Diabetes, psychiatric conditions and alcohol consumption: Cross-sectional and longitudinal associations in community samples

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Abstract

Background: Alcohol consumption is common in individuals with diabetes. Heavy alcohol consumption in individuals with diabetes is associated with an increased risk of developing diabetes-related complications, including neuropathy, retinopathy, nephropathy, and coronary artery disease (CAD). Although heavy alcohol consumption is associated with complications, little is known about patterns of alcohol use among individuals with diabetes. Furthermore, heavy drinking is more common among individuals with certain psychiatric conditions, including major depressive disorder (MDD), bipolar disorder (BD), or generalized anxiety disorder (GAD), compared to the general population, and these disorders are often comorbid with diabetes. Therefore, individuals with diabetes may be at an increased risk of heavy drinking if they have comorbid psychiatric conditions. Additionally, depression is related to an increased risk of diabetes-related complications. Thus, individuals with diabetes and depression who drink heavily may be at a particularly high risk of developing complications.

Objectives: The first manuscript aims to investigate how alcohol consumption patterns (frequency; quantity) may differ in those with or without MDD, BD, and GAD, in adults with diabetes compared to those without diabetes. The second manuscript aims to prospectively examine the association of frequency of alcohol use and depressive symptoms on the development of diabetes-related complications in adults with type 2 diabetes (T2D).

Methods: Data for the first manuscript were from the cross-sectional 2012 Canadian Community Health Survey-Mental Health, including 14,302 adult participants aged 40-79 (1698 with diabetes). Data were analyzed using hierarchical linear regression models. The second manuscript used data from the five waves of the Evaluation of Diabetes Treatment study, an annual telephone survey of 1413 insulin-naive adults aged 40-76 with T2D at baseline.

Longitudinal logistic regression analyses with generalized estimating equations were used to investigate the development of each complication over time. Both analyses were adjusted for various demographic, lifestyle, and health-related covariates.

Results: MDD and BD, but not GAD, significantly moderated the association between diabetes status and alcohol quantity, such that the presence of diabetes was strongly and negatively associated with alcohol use when individuals had MDD or BD, and weakly and negatively associated when individuals did not have MDD or BD. This interaction held after adjusting for covariates. There was no interaction with any of the psychiatric conditions and alcohol frequency. The second analysis showed that, even after adjusting for covariates, interactions between alcohol frequency and depressive symptoms were positively significantly related to increased odds of incident neuropathy and CAD, such that those with high depressive symptoms who drank the most frequently had the highest risk for neuropathy and CAD. However, this interaction was not significantly related to odds of developing retinopathy or nephropathy.

Conclusions: Among individuals with diabetes, those with comorbid MDD or BD may drink less than those without MDD or BD. This is different from research in the general population, in which individuals with MDD or BD tend to drink more. In addition, individuals with a combination of high depressive symptoms and a high frequency of drinking have a high risk of neuropathy and CAD. Future research is needed to further examine the possible differences among other diabetes-related complications, as well as the possible mechanisms associating diabetes, alcohol use, psychiatric conditions, and complications. This knowledge could help inform future prevention and intervention efforts on heavy alcohol use in individuals with diabetes and the development of diabetes-related complications.

Abrégé

Contexte: La consommation d'alcool est commune chez les personnes atteintes de diabète, mais la consommation excessive est associée à un risque accru de développer des complications liées au diabète, y compris la neuropathie, la rétinopathie, la néphropathie et la maladie coronarienne (MC). Mais, on sait peu sur les habitudes de consommation chez les personnes atteintes de diabète. La consommation est aussi plus commune chez les individus atteints de la dépression majeure (DM), le trouble bipolaire (TB) ou le trouble d'anxiété généralisé (TAG) relatif à la population générale. Ces troubles sont aussi souvent comorbides avec le diabète. Par conséquent, les personnes atteintes de diabète et de troubles psychiatriques comorbides risquent davantage de boire excessivement. De plus, la dépression est liée à un risque accru de complications. Ainsi, les personnes atteintes de diabète et de dépression qui boivent excessivement peuvent avoir un risque particulièrement élevé de développer des complications.

Objectifs: Le premier manuscrit vise à étudier comment les modes de consommation d'alcool (fréquence, quantité) peuvent différer chez ceux atteints ou non de DM, TB et TAG chez les adultes atteints de diabète relatif à ceux sans le diabète. Le deuxième manuscrit vise à examiner prospectivement l'association entre la fréquence de la consommation et les symptômes dépressifs sur le développement de complications chez les adultes atteints de diabète de type 2 (DT2).

Méthodes: Les données du premier manuscrit proviennent de l'Enquête sur la santé dans les collectivités canadiennes-santé mentale de 2012, incluant 14,302 adultes (1698 atteints de diabète). Les données ont été analysées à l'aide de modèles de régression linéaire hiérarchique. Le deuxième manuscrit a utilisé les données des cinq évaluations de l'Étude évaluation de traitements du diabète, un sondage annuel de 1435 adultes avec DT2 qui n'utilisent pas d'insuline. Des analyses longitudinales de régression logistique avec des équations d'estimation

généralisées ont été utilisées pour étudier le développement de chaque complication. Les deux analyses ont été ajustées pour des caractéristiques démographiques, de style de vie et liées à la santé.

Résultats: La DM et le TB, mais pas le TAG, ont modéré l'association entre l'état du diabète et la quantité d'alcool, de sorte que la présence du diabète était fortement associée à la consommation chez les personnes atteintes de DM ou TB et faiblement associée parmi ceux sans DM ou TB. Cette interaction a été effectuée lors de l'ajustement pour des facteurs de confusion. Il n'y avait aucune interaction entre les troubles psychiatriques et la fréquence de l'alcool. La deuxième analyse a démontré que, même lors de l'ajustement pour les facteurs de confusion, les interactions entre la fréquence de l'alcool et les symptômes dépressifs étaient positivement liées à une probabilité accrue de la neuropathie et la MC, de sorte que ceux avec des symptômes dépressifs élevés qui buvait le plus fréquemment ont eu le risque le plus élevé de la neuropathie et la MC. Cependant, cette interaction n'a pas été significativement liée à la probabilité de développer la rétinopathie ou la néphropathie.

Conclusions: Chez les personnes atteintes de diabète, ceux avec la DM ou le TB peuvent boire moins que celles qui n'ont pas la DM ou le TB. Ceci est l’inverse que la population générale, dans laquelle les personnes atteintes de DM ou TB ont tendance à boire d’avantage. De plus, les individus avec une combinaison de symptômes dépressifs élevés et une fréquence élevée de consommation ont un risque élevé de la neuropathie et la MC. De futures recherches devraient examiner les différences entre les autres complications, ainsi que les mécanismes associant le diabète, la consommation, les troubles psychiatriques et les complications. Ceci pourrait informer les futurs efforts de prévention et d'intervention sur la consommation excessive et le développement de complications.

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Preface and contribution of authors

As first author, I (**Randa Elgendy**) have contributed to the development of objectives and hypotheses, research design, statistical analyses, data interpretation, as well as drafting and revising of the two manuscripts in the present thesis. **Dr. Norbert Schmitz**, as thesis supervisor, contributed to the conceptualization, study design, interpretation of results, and critical revisions of both manuscripts. In addition, he obtained the dataset used in the first manuscript, 2012 Canadian Community Health Survey-Mental Health, was involved in data collection of the dataset used in the second manuscript, Evaluation of Diabetes Treatment study, and contributed to the statistical analyses for the second manuscript. He is a co-author on both manuscripts.

Dr. Sonya S. Deschênes and **Dr. Rachel J. Burns** were both involved in the study conception, interpretation of results, and critical revisions of both manuscripts. Dr. Rachel J. Burns was also involved in the data collection for the Evaluation of Diabetes Treatment study used in the second manuscript. Both of them are co-authors on the two manuscripts.

List of abbreviations and acronyms

T2D – Type 2 diabetes

T1D – Type 1 diabetes

MDD – Major depressive disorder

BD – Bipolar disorder

GAD – Generalized anxiety disorder

CAD – Coronary artery disease

DSM-IV-TR – Diagnostic and Statistical Manual, Fourth Edition, Text Revision

DSM-V – Diagnostic and Statistical Manual, Fifth Edition

CCHS-MH – Canadian Community Health Survey-Mental Health

WHO-CIDI – World Health Organization-Composite International Diagnostic Interview

SCID – Structured Clinical Interview for DSM Disorders

CI – Confidence interval

EDIT – Evaluation of Diabetes Treatment

OR – Odds ratio

PHQ-9 – Patient Health Questionnaire 9

AUDIT-C – Alcohol Use Disorders Identification Test-Concise

Chapter 1: Introduction

1.1 Rationale

Diabetes is a chronic illness that affects an estimated 3.5 million people in Canada, with this number expecting to grow to 4.9 million by 2026 (Canadian Diabetes Association, 2017). Individuals with diabetes have a shorter lifespan compared to the general population, and complications related to diabetes are associated with a greater number of hospitalizations and premature death (Public Health Agency of Canada, 2011). There are various lifestyle factors that are associated with diabetes-related complications, and one of particular interest is alcohol use (Bartoli et al., 2015).

Past research has shown that while alcohol use is slightly less common in the diabetes population (Ahmed, Karter, and Liu, 2006; Collins, Corcoran, & Perry, 2009; Ghitza, Wu, & Tai, 2013) compared to the general population (Lethbridge-Cejku, Schiller & Bernadel, 2004), heavy alcohol use and substance use disorders are still commonly found in individuals with diabetes (Fleming & Mundt, 2004; Fortney, Booth, & Curran, 1999; Ramsey & Engler, 2009; Wadland & Ferenchick, 2004). Individuals with diabetes who drink heavily may have specific characteristics. Of particular interest are individuals with psychiatric conditions, including major depressive disorder (MDD), bipolar disorder (BD), and generalized anxiety disorder (GAD), which are each commonly found in the diabetes population (Anderson, Freedland, Clouse, & Lustman, 2001; Grigsby, Anderson, Freedland, Clouse, & Lustman, 2002; Hermanns, Kulzer, Krichbaum, Kubiak, & Haak, 2005; Lin & Von Korff, 2008; McIntyre, Konarski, Misener, & Kennedy, 2005). Individuals with these psychiatric conditions are also more likely to engage in heavy alcohol use compared to the general population (McDonald & Meyer, 2011; Merikangas et al., 1998; Sonne & Brady, 1999). However, given that alcohol consumption is associated with

diabetes-related complications, it is unknown if diabetes populations would be similar to the general population in that individuals with psychiatric conditions tend to engage in heavy alcohol consumption (Emanuele et al., 1998).

Alcohol consumption is related to various outcomes in diabetes, including associations with diabetes-related complications (Deshpande, Harris-Hayes, & Schootman, 2008; Emanuele et al., 1998; Koppes, Dekker, Hendriks, Bouter, & Heine, 2006). The relation between alcohol use and complications depends on the particular level of alcohol consumed (Emanuele et al., 1998). Specifically, heavy alcohol use is associated with an increased risk of diabetes-related complications, such as neuropathy, retinopathy, nephropathy, and coronary artery disease (CAD; Emanuele et al., 1998; Koppes et al., 2006; Tanasescu, Hu, Willett, Stampfer, & Rimm, 2001). On the other hand, moderate alcohol use is associated with a decreased risk of the previously mentioned complications (Emanuele et al., 1998; Koppes et al., 2006; Solomon et al., 2000; Tanasescu, et al., 2001; Valmadrid, Klein, Moss, Klein, & Cruickshanks, 1999).

In addition to alcohol use, certain psychiatric conditions, such as depression, are also associated with diabetes-related complications (Bartoli et al., 2015; De Groot, Anderson, Freedland, Clouse, & Lustman 2001; Deschênes, Burns, Pouwer, & Schmitz, 2017). Specifically, past literature has shown that high depressive symptoms are related to an increased risk of neuropathy, retinopathy, nephropathy, and CAD (Black, Markides, & Ray, 2003; Lin et al., 2009; Lin et al., 2010; Sieu et al., 2011). Given that both heavy alcohol consumption (Emanuele et al., 1998; Koppes et al., 2006; Tanasescu et al., 2001) and high depressive symptoms (Black et al., 2003; Lin et al., 2009; Lin et al., 2010; Sieu et al., 2011) can increase the risk of complications, and that heavy alcohol consumption and high depressive symptoms commonly co-occur (Currie, et al., 2005; Grant & Harford, 1995; Grant, et al., 2004), individuals with

diabetes and both heavy alcohol consumption and high depressive symptoms may be at a particularly high risk for complications.

1.2 Thesis objectives

The first objective of this thesis is to describe alcohol consumption patterns (frequency; quantity) among adults with type 1 (T1D) or type 2 diabetes (T2D) compared to adults without diabetes, and to examine how these patterns may differ in those with or without psychiatric conditions (MDD, BD, or GAD). The second objective is to examine the longitudinal relation of frequency of alcohol consumption and depressive symptoms on the incidence of diabetes-related complications in a sample of adults with T2D.

This thesis contains seven chapters. The second chapter includes background information on diabetes, psychiatric conditions, alcohol consumption, and diabetes-related complications. The third chapter contains the first manuscript, a cross-sectional examination of the relation between alcohol consumption and psychiatric conditions in the diabetes population, compared to the non-diabetes population. The fourth chapter comprises of text linking the two manuscripts. The fifth chapter contains the second manuscript, a longitudinal investigation of the development of diabetes-related complications in relation to frequency of alcohol use and depressive symptoms. The sixth chapter includes the restatement of the thesis objectives, summary of the research findings, strengths and limitations of the thesis, clinical implications, future directions for research, and a conclusion. The seventh chapter includes the references, excluding references for the two manuscripts, which can be found directly following each manuscript. Appendix I includes additional analyses for the second manuscript. Both manuscripts have been submitted for publication.

Chapter 2: Literature review

2.1 Psychiatric conditions

2.1.1 Definition of psychiatric conditions

Major depressive disorder (MDD), bipolar disorder (BD), and generalized anxiety disorder (GAD) are diagnosable psychiatric conditions (American Psychiatric Association, 2000). MDD and BD are mood disorders, whereas GAD is an anxiety disorder (American Psychiatric Association, 2000). According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), an individual must present with five out of nine of the following symptoms in order to receive a diagnosis of MDD: depressed mood; loss of interest or pleasure; weight or appetite changes; sleep changes; fatigue or loss of energy; guilt or worthlessness; decrease in concentration; and suicidality (American Psychiatric Association, 2000). At least one out of these nine symptoms must be depressed mood or loss of interest or pleasure (American Psychiatric Association, 2000). These symptoms must be present nearly every day within the past two weeks and cause significant impairment in functioning (American Psychiatric Association, 2000).

