Title: Smoking and cessation behaviours in a community sample with type-2 diabetes: associations with depression.

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Abstract

Background: Smoking is a highly prevalent behaviour practiced worldwide, associated with high levels of illness morbidity and mortality. It has been associated with the incidence of type-2 diabetes, as well as the progression of diabetes complications and increased disease specific and all-cause mortality. Smoking cessation is an important self-care recommendation in diabetes treatment guidelines, although it appears many continue to smoke. Moreover, smoking has been associated with depression. Depression is twice a prevalent in those with diabetes, and has been linked with poor regimen adherence, increased complications, morbidity and mortality. Little is currently known about the association or impact of smoking and depression in populations with chronic illnesses, and specifically in those with type-2 diabetes.

Aims: Using a Canadian community based sample with type-2 diabetes, to determine: 1) Important differences in sociodemographic, health and disease related characteristics across smoking status; 2) Investigating the relationship between smoking status and depression while controlling for potential confounding factors; 3) Determining differences in the population according to cessation status and cessation attempts; and 4) Determining if there is a link between depression status and smoking cessation.

Results: Smoking prevalence was similar to rates found in the general population, and appeared to be stable over a 4-year period. Current moderate-heavy smokers differed on sociodemographic characteristics, and were more likely to have more diabetes complications, more comorbid chronic illness and be less physically active. Moderate-heavy smoking was associated with depression in both cross-sectional and longitudinal analyses, controlling for baseline depression. Smoking cessation status also differed across sociodemographic characteristics. Unsuccessful quitters were more likely to rate their health as fair/poor and report more disability affected days in the past month. Finally, unsuccessful

quitters were significantly associated with depression syndrome as compared to successful quitters, after controlling for sociodemographic, health and disease related variables.

Conclusion: Consistent with findings from the general population, current smokers, and specifically current heavy daily smoking was associated with elevated symptoms of depression. This association appeared to be stable over time, producing a number of negative health and functional outcomes in these individuals. Given this increased risk of morbidity and mortality faced by individual's with diabetes, this strong association of smoking and depression is that much more dangerous. Clinician's should therefore counsel these individuals to give up smoking as soon as possible, following diabetes treatment regimen guidelines. In addition, there is the prevailing notion that individuals with depression may be unmotivated to quit smoking and therefore counselling these individuals might be fruitless. In our study, the association between smoking and depression was extended to include unsuccessful quitters, who also had elevated prevalence rates of depression compared to successful quitters and non-attempters. That successful quitters had lower depression than those who continued to smoke replicates findings from the general population. We did however extend this finding by contrasting those unsuccessful quitters to non-attempters. In our study, unsuccessful quitters had the highest prevalence of depression. This would appear to indicate that those with depression who smoke may be motivated to quit, but unable to do successfully accomplish this task. Clinician's should therefore be prepared to assess and offer smoking cessation advice to those with depression, while also preparing to provide these individuals with additional support during the quit process.

Résumé

Contexte: Il est bien connu que le tabagisme, un comportement répandu et pratiqué dans le monde entier, est associée à des taux élevés de morbidité et de mortalité. Récemment, de multiples études ont démontré que le tabagisme est également associé à l'incidence du diabète de type 2, ainsi que les complications du diabète et l'augmentation de la mortalité spécifique et toutes causes. La cessation du tabagisme est une recommandation de soins importante dans les guides de traitement du diabète. En dépit de l'importance accordée à la cessation, beaucoup continuent à fumer. Le tabagisme est aussi associé avec la dépression. La dépression est deux fois plus répandue chez les personnes atteintes de diabète et a été lié à la mauvaise observance du régiment de traitement, à l'augmentation des complications, de la morbidité et de la mortalité. Présentement, les données sont insuffisantes pour conclure qu'il existe une association concrète entre le tabagisme et la dépression chez les populations souffrantes de maladies chroniques, le diabète de type-2 en particulier.

Objectifs: Pour cette étude, nous avons mené une enquête auprès des adultes québécois ayant le diabète de type 2, afin de déterminer: 1) les différences importantes dans les caractéristiques sociodémographiques, et l'état de santé selon le statut de fumeur, 2) la relation entre le tabagisme et la dépression en tenant compte des autres variables démographiques et liées à l'état de santé; 3) les différences déterminantes dans la population en fonction de cessation et les tentatives de sevrage, et 4) déterminer s'il existe un lien entre l'état de dépression et la cessation.

Résultats: La prévalence du tabagisme dans notre population était égale à la prévalence observée dans l'ensemble de la population canadienne, et semblait être stable sur une période de 4 ans. Les fumeurs excessifs actuels se différaient sur les caractéristiques sociodémographiques, et étaient plus susceptibles d'être moins actifs physiquement, avoir plus de complications du diabète et d'autres maladies chroniques. Le tabagisme excessif a été associé à la dépression dans les analyses transversale et

longitudinales, tout en tenant compte de la dépression de base. L'état de cessation du tabagisme différait aussi à travers des caractéristiques sociodémographiques. La catégorie de 'sevrage non-réussite' étaient plus susceptibles d'évaluer leur santé comme moyen / pauvres et ont reporté plus de jours affecté par l'incapacité au cours du dernier mois. Enfin, la dépression a été associé à une probabilité accrue chez la groupe 'sevrage non-réussite', comparé aux ex-fumeurs ('sevrage réussite'). Les analyses ont été effectuées en tenant comptes des variables sociodémographiques, de santé et de maladie.

