec – some post secondary education; Post-secondary grad – post seconadary education graduate

5.4.2 DSM IV diagnoses and BMI status

Table 5-4. DSM-IV diagnoses and the risk of overweight/obesity

	Crude models RRR (95%CI)			[a]Adjusted models RRR (95%CI)		
	Underweight vs normal weight	**Overweight vs normal weight**	**Obese vs normal weight**	**Underweight vs normal weight**	**Overweight vs normal weight**	**Obese vs normal weight**
AUD (Model 1)						
12month	0.81 (0.42-1.58)	1.02 (0.77-1.35)	0.84 (0.53-1.34)	0.71 (0.35-1.44)	1.03 (0.82-1.46)	0.90 (0.56-1.44)
Lifetime	0.90 (0.62-1.31)	**1.42** (1.25-1.61)**	**1.35** (1.17-1.56)**	0.92 (0.63-1.34)	**1.23** (1.08-1.41)**	**1.21** (1.03-1.41)*
CUD (model 2)						
12months	**2.27** (1.02-5.06)*	0.52 (0.46-1.01)	0.52 (0.27-1.00)	2.01 (0.83-4.86)	0.77 (0.50-1.19)	0.60 (0.30-1.19)
Lifetime	1.15 (0.67-1.97)	0.92 (0.76-1.12)	0.95 (0.75-1.20)	1.04 (0.59-1.85)	**0.79** (0.63-0.99)*	0.80 (0.61-1.04)
DUD (model 3)						
12months	**0.003** (0.002-0.01)**	**0.42** (0.25-0.71)**	1.03 (0.54-1.96)	**0.004** (0.001-0.01)**	**0.44** (0.27-0.74)*	1.16 (0.60-2.24)
Lifetime	1.09 (0.64-1.88)	1.08 (0.85-1.38)	1.22 (0.91-1.63)	0.90 (0.49-1.64)	0.98 (0.75-1.27)	1.05 (0.77-1.43)
MDE (model 4)						
12months	1.30 (0.82-2.07)	**0.77** (0.61-0.97)*	1.09 (0.86-1.39)	0.98 (0.61-1.57)	0.90 (0.71-1.16)	1.24 (0.97-1.59)
Lifetime	1.14 (0.77-1.67)	0.98 (0.84-1.14)	**1.23** (1.04-1.47)*	1.00 (0.67-1.48)	1.10 (0.94-1.30)	**1.30** (1.08-1.56)**

Significant values are marked in bold print
* p-value < =0.05
** p-value <0.01

[a]Adjusted for age, gender, marital status, highest level of education, race, smoking status, history of any mental health disorder, family history of mental health disorder in multivariate models
AUD - Alcohol use disorders is defined DSM-IV Alcohol Abuse /or Dependence diagnoses
CUD - Cannabis use disorders is defined DSM-IV Cannabis Abuse /or Dependence diagnoses (lifetime).
DUD - Drug use disorders is defined as DSM-IV diagnoses of drug abuse/or dependence diagnoses on opiates, sedatives, tranquilizers, amphetamines hallucinogens, heroin, cocaine, inhalants, and/or other drugs except cannabis (lifetime)
MDE - Major Depression is defined DSM-IV diagnosis of major depressive episode (lifetime).

The main associations between BMI and substance use disorders or major depression are shown in Table 5-4. Lifetime major depression is associated with a higher risk of being obese compared with normal weight. Individuals with lifetime alcohol use disorder had higher risk of being overweight or obese compared to normal weight. Lifetime CUD and 12-month DUD were associated with decreased risk of overweight, hence inversely proportional.

Table 5-5 shows the lifetime diagnosis of comorbid SUD with major depression predicting obesity and overweight. Here, the comparison groups are either no diagnosis (ND), isolated diagnosis of SUD (AUD, CUD, DUD) or MDE (without the other) and comorbid SUD with MDE. Adults with co-morbid AUD or DUD with major depression had significantly higher associated risk of being obese compared to ND. Isolated diagnosis of CUD without co-occurring major depression was found to reduce the risk of overweight and obesity by about 30% compared to ND. Compared to isolated diagnosis of CUD or DUD, individuals with comorbid SUD (CUD or DUD) with MD had about 2 times higher risk of being obese.

Table 5-5. Lifetime comorbid SUD with major depression predicting overweight/obesity

	Underweight vs normal weight RRR (95%CI)			*Overweight vs normal weight RRR (95%CI)*			*Obese vs normal weight RRR (95%CI)*		
	Ref= ND	*Ref = SUD*	*Ref = MD*	*Ref = ND*	*Ref = SUD*	*Ref = MD*	*Ref = ND*	*Ref = SUD*	*Ref = MD*
Alcohol and major depression (model 1)									
ND	1	1.22 (0.82-1.82)	1.14 (0.78-1.67)	1	**0.81** (0.70-0.94)**	0.92 (0.76-1.12)	1	**0.82** (0.69-0.97)*	**0.76** (0.61-0.94)*
AUD only	0.82 (0.55-1.22)	1	0.93 (0.56-1.55)	**1.24** (1.07-1.43)**	1	1.14 (0.91-1.42)	**1.22** (1.03-1.46)*	1	0.93 (0.71-1.20)
MDE only	0.88 (0.60-1.28)	1.07 (0.64-1.78)	1	1.09 (0.90-1.32)	0.88 (0.70-1.10)	1	**1.32** (1.06-1.65)*	1.08 (0.84-1.40)	1
AUD & MDE	1.16 (0.51-2.65)	1.42 (0.58-3.46)	1.33 (0.56-3.14)	1.23 (0.94-1.62)	1.00 (0.75-1.33)	1.13 (0.83-1.55)	**1.38**(1.02-1.86)*	1.13 (0.82-1.55)	1.04 (0.73-1.48)
Cannabis and major depression (model 2)									
ND	1	0.93 (0.49-1.76)	1.04 (0.62-1.73)	1	**1.41** (1.09-1.84)**	1.10 (0.89-1.35)	1	**1.54** (1.12-2.10)**	1.00 (0.79-1.26)
CUD only	1.07 (0.57-2.04)	1	1.11 (0.59-2.10)	**0.71** (0.54-0.92)**	1	0.78 (0.59-1.03)	**0.65** (0.48-0.89)	1	**0.65** (0.46-0.92)**
MDE only	0.97 (0.58-1.62)	0.90 (0.48-1.69)	1	0.91 (0.74-1.12)	1.29 (0.97-1.70)	1	1.00 (0.79-1.26)	**1.53** (1.09-2.16)*	1
CUD & MDE	1.01 (0.20-5.17)	0.94 (0.17 -5.18)	1.05 (0.21-5.26)	1.01 (0.67-1.56)	1.44 (0.91-2.28)	1.11 (0.72-1.73)	1.40 (0.88-2.20)	**2.14** (1.28-3.59)**	1.40 (0.87-2.23)
Drugs (excluding cannabis) and major depression (model 3)									
ND	1	0.81 (0.44-1.49)	0.91 (0.60-1.38)	1	0.92 (0.67-1.26)	0.89 (0.75-1.06)	1	1.03 (0.70-1.53)	**0.81** (0.67-0.99)*
DUD only	1.24 (0.67-2.29)	1	1.13 (0.54-2.35)	1.09 (0.79-1.49)	1	0.97 (0.68-1.37)	0.97 (0.65-1.43)	1	0.79 (0.52-1.21)
MDE only	1.10 (0.72-1.67)	0.89 (0.43-1.85)	1	1.12 (0.94-1.34)	1.03 (0.73-1.46)	1	**1.23 (1.01-1.50)***	1.27 (0.83-1.94)	**1**
DUD & MDE	0.42 (0.14-1.23)	0.34 (0.10-1.13)	0.38 (0.12-1.20)	1.04 (0.70-1.53)	0.95 (0.59-1.55)	0.92 (0.61-1.39)	**1.86 (1.21-2.85)****	**1.92 (1.09-3.38)***	1.52 (0.96-2.39)

Significant values are marked in bold print
* p-value < =0.05
** p-value <0.01
1 – reference category
Models adjusted for age, gender, marital status, highest level of education, race, smoking status, history of any mental health disorder, family history of mental health disorder in multivariate models
ND – no diagnosis; AUD - Alcohol use disorders is defined DSM-IV Alcohol Abuse /or Dependence diagnoses.; CUD - Cannabis use disorders is defined DSM-IV Cannabis Abuse /or Dependence diagnoses.; DUD - Drug use disorders is defined as DSM-IV diagnoses of drug abuse/or dependence diagnoses on opiates, sedatives, tranquilizers, amphetamines hallucinogens, heroin, cocaine, inhalants, and/or other drugs except cannabis.; MDE - Major Depression is defined DSM-IV diagnosis of major depressive episode. SUD – AUD (model 1), CUD (model 2) and DUD (model 3)

5.5 Discussion and Conclusion

This study examined the relationship between overweight/obesity and substance use disorders with underlying major depression. The inverse relationship between BMI and substance use found in previous studies (Gruchow, Sobocinski, Barboriak, & Scheller, 1985; Lahti-Koski, Pietinen, Heliovaara, & Vartiainen, 2002; Liu, Serdula, Williamson, Mokdad, & Byers, 1994; Kleiner, et al., 2004; Gearhardt & Corbin, 2009; Warren, Frost-Pineda, & Gold, 2005; Pickering, et al., 2011; Gearhardt, Harrison, & McKee, 2012; Le Strat & Le Foll, 2011) continued to exist for cannabis use disorder and drug use disorders in our study.

This could be explained by the hypothesis that food and drug intake may be regulated by the same neurobiological pathways (dopaminergic reward system and endogenous opioid system), competing for the same target brain site, hence inversely related – increased illicit drug associated with decreased BMI (Volkow, et al., 2008; Volkow & Wise, 2005; Di Chiara & Imperato, 1988; MacDonald, et al., 2004). It is important to note that behaviours such as cravings, loss of control (Gearhardt, Corbin, & Brownell, 2009) underlie excessive food consumption and substance use disorders. Some authors suggest that consequent to deficiencies in these neural reward systems, compensating behaviour in the form of increased food or drug intake may occur (Trinko, Sears, Guarnieri, & DiLeone, 2007; Johnson & Kenny, 2010). Another explanation stem from the fact that substance use disorders increase vulnerability to malnutrition which worsens with chronic disruption of eating habits, anorexia, and infections (Santolaria-Fernández, et al., 1995). Malnutrition could also occur through neglect of physical health, including insufficient calorie intake arising from the adverse effects of substance use disorder (McIntyre, et al., 2007; Nazrul Islam, Jahangir, Ahmed, & Ahsan, 2002). This inverse relationship found in our study provides further evidence to support the similarities between problematic food consumption and addiction (Volkow, Wang, Fowler, & Telang, 2008; Gearhardt, Corbin, & Brownell, 2009).

Major depression was associated with an increased risk of obesity and this was consistent with previous studies ((Pickering, et al., 2011; McLaren, Beck, Patten, Fick, & Adair, 2008). Two hypothesized psychosocial models explain this finding. The self-appraisal model where stigma following overweight/obesity promotes low self-esteem and negative self-image,

resulting in major depression (Puhl & Brownell, 2003). The fitting norms of appearance model is a consequence of societal values for thinness (McLaren, Beck, Patten, Fick, & Adair, 2008; Paeratakul, White, Williamson, Ryan, & Bray, 2002; Smolak & Striegel Moore, 2002). This argues that fitting the norm for weight becomes stressful for the overweight and obese as dieting is often unsuccessful resulting in major depression (Pickering, et al., 2011). In addition, our finding could reflect emotional overeating linked with suppressed mood (McLaren, Beck, Patten, Fick, & Adair, 2008), differential reporting of atypical depression (e.g., increased appetite, weight gain) and biological factors such as genetic susceptibility to both overweight and major depression (Comings, Gade, MacMurray, Muhlema, & Peters, 1996).

Inconsistent with a recent study (Gearhardt, Harrison, & McKee, 2012), comorbid SUDs (AUD, DUD) with depression compared with no diagnosis increased the risk of obesity in our study. In addition, our study showed a 2-fold associated increase in the risk of obesity in comorbid SUD (CUD, DUD) with major depression compared to the SUD (CUD, DUD) only. Thus, the inverse relationship between DUD and BMI ceased to exist in the presence of major depression in this population. This could be due to major depression mediating the effect on BMI. Another possible explanation is the contribution of the subtypes of depression. Atypical depression is associated with hypersomnia and weight gain and an increased likelihood of substance dependence (Matza, Revicki, Davidson, & Stewart, 2003). Thus, a combined effect could occur. Alcohol use disorder was associated with increased risk of overweight/obesity as seen in other studies (McLaren, Beck, Patten, Fick, & Adair, 2008). This can be explained by one component of substance use, that is, excessive calorie intake due to alcohol consumption (McLaren, Beck, Patten, Fick, & Adair, 2008).

The large sample size being representative of the Canadian population is a major strength of this study. Another strong point was that the diagnoses of substance use disorders and major depressive episodes were derived from DSM IV criteria. Other strengths include accounting for missing values with multiple imputation and for the complex data structure with survey weights, enabling generalizability. Limitations of this study include the cross-sectional study design which does not allow for causal inference. Further studies would be required to assess causality. Individuals living on reserves and other Aboriginal settlements, in institutions and full-time members of the Canadian Forces were excluded from the data. Since these populations account

for about 3% of the total population, our study may have underestimated the true strength of associations found in these conditions. This study was based on self-reported data, thus could be compromised by recall-bias and under-reporting.

In conclusion, the inverse relationship observed in other studies between substance use disorders and obesity ceased to exist in the presence of an underlying common risk factor, major depression. It is imperative that health professionals are aware of the associations that exist between substance-related behaviors, problematic food intake, and depression.

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Appendix A. Missing values analysis

Table A.1 Summary of missing values

Variables	Observed	Missing	Imputed	Total
Marital status	22824	57	57	22881
Educational status	22774	107	107	22881
Race	22787	94	94	22881
Income	22873	8	8	22881
Body mass index	22308	573	573	22881
12-month CUD	22691	190	190	22881
Lifetime CUD	22686	195	195	22881
12-month DUD	22622	259	259	22881
Lifetime DUD	22617	264	264	22881
12-month AUD	22530	351	351	22881
Lifetime AUD	22513	368	368	22881
12-month MDE	22730	151	151	22881
Lifetime MDE	22727	154	154	22881
Smoking status	22866	15	15	22881
Family history of mental illness	22630	251	251	22881
Personal history of mental illness	22197	684	684	22881

CUD- cannabis us disorder; AUD- alcohol use disorder; DUD – other drugs (excluding cannabis) use disorder; MDE – major depressive episode

Test for Missing Completely At Random (MCAR)

Little's MCAR test: Prob > chi-square = 0.0000

Data is not MCAR

Table A.2 Association of predictor variables and missingness in Body Mass Index

Variables	Chi square p-value
Province of residence	<0.0001
Age	0.001
Sex	<0.0001
Marital status	<0.0001
Educational status	<0.0001
Race	0.08
Income	<0.0001
12-month CUD	0.05
Lifetime CUD	<0.0001
12-month DUD	0.04
Lifetime DUD	<0.001
12-month AUD	0.06
Lifetime AUD	<0.0001
12-month MDE	0.4
Lifetime MDE	0.08
Smoking status	0.008
Family history of mental illness	<0.0001
Personal history of mental illness	<0.0001

CUD- cannabis us disorder; AUD- alcohol use disorder; DUD – other drugs (excluding cannabis) use disorder; MDE – major depressive episode

CHAPTER 6. ALCOHOL DEPENDENCE AND THE PERSISTENCE OR RECURRENCE OF MAJOR DEPRESSION

6.1 Introduction

Alcohol use disorders (AUD) are some of the most prevalent disorders worldwide (Grant, et al., 2004b; Kessler, Chiu, Demler, Merikangas, & Walters, 2005) and they frequently co-occur at significantly higher levels with major depression (Sullivan, Fiellin, & O'Connor, 2005; Swendson & Merikangas, 2000). In the 2016 Global Burden of Disease study, alcohol use was estimated to be the 7th-leading risk factor in terms of disability-adjusted life-years (DALYs) (GBD 2016 Risk Factors Collaborators, 2017; GBD 2016 Alcohol Collaborators, 2018) while major depressive disorder was amongst the five leading causes of years lived with disability (YLD) (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Comorbid AUD with depression is associated with an earlier onset of alcohol dependence and higher prevalence rates of drug dependence (Schuckit, et al., 1997; Brière, Rohde, Seeley, & Daniel Klein, 2014), poor outcomes in those entering treatment for drug and alcohol problems (Hasin, et al., 2002), and increased relapse rate following AUD treatment (Cornelius J. R., et al., 1995). This comorbidity is also associated with an increased likelihood of completed suicides, suicide attempts, and severity of suicidality in terms of frequency and duration of suicidal thoughts, death wishes and intent to take lethal actions (Preuss, et al., 2002; Britton, et al., 2015; Brière, Rohde, Seeley, & Daniel Klein, 2014; Cornelius J. R., et al., 1995).