BD is another mood disorder (American Psychiatric Association, 2000). In this thesis, an individual was considered to have BD if they had BD I, BD II, or hypomania (Statistics Canada, 2014). The primary symptom of BD I is mania, or cycling episodes of mania and depression (American Psychiatric Association, 2000). Mania is defined as a period of abnormally elevated or irritable mood, for at least one week or requiring hospitalization (American Psychiatric Association, 2000). In addition, at least three of the following symptoms must be present during the period of the episode: elevated self-esteem or grandiosity; reduced need for sleep; increased talkativeness; racing thoughts; increased distractibility; elevations in goal-directed behaviours or

psychomotor agitation; and excessive involvement in pleasurable activities that may result in negative consequences (American Psychiatric Association, 2000). If the individual only has an irritable and not elevated mood, then at least four of the seven aforementioned symptoms must be present (American Psychiatric Association, 2000). The episodes of depression in BD I present with the same symptoms as those in MDD (American Psychiatric Association, 2000). The symptoms of BD I must cause significant impairment in functioning (American Psychiatric Association, 2000).

Hypomania is characterized by a milder state of mania, in which the symptoms do not cause impairment in functioning or require hospitalization, but are still observable by others (American Psychiatric Association, 2000). At least three of the seven aforementioned symptoms must be present for at least one week, and four symptoms must be present if the mood is only irritable and not elevated (American Psychiatric Association, 2000). Although hypomania is not a separate disorder and is a symptom of BD II, the 2012 Canadian Community Health Survey-Mental Health (CCHS-MH) dataset used in the first manuscript included hypomania, BD I, and BD II in its BD algorithm (Statistics Canada, 2014). Therefore, in order to be consistent with the CCHS-MH, the same BD algorithm is used in the present thesis. BD II is characterized by one or more episodes of depression and one or more episodes of hypomania (American Psychiatric Association, 2000). The episodes of depression in BD II present with the same symptoms as those in MDD (American Psychiatric Association, 2000). The symptoms of BD II must cause significant impairment in functioning (American Psychiatric Association, 2000).

GAD is an anxiety disorder that is characterized by excessive anxiety or worry about a variety of different activities or events occurring on most days in the past six months, as well as trouble controlling the anxiety or worry (American Psychiatric Association, 2000). Additionally,

at least three of the following symptoms must be present: feelings of restlessness or on edge; easily becoming tired; difficulty concentrating; irritability; muscle tension; and difficulties in sleeping (American Psychiatric Association, 2000). Significant impairment in functioning should also be present (American Psychiatric Association, 2000).

The fifth version of the DSM (DSM-V) was released in 2013 and includes slight changes to the criteria for MDD, BD, and GAD. The DSM-IV-TR criteria excluded an MDD diagnosis for individuals who have recently experienced the death of a loved one and are currently going through a bereavement period of less than two months (American Psychiatric Association, 2000). However, this exclusion was removed in the DSM-V and replaced with a note intended to help clinicians differentiate between symptoms of bereavement and symptoms of MDD (American Psychiatric Association, 2013). Additionally, the DSM-IV-TR diagnosis of the BD I cycling episodes of mania and depression required that individuals meet diagnostic criteria for both mania and MDD (American Psychiatric Association, 2000). However, the DSM-V removed this criterion and instead added a specifier of "with mixed features", which can be added to episodes of mania and hypomania to depict the presence of symptoms of MDD (American Psychiatric Association, 2013). This specifier can also be added to an MDD diagnosis to depict the presence of manic or hypomanic symptoms (American Psychiatric Association, 2013). Other related BD diagnoses have been added for individuals who do not fulfill the duration requirements of BD I and BD II (American Psychiatric Association, 2013). Lastly, the DSM-IV diagnosis of GAD excluded individuals who solely presented with symptoms of GAD during an episode of MDD or another mood disorder, but this exclusion has been removed in the DSM-V (American Psychiatric Association, 2013). Nevertheless, the measures of MDD, BD, and GAD in this thesis are based on DSM-IV-TR criteria (American Psychiatric Association, 2000).

2.1.2 Measurement of psychiatric conditions

Depression can be measured using clinical interviews, carried out by a clinician or trained lay interviewer, or self-report questionnaires (Lloyd, Pouwer, & Hermanns, 2012). Clinical interviews, such as the Structured Clinical Interview for DSM Disorders (SCID; First, Spitzer, Gibbon, & Williams, 1996), are based on DSM-IV-TR criteria and are used to assess the presence of MDD (Lloyd et al., 2012). Although they are considered the "gold standard" to measure depression, there is a lack of available clinicians; therefore, structured clinical interviews using trained lay interviewers are commonly employed in research examining MDD (Wittchen, 1994). These structured clinical interviews performed by trained interviewers, such as the World Health Organization version of the Composite International Diagnostic Interview (WHO-CIDI; Kessler & Ustün, 2004), are less exhaustive but still have high reliability and validity compared to interviews carried out by clinicians, such as the SCID (First et al., 1996; Wittchen, 1994). However, structured interviews by trained interviewers can be time consuming and expensive, therefore, self-report questionnaires are often used in research (Lloyd et al., 2012). Furthermore, structured clinical interviews, such as the WHO-CIDI, examine episodes of MDD in the past year or over the lifetime (Kessler & Ustün, 2004), whereas self-report questionnaires usually focus on the past week or two (Kroenke, Spitzer, & Williams, 2001; Smarr & Keefe, 2011).

This thesis used both structured clinical interviews by trained lay interviewers and self-report questionnaires to assess depression. A modified version of the WHO-CIDI (Kessler & Ustün, 2004), which is a standardized clinical interview given by trained lay interviewers, was employed to evaluate past 12-month MDD in the first manuscript (modified by Statistics Canada, 2014). The second manuscript included the Patient Health Questionnaire-9 (PHQ-9), a self-

report questionnaire based on the DSM-IV-TR criteria, to evaluate depressive symptoms in the past two weeks (Kroenke et al., 2001). Although self-report questionnaires can also be used to assess anxiety and bipolar disorder symptoms (Andrews, Mahoney, Hobbs, & Genderson, 2016; Miller, Johnson, & Eisner, 2009), this thesis used modified versions of the WHO-CIDI clinical interviews to evaluate GAD and BD (modified by Statistics Canada, 2014).

2.2 Alcohol

2.2.1 Definition and measurement of alcohol consumption

Alcohol use is common in the Canadian population, with 70-80% of the population over the age of 15 consuming any alcohol in the past year (Thomas, 2012). Similar to psychiatric conditions, alcohol consumption can be measured using self-report questionnaires (Sobell & Sobell, 1995). Different aspects of alcohol consumption can be measured, including quantity, frequency, and a composite combining quantity and frequency (Sobell & Sobell, 1995). Alcohol quantity can be measured as the number of drinks per day or the grams of alcohol consumed per day (Sobell & Sobell, 1995). On the other hand, alcohol frequency is the number of drinking occasions per week or per month (Sobell & Sobell, 1995). A composite of alcohol quantity and frequency assesses the average number of drinks consumed in a specified time frame (Sobell & Sobell, 1995). In addition to retrospective quantity and frequency measures, daily diaries can be used to measure alcohol consumption everyday within a specified time frame (Sobell & Sobell, 1995), although they are limited in that they are more expensive, have more missing data, and put a higher burden on participants compared to retrospective self-report questionnaires (Leigh, 2000). Lastly, clinical interviews can also be used to measure alcohol use disorders (Aj, & Saitz, 2004). However, only alcohol quantity (number of drinks per day) and frequency self-report measures were used in the present thesis.

2.2.2 Alcohol and psychiatric conditions

Rates of heavy drinking are higher in individuals with psychiatric conditions, including MDD, BD, and GAD, compared to the general population (McDonald & Meyer, 2011; Merikangas et al., 1998; Patten & Charney, 1998; Sonne & Brady, 1999). There is evidence for a bidirectional association, such that psychiatric conditions may lead to heavy drinking, and heavy drinking may also lead to psychiatric conditions (Boden & Fergusson, 2011; Kushner, Abrams, & Borchardt, 2000; Strakowski & DelBello, 2000). According to affect regulation theory, individuals with these psychiatric conditions may drink alcohol in order to alleviate their negative affect (Cooper, Frone, Russell, & Mudar, 1995). Furthermore, individuals with BD having a manic episode may also use alcohol to enhance positive emotions (Cooper et al., 1995). Additionally, given that sleep disturbances are a potential symptom of MDD, BD, and GAD (American Psychiatric Association, 2000), individuals with these psychiatric conditions may use alcohol as a method to regulate their sleep (Canham & Mauro, 2016; Crum, Storr, Chan, & Ford, 2004).

On the other hand, heavy alcohol use may lead to changes in nervous system activation, metabolic factors, and biological factors, which may then lead to increased risk for psychiatric conditions (Boden & Fergusson, 2011; Kushner et al., 2000; McEachin, Keller, Saunders, & McInnis, 2008; Wang & Patten, 2002; Strakowski & DelBello, 2000). In addition, heavy alcohol use may lead to interferences in an individual's employment, family, and social life, and this stress may in turn lead to an increased risk of psychiatric conditions (Boden & Fergusson, 2011; Foster, Powell, Marshall, & Peters, 1999; Kushner, Sher, & Beitman, 1990; Strakowski & DelBello, 2000). In addition to the bidirectional relation, it is possible that both psychiatric conditions and heavy alcohol use may be caused by shared factors, such as environmental stress

or genetics (Kushner et al., 2000; Saunders, Zhang, Copeland, Mclnnis, & Zöllner, 2009; Sjöholm et al., 2010; Strakowski & DelBello, 2000).

2.3 Diabetes

2.3.1 Definition and epidemiology of diabetes

Diabetes mellitus, commonly known as diabetes, is a chronic metabolic disorder that occurs when the body does not properly produce or use insulin, leading to high levels of glucose, or sugar, in the blood (Public Health Agency of Canada, 2011). There are two main types of diabetes: type 1(T1D) and type 2 diabetes (T2D), with 90% of diabetes cases being T2D (Olokoba, Obateru, & Olokoba, 2012; Public Health Agency of Canada, 2011). In T1D, the immune system attacks beta cells in the pancreas, resulting in little or no insulin release in the body (Public Health Agency of Canada, 2011). It most commonly develops before the age of 20, with risk factors including both genetics and an autoimmune reaction in the pancreatic beta cells (Musselman, Betan, Larsen, & Phillips, 2003).

On the other hand, in T2D, there is not enough insulin produced, or the body cannot properly use the insulin that is produced (Public Health Agency of Canada, 2011). It most commonly develops in adults, although recently it has also been occurring in children (World Health Organization, 2016). Risk factors for T2D consist of both modifiable and non-modifiable risk factors (Olokoba et al., 2012). Non-modifiable risk factors include genetics (Herder & Roden, 2011), ethnic group or race (Egede & Dagogo-Jack, 2005; Zimmet, Alberti, & Shaw, 2001), childhood adversity (Danese & Tan, 2014; Rich-Edwards et al., 2010), a family history of diabetes (Wilson et al., 2007), a history of gestational diabetes, and low birth weight (Norris et al., 2012). Age is also a non-modifiable risk factor, with middle-aged adults having the highest risk for T2D (Egede & Dagogo-Jack, 2005; Zimmet et al., 2001). Modifiable risk factors include

obesity, a lack of physical activity, smoking, heavy alcohol use (Olokoba et al., 2012), and depression (Musselman et al., 2003). Low socioeconomic status may also increase the risk of T2D, given that low socioeconomic status is associated with obesity, lack of physical activity, smoking, heavy alcohol use, and depression (Everson, Maty, Lynch, & Kaplan, 2002). Furthermore, risk factors for T2D include cardiometabolic risk factors, which are a group of metabolic and immune-inflammatory factors that can contribute to the risk of T2D and cardiovascular disease (Leiter et al., 2011). These cardiometabolic risk factors include hypertension, high triglycerides, atypical lipid metabolism, systemic inflammation, and poor glucose control (Leiter et al., 2011).

There were approximately 3.5 million people in Canada with diabetes in 2016, and this is projected to increase to 4.9 million by 2026 (Canadian Diabetes Association, 2017). There are ethnic differences in the prevalence of diabetes, with higher rates in South Asian, African, Hispanic, and First Nations groups (Public Health Agency of Canada, 2011). Although there is no cure for diabetes, there are various ways that diabetes can be managed (Government of Canada, 2015). The treatment for T1D is insulin (Public Health Agency of Canada, 2011). The treatment for T2D involves dietary and physical activity planning, and may also include oral medication or insulin as the disease progresses (Hamdy, Goodyear, & Horton, 2001). However, if diabetes is not properly managed, diabetes-related complications and premature death can occur (Public Health Agency of Canada, 2011). Diabetes is the seventh leading cause of death in Canada (Government of Canada, 2015).

2.3.2 Diabetes-related complications

Improperly managed diabetes can lead to hyperglycemia, also known as high blood sugar (Public Health Agency of Canada, 2011). Over time, hyperglycemia can lead to diabetes-related

complications (Public Health Agency of Canada, 2011). Although there are a number of diabetes-related complications, the ones of particular interest in this thesis are neuropathy, retinopathy, nephropathy, and coronary artery disease (CAD; Public Health Agency of Canada, 2011), given that they are associated with depression and alcohol consumption.

Neuropathy, specifically peripheral neuropathy, occurs when the peripheral nerves are damaged by hyperglycemia (Public Health Agency of Canada, 2011). Given that these nerves go to the arms, hands, legs, and feet, the individual with peripheral neuropathy will feel abnormal sensations, such as tingling, burning, numbness, and sharp pain (Public Health Agency of Canada, 2011). Nerves that manage bodily functions, including bowel movements, can also be affected (National Institute of Neurological Disorders and Stroke, 2014). Peripheral neuropathy in the feet and toes can lead to foot ulceration and amputation (Public Health Agency of Canada, 2011). Additionally, peripheral neuropathy is associated with sexual dysfunction in both men and women, including erectile dysfunction, impairment in vaginal lubrication, and difficulty in achieving orgasm for both genders (Azadzoi & Siroky, 2010; Freeman, 2007).

Hyperglycemia in diabetes can lead to changes in the retina inside the eye, which is known as retinopathy (Public Health Agency of Canada, 2011). Retinopathy can lead to impaired vision or blindness (Public Health Agency of Canada, 2011). Nephropathy is another complication of diabetes and can occur over time when hyperglycemia damages the kidneys, leading to reduction in kidney functioning or complete kidney failure (Public Health Agency of Canada, 2011).

Hyperglycemia in individuals with diabetes can also increase risk for CAD, which is the most common type of heart disease (National Heart, Lung, and Blood Institute, 2014; Pistrosch, Natali, & Hanefeld, 2011). It occurs when the arteries bringing blood to the heart become

hardened, due to fatty deposits that have narrowed or blocked the arteries (Public Health Agency of Canada, 2011). This can then lead to a stroke or heart attack (Public Health Agency of Canada, 2011; National Heart, Lung, and Blood Institute, 2014).

2.3.3 Diabetes and psychiatric conditions

Several psychiatric conditions, including MDD, BD, and GAD, are more common in individuals with diabetes than in the general population (Deschênes, Burns, & Schmitz, 2015; Robinson, Luthra, & Vallis, 2013). In the Canadian diabetes population, the past year prevalence of MDD is about 6% (Levy, Burns, Deschênes, & Schmitz). On the other hand, the prevalence of past year MDD in the general Canadian population is approximately 3-4% (Deschênes et al., 2015; Patten et al., 2015). The association between diabetes and depression may be bidirectional (Mezuk, Eaton, Albrecht, & Golden, 2008; Renn, Feliciano, & Segal, 2011). This finding is consistent when using diagnostic measures for MDD and symptom scales for depressive symptoms (Mezuk et al., 2008; Renn et al., 2011).

Depression may increase the risk for diabetes through biological mechanisms, including increased hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system activation, increased inflammation, and cardiometabolic risk factors, which are all associated with a risk of diabetes (Champaneri, Wand, Malhotra, Casagrande, & Golden, 2010; Kan et al., 2013; Schmitz et al., 2016b; Silva, Atlantis, & Ismail, 2012). Depression may also increase risk for diabetes through behavioural mechanisms, including lack of physical activity, unhealthy diet, smoking, and alcohol use (Carnethon, Kinder, Fair, Stafford, & Fortmann, 2003; Silva et al., 2012). Conversely, diabetes can also increase the risk for depression through biological pathways, such as high blood glucose, insulin resistance, and increased HPA axis and sympathetic nervous system activation (Knol et al., 2007; Tabák, Akbaraly, Batty, & Kivimäki, 2014). The burden of

a diabetes diagnosis, diabetes self-care, and diagnoses of diabetes-related complications may also increase the risk for depression (Tabák et al., 2014). It is also likely that there is a common mechanism increasing the risk for both depression and diabetes, such as lack of physical activity, obesity, chronic stress, low socioeconomic status, inflammation, and vascular factors (Schmitz, Deschênes, Burns, & Smith, 2016a; Tabák et al., 2014).

BD and diabetes also commonly co-occur (McIntyre et al., 2005). Studies that have examined comorbid BD and diabetes generally examine the prevalence rate of diabetes in individuals with BD, rather than examining the prevalence rate of BD in individuals with diabetes (McIntyre et al., 2005). For example, one Canadian sample of individuals with BD revealed a prevalence rate of diabetes of approximately 12% (Ruzickova, Slaney, Garnham, & Alda, 2003), whereas the prevalence of diabetes is 9.2% in the general Canadian population (Canadian Diabetes Association, 2017). From a biological perspective, increased HPA axis and sympathetic nervous system activation, inflammation, insulin resistance, thyroid hormone changes, and obesity have all been studied as possible mechanisms linking BD and diabetes (Charles, Lambert, & Kerner, 2016; McIntyre et al., 2005). Psychotropic medications that are commonly used in the treatment of BD, particularly atypical antipsychotics, have also been associated with diabetes (Charles et al., 2016). Notably, atypical antipsychotics are sometimes used in the treatment of MDD and GAD (Maglione et al., 2011). There are also several behavioural links that have been studied in the association between BD and diabetes, such as lack of physical activity, unhealthy diet, smoking, and alcohol use (Charles et al., 2016; McIntyre et al., 2005). Additionally, BD is often accompanied with depressive symptoms and binge eating disorder, which may provide another pathway through which BD leads to diabetes (Charles et al., 2016; McIntyre et al., 2005).

Although there are several anxiety disorders, the one that is often comorbid with diabetes is GAD (Smith et al., 2013). In Canada, there was a past year prevalence rate of GAD of approximately 5% in individuals with diabetes (Levy et al., 2017). This is compared to the past year GAD prevalence rate of approximately 3% in the general Canadian population (Deschênes et al., 2015). However, the association between GAD and diabetes has been inconsistent, with studies showing positive (Demmer et al., 2015; Engum, 2007) or null relations (Edwards & Mezuk, 2012). Nevertheless, a possible link between GAD and diabetes, like MDD and BD, may be through increased HPA axis and sympathetic nervous system activation (Graeff & Zangrossi Junior, 2010). Individuals with diabetes may be worried about their diabetes self-management and fearful of complications or changes in blood sugar levels, which may lead to GAD (Cox et al., 1989). Additionally, GAD is often comorbid with MDD (Judd et al., 1998), thus when the two conditions co-occur, the mechanisms linking GAD and diabetes may be the same previously discussed biological (Champaneri et al., 2010; Kan et al., 2013; Knol et al., 2007; Silva et al., 2012; Tabák et al., 2014) and behavioural mechanisms (Carnethon et al., 2003; Silva et al., 2012; Tabák et al., 2014) linking MDD and diabetes (Grigsby et al., 2002).

2.3.4 Diabetes and alcohol

In addition to psychiatric conditions, alcohol use is another modifiable risk factor for diabetes (Olokoba et al., 2012). Alcohol use has been shown to have a U-shaped relation with diabetes, such that alcohol abstainers and heavy drinkers are at a similarly high risk for diabetes, whereas moderate drinkers are at a decreased risk (Baliunas et al., 2009; Carlsson, Hammar, & Grill, 2005). When assessing alcohol abstainers, it is possible that former drinkers may begin abstaining from alcohol due to health concerns (Baliunas et al., 2009; Shaper, Wannamethee, Walker, 1988). Therefore, it is possible that their increased risk of diabetes may be a result of

pre-existing health conditions and not a result of abstaining from alcohol (Baliunas et al., 2009; Shaper et al., 1988). However, even when including only lifetime abstainers and excluding former drinkers, there is still a U-shaped association such that lifetime abstainers and heavy drinkers are at a higher risk for diabetes (Baliunas et al., 2009). This decreased risk of diabetes for moderate drinkers compared to heavy drinkers and alcohol abstainers may be due to an increase in insulin sensitivity with moderate drinking (Bell, Mayer-Davis, Martin, D'agostino, & Haffner, 2000; Hendriks, 2007). On the other hand, heavy alcohol use may lead to decreased insulin sensitivity and impaired glucose metabolism, which may then increase the risk of diabetes (Avogaro et al., 1987; Bell et al., 2000; Shah, 1988). Heavy alcohol use is also associated with lifestyle and health-related factors that may lead to diabetes, such as poor diet, smoking (Adams, Barry, & Fleming, 1996; Ma, Betts, & Hampl, 2000), and obesity (Breslow & Smothers, 2005).

Research has shown that alcohol use is less common in the diabetes population compared to the general population (Ahmed et al., 2006; Ghitza et al., 2013; Ramsey & Engler, 2009). Although this has not been examined in a representative Canadian sample, in a large representative sample in the United States, the prevalence of any current alcohol consumption in the adult diabetes population was approximately 51% (Ahmed et al., 2006). On the other hand, the prevalence of current alcohol consumption was approximately 62% in the United States general population (Lethbridge-Cejku et al., 2004).

Nevertheless, other studies have shown that alcohol use disorders are still common in individuals with diabetes (Fleming & Mundt, 2004; Fortney et al., 1999; Ramsey & Engler, 2009; Wadland & Ferenchick, 2004). In one sample of adults with diabetes, the rate of a current DSM-IV-TR alcohol use disorder was 1%, whereas the rate of a current alcohol use disorder in

adults without diabetes was 5% (Fleming & Mundt, 2004). In the same study, the rate of a lifetime alcohol use disorder was 40% in the diabetes sample, whereas the rate of a lifetime alcohol use disorder was 48% in the non-diabetes sample (Fleming & Mundt, 2004). Furthermore, a study examining at-risk or heavy drinking found the rate to be about 13% in a diabetes population (Engler, Ramsey, & Stein, 2008) compared to 30% in the general population (National Institute on Alcohol Abuse and Alcoholism, 2005). Although heavy alcohol use is lower among individuals with diabetes than in the general population, heavy alcohol use and alcohol use disorders are still present in the diabetes population and are related to several negative outcomes, including increased risk of diabetes-related complications (Emanuele et al., 1998; Munukutla et al., 2016), and thus should be further investigated.

2.3.5 Diabetes-related complications, depressive symptoms and alcohol

Alcohol use is associated with diabetes-related complications (Deshpande et al., 2008; Emanuele et al., 1998). Heavy alcohol use is associated with an increased risk for cardiovascular disease, whereas moderate alcohol use is associated with decreased risk for cardiovascular disease (Emanuele et al., 1998; Koppes et al., 2006; Pitsavos et al., 2005; Soinio, Laakso, Lehto, Hakala, & Rönnemaa, 2003; Solomon et al., 2000; Tanasescu et al., 2001; Valmadrid et al., 1999). This association between alcohol use and cardiovascular disease has been described as a J-shaped relation (Pitsavos et al., 2005). However, associations between alcohol consumption and neuropathy, retinopathy, and nephropathy have yielded mixed results (Howard, Arnsten, & Gourevitch, 2004). Studies have shown negative (Giuffre, Lodato, & Dardanoni, 2004), positive (Adler et al., 1997; Klein, Klein, & Moss, 1993; McCulloch, Campbell, Prescott, & Clarke, 1980; Young, McCulloch, Prescott, & Clarke, 1984) and null (Franklin, Shetterly, Cohen, Baxter, & Hamman, 1994; Moss, Klein, & Klein, 1994) associations. Moreover, moderate

alcohol consumption has been associated with decreased risk of retinopathy and nephropathy in T1D and T2D (Beulens et al., 2008; Blomster et al., 2014; Howard et al., 2004; Fenwick et al., 2015; Munukutla et al., 2016). Although the protective effect of moderate alcohol consumption has not been shown with neuropathy in individuals with T2D, research in individuals with T1D has shown a decreased risk of neuropathy in those who drink moderately (Beulens et al., 2008).

Although acute alcohol consumption may not be associated with any major changes in glucose in individuals with T2D, chronic heavy alcohol consumption is related to insulin resistance, lipid level abnormalities, mitochondrial dysfunction, and changes in cell signalling and oxidative stress (Emanuele et al., 1998; Munukutla et al., 2016; Pietraszek, Gregersen, & Hermansen, 2010). Additionally, heavy alcohol consumption is associated with hypoglycemia when consumed on an empty stomach, and is associated with hyperglycemia when consumed with food (Emanuele et al., 1998; Munukutla et al., 2016). Moreover, those who engage in heavy alcohol consumption also tend to have poorer self-management behaviours, poorer adherence to medication, poorer diets, and engage in less exercise compared to those who do not engage in heavy alcohol consumption (Ahmed et al., 2006; Leung, Zhang, Lin, Clark, 2011; Thomas et al., 2012; Walter, Wagner, Cengiz, Tamborlane, & Petry 2017).

In addition to heavy alcohol use, high depressive symptoms in individuals with diabetes can also increase the risk of diabetes-related complications (Bartoli et al., 2015; De Groot et al., 2001; Deschênes et al., 2017). In two meta-analyses, high depressive symptoms were associated with the diabetes-related complications of neuropathy, retinopathy, nephropathy, and macrovascular complications, such as heart disease, in individuals with T2D (Bartoli et al., 2015; De Groot et al., 2001). Furthermore, longitudinal studies have shown that among individuals with T2D, those with high depressive symptoms were at an increased risk of incident

neuropathy, retinopathy, nephropathy, and heart disease (Black et al., 2003; Lin et al., 2009; Lin et al., 2010; Sieu et al., 2011).

Several mechanisms through which high depressive symptoms could lead to diabetes-related complications have been proposed (Ciechanowski, Katon, & Russo, 2000; Golden, 2007; Gonzalez et al., 2008; Lin et al., 2004; Lustman, Penckofer, Clouse, 2007). Similar to one of the proposed biological mechanisms for high depressive symptoms leading to diabetes, among individuals with T2D, high depressive symptoms may lead to complications through increased HPA axis and sympathetic nervous system activation (Golden, 2007; Lustman et al., 2007). Additionally, high depressive symptoms are associated with proinflammatory responses, insulin resistance, hypoglycemia, and hyperglycemia, which may then increase risk of complications (Golden, 2007; Lustman et al., 2007). On the other hand, similar to the behavioural mechanisms that may link high alcohol use with complications, behavioural factors linking high depressive symptoms and complications include poor diabetes management, poor adherence to medication, unhealthy diet, and lack of exercise (Ciechanowski et al., 2000; Gonzalez et al., 2008; Lin et al., 2004).

2.4 Addressing knowledge gaps in the literature

This thesis intends to further the extant research regarding the association between diabetes, alcohol use, psychiatric conditions, and diabetes-related complications. There is a lack of research on the patterns of alcohol use in individuals with diabetes, and the characteristics of individuals with diabetes who drink heavily. Given that psychiatric conditions are related to diabetes and heavy drinking (Deschênes et al., 2015; McDonald & Meyer, 2011; Merikangas et al., 1998; Patten & Charney, 1998; Robinson et al., 2013; Sonne & Brady, 1999), the first aim of this thesis is to provide a description of patterns of alcohol quantity and frequency among adults

with diabetes compared to adults without diabetes, and how these patterns may differ in the presence of MDD, BD, or GAD. Additionally, heavy alcohol use and certain psychiatric conditions, particularly depression, have been associated with an increased risk of diabetes-related complications (Adler et al., 1997; Black et al., 2003; Klein et al., 1993; Lin et al., 2009; Lin et al., 2010; McCulloch et al., 1980; Pitsavos et al., 2005; Sieu et al., 2011; Soinio et al., 2003; Young et al., 1984). However, although heavy alcohol use and depression commonly co-occur (Currie, et al., 2005; Grant & Harford, 1995; Grant, et al., 2004), their combined risk on complications has not yet been examined. Therefore, the second aim of this thesis is to examine the interaction of depressive symptoms and frequency of alcohol consumption on the development of neuropathy, retinopathy, nephropathy, and CAD over time in adults with T2D.

Chapter 3: Manuscript 1

Do mental disorders moderate the association between diabetes status and alcohol consumption?

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3.1 Abstract

Alcohol use is common in individuals with diabetes. Although heavy alcohol consumption is associated with diabetes-related complications, little is known about patterns of alcohol use among people with diabetes. Heavy drinking is more common among people with major depressive disorder (MDD), bipolar disorder (BD), and generalized anxiety disorder (GAD) than in the general population, and these disorders are often comorbid with diabetes. Therefore, individuals with diabetes may be at an increased risk of heavy drinking if they have comorbid MDD, BD, or GAD. The present study tested the hypothesis that mental disorders moderate the association between diabetes status and alcohol consumption. Specifically, the presence of diabetes was expected to be positively associated with alcohol quantity (drinks per day), and alcohol frequency (drinking occasions per week/month) when individuals had MDD, BD, or GAD, but a negative association was expected when individuals did not have MDD, BD, or GAD. 14,302 adult participants aged 40-79 were included from the cross-sectional 2012 Canadian Community Health Survey-Mental Health (1,698 with diabetes). Data were analyzed using hierarchical linear regression models. MDD and BD, but not GAD, significantly moderated the association between diabetes status and alcohol quantity, such that the presence of diabetes was strongly negatively associated with alcohol use when individuals had MDD or BD, and weakly negatively associated when individuals did not have MDD or BD. There was no interaction with any of the mental disorders and alcohol frequency. This study of a large, representative Canadian sample suggests that among individuals with diabetes, those with comorbid MDD or BD drink less than those without MDD or BD. This is inconsistent with research from the general population suggesting that people with MDD or BD tend to drink

more. Further investigation of this association is needed and could help inform future alcohol-related interventions among individuals with diabetes.