Alcohol dependence and major depression occur commonly together (Regier, et al., 1990; Grant & Harford, 1995; Brière, Rohde, Seeley, & Daniel Klein, 2014; Grant B. F., et al., 2004a; Grant, et al., 2015) and this comorbidity is particularly high in patient samples (Lynskey M. T., 1998; Britton, et al., 2015). With depression, the risk of alcohol dependence is higher than in the general population (Kessler, et al., 1996; Brière, Rohde, Seeley, & Daniel Klein, 2014) and, depression is more prevalent with alcohol dependence than without alcohol dependence (Kessler, et al., 1997; Britton, et al., 2015). Evidence suggests an increased prevalence of major depression among patients seeking treatment for addiction (Miller, Klamen, Hoffman, & Flaherty, 1996; Schuckit, et al., 1997; Britton, et al., 2015). For example, the Collaborative Study on the Genetics of Alcoholism (COGA) found a lifetime prevalence of major depressive disorder

among treatment-seeking alcoholics to be 42.2% while the prevalence prior to alcohol dependence was 5.3% and prevalence occurring outside of the context of alcohol dependence was 11.5% (Schuckit, et al., 1997).

Depression was predicted by the World Health Organization (WHO) to be the second most important factor influencing the global burden of disease by 2020 and the principal cause in developed countries by 2030 (Lépine & Briley, 2011; World Health Organization, 2004). The major clinical problems associated with depression resulting in significant personal and public health consequences are persistence and recurrence (Judd, 1997; Burcusa & Iacono, 2007). About half of those who recover from the first episode of major depression, would have at least one additional event in their lifetime and nearly 80% of those with a history of two events will have another recurrence (Burcusa & Iacono, 2007; American Psychiatric Association, 2000; Kupfer, Frank, & Wamhoff, 1996). The long-term course or persistence and recurrence often associated with depression is one of the reasons it is a burden (Balkrishnan, Joish, Yang, Jayawant, & Mullins, 2008; Fostick, Silberman, Beckman, Spivak, & Amital, 2010; Judd, et al., 2000; Burcusa & Iacono, 2007). Previous studies suggest there may be differences in risk factors, neurobiological basis and therapeutic response between major depression and recurrent or persistent major depression (Holzel, Harter, Reese, & Kriston, 2011; de Maat, Dekker, Schoevers, & de Jonghe, 2007; Szádóczky, Fazekas, Rihmer, & Arató, 1994; Burcusa & Iacono, 2007). Using the 'dynamic stress-vulnerability model' (Ormel & Neeleman, 2000), Spijker et al. (2004) classified the many risk factors of persistent major depression identified in the literature (Table 6-1) (Spijker, et al., 2004).

Table 6-1. Potential determinants of the persistence of major depression from literature

Determinants	Results
Demographic factors	
Age	*Older* (Sargeant, Bruce, Florio, & Weismann, 1990); *Younge*r (Spijker, Bijl, De Graaf, & Nolen, 2000)
Gender	*Female* (Sargeant, Bruce, Florio, & Weismann, 1990; Keitner, Ryan, Miller, & Norman, 1992), *No association* (Simpson, Nee, & Endicott, 1997)
Social Vulnerability factors	
Education	*Low level* (Sargeant, Bruce, Florio, & Weismann, 1990)
Social economic status	*Low* (Keller, 1994)
Marital status	*Married* (Keller, 1994), *no partner* (Mueller, et al., 1996)
Psychobiological vulnerability factors	
Youth experiences	*Childhood adversity* (Brown & Moran, 1994; Brown, Harris, Hepworth, & Robinson, 1994) *High neuroticism* (Scott, Eccleston, & Boys, 1992; Keitner, Ryan, Miller, & Norman, 1992)
Personality characteristics	*low mastery* (Spijker, Bijl, De Graaf, & Nolen, 2000)
Previous psychiatry illness	*Other psychiatry illness* (Keller, 1994)
Somatic illness	*Presence of somatic illness* (Keitner, Ryan, Miller, & Norman, 1992)
Sustaining factors	
Negative life events	*Multiple* (Spijker, Bijl, De Graaf, & Nolen, 2000) *No association* (Paykel, Cooper, Ramanda, & Hayhurst, 1996)
Ongoing difficulties	*Interpersonal difficulties* (Brown & Moran, 1994; Brown, Harris, Hepworth, & Robinson, 1994)
Social support	*Lack of support* (Brown, Harris, Hepworth, & Robinson, 1994) *No association* (Paykel, Cooper, Ramanda, & Hayhurst, 1996)
Illness-related factors	
Severity of depression	*Severe* (Sargeant, Bruce, Florio, & Weismann, 1990; Spijker, Bijl, De Graaf, & Nolen, 2000; Keller, 1994; Mueller, et al., 1996; Ramana, et al., 1995; Furukawa, Kiturama, & Takahashi, 2000; Mueller, et al., 1994)
Comorbidity	*With dysthymia* (Keller, 1994) *Anxiety disorders* (Ormel, Oldehinkel, Brilman, & van den Brink, 1993) *Alcohol dependence* (Mueller, et al., 1994), *No association* (Spijker, et al., 2004; Garcia-Toro, et al., 2013),
Previous episodes	*Multiple* (Sargeant, Bruce, Florio, & Weismann, 1990), *No association* (Keller, 1994)
Duration of previous episodes	*Long* (Sargeant, Bruce, Florio, & Weismann, 1990; Spijker, Bijl, De Graaf, & Nolen, 2000; Scott, Eccleston, & Boys, 1992; Ramana, et al., 1995)

Adapted with permission from: (Spijker, et al., 2004)

Previous studies suggest the characteristics of the index episode of depression such as the severity, duration, comorbidity with other psychiatric disorders and suicidality as the strongest predictors of recurrence or persistence (Burcusa & Iacono, 2007; Barkow, et al., 2003; Spijker & Nolen, 1998). The review by Burcusa and Iacono (2007) point to severity as an indicator for recurrence whether assessed using the International Classification of Disease (ICD) severity, Diagnostic and Statistical Manual of Mental Disorders (DSM) severity, presence of higher number of symptoms, higher Becker Depression Inventory (BDI) scores, higher Hamilton rating scale scores or the presence of certain symptoms such as suicidality (Burcusa & Iacono, 2007; Kessing, 2004). The more severe the first episode, the more likely there would be a recurrence or persistence.

Evidence of symptom exacerbation, disruptive behaviors, decreased social functioning, treatment nonadherence, poor response to conventional treatment, recurrence, increased service utilization and hospitalizations (Hobbs, Kushner, Lee, Reardon, & Maurer, 2011; Kushner, et al., 2005; Grant, et al., 2004b; Petrakis, Gonzalez, Rosenheck, & Krystal, 2002; Gilman & Abraham, 2001; Salloum & Thase, 2000; Owen, Fischer, Booth, & Cuffel, 1996; Volkow, Baler, Compton, & Weiss, 2014; Odlaug, et al., 2016) support the adverse consequences of substance use disorder on the course of severe mental illness. However, studies have been inconsistent in showing the relationship between alcohol dependence and persistent or recurrent depression. While some researchers have found an association between substance use disorders and recurrent depression, suggesting a resolution of depressive symptoms and consequent loss of depressive diagnosis with abstinence from alcohol, others have not (Garcia-Toro, et al., 2013; Spijker, et al., 2004; Mueller, et al., 1994; Barkow, et al., 2003; Alpert, Maddocks, Rosenbaum, & Fava, 1994; Coryell, Endicott, & Keller, 1991; Brown & Schuckit, 1988).

Comorbid alcohol dependence and major depression was found to predict treatment seeking (Kaufmann, Chen, Crum, & Mojtabai, 2014; Wu, Kouzis, & Leaf, 1999), and higher rates of treatment seeking most likely reflects greater disorder severity (Blanco, et al., 2010; Kessler, et al., 1996; Klein, Schwartz, Rose, & Leader, 2000; McFarland & Klein, 2005; Olfson, Liu, Grant, & Blanco, 2012; Rush, et al., 2009); therefore, studies based on patient samples may overestimate the association between alcohol dependence and major depression in the general population due to the inadvertent selection of more severe cases into treatment (Berkson, 1946).

To expand current knowledge on this topic, this study was aimed to determine if comorbid alcohol dependence predicts the persistence or recurrence of major depression in a cohort sample of the general Canadian population.

6.2 Objectives

This study aimed to first, determine if concurrent alcohol dependence predicts persistence or recurrence of major depression after 6 years and 16 years of follow-up. Second, to determine other factors that predict persistent or recurrent major depression after 6 years and 16 years of follow-up.

6.3 Methods

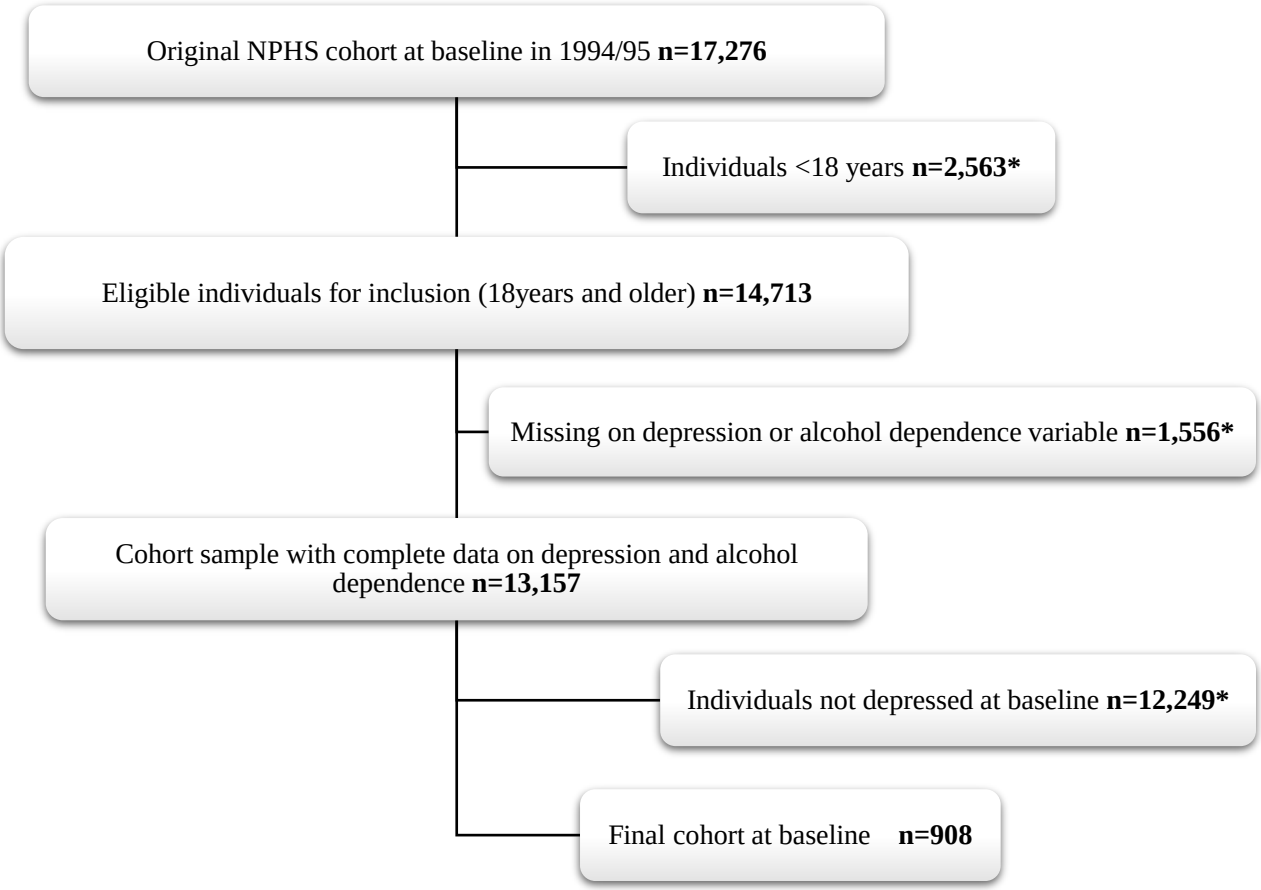
6.3.1 Data Source and study cohort

Data came from the longitudinal National Population Health Survey (NPHS, 1994/1995-2010/2011), a nationally representative prospective epidemiologic survey (Statistics Canada, 2012). Detailed information on the NPHS methodology is available on the Statistics Canada web page (Statistics Canada, 2012). Briefly, the participants of the longitudinal NPHS were individuals 12 years and older, resident in the ten Canadian provinces in 1994/1995. Criteria for exclusion from the survey were living in certain remote areas, institutions, and reserves. In addition, full-time members of the Canadian were not included. The population comprised of 17,276 participants who were re-interviewed every 2 years for 9 cycles (cycles 1 to 9) (Statistics Canada, 2012).

This secondary analysis of the NPHS data included only individuals 18years and older who met criteria for a diagnosis of 12-month major depressive episode at baseline (n=908) (Figure 6-1). The age restriction was because the structured instrument for the diagnosis of major depression, the World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF) based on DSM-III-R criteria, was administered to individuals 18years and older (Statistics Canada, 2009). This study focused on cycles 4 (6years from baseline) and 9 (16 years from baseline). The follow-up period ended in cycle 9. Cycle 4 was added to this analysis due to a significant loss to follow-up in cycle 9 (Figure 6-2). The estimated response rates reported by

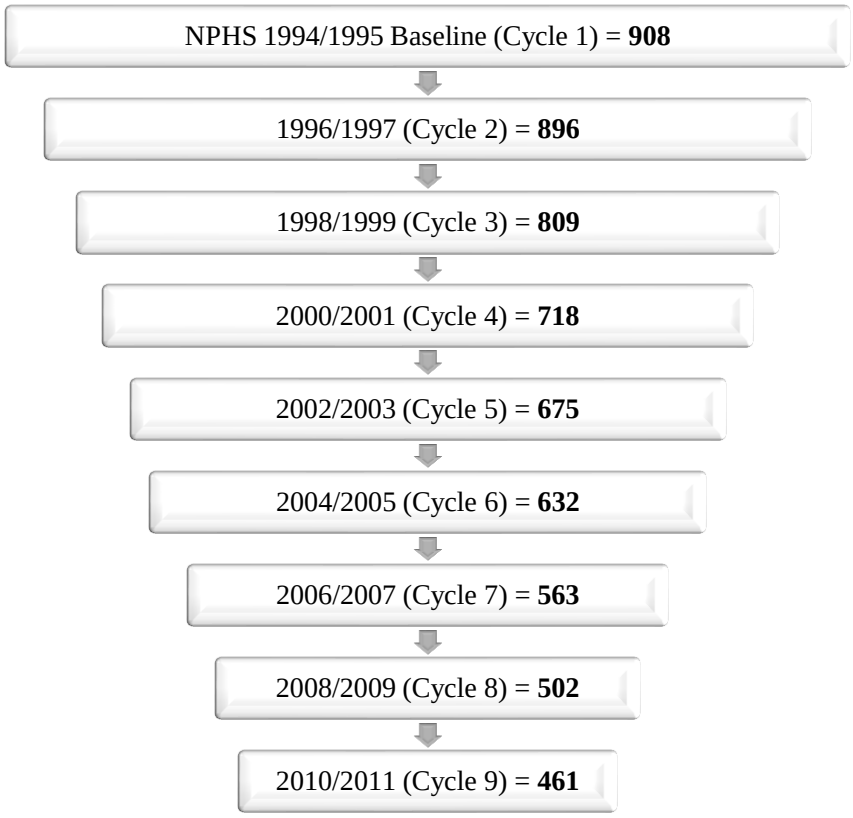
Statistics Canada were 84.9% and 69.7% for cycles 4 and 9 respectively (Statistics Canada, 2012).