Keywords

Diabetes, major depressive disorder, bipolar disorder, generalized anxiety disorder, alcohol

3.2 Introduction

3.2.1 Rationale

Heavy alcohol use is associated with various health risks in individuals with diabetes, including weight gain, metabolic dysregulations, and macrovascular and microvascular complications (Canadian Diabetes Association, 2013; Emanuele, Swade, & Emanuele, 1998), thus an understanding of drinking patterns in these individuals is needed. Research on alcohol use patterns among people with diabetes, however, is limited.

Alcohol consumption is less common in adults with diabetes compared to the general population (Ahmed, Karter, and Liu, 2006; Collins, Corcoran, & Perry, 2009; Ghitza, Wu, & Tai, 2013; Ramsey & Engler, 2009). In a large sample in the United States, about 50% of individuals with diabetes consumed alcohol (Ahmed et al., 2006), compared to the approximately 60% of people in the general population reported in previous surveys (Lethbridge-Cejku, Schiller, & Bernadel, 2004). However, some studies have also shown that heavy drinking and substance use disorders are commonly found in adults with diabetes (Fleming & Mundt, 2004; Fortney, Booth, & Curran, 1999; Ramsey & Angler, 2009; Wadland & Ferenchick, 2004). Therefore, findings about the rates of alcohol use among people with diabetes are mixed, and may be the result of a specific subgroup of adults with diabetes who drink heavily.

One subgroup to consider is individuals with mental disorders, such as major depressive disorder (MDD), bipolar disorder (BD), and generalized anxiety disorder (GAD), given that these mental disorders are more common in diabetes populations than in the general population (Anderson, Freedland, Clouse, & Lustman, 2001; Grigsby, Anderson, Freedland, Clouse, & Lustman, 2002; Hermanns, Kulzer, Krichbaum, Kubiak, & Haak, 2005; Lin & Von Korff, 2008; McIntyre, Konarski, Misener, & Kennedy, 2005). Moreover, heavy drinking is more common in

individuals with these mental disorders than in the general population (McDonald & Meyer, 2011; Merikangas et al., 1998; Sonne & Brady, 1999). Affect regulation theory proposes that individuals with mental disorders may use alcohol to alleviate their negative emotions or, in the case of the manic state in BD, enhance their positive emotions (Cooper, Frone, Russell, & Mudar, 1995). However, given that individuals with diabetes must control their blood sugar and reduce the risk of diabetes-related complications, which can be affected when drinking alcohol, it is unclear if a similar association between mental disorders and drinking would be found in individuals with diabetes (Emanuele et al., 1998).

Only one study to date has examined the association between alcohol use and anxiety or depressive symptoms among individuals with diabetes (Knychala, Jorge, Muniz, Faria, & Jorge, 2015). The study showed that among adolescents and adults aged 40 and below with type 1 diabetes, heavy drinking was more common in those with high anxiety or depressive symptoms (Knychala et al., 2015). However, associations between mental disorders in adult populations with both type 1 and type 2 diabetes should be examined because risk factors for type 2 diabetes include unhealthy lifestyle behaviours, such as excessive alcohol use (Ghitza et al., 2013), and heavy alcohol use is also associated with poorer health outcomes in adults over 40 years old (National Institute on Alcohol Abuse and Alcoholism, 2000). In addition, given that anxiety and depressive symptoms were measured by questionnaires, it is unclear if these results would hold when diagnostic interviews are used. Furthermore, BD is another mental disorder that is often comorbid with diabetes (McIntyre, Konarski, Misener, & Kennedy, 2005) and associated with heavy drinking in the general population (McDonald & Meyer, 2011; Sonne & Brady, 1999), thus the association between BD and alcohol in a diabetes population should also be examined.

The present study examines the association between diabetes, mental disorders, and alcohol use in an adult population, using diagnostic interviews for MDD, BD, and GAD.

3.2.2 Objective and hypothesis

The aim of this study was to describe alcohol consumption patterns among adults with diabetes compared to those without diabetes, and examine how these patterns may differ in those with or without MDD, BD, or GAD. It was hypothesized that MDD, BD, and GAD would moderate the association between diabetes status and alcohol consumption, such that the presence of diabetes would be positively associated with alcohol use when individuals had MDD, BD, or GAD, and negatively associated when individuals did not have MDD, BD, or GAD.

3.3 Methods

3.3.1 Dataset

Data came from the cross-sectional 2012 Canadian Community Health Survey-Mental Health (CCHS-MH; Statistics Canada, 2013). This dataset includes participants aged 15 or older across the ten provinces of Canada (Statistics Canada, 2013). 29,088 participants consented to participate and 25,113 completed the survey, with a response rate of 68.9% (Statistics Canada, 2013). The exclusion criteria were individuals living on First Nations reserves, full-time members of the Canadian Armed Forces, and those who were institutionalized (Statistics Canada, 2013).

The survey aimed to produce generalizable data by age and sex at the provincial and national levels (Statistics Canada, 2013). Interviews were conducted between January and December 2012 and the majority of participants (87%) were interviewed face-to-face. Telephone interviews were conducted only when it was not possible to conduct the interview in person

(Statistics Canada, 2013). To examine the relation between diabetes status, mental disorders, and alcohol in adults in the present study, the age range of the dataset was restricted to 40-79 years (*n* = 14,302).

3.3.2 Measures

Diabetes status. To determine diabetes status, participants were asked if they have ever been diagnosed with diabetes by a health professional. Responses were dichotomous (0 = "*no*", 1 = "*yes*") and the type of diabetes was not differentiated (Statistics Canada, 2014).

Mental disorders. Past year MDD, BD, and GAD were evaluated using the World Health Organization Composite International Diagnostic Interview (WHO-CIDI; Kessler & Ustün, 2004), which was modified for use in the CCHS-MH 2012 (Statistics Canada, 2014). The WHO-CIDI is based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria (American Psychiatric Association, 2000). Algorithms were used to categorize participants as either meeting or not meeting diagnostic criteria for each of MDD, BD, or GAD in the past year (Statistics Canada, 2014).

Alcohol use. Participants' quantity and frequency of drinking over the past year was assessed. Participants were first asked if they consumed any alcohol over the past year. Those who drank alcohol in the past year were then asked *"During the past 12 months, how often did you drink alcoholic beverages?"* Responses were made on an 8-point scale (1=*"less than once a month"*, 8= *"everyday")*. Quantity of alcohol consumed was assessed with the item *"On the days you drank in the past 12 months, about how many drinks did you usually have per day?"* Responses were made using a 10-point scale from *"1"* to *"10 or more"*. These two alcohol consumption variables were examined separately in order to capture the variability in drinking patterns (Statistics Canada, 2014).

Covariates. The following covariates were included in the analyses: age, sex, highest level of education (less than secondary, secondary, other post-secondary, post-secondary), number of comorbid chronic conditions (0, 1, 2, 3 and above), past year prescription or over the counter medication use (yes, no), past year nonmedical or illicit drug use (yes, no), and smoking status (daily, occasional, not at all).

3.3.3 Statistical analyses

To test the hypothesis that mental disorders moderate the association between diabetes status and alcohol consumption, hierarchical multiple linear regression analyses were conducted. Moderation examines if the relation between the predictor (diabetes status) and outcome variable (alcohol use) changes across levels of the moderator variable (MDD, BD, and GAD). Separate analyses were conducted for each of the mental disorders and separately for alcohol quantity and frequency; a total of six models were tested. The covariates were entered in the first step of each regression. The main effects of diabetes and each mental disorder were entered in the second step, and the interaction between diabetes and the mental disorder was entered in the third step. Simple slopes at the two levels of the dichotomous moderator variable were examined for statistically significant interactions. Analyses were conducted using SPSS version 22 and simple slopes were analyzed in the PROCESS macro for SPSS, which calculates the two simple slopes at the two levels of the dichotomous moderator variable using the pick-a-point approach (Hayes, 2013).

3.4 Results

3.4.1 Participant characteristics

The present analyses included 14,302 participants, 1,698 of whom reported having

diabetes. Participant characteristics are in Table 1. Table 2 describes the means of each diabetes status by mental disorder by alcohol use group.

3.4.2 Hypothesis testing

MDD as a moderator of the association between diabetes status and alcohol use. First, MDD was tested as a moderator of the relation between diabetes status and alcohol quantity (see Table 3). The main effect of diabetes status and the interaction between MDD and diabetes were statistically significant. The interaction explained 0.03% of the variance in alcohol quantity, with the overall model accounting for 12.69% of the variance. Analysis of the simple slopes revealed that diabetes status and alcohol quantity were negatively related among individuals without MDD (B = -.31, SE = .05, p < .000, 95% CI [-.40, -.26]). Diabetes status and alcohol quantity were more strongly negatively related among individuals with MDD (B = -.71, SE = .18, p < .000, 95% CI [-1.07, -.36]). See Figure 1 for the simple slopes of the model.

Next, MDD was tested as a moderator of the association between diabetes status and alcohol frequency (see Table 3). Diabetes was significantly positively related to alcohol frequency, whereas MDD was significantly negatively related to alcohol frequency. The overall model explained 8.60% of the variance in alcohol frequency. The interaction between MDD and diabetes was not statistically significant and did not account for any additional variance in alcohol frequency.

BD as a moderator of the association between diabetes status and alcohol use. BD was then tested as a moderator in the relation between diabetes status and alcohol quantity (see Table 3). The main effects of BD and diabetes, as well as the interaction between them, were statistically significant. The overall model explained 12.81% of the variance in alcohol quantity and the interaction explained an additional 0.05% of the variance. Analysis of the simple slopes

showed that diabetes status and alcohol quantity were negatively related among individuals without BD (B = -.32, SE = .05, p < .000, 95% CI [-.41, -.23]). Diabetes status and alcohol quantity were more strongly negatively related among individuals with BD (B = -1.29, SE = .33, p < .000, 95% CI [-1.93, -.65]). See Figure 2 for the simple slopes of the model.

Next, BD was tested as a moderator in the relation of diabetes and alcohol frequency. Diabetes was significantly negatively related to alcohol frequency, whereas BD was not significantly related to alcohol frequency. The overall model accounted for 8.53% of the variance in alcohol frequency scores. The interaction between BD and diabetes was not statistically significant and did not explain any additional variance in alcohol frequency.

GAD as a moderator of the association between diabetes status and alcohol use. GAD was then tested as a moderator in the association between diabetes status and alcohol quantity (see Table 3). Diabetes was negatively associated with alcohol quantity, whereas GAD was not significantly associated with alcohol quantity. The overall model accounted for 12.74% of the variance in alcohol quantity scores. The GAD by diabetes interaction was not statistically significant and accounted for an additional .01% of the variance in alcohol quantity.

Lastly, GAD was tested as a moderator in the relation between diabetes status and alcohol frequency (see Table 3). Both GAD and diabetes were significantly negatively related to alcohol frequency. The overall model explained 8.63% of the variance in alcohol frequency scores. The interaction between GAD and diabetes was not statistically significant and did not explain any additional variance in alcohol frequency.

3.5 Discussion

The present study examined the relation between diabetes status, mental disorders, and alcohol consumption. MDD and BD, but not GAD, moderated the relation between diabetes

status and alcohol quantity. The presence of diabetes was associated with a lesser number of drinks consumed among individuals without MDD or BD; however, this association was stronger among those with MDD or BD. This finding is inconsistent with previous research in the general population, showing that individuals with MDD or BD tend to consume a greater number of drinks compared to those without MDD or BD (McDonald & Meyer, 2011; Merikangas et al., 1998; Sonne & Brady, 1999). Therefore, the hypothesis that MDD and BD moderate the association between diabetes status and alcohol quantity was partially supported, given that the moderation did not occur in the hypothesized direction. In addition, the hypothesis that GAD would moderate the relation between diabetes status and alcohol quantity was not supported.

One reason for the unexpected direction of drinking in individuals with comorbid diabetes and MDD or BD could be explained by alcohol expectancies, which are the expected consequences of alcohol use (Cooper et al., 1995). In the general population, individuals with MDD or BD may expect that drinking will relieve their negative affect (Cooper et al., 1995). Alternatively, individuals with diabetes may instead expect that alcohol will worsen their diabetes, and thus may avoid drinking when they have MDD or BD. However, although alcohol expectancies have been examined in the general population (Cooper et al., 1995), they have not been examined in a diabetes population.

Contrary to the hypothesis, the relation between diabetes status and alcohol frequency was not moderated by MDD, BD, or GAD. A possible explanation for why different results were obtained with alcohol quantity and frequency may be because many past studies have examined alcohol quantity and frequency together, rather than separate, as a measure of overall heavy drinking or substance use (Goldsmith, Tran, Smith, & Howe, 2009; Knychala et al., 2015;

Merikangas et al., 1998). They were analyzed separately in the present study given that there is not much known about drinking patterns in individuals with diabetes and comorbid mental disorders, and pertinent information could be missed when only using a composite score (Apao & Damon, 1982). Prior studies that have examined alcohol quantity and frequency separately have shown either no correlation or a negative correlation with depression and anxiety and alcohol frequency, and a positive correlation with alcohol quantity (Graham, Massak, Demers, & Rehm, 2007; Kalodner, Delucia, & Ursprung, 1989). These studies suggest that frequency may be affected by factors other than mental disorders, such as access to alcohol, and quantity may be more relevant to depression and anxiety (Graham et al., 2007; Kalodner et al., 1989). However, alcohol frequency and quantity have not been previously examined separately in relation to BD. Nevertheless, this corresponds with the lack of interaction between diabetes status and MDD, BD, and GAD on alcohol frequency in the present study.

The results of the present study also do not correspond with the previous study that examined mental disorders and alcohol use in a type 1 diabetes population (Knychala et al., 2015). This could be because middle-aged and older adults tend to drink less than adolescents and younger adults (Chan, Neighbors, Gilson, Larimer, & Marlatt, 2007; Windle, 2003). The current study also incorporated both type 1 and type 2 diabetes. Thus, it is possible that the majority of participants had type 2 diabetes and their drinking patterns may have been different than those with type 1 (National Institute on Alcohol Abuse and Alcoholism, 2000). However, type of diabetes was not collected in the current data, so the distribution of the types of diabetes cannot be determined.