Figure 6-1. Cohort sample derivation



Excluded from the analysis
NPHS – National Population Health Survey

Figure 6-2. Cohort sample follow-up chart



NPHS- National Population Health Survey

6.3.2 Measures

Major Depressive Episode (MDE)

Major depressive episode was assessed at baseline (1994/1995) using the World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF) based on DSM-III-R criteria (Statistics Canada, 2009).

The past year MDE was evaluated on the same cohort every 2years. Six-year and 16-year persistence or recurrence of major depression were defined as meeting the diagnosis of MDE at cycle 4 (2000/2001) and at cycle 9 (2010/2011) respectively. The positive diagnosis of MDE in the subsequent cycles represent persistent episodes and, in some instances, recurrence – but it was not possible to distinguish between these two possibilities.

Alcohol dependence

Alcohol dependence was assessed at cycle 2 (1996/1997) using World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF) based on DSM-III-R criteria (Statistics Canada, 2009). Alcohol dependence was not assessed at baseline.

Other measures

These were assessed at baseline. These measures are listed in table 6-2 and were identified as covariates using the table adopted from (Spijker, et al., 2004) (Table 6-1).

Table 6-2. Potential covariates for model building

Risk factors for persistent major depression from the literature	Proxy covariates from the data
Demographic factors	*Age* *Gender*
Social Vulnerability factors	*Education* *Social economic status* (dwelling owned used as proxy) *Marital status*
Psychobiological vulnerability factors	
Youth experiences	*Childhood and adult stress index* - this measures the number of traumatic events respondents have been exposed to during their childhood, adolescence or adulthood. Higher values indicate more stressors/ traumatic events respondent has been exposed to in childhood/adolescent (Statistics Canada, 2009)
Personality characteristics	*Mastery index, Self-esteem index scores*. Higher scores indicate better mastery or self esteem (Statistics Canada, 2009)
Somatic illness	*Presence of chronic physical illness*
Sustaining factors	
Negative life events	*Recent life events score* (the events included in the survey were physical abuse, unwanted pregnancy, abortion or miscarriage, major financial difficulties, and serious problems at work or in school) (Statistics Canada, 2009).
Ongoing difficulties	*Family stress index* (the stressors include activity overload, financial difficulties and problems with relationships in day-to-day encounters) (Statistics Canada, 2009).
Social support	*Perceived social support*
Illness-related factors	
Duration of previous episodes	*Number of weeks felt depressed*

6.3.3 Statistical analyses

All statistical analyses were carried out using STATA version 14.0. First, baseline and cohort samples were used to describe participants sociodemographic characteristics and risk

factors for persistent or recurrent major depression. Second, Modified Poisson models were used to fit the data. The Modified Poisson model is an effective way of estimating the Relative Risk (RR) of binary data in a cohort (Zou, 2004).

The RR for the persistence or recurrence of MDE, the main outcome of interest was assessed for 6 years (model 1) and 16 years (model 2) of follow-up. The modelling was carried out in two stages for each model. First, all covariates were assessed independently as potential predictors of persistent or recurrent major depression. In stage two, covariates that were independent risk factors or met a significance level of $p<0.25$ were included in a multivariate model. The multivariate Modified Poisson models were built using stepwise analyses with backward elimination of covariates. Covariates that were eliminated were assessed for confounding and re-entered into the model if found to confound the RR for alcohol dependence. Biologically, plausible interactions for gender and alcohol dependence, smoking and alcohol dependence were tested for each model but were not significant. Deviance and Pearson goodness-of-fit were tested on each model to justify the use of Poisson models. The post-estimation command 'fitstat' in Stata 14 was used to compute other measures of fit and to compare models with interaction term and models without the interaction term. Sensitivity analysis was done to assess the presence of a difference in the response to major depression between those that were lost to follow-up and those that remained in the study (Appendix 1).

6.4 Results

6.4.1 Participants characteristics

At baseline, about half of the cohort sample were aged 25-44years, a third were males and married while two-thirds had a chronic condition (Table 6-3). After 6 years (cycle 4) and 16years (cycle 9), about 20% and 49% of participants were lost to follow-up (Figure 6-2).

Table 6-3. Participants characteristics of the NPHS and cohort sample at baseline

	Baseline Cohort Sample Frequency (%) N =908	Baseline NPHS Sample Frequency (%) N =14,713
Age		
18 to 24 years	149 (16.4)	2258 (15.4)
25 to 44 years	442 (48.7)	5828 (39.6)
45 to 64 years	231 (25.4)	3887 (26.4)
65 years and above	86 (9.5)	2740 (18.6)
Sex		
Male	288 (31.7)	6733 (45.8)
Female	620 (68.3)	7980 (54.2)
Marital status		
Married	325 (35.8)	7254 (49.3)
Common-law/ with a partner	63 (6.9)	968 (6.6)
Widowed	80 (8.8)	1380 (9.4)
Divorced or Separated	173 (19.1)	1445 (9.8)
Single/ never married	267 (29.4)	3662 (24.9)
Highest level of education		
<secondary	239 (26.3)	4721 (32.2)
Secondary grad	137 (15.1)	2184 (14.9)
Some post-secondary	269 (29.6)	3545 (24.2)
Post-secondary grad	263 (29.0)	4224 (28.8)
Chronic condition		
No	279 (30.7)	6215 (42.3)
Yes	629 (69.3)	8475 (57.7)
Alcohol dependence		
No	879 (96.8)	12,875 (97.9)
Yes	29 (3.2)	282 (2.1)
Total household income (CDN$)		
<15,000	220 (24.2)	2646 (18.9)
15,000-29,999	247 (27.2)	3572 (25.5)
30,000-49,999	210 (23.1)	3817 (27.2)
50,000-79,999	160 (17.6)	2762 (19.7)
80,000 or more	71 (7.8)	1241 (8.8)
Dwelling owned by a household member		
No	387 (42.6)	4592 (31.2)
Yes	521 (57.4)	10,115 (68.8)
Self-esteem index		
Self-esteem index <18	299 (32.9)	1826 (13.5)
Self-esteem index = 18	190 (20.9)	3506 (25.8)
Self-esteem index 19-22	266 (29.3)	4434 (32.7)
Self-esteem index 23-24	153 (16.9)	3804 (28.0)
Mastery index		
Mastery index <17	407 (44.8)	2960 (21.9)
Mastery index 17-19	212 (23.4)	3421 (25.3)
Mastery index 20-21	157 (17.3)	3396 (25.2)
Mastery index 22-28	132 (14.5)	3728 (27.6)
Type of smoker		
Never Smoked	256 (28.2)	5286 (37.1)
Daily	374 (41.2)	3851 (27.0)
Former daily/ Occasionally but former daily	201 (22.1)	3781 (26.5)
Always/ former occasional	77 (8.5)	1331 (9.3)
Recent life events scores		
No recent life events	397 (43.7)	8738 (66.7)
<3 recent life events	400 (44.1)	3866 (29.5)
3 or more recent life events	111 (12.2)	488 (3.7)
Childhood and adult stress index		
No traumatic events	260 (28.6)	6696 (51.2)
<3 traumatic events	414 (45.6)	5060 (38.7)
3 or more traumatic events	234 (25.8)	1329 (10.2)

Perceived social support index		
No social support	38 (4.2)	133 (1.0)
Minimal social support	37 (4.1)	256 (1.9)
Some social support	162 (17.8)	1914 (14.2)
Adequate social support	671 (73.9)	11,234 (83.0)
Number of weeks felt depressed		
Did not feel depressed	x	12,341 (91.1)
Felt depressed for <6 weeks	418 (46.0)	573 (4.2)
Felt depressed for 6-52 weeks	490 (54.0)	626 (4.6)
Family stress index		
No stress	584 (64.3)	9983 (76.3)
Some stress	267 (29.4)	2752 (21.0)
Stress overload	57 (6.3)	356 (2.7)
Activities prevented by pain		
No pain or discomfort	618 (68.1)	11,647 (82.1)
Pain does not prevent activities	51 (5.6)	697 (4.9)
Pain prevents few activities	81 (8.9)	813 (5.7)
Pain prevents some activities	76 (8.4)	552 (3.9)
Pain prevents most activities	82 (9.0)	478 (3.4)

NPHS- National Population Health Survey
< Secondary- less than secondary education; Secondary grad- secondary education graduate; Some post sec – some post secondary education; Post-secondary grad – post secondary education graduate
x – All participants in the cohort were depressed at baseline

6.4.2 Alcohol dependence and 6-year persistence or recurrence of major depression

After 6 years (cycle 4), 718 participants remained in the study (Figure 6-2). A hundred and twenty-four (124) participants out of 908 depressed participants at baseline, met the criteria for MDE at this time. This accounted for 17.3% of the participants who were still in the study at cycle 4. Overall, 13.7% of the baseline cohort continued to have MDE after 6years. The presence of alcohol dependence gave a three-fold increase in the risk of having persistent or recurrent depression (Table 6-4). Other factors predicting the risk of persistent or recurrent depression were being a female, a daily smoker, having pain that prevents activities and experiences of 3 or more traumatic life events. A self-esteem index of 23 and above reduced the risk of persistent or recurrent depression by 46%.

Table 6-4. Alcohol dependence, other risk factors for 6-year persistent or recurrent major depression

		[a]Adjusted	
	Crude RR (95%CI)	**RR (95%CI)**	**Statistic (p-value)**
Alcohol dependence			
No	1	1	
Yes	**2.54** (1.46-4.41)**	**3.03** (1.68-5.48)**	
Age			0.06
18 to 24 years	1	1	
25 to 44 years	1.33 (0.85-2.08)	1.37 (0.82-2.28)	
45 to 59 years	0.79 (0.45-1.38)	0.84 (0.44-1.61)	
60 years and above	0.59 (0.23-1.49)	0.97 (0.35-2.68)	
Sex			
Male	1	1	
Female	1.39 (0.95-2.04)	**1.53** (1.02-2.29)*	
Marital status			
Married	1	1	
Common-law/ with a partner	1.29 (0.69-2.40)	0.81 (0.41- 1.59)	
Widowed	.053 (0.22-1.28)	0.62 (0.24-1.56)	
Divorced or Separated	1.48 (0.98-2.23)	1.01 (0.65-1.56)	
Single/ never married	1.07 (0.71-1.61)	0.86 (0.53-1.38)	
Highest level of education			0.90
<secondary	1	X	
Secondary grad	0.77 (0.44-1.35)		
Some post-secondary	0.97 (0.64-1.46)		
Post-secondary grad	0.83 (0.54-1.28)		
Dwelling owned by a household member			
No	1	1	
Yes	**0.61** (0.44-0.83)**	0.74 (0.53-1.03)	
History of chronic condition			
No	1	X	
Yes	1.13 (0.79-1.61)		
Self-esteem index			<0.0001
Self-esteem index <18	1	1	
Self-esteem index = 18	**0.56** (0.36-0.87)**	0.73 (0.47-1.12)	
Self-esteem index 19-22	**0.49** (0.32-0.74)**	**0.59** (0.40-0.89)**	
Self-esteem index 23-24	**0.43** (0.25-0.74)**	**0.54** (0.32-0.92)*	
Mastery index			
Mastery index <17	1	X	
Mastery index 17-19	**0.56** (0.36-0.86)**		
Mastery index 20-21	0.64 (0.40-1.01)		
Mastery index 22-28	**0.43** (0.23-0.77)**		
Type of smoker			0.02
Never Smoked	1	1	
Daily	**2.05** (1.34-3.12)**	**1.58** (1.03-2.43)*	
Former daily/ Occasionally but former daily	1.09 (0.62-1.91)	1.09 (0.63-1.87)	
Always/ former occasional	1.50 (0.78-2.88)	1.24 (0.63-2.44)	
Recent life events scores			0.43
No recent life events	1	1	
<3 recent life events	**1.59** (1.11-2.27)*	1.19 (0.81-1.76)	
3 or more recent life events	1.47 (0.88-2.47)	0.92 (0.54-1.57)	
Childhood and adult stress index			0.03
No traumatic events	1	1	
<3 traumatic events	**1.68** (1.05-2.69)*	1.38 (0.87-2.19)	
3 or more traumatic events	**2.67** (1.66-4.28)**	**1.72** (1.04-2.83)*	
Perceived social support index			
No social support	1	X	
Minimal social support	0.78 (0.19-3.14)		
Some social support	1.54 (0.59-4.02)		
Adequate social support	1.06 (0.42-2.66)		
Number of weeks felt depressed			
Felt depressed for <6 weeks	1	X	
Felt depressed for 6-52 weeks	1.25 (0.90-1.74)		

Family stress index			0.68
No stress	1	1	
Some stress	**1.40** (1.01-1.96)*	1.08 (0.76-1.52)	
Stress overload	1.11 (0.57-2.16)	0.73 (0.37-1.46)	
Activities prevented by pain			0.03
No pain or discomfort	1	1	
Pain does not prevent activities	1.33 (0.69-2.55)	0.95 (0.54-1.68)	
Pain prevents few activities	1.19 (0.68-2.07)	0.96 (0.59-1.56)	
Pain prevents some activities	1.35 (0.77-2.39)	1.14 (0.63-2.06)	
Pain prevents most activities	**2.13** (1.37-3.31)**	**1.70** (1.06-2.71)*	

a – adjusted in a multivariate model
x – lost in multivariate analysis
Significant values are marked in bold print
* p-value < =0.05
** p-value <0.001
< Secondary- less than secondary education; Secondary grad- secondary education graduate; Some post sec – some post secondary education; Post-secondary grad – post secondary education graduate

6.4.3 16-year persistence or recurrence of major depression

After 16 years of follow-up (cycle 9), 461 (51%) participants remained in the study (Figure 6-2). Seventy-nine of them (17.14%) still met the criteria for MDE, that is 8.7% of the baseline cohort of 908 depressed participants continued to have depression after 16 years. Alcohol dependence remained a risk factor for the persistence or recurrence of major depression with a three-fold increase in the risk compared to those who were not alcohol dependent (Table 6-5). There was a two-fold increase in the risk of persistent or recurrent depression if participants had pain preventing activities compared to no pain or discomfort. After 16years of follow-up, being divorced or separated at baseline compared to being married was associated with a reduction in the risk of persistent or recurrent depression by 62%.