A strength of the present study was the use of a large, representative Canadian sample that included diagnostic assessments of MDD, BD, and GAD rather than questionnaire-based

symptom assessments. It also included questions on both alcohol quantity and frequency and included a comprehensive set of covariates in the models. Furthermore, this was the first study to examine mental disorders as moderators in the relation between diabetes status and alcohol use in middle aged and older adults.

There are also important limitations to consider. Although this study included both type 1 and type 2 diabetes participants, there was no distinction between them, so it is unknown whether or not the moderating effect of mental disorders on alcohol quantity would be different between diabetes types. There was also limited information on diabetes, including information regarding poor diabetes control and complications, which have been associated with drinking (Canadian Diabetes Association, 2013; Emanuele et al., 1998), thus the relation between alcohol and mental disorders may differ for these individuals. The CCHS-MH also excluded individuals who were institutionalized, lived on First Nations reserves, and were in the Armed Forces, and these groups have been shown to have higher rates of mental disorders and heavy alcohol use (Blashki & Brown, 2005; Farrell et al., 1998; Fiest, Currie, Williams, & Wang, 2011; Jones, Rona, Hooper, & Wesseley, 2006; Whitehead & Hayes, 1998). Although the CCHS-MH is generalizable across age and sex, the majority of the participants were Caucasian, therefore this study is not generalizable to other ethnicities, which have been shown to engage in heavier drinking (Chartier & Caetano, 2009). The current study was also cross-sectional, thus the direction of the association between diabetes status, mental disorders, and alcohol use could not be examined. Additionally, the measure of alcohol use was limited in that the item assessing frequency uses broad categories (e.g. less than once a month, once a month, etc.). Therefore, it is difficult to combine the quantity and frequency items in a meaningful way. Accordingly, quantity and frequency were examined separately to be able to obtain interpretable information

regarding how many drinks and how often drinks are being consumed in this sample. Future research should further investigate the association between diabetes, mental disorders, and alcohol use using an alcohol use measure that is more comprehensive.

3.6 Conclusion

Individuals with diabetes consumed a lesser quantity of alcohol in comparison to those without diabetes when they did not have MDD or BD, and this relation was even stronger for individuals with diabetes and comorbid MDD or BD. Overall, individuals with diabetes consumed a lesser quantity of alcohol than individuals without diabetes, which corresponds with what has been shown in previous research (Ahmed et al., 2006). However, those with diabetes and comorbid MDD or BD consumed less than those with diabetes without MDD or BD, which is inconsistent with findings from the general population (Graham et al., 2007; Kalodner et al., 1989; Stewart, Morris, Mellings, & Komar, 2006). The current study expanded the knowledge in the relation between mental disorders and alcohol use in a specific population, particularly those with diabetes. Further replication and investigation of why these drinking patterns differ is needed. Moreover, future research should examine if the association between mental disorders, alcohol use, and diabetes can be explained by alcohol expectancies, as well as analyze the mechanism of this association longitudinally to examine changes in mental disorders and alcohol use. The knowledge of why individuals with diabetes consume alcohol, and of why there is a difference in alcohol consumption patterns between individuals with and without mental disorders, could help inform future alcohol-related interventions in the diabetes population.

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3.8 Tables and figures

Table 1

Sample characteristics for demographic, predictor, and outcome variables

Variables	Diabetes (*n* = 1698)	No Diabetes (*n* = 12598)	Total (*N* = 14302)
	n (%)	n (%)	n (%)
Age range			
40-49	170 (10)	3221 (25.3)	3361 (23.5)
50-59	388 (22.9)	3811 (30.2)	4201 (29.4)
60-69	646 (38)	3474 (27.6)	4124 (28.8)
70-79	494 (29.1)	2122 (16.8)	2616 (18.3)
Sex, female	876 (51.6)	6905 (54.8)	7783 (54.4)
Highest level of education			
< Than secondary	539 (31.9)	2255 (18.0)	2796 (19.6)
Secondary	268 (15.9)	1963 (15.7)	2231 (15.7)
Other post-secondary	75 (4.4)	573 (4.6)	648 (4.6)
Post-secondary	807 (47.8)	7748 (61.8)	8558 (60.1)
Number of chronic conditions (excl. diabetes)			
0	228 (13.5)	4584 (36.6)	4812 (33.9)
1	462 (27.4)	3730 (29.8)	4194 (29.5)
2	426 (25.2)	2366 (18.9)	2792 (19.7)
3+	573 (33.9)	1837 (14.7)	2410 (17.0)
Type of smoker			
Daily	251 (14.8)	2361 (18.7)	2615 (18.3)
Occasional	49 (2.9)	454 (3.6)	503 (3.5)
Not at all	1398 (82.3)	9771 (77.6)	11171 (78.2)
Medication use, yes	272 (16.0)	1541 (12.2)	1813 (12.7)
Drug use, yes	188 (11.2)	1505 (12.1)	1695 (12.0)
MDD, yes	104 (6.2)	592 (4.7)	697 (4.9)
BD, yes	33 (2.0)	157 (1.3)	190 (1.3)
GAD, yes	78 (4.7)	377 (3.0)	455 (3.2)
Any alcohol use, yes	1042 (61.4)	9873 (78.4)	10918 (76.4)
Alcohol frequency			
< 1/month	419 (40.3)	2353 (23.8)	2772 (25.4)
1/month	90 (8.7)	829 (8.4)	919 (8.4)
2-3/month	131 (12.6)	1433 (14.5)	1564 (14.3)
1/week	131 (12.6)	1493 (15.1)	1624 (14.9)
2-3/week	122 (11.7)	1937 (19.6)	2060 (18.9)
4-6/week	60 (5.8)	861 (8.7)	922 (8.4)
Everyday	87 (8.4)	963 (9.8)	1051 (9.6)
Number of drinks/day, mean (SD)	2.2 (1.9)	2.3 (1.8)	2.3 (1.8)

Table 2

Mean alcohol quantity and frequency for diabetes status by mental disorders

	Alcohol quantity	Alcohol frequency
	M (SD)	*M (SD)*
MDD		
No diabetes or MDD	1.58 (1.79)	2.87 (2.30)
MDD only	1.95 (2.41)	2.49 (2.27)
Diabetes only	1.09 (1.70)	1.86 (2.17)
Both MDD and diabetes	1.07 (1.92)	1.43 (1.89)
BD		
No diabetes or BD	1.58 (1.80)	2.86 (2.30)
BD only	2.57 (2.95)	2.68 (2.30)
Diabetes only	1.08 (1.72)	1.83 (2.15)
Both BD and diabetes	1.09 (1.59)	1.67 (2.29)
GAD		
No diabetes or GAD	1.59 (1.81)	2.87 (2.31)
GAD only	1.83 (2.34)	2.32 (2.22)
Diabetes only	1.08 (1.70)	1.85 (2.16)
Both GAD and diabetes	.99 (1.87)	1.31 (1.90)

Table 3

MDD, BD, and GAD as moderators of the association between diabetes status and alcohol use

	Alcohol quantity			*Alcohol frequency*		
	B (SE)	*p*	*95% CI*	*B (SE)*	*p*	*95% CI*
MDD						
Model 1: MDD	.14 (.08)	.072	-.01, .29	.23 (.10)	.022*	-.42, -.03
Model 1: Diabetes	-.31 (.05)	.000**	-.40, -.22	-.85 (.06)	.000**	-.97, -.73
Model 2: MDD x Diabetes	-.41 (.19)	.031*	-.77, -.04	.00 (.24)	.997	-.48, .49
BD						
Model 1: BD	.53 (.14)	.000**	.25, .80	-.11 (.18)	.552	-.47, .25
Model 1: Diabetes	-.32 (.05)	.000**	-.41, -.23	-.85 (.06)	.000**	-.97, -.73
Model 2: MDD x Diabetes	-.97 (.33)	.003**	-1.62, -.33	-.09 (.43)	.843	-.92, .75
GAD						
Model 1: GAD	.01 (.10)	.931	-.18, .19	-.38 (.12)	.002**	-.62, -.14
Model 1: Diabetes	-.32 (.05)	.000	-.42, -.23	-.86 (.06)	.000**	-.98, -.74
Model 2: GAD x Diabetes	-.31 (.22)	.159	-.74, .12	.11 (.29)	.700	-.45, .67

Notes. MDD, major depressive disorder; BD, bipolar disorder; GAD, generalized anxiety disorder.

Models adjusted for the following covariates: age, sex, highest level of education, number of comorbid chronic conditions, prescription or over the counter medication use, nonmedical or illicit drug use, and smoking status.

Data not skewed. For comparison, sensitivity analyses with transformed alcohol quantity and frequency yielded similar results.

*$p < .05$

**$p < .01$

Figure 1

Simple slopes for MDD by diabetes status on alcohol quantity

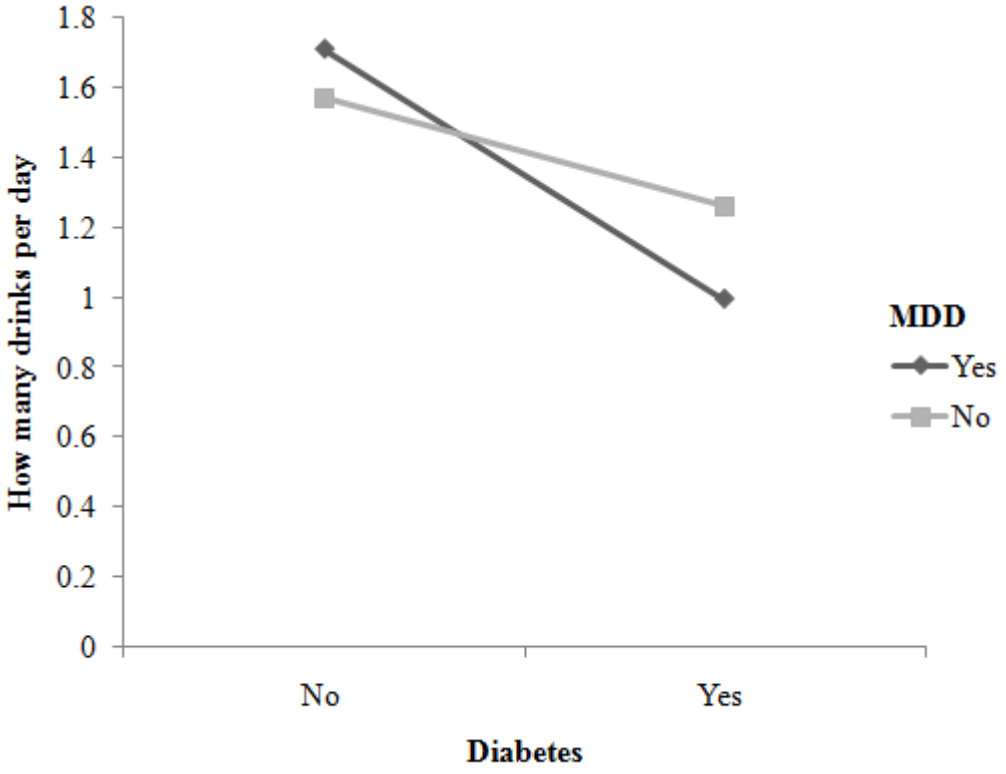
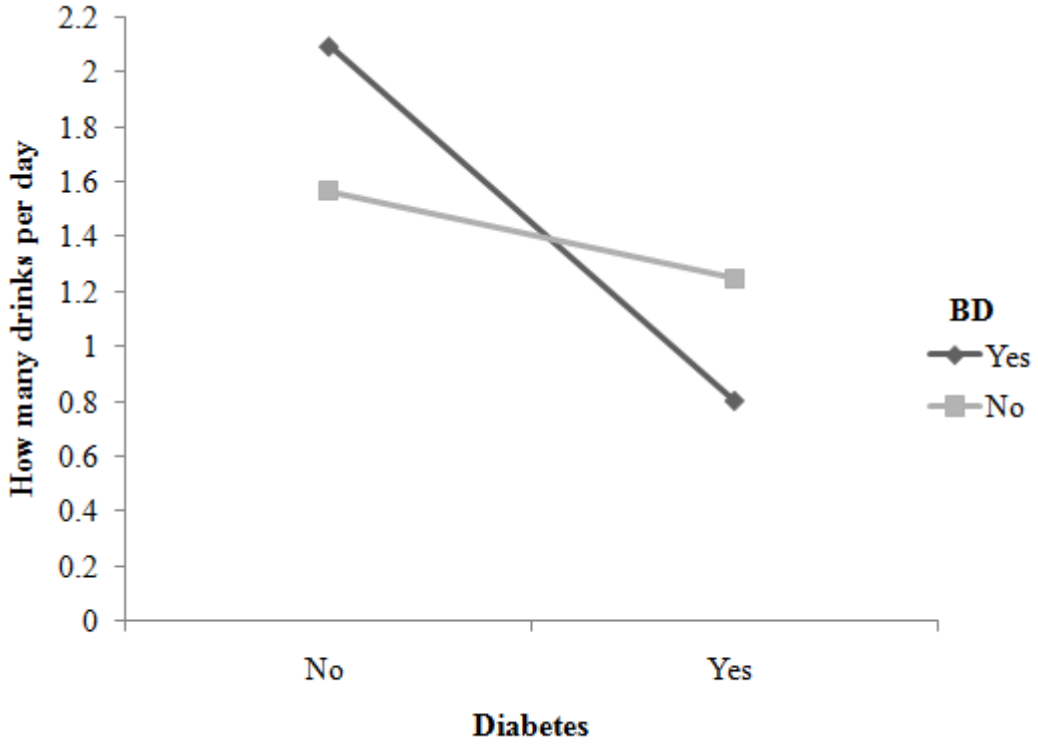


Figure 2

Simple slopes for BD by diabetes status on alcohol quantity



Chapter 4: Bridge

The first manuscript describes cross-sectional patterns of alcohol consumption in relation to diabetes status, and how the presence of MDD, BD, or GAD may alter this relation. Although the direction of the association found was not as expected, examination of alcohol use and psychiatric conditions in individuals with diabetes still needs to be further examined, as heavy alcohol use and particular psychiatric conditions, namely depression, are associated with diabetes-related complications (Adler et al., 1997; Black et al., 2003; Klein et al., 1993; Lin et al., 2009; Lin et al., 2010; McCulloch et al., 1980; Pitsavos et al., 2005; Sieu et al., 2011; Soinio et al., 2003; Young et al., 1984). However, given that heavy alcohol use and depression are often comorbid (Currie, et al., 2005; Grant & Harford, 1995; Grant, et al., 2004), it may be beneficial to examine alcohol use and depression together when evaluating the risk of complications, rather than examining alcohol use and depression separately. Furthermore, longitudinal research is needed in order to examine how the combination of alcohol use and depression relate to the risk of developing complications.