Table 6-5. Alcohol dependence, other risk factors for 16-year persistent or recurrent major depression

	Crude RR (95%CI)	[a]Adjusted	
		RR (95%CI)	Statistic (p-value)
Alcohol dependence			
No	1	1	
Yes	**2.41** (1.09-5.29)*	**3.17** (1.15-8.77)*	
Age			0.07
18 to 24 years	1	1	
25 to 44 years	1.29 (0.74-2.24)	1.16 (0.64-2.10)	
45 to 59 years	0.67 (0.32-1.42)	0.49 (0.22-1.12)	
60 years and above	0.60 (0.18-1.95)	0.48 (0.13-1.73)	
Sex			
Male	1	1	
Female	1.23 (0.76-1.97)	1.39 (0.85-2.27)	
Marital status			0.003
Married	1	1	
Common-law/ with a partner	0.97 (0.41-2.29)	0.86 (0.31-2.37)	
Widowed	0.47 (0.12-1.83)	0.63 (0.15-2.85)	
Divorced or Separated	0.62 (0.32-1.21)	**0.38** (0.19-0.74)**	
Single/ never married	1.22 (0.79-1.90)	1.10 (0.66-1.84)	
Highest level of education			
<secondary	1	X	
Secondary grad	0.82 (0.34-1.96)		
Some post-secondary	1.52 (0.82-2.80)		
Post-secondary grad	1.28 (0.69-2.39)		
Dwelling owned by a household member			
No	1	1	
Yes	**0.63** (0.42-0.94)*	0.69 (0.44-1.07)	
History of chronic condition			
No	1	1	
Yes	1.57 (0.98-2.51)	1.32 (0.80-2.18)	
Self esteem index			
Self-esteem index <18	1	X	
Self-esteem index = 18	0.81 (0.46-1.41)		
Self-esteem index 19-22	0.69 (0.41-1.14)		
Self-esteem index 23-24	0.72 (0.40-1.30)		
Mastery index			0.01
Mastery index <17	1	1	
Mastery index 17-19	**0.48** (0.25-0.91)*	**0.47** (0.25-0.90)*	
Mastery index 20-21	0.66 (0.37-1.16)	0.68 (0.38-1.25)	
Mastery index 22-28	0.73 (0.41-1.28)	0.82 (0.48-1.40)	
Type of smoker			0.03
Never Smoked	1	1	
Daily	1.35 (0.83-2.20)	1.15 (0.70-1.89)	
Former daily/ Occasionally but former daily	1.29 (0.74-2.24)	1.28 (0.74-2.22)	
Always/ former occasional	0.33 (0.08-1.35)	**0.23** (0.06-0.95)*	
Recent life events scores			0.51
No recent life events	1	1	
<3 recent life events	1.24 (0.79-1.95)	1.09 (0.69-1.72)	
3 or more recent life events	1.53 (0.86-2.72)	0.90 (0.49-1.66)	
Childhood and adult stress index			0.58
No traumatic events	1	1	
<3 traumatic events	1.18 (0.69-2.00)	1.30 (0.78-2.19)	
3 or more traumatic events	**1.86** (1.09-3.19)*	1.32 (0.74-2.37)	
Perceived social support index			0.002
No social support	1	1	
Minimal social support	0.38 (0.08-1.70)	0.27 (0.05-1.32)	
Some social support	**0.24** (0.08-0.74)*	**0.20** (0.07-0.57)*	
Adequate social support	0.64 (0.30-1.38)	0.52 (0.24-1.14)	
Number of weeks felt depressed			
Felt depressed for <6 weeks	1	X	
Felt depressed for 6-52 weeks	1.12 (0.74-1.68)		

Family stress index			0.21
No stress	1	1	
Some stress	**1.70** (1.13-2.56)**	1.27 (0.82-1.98)	
Stress overload	1.00 (0.39-2.58)	0.53 (0.20-1.45)	
Activities prevented by pain			0.001
No pain or discomfort	1	1	
Pain does not prevent activities	1.02 (0.39-2.64)	0.63 (0.22-1.77)	
Pain prevents few activities	**2.70** (1.67-4.39)**	**2.24** (1.39-3.63)**	
Pain prevents some activities	**2.19** (1.15-4.16)*	1.89 (0.94-3.78)	
Pain prevents most activities	1.85 (0.88-3.89)	**2.23** (1.08-4.62)*	

a – adjusted in a multivariate model
x – lost in multivariate analysis
Significant values are marked in bold print
* p-value < =0.05
** p-value <0.001
< Secondary- less than secondary education; Secondary grad- secondary education graduate; Some post sec – some post secondary education; Post-secondary grad – post secondary education graduate

6.5 Discussion

6.5.1 Alcohol dependence

This study showed the risk for persistence or recurrence of major depression was three times higher with concurrent alcohol dependence. This supports the evidence that comorbidity is one of the strongest predictors of persistent or recurrent major depression (Spijker & Nolen, 1998; Mueller, et al., 1994; Burcusa & Iacono, 2007; Barkow, et al., 2003; Segal, Pearson, & Thase, 2003). This also supports the evidence of the adverse effects of substance use disorders on the course of severe mental illness (Owen, Fischer, Booth, & Cuffel, 1996; Dixon, McNary, & Lehman, 1998; Mueser, Bellack, & Blanchard, 1992; Volkow, Baler, Compton, & Weiss, 2014; Hobbs, Kushner, Lee, Reardon, & Maurer, 2011). Alcohol dependence could increase the risk of persistent or recurrent depression by increasing the likelihood of symptom exacerbation, decreased social functioning and treatment nonadherence (Owen, Fischer, Booth, & Cuffel, 1996; Dixon, McNary, & Lehman, 1998; Mueser, Bellack, & Blanchard, 1992; Burcusa & Iacono, 2007).

Several possible mechanisms postulated for the co-occurrence of alcohol dependence and major depression could explain the findings of this study. However, two theories receive more recognition: the disorder inducing theory and overlapping predisposition theory. The disorder inducing theory believes one disorder causes the other and lends itself to the self-mediation theory, where major depression is being treated with alcohol to suppress symptoms (Khantzian, 1985; Merikangas, et al., 2008; Maremmani, Perugi, Pacini, & Akiskal, 2006; MacDonald, Baker, Stewart, & Skinner, 2000). In contrast, in substance-induced mood disorder, major

depression becomes a consequence of alcohol dependence (American Psychiatric Association, 2000). The overlapping predisposition consists of the idea of a common underlying vulnerability to alcohol dependence and major depression. This common vulnerability may be genetic and/or environmental (Goldman, Orozi, & Ducci, 2005; Kendler, Prescott, Myers, & Neale, 2003) with possible predisposition of individuals high in the vulnerability to not only the recurrent major depressive episodes, but also to the significant psychosocial risk factors that often accompany recurrence or persistence such as the co-occurrence of alcohol dependence (Canadian Centre on Substance Abuse, 2009; Edvardsen, et al., 2008; Agrawal & Lynskey, 2014; Li & Burmeister, 2009; Stewart & Conrod, 2008b; Agrawal & Lynskey, 2008; Burcusa & Iacono, 2007).

Irrespective of the pathway involved in causing the comorbid occurrence of major depression and alcohol dependence, once it is formed, a vicious cycle where one disorder maintains or worsens the other, may have been triggered (Stewart & Conrod, 2008; Stewart & Conrod, 2008b). In other words, if one were to treat one disorder without addressing the other, the risk of relapse, recurrence, or persistence would be very high (Canadian Centre on Substance Abuse, 2009; Stewart & O'Connor, 2009; Foa & Kozak, 1986; Forbes, Creamer, Hawthorne, Allen, & McHugh, 2003; Bruce, et al., 2005; Kushner, et al., 2005; Driessen, et al., 2001; Book, McNeil, & Simpson, 2005) resulting in increased health care utilization and costs (Willinger, Lenzinger, Hornik, Fischer, & Meszaros, 2002).

6.5.2 Other risk factors

Childhood and adult stress index was associated with an increased risk for persistent or recurrent major depression. This prospective finding which is a measure of the number of traumatic events respondents have been exposed to during their childhood, adolescence or adulthood, is in line with previous findings (Garcia-Toro, et al., 2013; Johnstone, et al., 2009; Klein, et al., 2009; Perez-Fuentes, et al., 2013; Sugaya, et al., 2012). Traumatic events such as physical and sexual abuse increase the prevalence, risk, and chronicity of depression (Perez-Fuentes, et al., 2013; Klein, et al., 2009). Physiologic dysregulation which results from stressful events during development also increases the risk of chronic conditions such as depression (Friis, Wittchen, Pfister, & Lieb, 2002; Gonzalez, et al., 2012; Choi, DiNitto, Marti, & Choi, 2017; Merrick, et al., 2017) and possibly treatment resistance (Klein, et al., 2009; Nemeroff, et al., 2003; Perez-Fuentes, et al., 2013; Sugaya, et al., 2012). Parental psychopathology, abuse, and the

resultant chaotic family environment could interfere with normal childhood development, coping mechanisms and self-esteem leading to future and severe psychopathology (Garcia-Toro, et al., 2013).

Consistent with previous findings, pain, smoking, lack of social support, low mastery or low self-esteem were associated with persistent or recurrent depression (Patten, et al., 2010; Bottomley, et al., 2010; Burcusa & Iacono, 2007; Spijker, Bijl, De Graaf, & Nolen, 2000; Keitner, Ryan, Miller, & Norman, 1992). Social vulnerability factors such as education and socioeconomic status were not associated with persistence or recurrence, consistent with findings from the Netherlands (Spijker, et al., 2004), but inconsistent with findings from the USA (Keller, 1994; Sargeant, Bruce, Florio, & Weismann, 1990; Mueller, et al., 1996). This may reflect the income inequality in these countries with the US having more income inequality than the Netherlands and Canada (The Conference Board of Canada, 2018).

The risk of persistent or recurrent depression was increased in females after 6years of follow-up, consistent with previous findings (Sargeant, Bruce, Florio, & Weismann, 1990; Keitner, Ryan, Miller, & Norman, 1992) but after 16years of follow-up, gender became a confounder. Age was not a determinant of persistent depression contrary to previous findings (Spijker, Bijl, De Graaf, & Nolen, 2000; Sargeant, Bruce, Florio, & Weismann, 1990; Spijker, et al., 2004) but a confounder. There was no association between the duration of the most recent episode (number weeks depressed) and persistent depression. This was consistent with previous findings of no associated risk of recurrence with the duration of the index episode (Burcusa & Iacono, 2007; Kaminski & Garber, 2002; O'Leary, Costello, Gormley, & Webb, 2000). This finding can be explained by the fact that the index episode may not be the first episode and results may simply be reflecting treatment response of participants (Gonzales, Lewinsohn, & Clarke, 1985). Also, our findings may be affected by recall bias.

One of the strengths of this study is that this prospective analysis was based on a nationally representative sample of the Canadian population giving an inference among individuals irrespective of their health-seeking behaviors and severity of their conditions. The diagnoses of alcohol dependence and MDE were derived using structured diagnostic instruments based on DSM III-R criteria. Limitations of this study include the loss to follow-up. Diagnosis of depression and alcohol dependence were interview-based, possibly introducing recall bias.

Assessing participants characteristics at baseline as an indication for persistence or recurrence over a long time (6 years and 16 years) is a drawback in this analysis. In addition, an important determinant of prognosis, the severity of the index MDE, was not assessed in the data.

6.6 Conclusion

The significant overlap in the mechanisms leading to alcohol dependence and major depression, the adverse effects of dependence on the course of major depression and the increased health care utilization caused by this comorbidity, is a public health concern. It is therefore of utmost importance to treat both disorders simultaneously to improve treatment outcome and reduce health care costs.

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Appendix A. Loss to follow-up

Table A.1 Association of predictor variables and missingness in MDE at cycle 4 and 9

Variables	Chi square p-value	
	MDE at cycle 4	**MDE at cycle 9**
Province of residence	0.59	0.75
Age	0.93	0.74
Sex	0.86	0.98
Marital status	0.43	0.05
Educational status	0.79	0.19
Income	0.53	0.35
History of chronic disease	0.91	0.29
Recent life events scores	0.25	0.65
Childhood and adult stress index	0.05	0.04
Dwelling owned	0.21	0.29
Alcohol dependence	0.88	0.25
Self esteem index	0.36	0.75
Mastery index	0.96	0.72
Number of weeks felt depressed	0.11	0.91
Perceived social support	0.06	0.23
Type of smoker	0.94	0.52
Pain preventing activities	0.53	0.42
Family stress index	0.04	0.22

MDE – major depressive episode

CHAPTER 7. A SYSTEMATIC REVIEW AND META-ANALYSIS OF COMORBID SUBSTANCE USE DISORDERS, CANNABIS USE DISORDERS WITH MAJOR DEPRESSION

7.1 Introduction

Substance use disorders (SUDs) are highly co-morbid with other psychiatric disorders in both the general population and in patient populations (Buckley & Brown, 2006; Compton, Thomas, Stinson, & Grant, 2007; Conway, Montoya, & Compton, 2007; de Leon & Diaz, 2005; Grant, et al., 2004; Jane-LIopis & Matytsina, 2006; Kessler, et al., 2003; Regier, et al., 1990) and are usually associated with poor treatment outcomes resulting in severe illnesses and increased health service utilization (Kessler, et al., 1994; Kessler R. , 2004; Merikangas & Gelernter, 1990). Epidemiological patterns of several population-based studies (Grant & Harford, 1995; Kessler, et al., 1996a; Kessler, et al., 1997; Kessler, et al., 2001; Regier, et al., 1990; Grant, et al., 2004; Grant, et al., 2016) consistently found comorbid associations between mental health disorders and substance use disorders, and at much higher rates than chance levels.

Comorbid substance use and psychiatric disorders have been investigated extensively in large epidemiological studies: the Epidemiological Catchment Area (ECA) surveys in the United States of America (Regier, et al., 1990), the International Consortium in Psychiatric Epidemiology (ICPE) (Kessler, et al., 2001), the US National Comorbidity Survey (NCS) (Kessler, et al., 1996a), the Canadian Community Health Survey: Mental Health and Well-Being (CCHS 1.2) (Currie, et al., 2005; Rush, Urbanoski, Bassani, Castel, & Wild, 2008), the National Longitudinal Alcohol Epidemiologic Survey (NLAES) (Grant B. , 1995), the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Bijl, Ravelli, & Van Zessen, 1998) and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Compton, Thomas, Stinson, & Grant, 2007; Hasin, et al., 2016). Even though these surveys have demonstrated independently, the prevalence and associations of substance use and psychiatric disorders, a meta-analysis of these associations is necessary.

Comorbidity research has produced a range of prevalence rates (Grant, et al., 2004; Kessler, et al., 2003; Currie, et al., 2005; Schuckit, et al., 1997). Although definitive comparisons across studies are made impossible by methodological differences, Jane-LIopis & Matytsina

(2006) in their review found prevalence estimates overlap of 7% to 45% and 17% to 55% for mood or anxiety disorders with alcohol dependence and drug dependence respectively. These variations can be explained by the fact that the diagnostic criteria for major depression and substance use disorders have changed over the years and the overlap in symptomatology have been handled differently in different surveys (Currie, et al., 2005). In addition, a variety of instruments and different versions of the same instrument have been used in epidemiological surveys (Currie, et al., 2005; Hasin, et al., 1997), with advancements in some of these instruments such as the World Health Organization – Composite International Diagnostic Interview, WHO-CIDI resulting fewer false positives, hence reduced prevalence of comorbidity (Kessler, et al., 2003). In the Collaborative Study on Genetics of Alcoholism (COGA), the relationships between Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, DSM-III-R and International Classification of Diseases, ICD-10 diagnostic criteria were evaluated for substance use disorders (Schuckit, et al., 1994). While analyses revealed similarity in the proportions of individuals diagnosed with the three systems for substance dependence (kappa 0.54-0.83), they were largely disparate for substance abuse or harmful alcohol use (kappa rarely exceeding 0.1) (Schuckit, et al., 1994).

Comorbid associations have been postulated to occur either by one disorder inducing the other or the individual having a shared vulnerability to both disorders (Canadian Centre on Substance Abuse, 2009). Concurrent disorders tend to be more frequent in treatment samples than in the general population (Weaver, et al., 2003). Treatment samples are often biased by the increased help-seeking behavior of individuals with comorbid, more severe and protracted mental health disorders (Berkson, 1946; Regier, et al., 1990; Rounsaville, Dolinsky, Babor, & Meyer, 1987). General population-based studies, therefore, provide more robust and generalizable estimates of the comorbidity distribution of SUDs and mental health disorders.

A previous systematic review of comorbid substance use disorders and mental health disorders in studies between 1998 and 2005, did not include a meta-analysis (Jane-LIopis & Matytsina, 2006). Another systematic review on comorbid substance use and mental health disorders had a meta-analysis and was based on studies between 1990 and 2014 included 22 studies from national epidemiological surveys and community-based samples of predominantly large urban centres (Lai, Cleary, Sitharthan, & Hunt, 2015). This may have introduced some

form of bias as there are disparities in access to care between rural and urban residents (Loftus, Allen, Call, & Everson-Rose, 2018).

To expand knowledge, our current systematic review with meta-analysis was intended to assess the prevalence and strength of associations between comorbid substance use disorders, cannabis use disorders with major depression in nationally representative samples. Since comorbidity is a significant predictor of treatment seeking (Wu, Kouzis, & Leaf, 1999), nationally representative studies where chosen to avoid including studies based on patient samples that may overestimate the comorbid associations (Berkson, 1946). In addition, national surveys were chosen to avoid population dynamics such as rural versus urban and the influence on comorbid treatment access and estimates. Nationally representative studies were defined as studies whose original participants were from national surveys capturing both rural and urban residents and stated by the authors as nationally representative. Our interest in cannabis stems from the fact that it is still the most frequently used controlled substance across the globe (United Nations Office on Drugs and Crime, 2016) and a significant political, health and law-enforcement issue. After alcohol, cannabis is the most consumed substance with several countries moving to its legalization and contemplating how its medical uses fit into the equation (Canadian Centre on Substance Abuse, 2017; United Nations Office on Drugs and Crime, 2016). In Canada, cannabis legalization took place on the 17th of October 2018, and this legalization is thought to replace a failed model that increased organized criminal activities and vulnerability to children (Tasker, 2018). Evidence of the negative health effects of cannabis appear to be inconsistent (Canadian Centre on Substance Abuse, 2017). A systematic review with a pooled effect could help to clarify the nature and extent of the relationship between substance use disorder, cannabis use disorder and major depression.

7.2 Objectives

In this study, we aimed to conduct a systematic review and meta-analyses assessing the prevalence and strength of associations between comorbid substance use disorders (alcohol use disorders, drug use disorders – all illicit drugs of abuse) with major depressive episodes (MDE), comorbid cannabis use disorders (CUDs) with MDE in nationally representative population-based surveys.

7.3 Methods

The methods were based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati, et al., 2009; Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

7.3.1 Data sources and search strategy

A computerized search of the following bibliographic databases: MEDLINE, CINAHL, PsycINFO and EMBASE was conducted using the following search terms: (co-morbid* or comorbid* or co-occur*) OR diagnosis or dual diagnosis(psychiatry), AND (alcohol* or cannabis* or marijuana* or drug* or substance* or SUD) OR (mental health or mental illness or bipolar or depress* or mood disorder) AND (epidemiology or prevalence or incidence or occurrence), for population surveys of humans in English, published online between January 1st 1980 and May 31st 2018. Further search of related articles of selected authors (e.g. de Graaf, Grant, Kessler, Merikangas, Reiger, Conway and Swendson), the reference list of included studies and a previous meta-analysis on comorbid substance use, anxiety and mood disorders (Lai, Cleary, Sitharthan, & Hunt, 2015) was done. Gray literature for dissertations, conference abstracts, formally unpublished journal articles and books were made. Inclusion criteria were publications in English Language, original research, nationally representative samples, and non-clinical randomly selected adult populations. Studies whose target population were a close representation of the national population were assessed as nationally representative. Exclusion criteria were studies done on clinical/ patient samples, restricted geographic area or population of a country, children and adolescent.

7.3.2 Selection criteria

Two independent raters (Vivian Onaemo and Muzi Li) excluded materials that were irrelevant to the review and assessed for risk of bias using the tool developed by Hoy et al (2012). The first, second and third rounds of exclusions were based on the articles' titles, abstracts and full texts respectively. If there were any disagreements or uncertainties at the first and second rounds, a full text review was done. Disagreements with full text review were resolved by a third rater (Carl D'Arcy). Articles were chosen if they were original research on adults, randomly selected national representative surveys. Children and adolescent studies were excluded because interviews on them are usually complicated with consent and proxy issues.

Studies on subpopulations such as specific cities (e.g. Ontario (Offord, et al., 1996), Munich (Wittchen, Essau, von Zerssen, Krieg, & Zaudig, 1992), limited age (e.g. middle-aged), gender-specific or other specific groups (e.g. veterans), race (Merikangas, et al., 1998), other comorbidities (e.g. diabetes), institutionalized, homelessness, specific demographics (e.g. students, nurses) were excluded as they were not nationally representative. Studies were also screened based on the diagnostic criteria used. All included studies were based on structured diagnostic instruments.

7.3.3 Data abstraction

The two raters (VO and ML) independently abstracted using a semi-structured form for the study characteristics such as the name of study, name of survey, authors, setting (country), year survey was conducted, year of publication, journal, sample size, age range, diagnostic criteria used, type of SUD and psychiatric disorders (major depression).

Data abstraction for meta-analysis included the comorbidity prevalence, odds ratios (ORs) and 95% confidence intervals of major depression and SUDs (alcohol, drugs), and major depression and CUDs.

7.3.4 Meta-analysis

STATA version 14 was used to estimate the pooled ORs of selected articles in four separate meta-analyses.

- Substance use disorders[2] (SUD) and major depression (MD)
- Substance abuse[3] and MD
- Substance dependence and MD
- Cannabis use disorders (CUD) and MD

[2] Substance use disorders (alcohol, illicit drugs) refers to substance abuse and /or dependence (American Psychiatric Association, 1994).

[3] "Substance abuse refers to the harmful or hazardous use of psychoactive substances (alcohol and illicit drugs) while substance dependence is a cluster of behavioural, cognitive, and psychological phenomena (difficulties controlling its use or the strong desire to use, persisting in its use despite harmful consequences, higher priority given to the drug use than other activities or obligations, increased tolerance, physical withdrawal) that develop secondary to repeated use of the substance" (World Health Organization, 2018).

In these analyses, substance use disorder is comprised of alcohol use disorders (AUD) and illicit drug use disorders (DUD). Substance abuse is comprised of alcohol abuse and illicit drug abuse while substance dependence is comprised of alcohol dependence and illicit drug dependence. Cannabis use disorder is comprised of cannabis use disorder, cannabis abuse and cannabis dependence. All diagnoses were derived using structured diagnostic instruments in the primary studies.

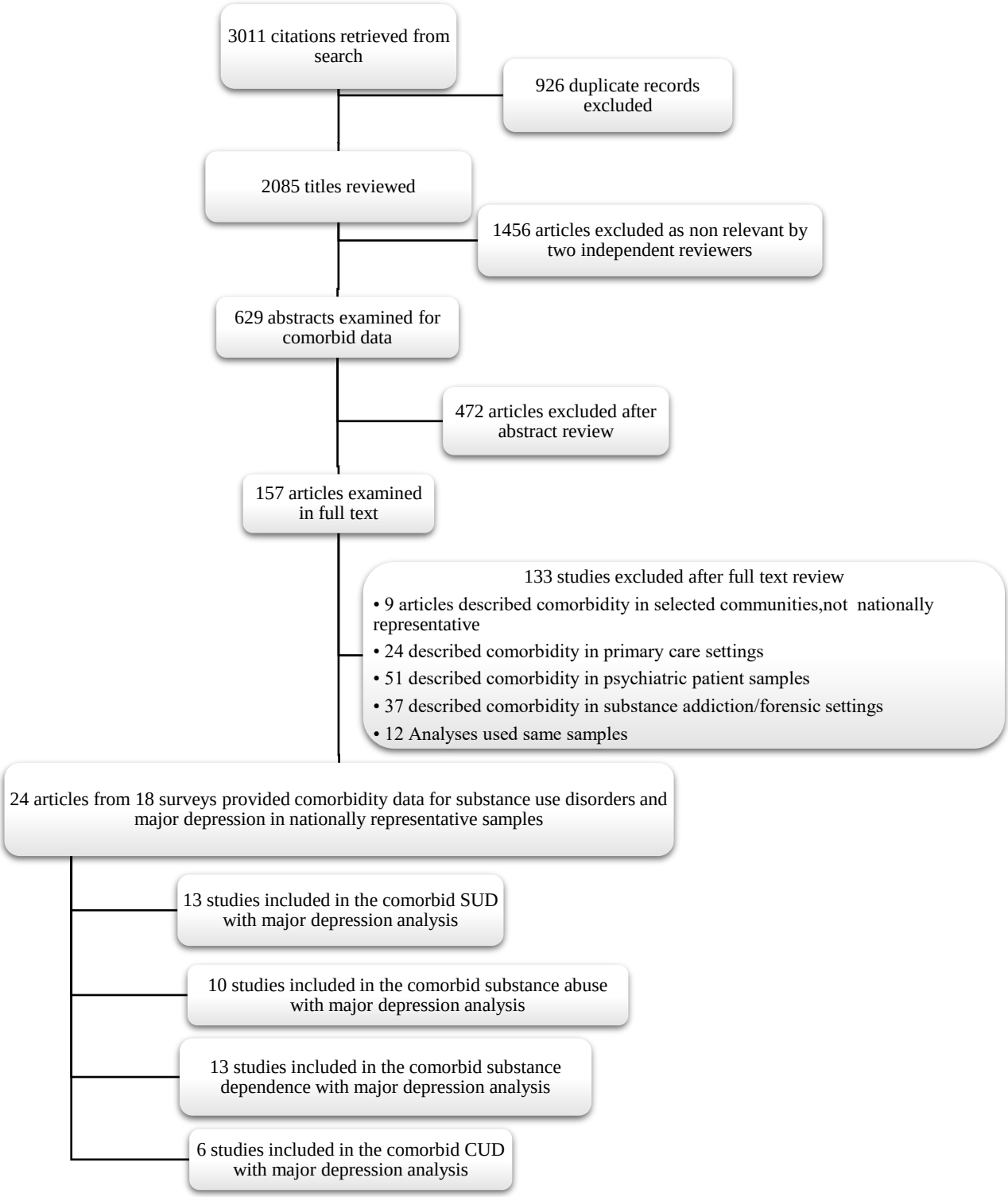
Since the prevalence would likely vary between populations of different nationalities and characteristics, we evaluated heterogeneity with DerSimonian and Laird I^2 Statistic to determine the degree of inconsistency across studies' results that is due to heterogeneity rather than chance (Higgins, Thompson, Deeks, & Altman, 2003). A random effects model was chosen over a fixed effects model when the percentage of total variation across studies was found to be significant. To avoid duplication, articles reporting odds ratios from the same survey were identified and one selected based on quality, estimates reported (lifetime chosen over 12-months) and date of publication (most recent chosen). Publication bias was accounted for with Egger's test and impact of study quality with meta-regression. Sensitivity analysis and meta-cumulative analysis were done to see the impact of individual studies on the overall estimate.

7.4 Results

7.4.1 Search findings

After removal of duplicates, a total of 2085 titles were identified (Figure 7-1). The two independent reviewers (VO and ML) judged 1456 articles as not relevant by title. The reviewers examined 629 articles for comorbid associations by abstract and excluded 472 articles. A full text review of 157 articles was done and 24 articles from 18 surveys were identified as describing comorbid prevalence and associations in nationally representative samples.

Figure 7-1. PRISMA flow diagram of search strategies and results. - Comorbid substance use disorder with major depression



7.4.2 Study characteristics

The settings, sample sizes and characteristics of respondents for the 24 articles included in this review are summarised in Table 7-1. Sample sizes ranged from 1555 in Puerto Rico to 43,093 in the USA with a total sample size of 300,104 for all 18 surveys included in the analysis. Surveys included were from the USA, Canada, Europe (Belgium, France, Germany, Italy, The Netherlands, Spain), The Netherlands, Great Britain, Australia, Puerto Rico, South Korea, Singapore, Thailand and Taiwan. Some national surveys that were repeated at a different time point with different respondents (NSMH&WB 1 and 2 (study ID 12 and 13), NSERC wave I and III (study ID 8 and 9), and NCS and NCS-R (study ID 6 and 7) were included as different studies while the one that was based on the same respondents (NSERC wave II) from a previous survey (NSERC wave I) was excluded.

The quality of the studies (Appendix 3) and risk for bias were assessed using an assessment scale modified from the Newcastle-Ottawa Scale (NOS) (Wells, et al., 2012) and the tool developed for prevalence studies by Hoy et al (2012). The assessment was based on the external validity (representativeness of the national population, sampling frame a true representation of the target population, random selection of participants, likelihood of non-response minimal) and internal validity (data collected directly from the subjects not proxy, assessment of exposure and outcome, acceptable case definition used in the study, the same mode of data collection for all subjects, numerator(s) and denominator(s) for the parameter of interest appropriate, appropriate control of confounding) of the studies (Hoy, et al., 2012; Wells, et al., 2012). One study (ESEMed) had a medium risk of bias while others were low.