The second manuscript investigates the longitudinal association of the combination of frequency of alcohol use and depressive symptoms on the incidence of diabetes-related complications. Given that the first manuscript examines patterns of association, it includes several psychiatric conditions. However, the second manuscript has a narrower scope with a focus on depression, given that past research has shown consistent associations between depression and diabetes-related complications (Black et al., 2003; De Groot et al., 2011; Lin et al., 2010). The first manuscript uses cross-sectional data whereas the second manuscript uses longitudinal assessments, which allows for the examination of the incidence of complications.

The first manuscript uses a clinical interview by trained lay interviewers to measure depression, the WHO-CIDI, whereas the second manuscript uses a self-report measure of depressive symptoms, the PHQ-9. It is often not feasible to use repeated measures of clinical interviews in large populations; therefore, self-report questionnaires are more suitable for longitudinal research. Nevertheless, the PHQ-9 has demonstrated a high sensitivity of .93 and a high specificity of .85 when assessed against the SCID, which is a "gold standard" clinical interview by clinicians (Wittkampf et al., 2009). Furthermore, both the WHO-CIDI and the PHQ-9 have been shown to be appropriate to use in individuals with diabetes (Lloyd et al., 2009). In terms of alcohol use measures, the first manuscript assesses patterns of both alcohol quantity and frequency, whereas only alcohol frequency is used in the second manuscript. Although the Alcohol Use Disorders Identification Test-Concise (AUDIT-C) questionnaire used in the second manuscript is a reliable and valid questionnaire, the alcohol quantity item does not assess alcohol abstainers (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998), and alcohol abstainers constitute a large portion of the diabetes population (Ahmed et al., 2006). Furthermore, this item assesses quantity "on a typical day", which may be interpreted differently between individuals who drink on occasion and individuals who drink regularly. However, although alcohol quantity was not included in the main analyses of the second manuscript due to the aforementioned limitations of that item, additional sensitivity analyses using alcohol quantity can be found in Appendix I.

Chapter 5: Manuscript 2

Alcohol use, depressive symptoms and the incidence of diabetes-related complications

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Running head: Alcohol, depressive symptoms and incident diabetes-related complications

At the time of this thesis, this manuscript was submitted to Diabetic Medicine.

Novelty statement:

- Heavy alcohol use and high depressive symptoms are each independently associated with diabetes-related complications in individuals with type 2 diabetes.
- The combination of high alcohol frequency and high depressive symptoms on complications has not been examined.
- This study examined the interaction of high alcohol frequency and high depressive symptoms on development of neuropathy, retinopathy, nephropathy, and coronary artery disease.

- Individuals with high depressive symptoms who drank the most frequently had the highest risk of incident neuropathy and coronary artery disease.
- Future preventions should examine both alcohol frequency and depressive symptoms when assessing risk of complications.

5.1 Abstract

Background: Heavy alcohol consumption in individuals with type 2 diabetes (T2D) is related to increased risk of diabetes-related micro- and macrovascular complications. Depressive symptoms may be relevant to consider in this relation, as high depressive symptoms are associated with increased risk of complications.

Aims: We aimed to investigate whether the interaction between depressive symptoms and alcohol frequency will be positively related to development of neuropathy, retinopathy, nephropathy, and coronary artery disease (CAD), such that those with high depressive symptoms and high alcohol frequency will be at increased risk for complications.

Methods: Data were from five waves of the Evaluation of Diabetes Treatment study, an annual survey including 1413 adults with T2D in Quebec, Canada. Data on alcohol frequency (number of drinking occasions), depressive symptoms, and complications were collected annually. Multiple logistic regression analyses with generalized estimating equations were used to investigate the development of each complication.

Results: After adjusting for sociodemographic, lifestyle, and diabetes-related covariates, the interaction between alcohol frequency and depressive symptoms was positively related to incidence of neuropathy and CAD, such that those with high depressive symptoms who drank the most frequently had the highest risk of neuropathy (OR = 1.02, p = .04, CI [1.00, 1.04]) and CAD (OR = 1.02, p = .03, CI [1.00, 1.04]). This interaction was not significantly related to retinopathy or nephropathy.

Conclusion: Individuals with high depressive symptoms and high frequency of alcohol consumption may have a particularly high risk of neuropathy and CAD. Future prevention efforts

should examine both alcohol frequency and depressive symptoms when evaluating risk of complications.

5.2 Introduction

5.2.1 Rationale

Alcohol use in individuals with type 2 diabetes (T2D) is associated with macrovascular and microvascular complications, and these complications can contribute to morbidity and mortality in individuals with T2D [1]. Heavy alcohol use is associated with an increased risk for macrovascular complications, such as cardiovascular disease, whereas moderate alcohol use is associated with decreased risk for cardiovascular disease [2].

Conversely, results of studies examining associations between alcohol consumption and microvascular complications, including neuropathy, retinopathy, and nephropathy are mixed; negative [3], positive [4,5,6] and null [7,8] associations have been found. Additionally, there is some evidence suggesting that moderate alcohol use is related to decreased risk of retinopathy and nephropathy in type 1 diabetes (T1D) and T2D [2,9,10], and decreased risk of neuropathy in T1D [9]. However, additional longitudinal research is necessary to further examine the association between alcohol use and microvascular complications.

When examining the association between alcohol consumption and complications, it may be relevant to consider depression, given that heavy alcohol use is more common in individuals with high depressive symptoms than in the general population [11]. Moreover, high depressive symptoms are more common in individuals with T2D compared to the general population [12] and are also associated with complications [13]. Specifically, past research has demonstrated that among individuals with T2D, those with high depressive symptoms were at an increased risk of developing neuropathy, retinopathy, nephropathy, and heart disease [14,15].

Heavy alcohol use and high depressive symptoms are often comorbid [11]. There is evidence that high depressive symptoms lead to increased alcohol use, and that chronic alcohol

use leads to high depressive symptoms [16]. Given that both heavy alcohol use and high depressive symptoms can increase the risk of complications, individuals who have both may have an even higher risk of complications. However, associations between the combination of alcohol use and high depressive symptoms and the development of complications have not yet been investigated.

5.2.2 Objective and hypothesis

The aim of the present study is to investigate the longitudinal association of frequency of alcohol use and depressive symptoms on the incidence of diabetes-related complications in a community-based sample of adults with T2D. It is expected that the interaction between depressive symptoms and alcohol frequency will be positively associated with the development of neuropathy, retinopathy, nephropathy, and coronary artery disease (CAD). Specifically, higher levels of both depressive symptoms and alcohol frequency will be associated with the highest risk of complications.

5.3 Methods

5.3.1 Dataset

The present study used data from five waves of the longitudinal Evaluation of Diabetes Treatment (EDIT) study, an annual telephone survey across Quebec, Canada [17]. It includes adult participants who were between 40 and 76 years old and insulin-naïve at baseline, with all participants having been diagnosed with T2D within 10 years before the baseline assessment. 2028 individuals completed the baseline assessment, 1691 individuals agreed to participate in follow-up interviews, and 1413 individuals who completed at least one follow-up assessment were included in the present study. Individuals who were included in this study drank slightly

more frequently than individuals who were excluded, but did not differ on depressive symptoms and complications at baseline.

5.3.2 Measures

Depression. Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9) at every wave [18]. This measure includes 9 items, each representing a depressive symptom corresponding with the diagnostic criteria for major depression outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [19]. Participants rate how often each symptom occurred in the past two weeks using a 4-point scale from 0 = "*not at all*" to 3 = "*nearly every day*". The scores for each item were summed to provide a total score for each participant, ranging from 0 to 27 [18]. This measure demonstrated good internal consistency in the current sample at all assessed time points (α_{BL} = .813, α_{F1} = .842, α_{F2} = .818, α_{F3} = .841).

Alcohol use. The Alcohol Use Disorders Identification Test-Concise (AUDIT-C) was also administered at every wave and includes 3 items assessing alcohol consumption and problematic drinking [20]. In the present study, only the item assessing alcohol frequency was used ("*How often did you have a drink containing alcohol in the past year?*") [20]. The alcohol quantity item was not examined, given that this item assesses quantity on a "typical day" [20], which may be perceived differently for individuals who drink occasionally compared to individuals who drink regularly.

Diabetes complications. EDIT included various dichotomous yes/no questions about chronic conditions, with one question assessing nephropathy by asking participants if they had been diagnosed by a physician with kidney disease. The remaining complications were measured using the Diabetes Complications Index (DCI), a self-report questionnaire that includes 17

dichotomous yes/no items assessing 6 common diabetes-related complications [21]. CAD, the most common type of heart disease, was indicated if participants reported they were diagnosed with CAD by a physician, had chest pain within the past six months, or had been told they had a heart attack by a physician. Neuropathy was indicated if participants reported numbness in their feet in the past six months or loss of bowel control or diarrhea in the past four months. Retinopathy was indicated if participants responded that they had ever been diagnosed with retinopathy or diabetic eye disease by a physician [21].

Covariates. The following variables, measured at the baseline assessment, were included as covariates in the adjusted model: age, sex, education (less than secondary, secondary, other post-secondary, post-secondary), marital status (married, living as married, never married, divorced/separated, widowed), and duration of diabetes. The use of oral medication for diabetes (yes/no) and smoking status (never, former, current) were time-varying and also included as covariates.

5.3.3 Statistical analyses

Longitudinal logistic regression analyses with generalized estimating equations (GEE) were used to examine associations between frequency of alcohol use, depressive symptoms, and the risk of incident diabetes-related complications [22]. GEE uses data from all time points and corrects for the repeated measures of each participant over time [22]. The autoregressive correlation matrix was specified for the model, given that the assessments in EDIT are conducted at equal time intervals of one year [22].

In the logistic regression based on GEE, the coefficient for time represents the change in the odds of having complications over time. The coefficient for depressive symptoms assesses the odds of having incident complications as depressive symptoms increase or decrease by one

unit from 0 to 27. The coefficient for alcohol frequency represents the odds of having incident complications as alcohol frequency increases or decreases by one unit. Finally, the coefficient for the interaction of depressive symptoms by alcohol frequency assessed their interaction on the odds of developing incident complications. Significant interactions were graphically examined for interpretation.

Analyses were adjusted for various covariates. The sociodemographic covariates, as well as diabetes duration, were all measured at baseline and are referred to as time-stationary covariates [22]. Use of oral medication and smoking, which were measured at every wave, are referred to as time-varying covariates, given that their values could change over time for each participant [22].

Separate models were computed for each of the four complications in order to determine which specific complications are associated with the interaction between alcohol frequency and depressive symptoms. Time, depressive symptoms, and alcohol frequency were entered in the first step of the unadjusted model. The interaction term of depressive symptoms by alcohol frequency was entered in the second step. Lastly, all covariates were added to compute the adjusted model. Analyses were conducted using SPSS version 22 and significant interactions were graphed in STATA version 14.

5.4 Results

5.4.1 Participant characteristics

At baseline, 1691 participants agreed to be contacted for follow-up. Of these, 13.7% completed one follow-up assessment, 13.5% completed two follow-up assessments, 18.2% completed three follow-up assessments, and 38.2% completed all four follow-up assessments. Participants were included in this study if they completed at least one follow-up, providing a

total sample of 1413. Baseline participant characteristics are shown in Table 1. However, the sample for each analysis differed because participants with a particular complication at baseline were excluded from the analyses predicting that complication (see Table 2).

5.4.2 Hypothesis testing

Neuropathy. There was a 9% increase in the odds of developing neuropathy for every unit increase in depressive symptoms, and a 10% decrease in the odds of developing neuropathy for every unit increase in alcohol frequency. The interaction between depressive symptoms and alcohol frequency was significantly positively associated with increased odds of developing neuropathy. When the model was adjusted for covariates, the odds of developing neuropathy were no longer significantly related to depressive symptoms. However, the association remained statistically significant for alcohol frequency and for the interaction between depressive symptoms and alcohol frequency (see Table 3).

To visualize the interaction of depressive symptoms and alcohol frequency on the odds of developing neuropathy, predicted probabilities of incident neuropathy were calculated for each combination of depressive symptoms and alcohol frequency [23]. Predicted probabilities are calculated based on the estimated marginal means derived from the model, and provide the estimated probability that an individual, at that particular combination of depressive symptoms and alcohol frequency, will develop neuropathy [23]. The probabilities of neuropathy were then graphed against depressive symptoms and alcohol frequency, using the continuous scales of both the alcohol frequency and depressive symptom measures [23]. As shown in Fig. 1, individuals with lower depressive symptoms have a lower risk for neuropathy, regardless of alcohol frequency. However, for individuals at higher depressive symptoms, those with higher alcohol frequency levels have a greater probability of neuropathy compared to those with lower alcohol

frequency levels. Finally, those with high depressive symptoms who drank the most frequently had the highest predicted probability of developing neuropathy.

Retinopathy. Neither depressive symptoms nor alcohol frequency were significantly associated with the incidence of retinopathy. Furthermore, there was no significant interaction between depressive symptoms and alcohol frequency on the odds of developing retinopathy. The adjusted model was similar (see Table 3).

Nephropathy. There was a 6% increase in the odds of developing nephropathy for every unit increase in depressive symptoms, although alcohol frequency was not significantly associated with the incidence of nephropathy. There was no significant interaction between depressive symptoms and alcohol frequency on the odds of developing nephropathy. When the model was adjusted for covariates, the odds of developing nephropathy were no longer significantly related to depressive symptoms. However, there was a significant 26% decrease in the odds of incident nephropathy for every unit increase in alcohol frequency. The interaction between depressive symptoms and alcohol frequency on the odds of developing nephropathy remained not significant in the adjusted model (see Table 3).

CAD. There was a 9% increase in the risk of developing CAD for every unit increase in depressive symptoms. There was no significant association between alcohol frequency and the odds of developing CAD. The interaction between alcohol frequency and depressive symptoms was significantly positively related to increased odds of developing CAD. When the model was adjusted for covariates, the odds of developing CAD were no longer significantly related to depressive symptoms. However, there was an 18% decrease in the odds of developing CAD for every unit increase in alcohol frequency. The interaction between depressive symptoms and

alcohol frequency remained positively significantly associated with the incidence of CAD (see Table 3).

The interaction between depressive symptoms and alcohol frequency was graphed to visualize their association with CAD, using predicted probabilities as was done in the graph with neuropathy [23]. As shown in Fig. 2, individuals with lower depressive symptoms have a similarly lower risk for CAD, regardless of alcohol frequency. However, for individuals at higher depressive symptoms, those with higher alcohol frequency levels have a greater probability of CAD compared to those with lower alcohol frequency levels. Finally, individuals with high depressive symptoms who drank the most frequently had the highest risk of CAD.

5.5 Discussion

The present study sought to determine if the interaction between depressive symptoms and frequency of alcohol use would be associated with an increased risk of diabetes-related complications. The hypothesis was partially supported, given that the combination of higher levels of both alcohol frequency and depressive symptoms were associated with the highest risk of incident neuropathy and CAD. Specifically, as shown in Fig. 1, the predicted probability of neuropathy is between 0.0 and 0.1 for individuals with low depressive symptoms (0-5) at any level of alcohol frequency. However, at higher levels of depressive symptoms, the predicted probability of neuropathy is dependent on alcohol frequency. For example, a depressive symptom score of 24 is associated with a predicted probability of neuropathy of 0.2 to 0.3 when alcohol frequency is low, but increases to 0.3 to 0.5 at higher levels of alcohol frequency. Similarly, as shown in Fig. 2, the predicted probability of CAD is between 0.0 and 0.2 for individuals with low depressive symptoms (0-5) at any level of alcohol frequency. However, at higher levels of depressive symptoms, the predicted probability of CAD is dependent on alcohol

frequency. For example, a depressive symptom score of 24 is associated with a predicted probability of CAD of 0.2 to 0.3 when alcohol frequency is low, but increases to 0.3 to 0.4 at higher levels of alcohol frequency. However, this interaction was not significantly related to incident retinopathy and nephropathy. Past research has shown that heavy alcohol use and high depressive symptoms are each independently positively related to neuropathy [4,14,15] and heart disease [2,14,15]. This study adds to the literature by demonstrating that the combination of high depressive symptoms and high alcohol frequency may lead to an even greater risk of neuropathy and CAD.

Several possible mechanisms may link alcohol consumption to diabetes-related complications [1,2,24]. Whereas acute alcohol consumption may not have any significant long-term effects on glucose in individuals with T2D, chronic heavy alcohol use may result in changes in glucose levels, insulin resistance, changes in lipid levels, mitochondrial dysfunction, and interference in cell signalling [1,2]. Additionally, individuals with T2D who drink heavily are also more likely to engage in poorer self-management behaviours, including poorer medication adherence, diet, and exercise, compared to those who drink less [24]. Through these metabolic, cell signalling, and self-management changes, heavy alcohol use can increase the risk of complications [1,2,24].

High depressive symptoms may also increase risk for complications through poorer diabetes management [25]. Specifically, individuals with T2D and high depressive symptoms tend to have poorer adherence to medication, diet, and exercise, compared to individuals with T2D alone [25]. Additionally, high depressive symptoms in individuals with T2D are associated with increased hypothalamic-pituitary-adrenal axis and sympathetic nervous system activation,

as well as increased insulin resistance and proinflammatory responses [26,27]. Through these possible pathways, high depressive symptoms may lead to complications [25,26,27].

The interaction between alcohol frequency and depressive symptoms was only associated with increases in the odds of developing neuropathy and CAD, and not for retinopathy and nephropathy. However, depressive symptoms and alcohol frequency were independently associated with nephropathy, implying that each of their associations do not change depending on the other. Conversely, alcohol frequency and depressive symptoms were not associated with retinopathy. However, the sample sizes for retinopathy and nephropathy were smaller than those for neuropathy and CAD, so it is possible that the sample sizes were not large enough to examine the interactions for these two complications. Future research should examine the interaction between alcohol frequency and depressive symptoms on the development of retinopathy and nephropathy in larger samples.

The association of moderate alcohol use with decreased risk of cardiovascular events has previously been shown [2], although the association of moderate alcohol use with decreased risk of neuropathy has only been found in T1D [9]. Although moderate alcohol use was not examined in this study, future research should examine the combination of moderate alcohol use and depressive symptoms on the incidence of complications.

The present study was the first, to our knowledge, to examine the combination of depressive symptoms and alcohol use on the incidence of diabetes-related complications. All participants were diagnosed with T2D within the past 10 years, thus the sample was relatively healthy at baseline, making it ideal for examining the development of complications as the illness progresses. Additionally, the analyses included a comprehensive list of covariates. Depressive symptoms and alcohol frequency were each measured using reliable and valid

questionnaires [18,20]. However, the measures are not clinical assessments and do not measure major depressive disorder or alcohol use disorder, and the interaction between major depressive disorder and alcohol use disorder on diabetes-related complications should be researched in future studies. Additionally, the study spanned 5 years, allowing for the examination of the incidence of complications. However, complications may develop later on as T2D progresses, thus it would be beneficial for future studies to examine longer time frames in the association between alcohol frequency, depressive symptoms, and complications.

The sample was large and community-based, but not necessarily representative. Previous research has found ethnic differences in depressive symptoms [28] and alcohol use [29] in individuals with T2D, as well as ethnic differences in diabetes-related complications [30]. Accordingly, future research should examine the risk of developing complications for those with high depressive symptoms and high frequency of alcohol use in a sample representative of ethnic diversity.

Although the alcohol use questionnaire used in this study is reliable and valid, it only provides response options in ranges for alcohol frequency [20]. This does not allow for determination of the specific number of days when drinking frequency is harmful. Additionally, some questions in the DCI include a reference interval of six months, whereas others have a reference interval of one month [21].

5.6 Conclusion

In conclusion, the combination of high depressive symptoms and high frequency of alcohol consumption were associated with the greatest risk of incident neuropathy and CAD. However, the interaction of alcohol frequency and depressive symptoms on the development of retinopathy and nephropathy should be further examined in a larger sample. Nevertheless, the

present findings underscore the importance of psychoeducation on alcohol use guidelines and the increased risk of a high frequency of alcohol use in the diabetes population. Moreover, the present results suggest that individuals should be screened not only for frequency of alcohol consumption, but also for depressive symptoms when evaluating the risk of diabetes-related complications, as the combination of high alcohol frequency and high depressive symptoms could lead to an even greater risk of neuropathy and CAD.

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Conflicts of interest

All authors have no potential conflicts of interest.

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5.8 Tables and figures

Table 1

Baseline participant characteristics for predictors and covariates

Variables	Total sample (*N* = 1413)
	n (%)
Age, mean (SD)	60.0 (8.4)
Sex, female	705 (49.9)
Highest level of education	
< Secondary	528 (37.8)
Secondary	438 (31.3)
Some post-secondary	118 (8.4)
Post-secondary	314 (22.5)
Marital status	
Married	740 (52.4)
Living as married	201 (14.2)
Never married	171 (12.1)
Divorced/separated	190 (13.5)
Widowed	109 (7.7)
Smoking status	
Current smoker (daily/occasional)	276 (19.5)
Former smoker	642 (45.4)
Never smoker	495 (35.0)
Diabetes duration (years)	
0-3	606 (43.2)
4-7	489 (34.8)
8-10	309 (22.0)
Pills for diabetes, yes	1283 (90.8)
Alcohol frequency	
Never	452 (32.1)
≤ Monthly	356 (25.2)
2-4/Month	273 (19.4)
2-3/Week	197 (14.0)
≥ 4/Week	132 (9.4)
Number of drinks/day, mean (SD)	1.3 (.7)
Depressive symptoms summary score, mean (SD)	4.1 (4.9)

Table 2

Number of participants included in analyses for each complication and number who developed each complication

Incident complication	Participants included	Number of incident cases
	n	*n* (%)
Neuropathy	1141	431 (37.8%)
Retinopathy	1280	101 (7.9%)
Nephropathy	1258	84 (6.7%)
CAD	1138	266 (23.4%)

Table 3

Interaction of depressive symptoms and alcohol frequency on incident complications

	Unadjusted Model			Adjusted Model		
	OR	*p*	95% CI	OR	*p*	95% CI
Neuropathy	(*n* = 1141)			(*n* = 1124)		
Dep.	1.09**	.00	1.06, 1.11	1.04	.07	.99, 1.09
Alc. Freq.	0.90*	.03	0.83, .99	.83**	.00	.73, .94
Dep. X Alc. Freq.	1.02*	.03	1.00, 1.04	1.02*	.04	1.00, 1.04
Retinopathy	(*n* = 1280)			(*n* = 1261)		
Dep.	1.01	.74	.96, 1.06	1.07	.11	.99, 1.16
Alc. Freq.	.89	.162	.76, 1.05	.92	.48	.74, 1.15
Dep. X Alc. Freq.	.97	.18	.93, 1.01	.97	.15	.93, 1.01
Nephropathy	(*n* = 1258)			(*n* = 1242)		
Dep.	1.06**	.00	1.02, 1.10	1.03	.52	.95, 1.11
Alc. Freq.	.82	.07	.67, 1.01	.74*	.02	.57, .94
Dep. X Alc. Freq.	1.02	.16	.99, 1.06	1.02	.22	.99, 1.06
CAD	(*n* = 1138)			(*n* = 1124)		
Dep.	1.08**	.00	1.05, 1.10	1.03	.37	.97, 1.08
Alc. Freq.	.93	.21	.84, 1.04	.82*	.01	.71, .96
Dep. X Alc. Freq.	1.02*	.04	1.00, 1.04	1.02*	.03	1.00, 1.04

Notes. Dep, depressive symptoms; alc. freq., alcohol frequency.
Time coefficients are not shown, and were not significant.
Adjusted model adjusted for the following covariates: age, sex, highest level of education, marital status, duration of diabetes, oral medication use, and smoking status.
*$p < .05$
**$p < .01$

Figure 1

The interaction of alcohol frequency by depressive symptoms on the proportion of individuals who developed neuropathy is depicted through the curved lines. The curves in the graph reveal how depressive symptoms are associated with the predicted probability of neuropathy for various levels of alcohol frequency, and how alcohol frequency is associated with the predicted probability of neuropathy for various levels of depressive symptoms.

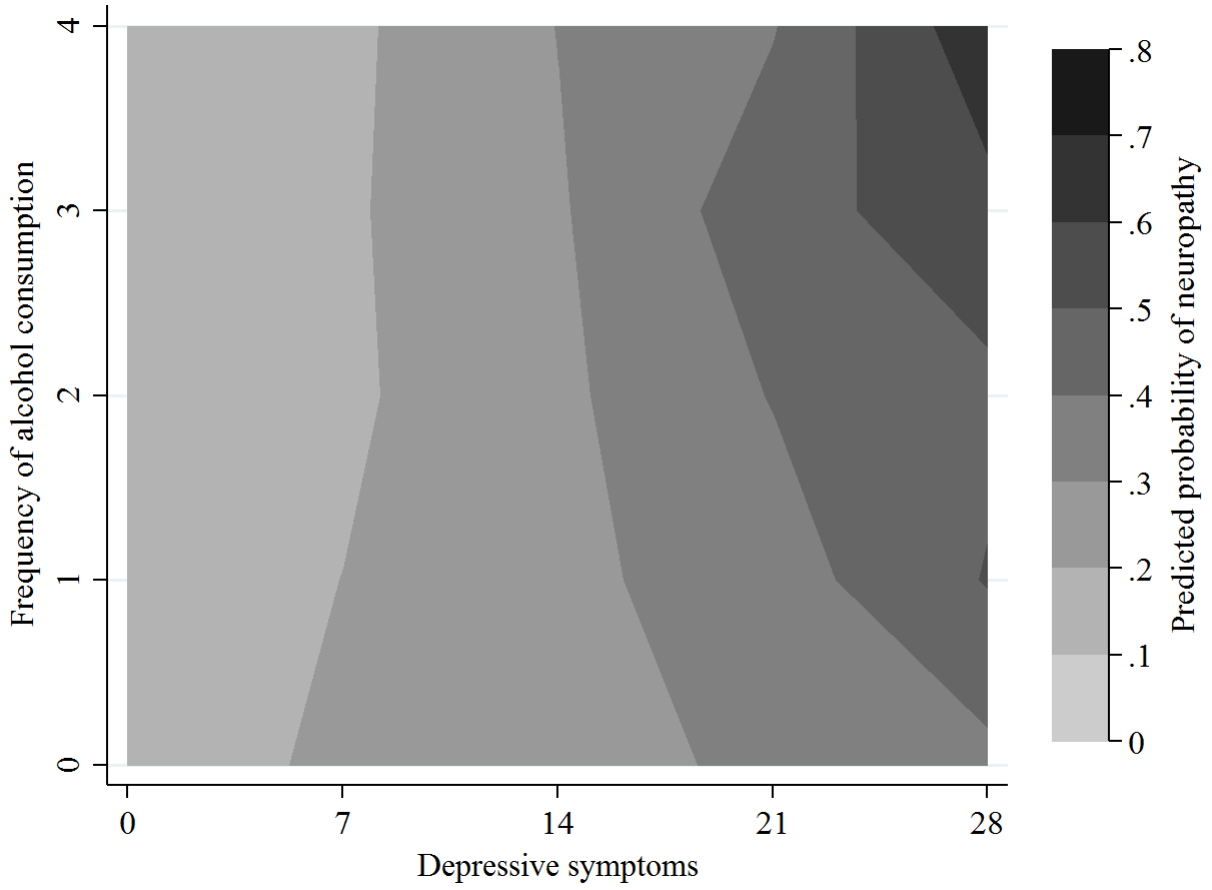
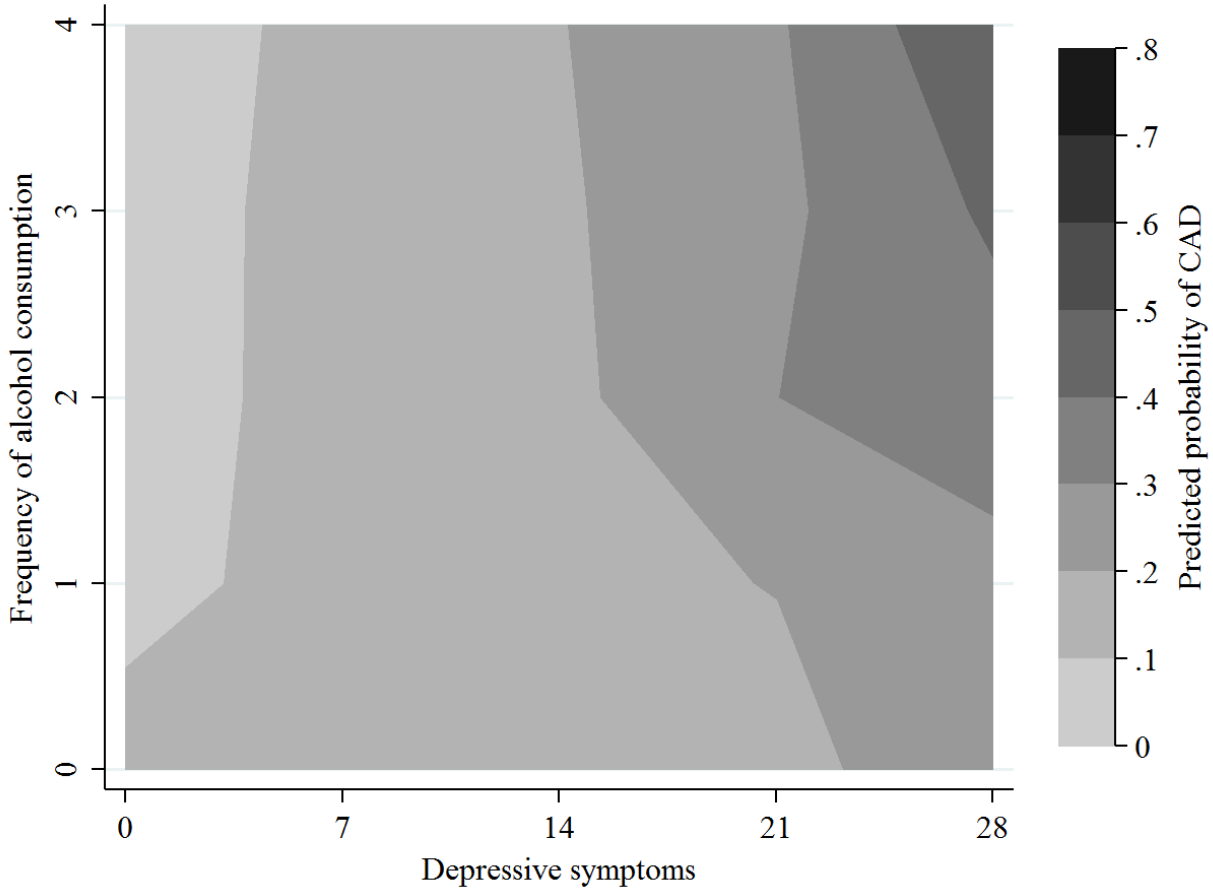


Figure 2

The interaction of alcohol frequency by depressive symptoms on the proportion of individuals who developed CAD is depicted through the curved lines. The curves in the graph reveal how depressive symptoms are associated with the predicted probability of CAD for various levels of alcohol frequency, and how alcohol frequency is associated with the predicted probability of CAD for various levels of depressive symptoms.