Table 7-1. Summary of study characteristics of included studies

Study ID	Survey name	Survey year	Setting	First author	Sample size	Age range (year)	Psychiatric disorders	SUDs	Diagnostic criteria	Risk of bias
1	Canadian Community Health Survey: Mental Health and Well-Being (CCHS 1.2)	2002	Canada	(Currie, et al., 2005)	36,984	15years and older	Major depression	Harmful alcohol use, alcohol dependence, drug dependence	WHM-CIDI (based on DSM-III-R)	Low; harmful alcohol use to mean alcohol abuse
2	Epidemiologic Study of Puerto Rico	1984	Puerto Rico	(Swendsen, et al., 1998)	1551	17-64years	Depression	AUD	DSM-III	Low
3	European Study of the Epidemiology of mental disorders (ESEMed)	2000	Belgium, France, Germany, Italy, The Netherlands, Spain	(Alonso, Lepine, & Scientific-Committee, 2007)	Phase 1 21,425 phase 2 8796	18years and older	Major depression	Alcohol abuse, alcohol dependence	CIDI 3.0	Medium: varied response rate across regions (46-79%), combined comorbidity indices
4	Korean Epidemiologic Catchment Area (KECA) study	2001	South Korea	(Chou, et al., 2012)	7867	18-65years	Major depression	Alcohol use disorders	K-CIDI 2.1	Low
5	Collaborative Psychiatric Epidemiology Studies (CPES)	2001-2003	United States	(Mericle, Ta Park, Holck, & Arria, 2012)	19,729	18years and older	Major depressive episode	SUD (AUD and DUD)	WHM-CIDI (based on DSM-IV)	Low
6	National Comorbidity Survey (NCS)	1990-1992	United States	(Kessler, et al., 1996b)	5,877	15-54years	Depression	Alcohol, drug, abuse, dependence, SUD	DSM-III-R	Low
7	National Comorbidity Survey Replication (NCS-R)	2001-2002	United States	(Kessler, et al., 2003)	5,554	18years and older	Major depressive ds	SUD	DSM-IV	Low
8a	National Epidemiologic Survey on Alcohol and Related Conditions (NSERC)	2001-2002	United States	(Conway, Compton, Stinson, & Grant, 2006)	43,093	18years and older	Major depression	DUD, abuse, dependence; CUD, abuse, dependence	AUDADIS-IV derived from DSM-IV	Low

8b				(Hasin, Goodwin, Stinson, & Grant, 2005)	43,093	18years and older	Major depressive ds	AUD, DUD, abuse, dependence	AUDADIS-IV derived from DSM-IV	Low
8c				(Stinson, Ruan, Pickering, & Grant, 2006)	43,093	18years and older	Major depression	CUD	AUDADIS-IV derived from DSM-IV	Low
9a	National Epidemiological Survey on Alcohol and Related Conditions (NESARC) III	2012-2013	United States	(Grant, et al., 2015)	36,309	18years and older	Major depression	AUD	AUDADIS-5 derived from DSM-5 criteria	Low
9b				(Grant, et al., 2016)	36,309	18years and older	Major depression	DUD	AUDADIS-5 derived from DSM-5 criteria	Low
9c				(Hasin, et al., 2016)	36, 309	18years and older	Major depression	CUD	AUDADIS-5 derived from DSM-5 criteria	Low
10	National Household Survey on Drug Abuse (NHSDA)	1994, 1995, 1996	United States	(Kandel, Huang, & Davies, 2001)	39,994	12years and older	Major depression	Alcohol, cannabis, drugs dependence	DSM-IV	Low
11a	National Longitudinal Alcohol Epidemiology Survey (NLAES)	1992	United States	(Grant B. , 1995)	42,862	18years and older	Major depression	DUD, abuse, dependence; CUD, abuse, dependence	AUDADIS-IV derived from DSM-IV	Low
11b				(Grant & Harford, 1995)	42,862	18years and older	Major depression	AUD, abuse, dependence	AUDADIS-IV derived from DSM-IV	Low
12	National Survey of Mental Health and Well Being (NSMH&WB)	1997	Australia	(Burns & Tesson, 2002)	10,641	Adults	Major depression	AUD	CIDI	Low

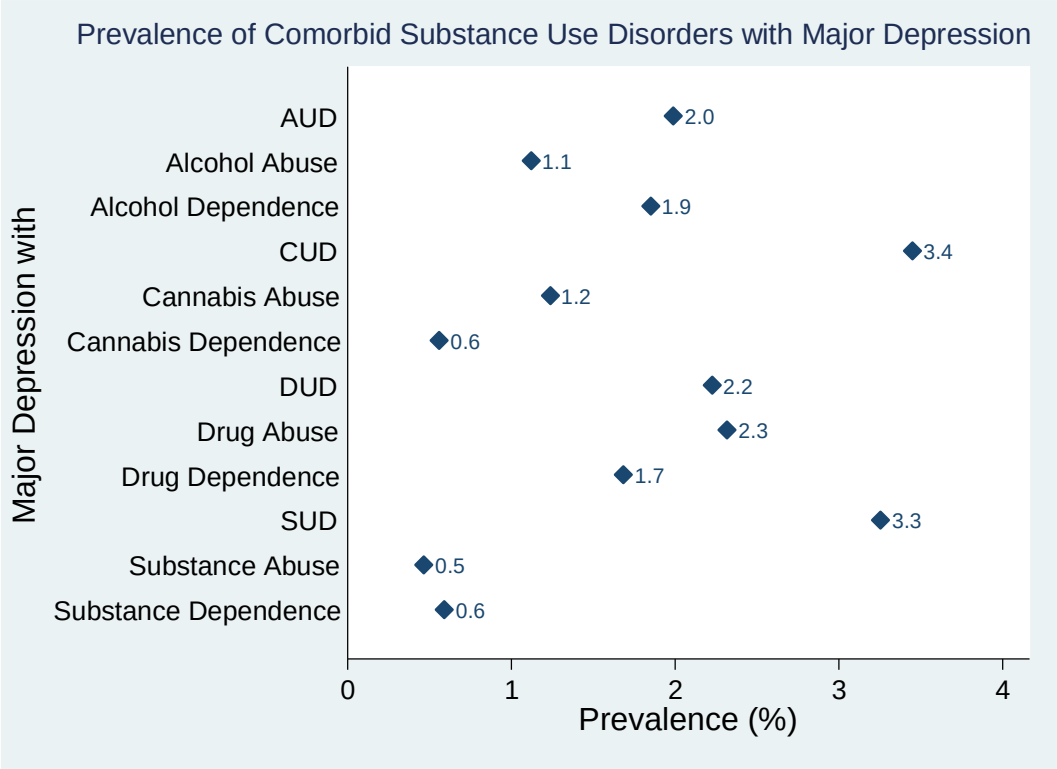
13a	National Survey on Mental Health and Well-being (NSMH&WB)	2007	Australia	(Teesson, et al., 2010)	8841	16-85years	Major Depressive Disorder	AUD	WMH-CIDI derived from DSM-IV	Low
13b				(Teesson, et al., 2012)	8841	16-85yeasr	Major depressive ds	CUD	WMH-CIDI derived from DSM-IV	Low
14	National Survey of Psychiatric Comorbidity	1995	Great Britain	(Farrell, et al., 2001)	10,018	16-64years	Depression	Alcohol dependence, drug dependence	ICD-10	Low
15	Netherlands Study of Depression and Anxiety (NESDA)	2004-2007	The Netherlands	(Boschloo, et al., 2011)	2981	18-65years	Depressive ds	Alcohol abuse, alcohol dependence	CIDI	Low
16	Taiwan Psychiatric Morbidity Survey (TPMS)	2003-2005	Taiwan	(Liao, et al., 2012)	10,135	18years and older	Major depressive disorder	SUD (AUD and DUD)	WHM-CIDI (based on DSM-IV)	Low
17	Thai National Mental Health Survey	2008	Thailand	(Suttajit, Kittirattanapaiboon, Junsirimongkol, Likhitsathian, & Srisurapanont, 2012)	17,140	15 and 59years	Major depressive disorder	AUD, DUD, SUD	MINI v5.0 based on DSM-IV	Low
18	The Singapore Mental Health Study	2009-2010	Singapore	(Subramaniam, et al., 2012)	6,616	18years and older	Major depressive ds	AUD	WMH-CIDI	Low

AUD, Alcohol use disorders; CUD, Cannabis use disorders; DUD, Drug use disorders; SUD, Substance use disorders; CIDI, Composite International Diagnostic Interview (CIDI); CIDI-SF (short form); DIS, diagnostic; WMH-CIDI, World Mental Health-CIDI; DSM, Diagnostic Statistical Manual of Mental Disorders; AUDADIS-IV, Alcohol Use Disorder and Associated Disabilities Interview Schedule – DSM-IV version; AUDADIS-5, The Alcohol Use Disorder and Associated Disabilities Interview Schedule-5.

7.4.3 Prevalence

The prevalence of major depression with SUDs, AUD, CUD and DUD are shown in Figure 7-2. Prevalence estimates were those of comorbid occurrence of substance use disorders with major depression. Comorbid substance use disorders with major depression are highly prevalent. Major depression co-occurring with cannabis or drug abuse is more prevalent than with cannabis or drug dependence while its co-occurrence with alcohol dependence is more prevalent than with alcohol abuse. Comorbid major depression with DUD and CUD are more prevalent than with AUD.

Figure 7-2. Prevalence of comorbid substance use disorder with major depression



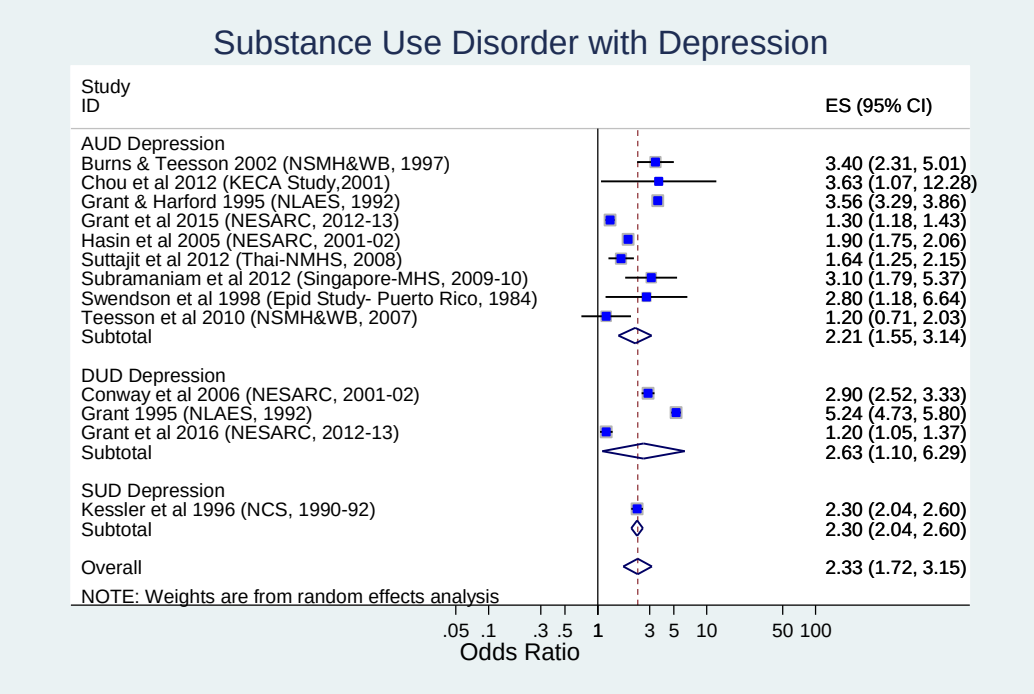
AUD, Alcohol use disorders; CUD, Cannabis use disorders, DUD, Drug use disorders, SUD, Substance use disorders

7.4.4 Meta-analysis

The forest plot for SUD (AUD, DUD and SUD) and major depression is shown in figure 7-3. The meta-analysis pooled OR for AUD and major depression was 2.21 (95%CI 1.55-3.14), for DUD was 2.63 (95% CI 1.10-2.63) and SUD was 2.30 (95%CI 2.04-2.60). Thirteen studies

gave a pooled OR for comorbid major depression with substance use disorder as 2.33 (95%CI 1.72-3.15), indicating that individuals with SUD are 2 times more likely to have comorbid major depression. There was no evidence of publication bias using the Egger's test (p=0.85). Due to a significant DerSimonian and Laird I^2 heterogeneity test (p<0.0001), a random effects analysis was chosen.

Figure 7-3. Comorbid substance use disorder with major depression

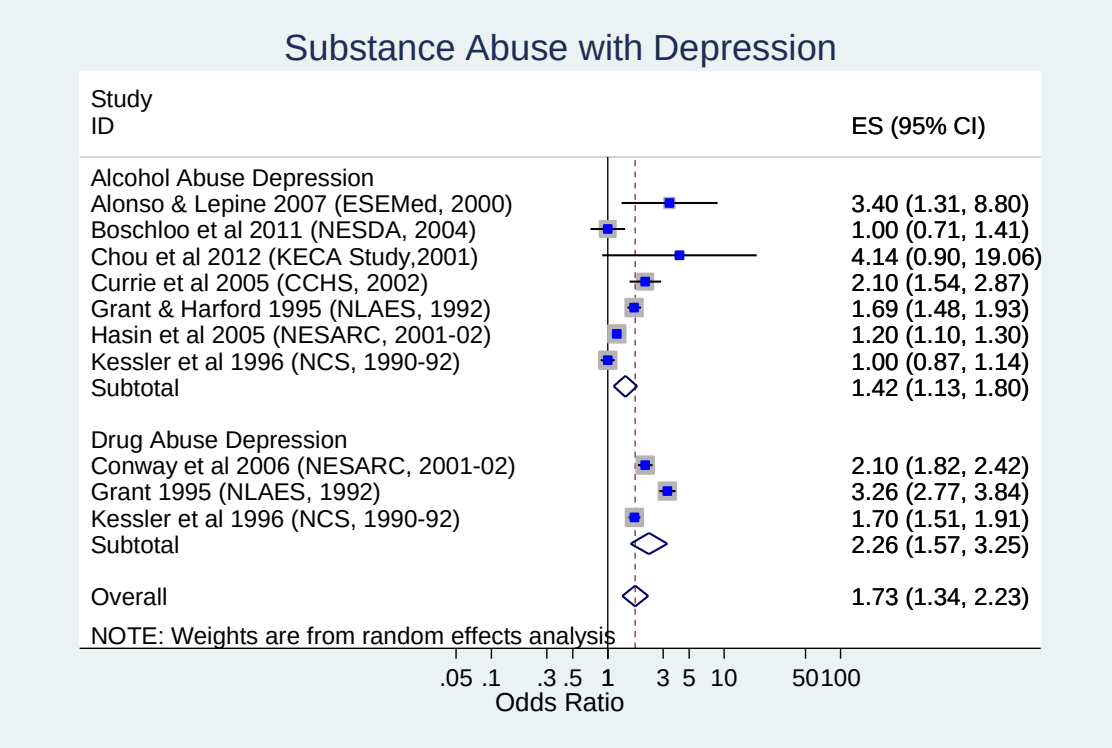


ES – estimate (OR); AUD - Alcohol use disorders; DUD - Drug use disorders; SUD - Substance use disorders

Figure 7- 4 shows the forest plot for substance abuse (alcohol abuse, drug abuse) with depression. Meta-analysis pooled OR on 10 studies for major depression with substance abuse was 1.73 (95% CI 1.34-2.23), for alcohol abuse with depression was 1.42 (95%CI 1.13-1.80) and for drug abuse with depression was 2.26 (95%CI 1.57-3.25). Chou et al (2012) in their study on the Korean Epidemiologic Catchment Area (KECA) 2001 survey and Boschloo et al (2011) in their study on the Netherlands Study of Depression and Anxiety (NESDA) 2004 survey did not find associations between comorbid alcohol abuse with major depression. Other studies included in the meta-analysis showed significant risk of comorbid depression with substance abuse. There

was no evidence of publication bias with Egger's test (p=0.37) and random effects analysis chosen due to a significant DerSimonian and Laird I^2 heterogeneity test (p<0.0001).

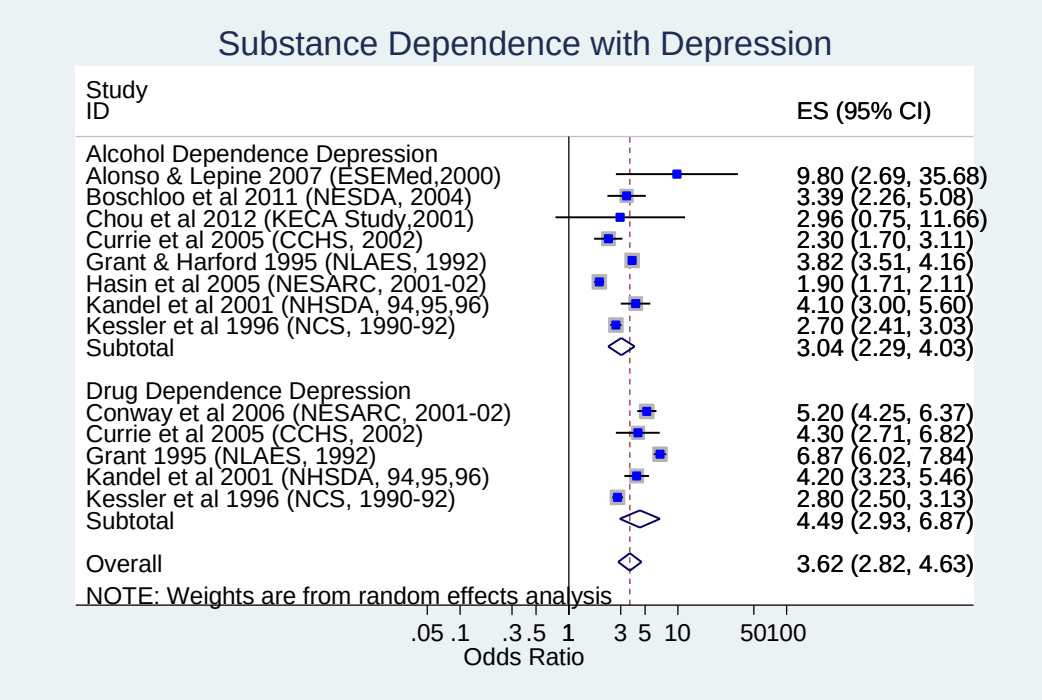
Figure 7-4. Comorbid substance abuse with major depression



ES – estimate (OR); AUD - Alcohol use disorders; DUD - Drug use disorders; SUD - Substance use disorders

The meta-analysis pooled OR for substance dependence (alcohol dependence, drug dependence) with major depression is shown in figure 7-5. The overall pooled estimate for 13 studies was 3.62 (95%CI 2.82-4.63) while that for alcohol dependence with major depression was 3.04 (95%CI 2.29-4.03) and drug dependence with major depression was 4.49 (2.93-6.87). This indicates a 3-folds and 4-folds increased risk of comorbid major depression with substance dependence and drug dependence respectively. DerSimonian and Laird I2 heterogeneity test was significant (p<0.0001) and a random effects analysis was chosen. Egger's test showed no evidence of publication bias (p=0.58).

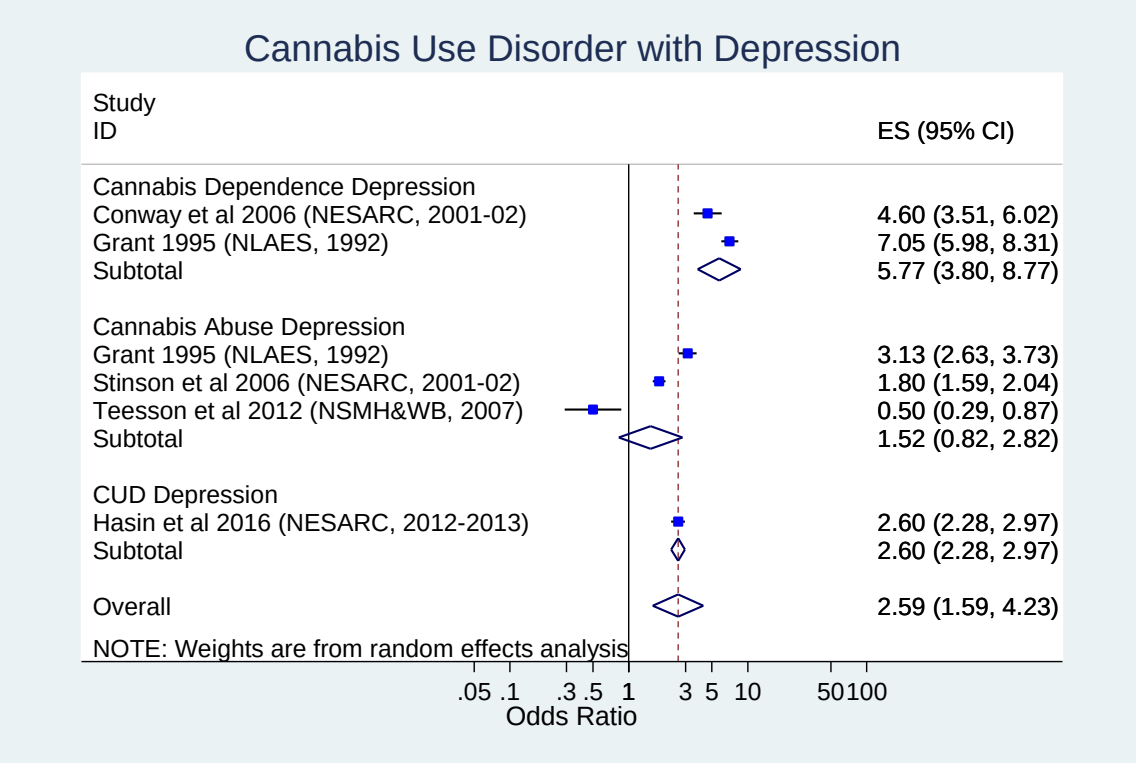
Figure 7-5. Comorbid substance dependence with major depression



ES – estimate (OR); AUD - Alcohol use disorders; DUD - Drug use disorders; SUD - Substance use disorders

In figure 7-6, the meta-analysis pooled OR for CUD (Cannabis abuse, cannabis dependence, CUD) with major depression was 2.59 (95%CI 1.59-4.23) on 6 studies while the pooled OR for cannabis dependence with depression was 5.77 (95%CI 3.8-8.77). In other words, individuals with CUD and cannabis dependence are 2 times and 5 times more likely to have comorbid major depression respectively. One study, Teesson et al (2012) based on the 2007 Australian National Survey of Mental Health and WellBeing found a significant reduction in the risk of comorbid major depression with cannabis abuse. Other studies in the analysis showed increased risk of having comorbid major depression with cannabis use disorders. The DerSimonian and Laird I^2 test for heterogeneity was significant ($p<0.0001$) and a random effects analysis was chosen. There was no evidence of publication bias with Egger's test ($p=0.97$).

Figure 7-6. Comorbid cannabis use disorder with major depression



ES – estimate (OR); AUD - Alcohol use disorders; DUD - Drug use disorders; SUD - Substance use disorders

7.5 Discussion

This systematic review and meta-analysis showed high prevalence and evidence of strong associations between substance use disorders (abuse, dependence or both) and major depression, irrespective of the type of substance use disorder (alcohol, drug or cannabis). Comorbid major depression with CUD and DUD were found to be more prevalent than with AUD. This corroborates previous findings of higher rates of comorbid mental health disorders with SUD and much higher rates in illicit drug use disorders than AUD (Jane-LIopis & Matytsina, 2006). Alcohol dependence was noted to be more prevalent than alcohol abuse unlike in cannabis and illicit drug use where the abuse is more prevalent than the dependence. This could be explained by the policies on alcohol and drugs. While alcohol is considered a legal substance, illicit drugs (and cannabis until recently in some countries including Canada) were not. This may have affected participants perception of abuse of these substances with under reporting of abuse relating to alcohol. In addition, since dependence is the severe form of the spectrum of alcohol

use disorder, individuals with alcohol dependence are therefore, more likely to acknowledge the problem as opposed to those with alcohol abuse.

The strongest associations of comorbidity were found between major depression and substance dependence (pooled OR, 95%CI - 3.62, 2.82-4.63) and, major depression and substance use disorder with pooled OR (95%CI) of 2.33 (1.72-3.15). In sub-analyses, major depression had very strong associations with cannabis dependence (OR, 95%CI - 5.77, 3.80-6.02), drug dependence (OR, 95%CI - 4.49, 2.93-6.87), alcohol dependence (OR, 95%CI - 3.04, 2.29-4.03), DUD (OR, 95%CI - 2.63, 1.10-6.29) and AUD (OR, 95%CI - 2.21, 1.55-3.14).

7.5.1 Substance use disorders with major depression

Major depression is significantly associated with substance use disorder (Figure 7-3) and this association was strongest for DUD. A closer inspection of the forest plot showed only one of the 13 studies included in the analysis (Teesson, et al., 2010) had a non-significant association between substance (alcohol) use disorder and depression (95%CI 0.71-2.03). Substance dependence was strongly associated with depression (Figure 7-5) and the strongest association was found for drug dependence. Only one of 13 studies did not show this association (Chou, et al., 2012) confirming the robustness of this association across countries of different population characteristics. These findings are consistent with a previous review finding of significant associations of comorbid SUDs with mood disorders across countries (Lai, Cleary, Sitharthan, & Hunt, 2015).

The strength of the association between major depression and substance abuse is weaker than that of dependence. This can be explained by the clinical differences and severity of substance abuse and substance dependence. Substance dependence which is defined as a cluster of behavioural, cognitive, and psychological phenomena is more severe and has a worse outcome such as comorbidity associations than substance abuse which is the harmful or hazardous use of substances (World Health Organization, 2018). This shows that dependence rather than abuse is the major driver in the association between substance use disorders and depression.

Several mechanisms have been postulated to mediate the co-occurrence of SUD and major depression. However, part of the difficulty in explaining how substance use disorders and depression co-occur is that the boundaries between different mood disorders and the variety of

substances make research and conclusions in this area quite a challenge (Canadian Centre on Substance Abuse, 2009). The onset of either of the disorders is also difficult to define (Canadian Centre on Substance Abuse, 2009). Comorbid associations of major depression and SUD are difficult to treat as there are several service barriers to overcome (McGovern, Xie, Segal, Siembab, & Drake, 2006; Mills, et al., 2012). Having both disorders affects the clinical course of both disorders and clinical outcomes, therefore, it is crucial to treat both conditions in an affected individual simultaneously (Canadian Centre on Substance Abuse, 2009) .

7.5.2 Cannabis use disorders with major depression.

Major depression was strongly associated with cannabis use disorders and this association was stronger with cannabis dependence (pooled OR 5.77). A closer inspection of the forest plot showed one of six studies found a reduction in the risk of comorbid associations of major depression and cannabis abuse (Teesson, et al., 2012). As the most frequently used controlled substance globally (United Nations Office on Drugs and Crime, 2016), this meta-analysis, confirms the findings from several studies that cannabis, especially the heavy use increases the risk of comorbid major depression (Arseneault, et al., 2002; Chen, Wagner, & Anthony, 2002; Cheung, et al., 2010; van Laar, van Dorsselaer, Monshouwer, & de Graaf, 2007; Degenhardt, Hall, & Lynskey, 2003; Fergusson, Horwood, & Swain-Campbell, 2002; Lynskey, et al., 2004; Hayatbakhsh, et al., 2007; Marmorstein & Iacono, 2011; Bovasso, 2001) and negatively affects the outcome of pharmacological treatment for depressive symptoms (Bricker, et al., 2007).

The possibility of several mechanisms leading to the occurrence of comorbid cannabis use disorder and major depression has been proposed. First, biological effects where cannabis causes multiple effects in brain chemistry, thus increasing the likelihood of depression (Degenhardt, Hall, & Lynskey, 2003; Hayatbakhsh, et al., 2007; van Laar, van Dorsselaer, Monshouwer, & de Graaf, 2007; Patton, et al., 2002; Dean, Sundram, Bradbury, Scarr, & Copolov, 2001). It is also biologically plausible that long-term cannabinoid consumption may alter the responsiveness of the serotonin system in ways consistent with depression (Hill, Sun, Tse, & Gorzalka, 2006; Tsou, Mackie, Sanudo-Pena, & Walker, 1999; Bhagwager, Rabiner, Sargent, Grasby, & Cohen, 2004; Drevets, et al., 1999; Sargeant, Bruce, Florio, & Weismann, 1990). Another mechanism is through shared vulnerability where common genetic and/or environmental vulnerabilities predispose some people to have impaired psychosocial adjustment

from which mental health problems could arise (Lynskey, et al., 2004; Degenhardt, Hall, & Lynskey, 2003). In addition, the adverse psychological consequences of cannabis use such as educational under-achievement, unemployment, and crime exacerbate this association (Marmorstein & Iacono, 2011; Lev-Ran, et al., 2014; Degenhardt, Hall, & Lynskey, 2003).

The results of this meta-analysis further confirm the association between SUDs and major depression found in an earlier meta-analysis (Lai, Cleary, Sitharthan, & Hunt, 2015) on alcohol use, illicit drug use, and depression. The methods for this meta-analysis differed from Lai et al (2015) as we excluded studies from sub-populations within a geographic boundary such as community-based epidemiological studies of target cities. Nevertheless, the findings of strong associations between substance use disorder and major depression in two meta-analyses irrespective of the study question and sample definition do confirm a robust association between substance use disorders and major depression.

7.5.3 Strengths and limitations

Consistently, strong associations between SUDs and major depression were demonstrated by the epidemiological studies used for these analyses. The methods for individual studies were relatively consistent, using surveys of face-to-face interviews from random samples of general populations at the national level. In addition, studies included used structured diagnostic methods to derive the diagnosis of major depression and substance use disorders. Limitations of this study include interview-based diagnoses which do not allow for the eliminating of differential diagnoses, possibly inflating prevalence and associations. Also, such interviews do not allow for detailed history from the respondent nor repeated visits to confirm a diagnosis. Data combined were from studies across different geographic regions, cultures with varied response rates. This could have introduced some selection bias. Adjustment of prevalence and associations of the comorbidity varied across studies. While some studies adjusted for either the demographic or socioeconomic factors, others did both. Furthermore, different modifications of different versions of the Diagnostic Statistical Manual (DSM) or International Classification of Diseases (ICD) diagnostic criteria and the varying depth of the interviews could have contributed to the heterogeneity of the study. Finally, the studies did not consider polysubstance use or comorbidity clusters of more than two disorders (Rosenthal, Nunes, & Le Fauve, 2012).

7.6 Conclusion

This systematic review of epidemiological studies spanning three decades shows that the comorbid association between major depression and substance use disorders is not only strong but highly prevalent. This study showed that individuals with substance dependence were three times at higher risk for comorbid depression. In light of recent legislative changes around the use of cannabis in Canada, the finding of this review that risks of depression increases substantially with heavy cannabis use is to be noted as an area of concern.

Further reviews on prospective studies, comorbidity clusters of polysubstance use would be needed to understand the causal relationships and patterns better to help develop better preventive strategies and interventions.

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Appendix A. Search Strategy

MEDLINE

1. (((((co-morbid* or comorbid* or co-occur* or diagnosis or dual diagnosis psychiatry,) and alcohol*) or cannabis* or marijuana* or drug* or substance* or SUD or mental health or mental illness or bipolar or depress* or mood disorder) and epidemiology) or prevalence or incidence or occurrence).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2. limit 1 to (english language and full text and yr="1980 - 2018")

CINAHL

1. co-morbid* or comorbid* or co-occur*) OR diagnosis or dual diagnosis(psychiatry), AND (alcohol* or cannabis* or marijuana* or drug* or substance* or SUD) OR (mental health or mental illness or bipolar or depress* or mood disorder) AND (epidemiology or prevalence or incidence or occurrence)

2. **Limiters** - Full Text; Abstract Available; Published Date: 19800101-20180531; English Language; Research Article; Exclude MEDLINE records; Human

3. **Search modes** - Find all my search terms

EMBASE

1. (((((co-morbid* or comorbid* or co-occur* or diagnosis or dual diagnosis psychiatry,) and alcohol*) or cannabis* or marijuana* or drug* or substance* or SUD or mental health or mental illness or bipolar or depress* or mood disorder) and epidemiology) or prevalence or incidence or occurrence).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

2. limit 1 to (full text and abstracts and human and Cochrane library and English language and yr="1980 - 2018")

PsychINFO

1. (((((co-morbid* or comorbid* or co-occur* or diagnosis or dual diagnosis psychiatry,) and alcohol*) or cannabis* or marijuana* or drug* or substance* or SUD or mental health or mental illness or bipolar or depress* or mood disorder) and epidemiology) or prevalence or incidence or occurrence).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

2. limit 1 to (human and English language and yr="1980 - 2018"

3. limit 2 to (full text and human and English language and abstracts and yr="1980 - 2018")

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Appendix C. Assessment of studies quality

First Author	National Repres-entation[1]	Close representation of target population[2]	Random selection[3]	Non-response bias minimal[4]	Data collection from subjects[5]	Case definition[6]	Assessment of exposure[7]	Assessment of outcome[8]	Data collection method the same[9]	Confounding control[10]	TOTAL	Risk of bias
Currie, et al., 2005	1	1	1	1	1	1	1	1	1	1	10	Low; harmful alcohol use to mean alcohol abuse
Swendsen, et al., 1998	1	1	1	1	1	1	1	1	1	1	10	Low
Alonso, et al., 2007	1	1	1	0	1	1	0	0	1	1	7	Medium: varied response rate across regions (46-79%), combined comorbidity indices
Chou, et al., 2012	1	1	1	1	1	1	1	1	1	1	10	Low
Mericle, et al., 2012	1	1	1	1	1	1	1	1	1	1	10	Low
Kessler, et al., 1996b	1	1	1	1	1	1	1	1	1	1	10	Low
Kessler, et al., 2003	1	1	1	1	1	1	1	1	1	1	10	Low
Conway, et al., 2006	1	1	1	1	1	1	1	1	1	1	10	Low
Hasin, et al., 2005	1	1	1	1	1	1	1	1	1	1	10	Low
Stinson, et al., 2006	1	1	1	1	1	1	1	1	1	1	10	Low
Grant, et al., 2015	1	1	1	1	1	1	1	1	1	1	10	Low
Grant, et al., 2016	1	1	1	1	1	1	1	1	1	1	10	Low

Hasin, et al., 2016	1	1	1	1	1	1	1	1	1	1	10	Low
Kandel, et al., 2001	1	1	1	1	1	1	1	1	1	1	10	Low
Grant, 1995	1	1	1	1	1	1	1	1	1	1	10	Low
Grant & Harford, 1995	1	1	1	1	1	1	1	1	1	1	10	Low
Burns & Tesson, 2002	1	1	1	1	1	1	1	1	1	1	10	Low
Teesson, et al., 2010	1	1	1	1	1	1	1	1	1	1	10	Low
Teesson, et al., 2012	1	1	1	1	1	1	1	1	1	1	10	Low
Farrell, et al., 2001	1	1	1	1	1	1	1	1	1	1	10	Low
Boschloo, et al., 2011	1	1	1	1	1	1	1	1	1	1	10	Low
Liao, et al., 2012	1	1	1	1	1	1	1	1	1	1	10	Low
Suttajit, et al., 2012	1	1	1	1	1	1	1	1	1	1	10	Low
Subramaniam, et al., 2012	1	1	1	1	1	1	1	1	1	1	10	Low

External validity

1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex? • 1 -Yes (LOW RISK): The study's target population was a close representation of the national population. • 0 - No (HIGH RISK): The study's target population was clearly NOT representative of the national population.
2. Was the sampling frame a true or close representation of the target population? • 1-Yes (LOW RISK): The sampling frame was a true or close representation of the target population. • 0 - No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.