Chapter 6: Discussion

6.1 Restatement of objectives

Heavy alcohol use is associated with an increased risk of various negative outcomes in individuals with diabetes, such as diabetes-related complications (Deshpande et al., 2008; Emanuele et al., 1998). However, research on patterns of alcohol use in individuals with diabetes is lacking. Furthermore, given that heavy alcohol use is also associated with psychiatric conditions (McDonald & Meyer, 2011; Merikangas et al., 1998; Sonne & Brady, 1999), it may be beneficial to examine psychiatric conditions when investigating patterns of alcohol consumption in individuals with diabetes. Therefore, the objective of the first manuscript was to assess patterns of alcohol consumption and how they differ based on diabetes status and the presence of MDD, BD, or GAD. Additionally, given that both heavy alcohol use and depression can individually increase the risk of diabetes-related complications (Adler et al., 1997; Black et al., 2003; Lin et al., 2010; Munukutla et al., 2016), it may be beneficial to examine the risk of complications in individuals with a combination of heavy alcohol use and depression. Thus the objective of the second manuscript was to assess the associations between high frequency of alcohol use and high depressive symptoms on the risk of CAD and various microvascular complications over time.

6.2 Summary of findings

The analysis of a large, representative sample in the first manuscript demonstrated that alcohol use was slightly less common in the diabetes sample compared to the non-diabetes sample. Specifically, approximately 61% of individuals with diabetes consumed any alcohol in the past year, whereas approximately 78% of individuals without diabetes, and 76% of the total sample, consumed any alcohol in the past year. When examining the association between

diabetes status and psychiatric conditions on alcohol use, individuals with diabetes consumed a lesser quantity of alcohol compared to those without diabetes when they did not have MDD or BD. Moreover, this association was even stronger for individuals with diabetes and comorbid MDD or BD. There was no significant interaction between alcohol frequency and BD or MDD, nor was there a significant interaction between diabetes status and GAD on alcohol quantity and frequency. These associations remained unchanged when adjusted for various sociodemographic, lifestyle, and health-related covariates.

The second manuscript revealed that among adults with T2D, individuals with high depressive symptoms who drank the most frequently had the highest risk of incident neuropathy and CAD. However, this increased risk of the combination of heavy alcohol frequency and high depressive symptoms was not found for incident retinopathy or nephropathy. These associations held when adjusted for relevant sociodemographic, lifestyle, and health-related covariates.

6.3 Strengths and limitations

This thesis utilized large datasets, the first being a representative community-based sample of the Canadian population and the second being a community-based sample in the Quebec population. Furthermore, the CCHS-MH dataset used in the first manuscript included clinical assessments of psychiatric conditions. In addition, the EDIT dataset used in the second manuscript included five years of assessment, allowing for the longitudinal examination of the risk of complications over time. Both datasets included valid and reliable questionnaires and a comprehensive set of covariates in the analyses.

Previous literature examining the association between alcohol use and the risk of diabetes-related complications has measured alcohol differently. Some studies have operationalized quantity as number of drinks or grams of alcohol consumed per day (Solomon et

al., 2000; Valmadrid et al., 1999), some have used frequency of drinking (Ajani et al., 2000), and some have used a composite of average consumption in a week (Blomster et al., 2014; Fenwick et al., 2015; McCulloch et al., 1980; Young et al., 1994). The first manuscript included two measures of alcohol use, allowing for the examination of separate patterns of quantity of drinks per day and frequency of drinking in the diabetes population. However, a composite of quantity and frequency was not utilized because the frequency is categorized such that the composite categories would be difficult to interpret meaningfully.

The main analysis in the second manuscript only included alcohol frequency and not quantity, because the alcohol quantity item in the AUDIT-C ("*How many drinks did you have on a typical day when you were drinking in the past year?*"; Bush et al., 1998) has several limitations. The item excludes individuals who abstain from alcohol, and by removing all the individuals at this lower end, it removes much of the variability in quantity scores. This variability is especially relevant in a diabetes population, as a large proportion of individuals with diabetes abstain from alcohol (Ahmed et al., 2006). In addition, the item asks for quantity "on a typical day", which could be interpreted differently between an individual who drinks once a year and an individual who drinks multiple times a week. Additional sensitivity analyses can be found in Appendix I examining the interaction between alcohol quantity and depressive symptoms on the incidence of diabetes-related complications. The additional analyses revealed no significant interactions between alcohol quantity and depressive symptoms on each of the complications. This suggests that different measures of alcohol consumption may be related to different types of complications and may not all be related to psychiatric conditions. However, future research using a more comprehensive measure of alcohol quantity is needed to be able to

examine how alcohol quantity and depressive symptoms interact on diabetes-related complications.

Binge drinking could not be assessed in both manuscripts due to the small number of participants who engaged in binge drinking. Specifically, about 60% of participants in the first dataset reported never binge drinking in the past 12 months, and 70-80% of participants in the second dataset reported never binge drinking throughout all time points. Similarly, although the CCHS-MH dataset used in the first manuscript did include measures of alcohol use disorders (Statistics Canada, 2014), there was insufficient power to examine the sample of individuals with diabetes, a psychiatric condition, and an alcohol use disorder. In addition, although the alcohol frequency questionnaire in the first dataset included an option for "everyday", the highest response option in the second dataset was "4 or more times a week", which does not allow for differentiation of individuals who drink everyday in the second manuscript (Bush et al., 1998).

6.4 Implications of findings

The findings from the first manuscript expand the extant literature by describing the drinking patterns in individuals with diabetes in a representative Canadian sample, and how drinking patterns differ based on the presence psychiatric conditions. The study suggests that the associations between alcohol consumption and psychiatric conditions observed in the general population may not extend to the diabetes population. The findings of the study should be replicated in other samples. Further investigation into why the associations between psychiatric conditions and alcohol consumption in individuals with diabetes differ from those observed in the general population is needed. Elucidating why the association between alcohol consumption and psychiatric conditions differs in individuals with diabetes could help inform future alcohol-related prevention and intervention efforts in the diabetes population.

The second manuscript contributed to the extant literature by examining the combination of frequency of alcohol use and depressive symptoms on diabetes-related complications, whereas previous research has only examined each one's independent association with complications (Adler et al., 1997; Black et al., 2003; Lin et al., 2010; Munukutla et al., 2016). The study revealed that individuals who drink the most frequently and have high depressive symptoms are at the highest risk of developing neuropathy and CAD. The implications of these findings are relevant to prevention efforts, by encouraging screening individuals with diabetes not only for their frequency of alcohol consumption, but also for depressive symptoms when assessing their risk for neuropathy and CAD. Furthermore, the findings of the study support the importance of psychoeducation regarding alcohol consumption guidelines and the risk of a high frequency of alcohol consumption among individuals with diabetes. Additionally, it could also inform intervention efforts, by encouraging interventions to address not only highly frequent alcohol use, but also high depressive symptoms in order to lower the risk for neuropathy and CAD.

6.5 Future directions

There are several possible avenues for future research to advance the understanding of alcohol use, psychiatric conditions, and diabetes-related complications. Given that the results of the first manuscript were not as expected, researchers should replicate the study in different samples to determine if similar results are obtained. Additionally, further investigation is needed into why the association between psychiatric conditions and alcohol use is different in the diabetes population compared to the general population. One possible direction for future research may be evaluating alcohol expectancies, or the expected consequences of alcohol consumption (Cooper et al., 1995), in individuals with diabetes. This examination may reveal that individuals with diabetes and MDD or BD have different alcohol expectancies than those

with MDD or BD in the general population, which may explain why alcohol consumption may relate to MDD and BD differently in these populations.

The interaction between high depressive symptoms and high frequency of alcohol consumption on the increased risk of neuropathy and CAD may possibly be explained by their overlapping mechanisms (Emanuele et al., 1998; Munukutla et al., 2016; Golden, 2007; Lustman et al., 2007; Pietraszek et al., 2010). Their common mechanisms include insulin resistance, changes in glucose levels (Emanuele et al., 1998; Munukutla et al., 2016; Golden, 2007; Lustman et al., 2007; Pietraszek et al., 2010), and poor diabetes self-management (Ahmed et al., 2006; Ciechanowski et al., 2000; Gonzalez et al., 2008; Leung et al., 2011; Lin et al., 2004; Thomas et al., 2012; Walter et al., 2017). Accordingly, it is possible that individuals who have high depressive symptoms and drink at a high frequency may have even worse insulin resistance, glucose level changes, and diabetes self-management compared to those with only high depressive symptoms or who only drink at a high frequency. Future research should investigate possible mechanisms of the combination of high depressive symptoms and high frequency of alcohol use on the risk of neuropathy and CAD, as well as examine the association of alcohol quantity, depressive symptoms, and diabetes-related complications using a more comprehensive measure than the AUDIT-C.

In addition, the interaction of alcohol frequency and depressive symptoms on the development of retinopathy and nephropathy should be further examined in a larger sample. Future research should investigate if the different associations between different complications are related to differing mechanisms of how alcohol and depressive symptoms each independently increase the risk for retinopathy and nephropathy, compared to how they increase the risk for neuropathy and CAD. Additionally, though previous research has found a protective effect for

moderate alcohol use on diabetes-related complications (Beulens et al., 2008; Blomster et al., 2014; Howard et al., 2004; Fenwick et al., 2015; Munukutla et al., 2016; Solomon et al., 2000; Tanasescu et al., 2001), the second manuscript could not examine this because of limited power. It would be beneficial for future research to examine how depressive symptoms and moderate alcohol use interact on diabetes-related complications.

The two manuscripts in this thesis both examined large, community-based samples. However, although the CCHS-MH dataset used in the first manuscript is representative by age and sex (Statistics Canada, 2013), neither the CCHS-MH nor EDIT are representative by ethnicity. Previous research has revealed that, among individuals with diabetes, ethnic differences exist in depressive symptoms (Wagner, Tsimikas, Abbott, de Groot, & Heapy, 2007), alcohol consumption (Vaeth, Caetano, & Durazo, 2014) and diabetes-related complications (Lanting, Joung, Mackenbach, Lamberts, & Bootsma, 2005). Within a representative, ethnically diverse diabetes population, future research should further investigate the patterns of alcohol consumption in the presence and absence of psychiatric conditions, as well as the combination of depressive symptoms and alcohol consumption on the risk of diabetes-related complications. This research could identify if there are potential ethnic differences in the association between psychiatric conditions, alcohol use, and complications.

6.6 Conclusion

In conclusion, the findings of this thesis provide evidence that drinking patterns may be associated to psychiatric conditions differently in the diabetes population compared to the general population. In addition, longitudinal analyses reveal that among individuals with T2D, those who consume alcohol at a high frequency and have high depressive symptoms have a particularly high risk of incident neuropathy and CAD. These drinking patterns and risk of

neuropathy and CAD remained after adjusting for various sociodemographic, lifestyle, and health-related covariates. Given the increasing prevalence of diabetes in the Canadian population, further investigation is required in order to assess the replicability of these findings, as well as advance the understanding of the associations between alcohol consumption, psychiatric conditions, and diabetes-related complications. This research could contribute to prevention and intervention efforts of diabetes-related complications, and thus prevent the morbidity and mortality that is associated with these complications.

Chapter 7: References

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Appendix I: Additional analyses

Manuscript 2: Supplemental table 1

Interaction of depressive symptoms and alcohol frequency on incident complications

	Unadjusted Model			Adjusted Model		
	OR	*p*	95% CI	OR	*p*	95% CI
Neuropathy	(*n* = 848)			(*n* = 840)		
Dep.	1.11**	.00	1.07, 1.14	1.10*	.04	1.01, 1.19
Alc. Quant.	.98	.88	.78, 1.24	.91	.59	.65, 1.28
Dep. X Alc. Quant.	1.00	.99	.94, 1.06	1.00	.90	.95, 1.07
Retinopathy	(*n* = 952)			(*n* = 941)		
Dep.	.98	.59	.90, 1.06	.95	.43	.84, 1.08
Alc. Quant.	1.36*	.04	1.01, 1.83	1.14	.58	.72, 1.81
Dep. X Alc. Quant.	1.02	.51	.95, 1.11	1.02	.52	.95, 1.10
Nephropathy	(*n* = 936)			(*n* = 927)		
Dep.	1.09**	.00	1.03, 1.14	1.13	.11	.97, 1.31
Alc. Quant.	.87	.64	.48, 1.57	.95	.91	.39, 2.34
Dep. X Alc. Quant.	.97	.58	.87, 1.08	.97	.62	.86. 1.09
CAD	(*n* = 840)			(*n* = 834)		
Dep.	1.09**	.00	1.06, 1.13	1.11*	.01	1.02, 1.20
Alc. Quant.	1.15	.25	.90, 1.48	1.23	.24	.87, 1.72
Dep. X Alc. Quant.	.98	.55	.93, 1.04	.99	.65	.93, 1.05

Notes. Alc. quant., alcohol quantity.
Time coefficients are not shown, and were not significant.
Adjusted model adjusted for the following covariates: age, sex, highest level of education, marital status, duration of diabetes, oral medication use, and smoking status.
*$p < .05$
**$p < .01$