3. Was some form of random selection used to select the sample, OR, was a census undertaken? • 1-Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). •0 - No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.
4. Was the likelihood of non-response bias minimal? • 1-Yes (LOW RISK): The response rate for the study was >/=75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders • 0 - No (HIGH RISK): The response rate was < 75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders

Internal validity

5. Were data collected directly from the subjects (as opposed to a proxy)? • Yes (LOW RISK): All data were collected directly from the subjects. • No (HIGH RISK): In some instances, data were collected from a proxy.
6. Was an acceptable case definition used in the study? • 1 - Yes (LOW RISK): An acceptable case definition was used. • 0 - No (HIGH RISK): An acceptable case definition was NOT used.
7. Assessment of exposure: use of structured clinical interview derived from structured diagnostic criteria for substance use disorders (DSM-III/IV/V, CIDI)? • 1 - Yes (LOW RISK) • 0 - No (HIGH RISK): questions from published health surveys/screening instruments, own system, symptoms described, no system, not specified, or self-reported
8. Assessment of outcome: use of structured clinical interview derived from structured diagnostic criteria for major depression (DSM-III/IV/V, CIDI)? • 1 - Yes (LOW RISK) • 0 - No (HIGH RISK): questions from published health surveys/screening instruments, own system, symptoms described, no system, not specified, or self-reported
9. Was the same mode of data collection used for all subjects? • 1 - Yes (LOW RISK): The same mode of data collection was used for all subjects. • 0 - No (HIGH RISK): The same mode of data collection was NOT used for all subjects
10. Appropriate methods to control confounding: • 1 - Yes (LOW RISK): multivariable adjusted OR including SES, education in models. • 0 - No (HIGH RISK): univariate analysis or controls for age/sex only.

CIDI - Composite International Diagnostic Interview; DSM- Diagnostic Statistical Manual

CHAPTER 8. CONCLUSION: IMPLICATION FOR TREATMENT, PREVENTION, POLICY AND RESEARCH

8.1 Recognizing the interaction between substance use disorders and mental health disorders

Co-occurring substance use disorders and mental health disorders share common biological, psychological and social risk factors and affect one another in clinically significant ways. They represent a major health challenge and public health concern in Canada and globally. They have been recognized by the World Health Organization as one of the major causes of disability in most regions of the world (World Health Organization, 2004; GBD 2016 DALYs and HALE Collaborators, 2017). And they have been linked to increased treatment seeking, health care utilization and social and economic costs (Willinger, Lenzinger, Hornik, Fischer, & Meszaros, 2002; Wu, Kouzis, & Leaf, 1999; Hjorthoj, et al., 2015; Kuyper, Hogg, Montaner, Schechter, & Wood, 2004; Canadian Substance Use Costs and Harms Scientific Working Group, 2018; Canadian Institute for Health Information, 2013; Canadian Institute for Health Information, 2012; O'Toole, Pollini, Gray, Bigelow, & Ford, 2007).

An essential first step to overcoming the barrier to effective management of patients with comorbid disorders is the recognition of this interaction. Several patients with mental disorders receiving treatment in mental health centres are using drugs while a large proportion of those in addiction care programs have significant mental health issues for which they receive scanty treatment (Canadian Centre on Substance Abuse, 2009; Canadian Institute for Health Information, 2012; RachBeisel, Scott, & Dixon, 1999). The interplay of comorbid disorders results in marked stress on the at-risk populations through their reduced ability to deal with daily hurdles and the shame associated with having a mental disorder. These persons have tendencies towards engaging in crime, living on the streets, socially marginalized and committing suicides (Canadian Centre on Substance Abuse, 2009).

This thesis demonstrated the strength of comorbid associations between substance use disorders and depression, the effect of concurrent alcohol dependence on the course of major depression, and the associated increased risk for suicide and disability in comorbidity. One major strength of this thesis is in the use of different epidemiological methods to support existing

literature on comorbid substance use disorders with major depression. The data sources were nationally representative surveys, robust and very well conducted by a renowned Canadian institution with expertise in data collection, Statistics Canada. The diagnosis of substance use disorders and major depression in all data sets were derived using structured interviews based on the Diagnostical and Statistical Manual of Mental Disorders (DSM)-IV and III-R criteria, while the complex data structures of the surveys were accounted for with survey weights in the analyses. The use of multiple imputation to account for missing values in chapters 4 ad 5 were important strengths in those chapters. The original studies in the systematic review were based on nationally representative, randomly selected samples and the diagnoses of substance use disorders and major depression were based on structured diagnostic criteria. Using nationally representative high-quality original studies, the systematic review was conducted to avoid overestimation of associations related to patient-seeking behaviours or access to health care. However, there are some limitations in this thesis. There is a possibility of selection bias with underestimation of associations due to the exclusion of some populations in the datasets. The use of cross-sectional surveys in some studies did not allow for causal inference of associations. In the systematic review, only publications in English language were included giving the potential for publication bias and the studies included were highly heterogeneous due to the diverse population characteristics, but this was accounted for in the analysis.

In studying the comorbid association of substance use disorders and major depression, we made assumptions that individuals have one SUD with major depression. While this may be true for some, it may not be for others. Understanding the nature, extent, and impact of polysubstance abuse comorbid with psychiatric illness or vice versa is necessary to manage individuals in these highly heterogeneous categories better. Given the significant overlap in comorbid substance use disorders and mental health disorders, it is crucial that co-occurring disorders are managed proactively and concurrently. A better understanding of these disorders and their interaction is essential to developing effective interventions.

8.2 Barriers to effective management of co-morbid mental health and substance use disorders

Several practical barriers preventing effective identification and coordination of services to achieve holistic care exist within and between systems of care making collaborations difficult. Such barriers would include stigma, structural barriers, different etiological and treatment conceptions, professional 'turf' protection, lack of clear communication, lack of clarity regarding roles and responsibilities of various stakeholders, competition between separate services and lack of an existing model to follow (Froy, 2009; Marel, et al., 2016; Rosenberg & Hickie, 2013; Muir, et al., 2009; Canadian Centre on Substance Abuse, 2009). The stigma associated with mental health and addiction particularly in rural settings, poses a major barrier to treatment access resulting in late presentation, social marginalization, homelessness and involvement in crime.

Referral, which is the act of referring a client to a more suitable provider beyond the skills and expertise of the clinician (Marsh, O'Toole, Dale, & Willis, 2013) could be a strength and a weakness in health service provision. Referring a patient is an ethical practice that ensures the appropriate needs of the patient are met (Marsh, O'Toole, Dale, & Willis, 2013); however, the pitfall to this is the potential risk for patients to disappear due to difficulties navigating through available services (Kay-Lambkin, Baker, & Lewin, 2004). Therefore, becoming a structural barrier.

Holistic care interventions such as healthy eating, cessation of other addictions (e.g., smoking), exercise, medication compliance, and healthy sleep patterns should be emphasized to overcome barriers and achieve holistic management of patients. Communication, collaborations and assertive follow-up are crucial, particularly with referrals, to ensure services referred to were provided (Marel, et al., 2016).

8.3 A case for integrated management of concurrent disorders

Four models have been suggested for the treatment of comorbid disorders (Marel, et al., 2016). In the sequential treatment model, one illness is treated first, then followed by the other condition. The choice of which disorder to treat first is mainly dependent on which condition is considered primary, severe or in some cases, addiction first (Marel, et al., 2016). Patients in the parallel treatment model have both disorders treated simultaneously but provided independently

of each other by different providers and/or services. The integrated treatment model comprises treatment of both disorders simultaneously by the same treatment provider or service allowing for the exploration of the relationship between the patient's addiction and psychiatric disorder (Marel, et al., 2016; Kelly & Daley, 2013; Canadian Centre on Substance Abuse, 2013b; Torrens, Rossi, Martinez-Riera, Martinez-Sanvisens, & Balbuena, 2012). In the stepped-care treatment model, there is a flexible matching of treatment intensity with case severity. Patients are initially started off on the least intensive and expensive treatment and stepped up to a more intensive or a different form of treatment, only when the treatment goal is not achieved by the less intensive (Marel, et al., 2016).

Although patients in treatment programs do receive care, the care provided is typically not well integrated and does nothing to counteract the course and outcome of the co-occurring problem, or the program may also completely exclude the other disorder. Most clients are left with significant unmet needs and helplessness, and in some cases, the presenting problem being treated, may not be the primary problem (Canadian Centre on Substance Abuse, 2009; Torrens, Rossi, Martinez-Riera, Martinez-Sanvisens, & Balbuena, 2012; Canadian Centre on Substance Abuse, 2013b; Kavanagh & Mueser, 2007; Mangrum, Spence, & Lopez, 2006).

The integrated treatment model for comorbid disorders offers superior benefits when compared to other treatment options (Marel, et al., 2016; Torrens, Rossi, Martinez-Riera, Martinez-Sanvisens, & Balbuena, 2012; Kelly & Daley, 2013; Mangrum, Spence, & Lopez, 2006; Kavanagh & Mueser, 2007; Canadian Centre on Substance Abuse, 2013b; Drake, Mercer-McFadden, Mueser, McHugo, & Bond, 1998). The delivery of integrated treatment by a single service or provider offers consistency in treatment and helps to ensure a single point of contact is established to build trust and avoid falling through the gaps of the system. In addition, the relationship between substance use disorders and mental health disorders is explored and communication gaps/breakdown between agencies do not interfere with treatment (Kavanagh, 2008; Marel, et al., 2016). Even though the integrated treatment approach is appealing, there is a paucity of research in this area comparing different models of treatment (Australian Institute for Primary Care, 2009). While some evidence supports better patient outcomes with the integrated model of care (Donald, Dower, & Kavanagh, 2005; Kelly & Daley, 2013; Mangrum, Spence, & Lopez, 2006; Torrens, Rossi, Martinez-Riera, Martinez-Sanvisens, & Balbuena, 2012), some

support the stepped-care approach (Baker & Dawe, 2005; Baker, et al., 2005; Kay-Lambkin F. J., Baker, McKetin, & Lee, 2010). However, the consensus of research evidence and clinical expertise is that the treatment of comorbid substance use and mental health disorders is insufficient if they are solely psychiatric focused or addiction focused (Kavanagh & Mueser, 2007; Canadian Centre on Substance Abuse, 2013b; Kelly & Daley, 2013; Torrens, Rossi, Martinez-Riera, Martinez-Sanvisens, & Balbuena, 2012).

In Canada, the existing management systems of addiction and mental health are largely independent irrespective of the setting and as such, the trainings, clinical guidelines and accreditation standards are separate. (hospitals, correctional facilities or community health services) (Canadian Centre on Substance Abuse, 2009; Canadian Centre on Substance Abuse, 2013b). The present treatment model is to treat addiction and mental disorders as isolated entities even when it is recognized that the most complicated patients with worse outcomes are those with co-occurring disorders (Fairbairn, Kerr, Li, Montaner, & Wood, 2007; Fulkerson, Harrison, & Beebe, 1999). Due to its fragmented mode of delivery developed to treat either the addiction or mental health issue solely as the primary focus, the system is not well prepared to manage both disorders concurrently leading to worse patient outcomes (Canadian Centre on Substance Abuse, 2009). Education, clinical guidelines and standards for addiction and mental health need to be integrated for better outcomes in the treatment and care of patients with comorbid disorders.

8.4 Prevention of comorbid substance use and mental health disorders: A Life Course Perspective

Evidence suggests a developmental course in the onset of comorbid disorders (Canadian Centre on Substance Abuse, 2009; Brière, Rohde, Seeley, & Daniel Klein, 2014; Burcusa & Iacono, 2007; Lubman, Cheetham, & Yucel, 2015); therefore, the importance of early recognition and prevention cannot be ignored. Comorbid disorders have been implicated to have common vulnerability factors, i.e. genetic and environmental determinants (Agrawal & Lynskey, 2014; Kendler, Prescott, Myers, & Neale, 2003; Burcusa & Iacono, 2007; Degenhardt, Hall, & Lynskey, 2003a; Lynskey, et al., 2004). Early identification of vulnerable populations could

potentially, avert the future emergence of a full-blown concurrent disorder (Canadian Centre on Substance Abuse, 2009).

A life course approach to the prevention of comorbid mental health and substance use disorders with a special focus on the developmental stages is recommended. A life course approach incorporates, 'the fetal origins hypothesis' which links intrauterine exposure and conditions to later development of adult chronic disease (Barker, 1998), parenting, infancy, childhood, adolescence, and adulthood to aging in prevention efforts. Previous studies suggest that the crucial stages of growth when environmental exposures do the most harm to health with long-term health consequences are in-utero, early infancy, childhood, and adolescence (Ben-Shlomo & Kuh, 2002; World Health Organization and International Longevity Centre-UK, 2000). In addition, in childhood and adolescence are critical developmental phases when important cognitive and psychosocial skills are easily obtained (World Health Organization and International Longevity Centre-UK, 2000; Ben-Shlomo & Kuh, 2002). Life course trajectories with consequences for health in adulthood are greatly impacted by the development of these skills and abilities (World Health Organization and International Longevity Centre-UK, 2000).

Adult health and disease risk are shaped by the socio-economic conditions through-out life because, health-damaging exposures, health-enhancing opportunities and individual's response to either are socioeconomically determined (Ben-Shlomo & Kuh, 2002; Kuh & Ben-Shlomo, 1997). A life course perspective in the prevention of comorbid SUD with major depression helps to identify the times of intervention that would be effective and the chains of risk that can be broken (World Health Organization and International Longevity Centre-UK, 2000).

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