Conclusion: Comparativement aux conclusions de la population générale, les fumeurs excessifs sont associé à la dépression dans les études transversale et longitudinales, indiquant que le tabagisme excessif peut également contribuer à un plus haut taux de problème de santé mentale observé dans cette population. Les personnes avec la diabète one déja un risque acrru de morbidité et de mortalité, alors cette association entre la tabagisme et la depression est encore plus dangereux. Les fournisseurs de soins de santé doivent alors être attentifs envers ces patients pour éviter des problèmes de santé et de fonctionne. De même, l'état de cessation du tabagisme était associé à la dépression. L'idée répandue que les gens souffrant de la depression ne sont pas motive d'arreter de fumer est cependent mis en question. Dans notre etudes, les gens de la catégorie de 'sevrage non réussite' avaient une perception plus pauvres par rapports à leur santé. En outre, les personnes classifiées 'sevrage non-réussite' ont une prévalence élevée de la dépression, et possèdent une probabilité accru pour la dépression par rapport aux ex-fumeurs (sevrage réussite). Les fumeurs atteints de diabète du type-2 devraient être encouragés à la cessation afin d'éviter les résultats négatifs sur la santé physique et mentale. Les fournisseurs de soins de santé offrant des conseils de cessation devraient tenir compte des différences dans les caractéristiques sociodémographiques et de la maladie lors de l'élaboration des interventions. Par ailleurs, la dépression doit être considérée étant donné qu'il est fortement et indépendamment associée

au tabagisme actuel et a un impact considérable sur le sevrage tabagique dans cette population à risque.

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Contributions of Authors

As first author on all 3 manuscripts presented, I (**Matthew Clyde**) made significant contributions to the formulation, creation and presentation of the accompanying material. I was responsible for the ideas, writing and analyses presented in the manuscripts.

Dr. Norbert Schmitz provided substantial contributions to the theoretical formulation for all 3 papers, as well as substantial input with regards to the interpretation, reporting, content and presentation of the findings in the 3 manuscripts.

Dr. Kimberley Smith provided substantial input in both the theoretical formation, as well as interpretations presented in the 3 manuscripts. Dr. Smith was also an important contributor to the revision of all 3 manuscripts.

Geneviève Gariépy provided substantial input in both the interpretation and analyses of the statistics presented in all 3 manuscripts. Additionally, she was an important contributor to the revision of all 3 manuscripts.

Chapter 1 – Background and Study Objectives

1.1 Introduction - Smoking

Cigarette smoking is a widely practiced behaviour worldwide. The World Health Organization often refers to the use of tobacco as an epidemic(World Health Organization, 2013c), and the statistics continue to mount in support of the use of this term. Responsible for nearly 6 million deaths worldwide every year (including non-users affected via second-hand exposure), up to one half of all users will eventually die due to a tobacco related cause. Current projections(Mathers & Loncar, 2006), should tobacco use go unchecked, estimate nearly 8 million people will die each year thanks to complications associated with smoking. Given that each cigarette is made up of roughly 4000 compounds(Fowles, Bates, & Noiton, 2000), including agents like nicotine which produce addiction, the broad spectrum of complications and poor outcomes associated with tobacco use begin to make sense.

In spite of major decreases in the previous 2 decades, smoking remains a prevalent behaviour both in Western society and around the world. Smoking prevalence now appears to have reached a floor, with year over year prevalence estimates in the past decade slowing, having become stagnant over the past several years Data from a Canadian perspective illustrate this(Health Canada, 2010), as current smoking prevalence declined nearly 20% between 1985-2011. However, focusing on data since the turn of the millennium, declines have slowed considerably, yielding modest 1% reductions earlier in the decade, and stable rates today. Currently, Statistics Canada(Statistics Canada, 2012) estimates that approximately 20% of Canadians aged 12 and over smoke, representing over 5 million smokers. Smoking not only infers health dangers to users, but also functions as an environmental health hazard for those impacted as second hand smokers. Consequently, tobacco use is extremely taxing on the Canadian health system, with direct and indirect costs estimated at upwards of $17 billion dollars annually(Reid &

Hammond, 2009). While indirect measures have been implemented to prevent smoking in public places (i.e. banning the use in restaurants and work environments), the burden on current smokers is to quit.

Given the high degree of morbidity associated with cigarettes, smoking cessation immediately becomes a component in treatment guidelines upon the diagnosis of numerous illnesses. Unfortunately, due to the addictive nature of cigarettes, quitting is often easier said than done. Numerous studies focusing on smoking cessation and relapse support this claim, demonstrating that although nearly 50% of smokers will make a cessation attempt in any given year, fewer than 10% will succeed(Lee & Kahende, 2007). Multiple factors have been identified as potentially important during this process, including non-modifiable factors such as demographics (e.g. age and gender)(Lee & Kahende, 2007), and smoking related characteristics (Hyland et al., 2006) such as number of cigarettes smoked per day, the number of previous cessation attempts, degree of nicotine dependence, as well as the presence of comorbid mental illness(Lawrence, Mitrou, & Zubrick, 2009). However, one of the strongest indicators of making a cessation attempt is concern for health, often related to the diagnosis of a medical illness(Twardella et al., 2006).

1.11 Smoking and illness

The 2004 Surgeon General's report(US Department of Health & Human Services, 2004) focused on the relationship between smoking and health consequences. It summarized the evidence in support of a causal relationships between smoking and many illnesses, including cancers, cardiovascular diseases, and pulmonary disease. It concluded that smoking negatively impacts nearly every organ in the body, while providing evidence that cessation remains the only effective way to combat the impact of cigarette use on the body. The 2010 report(US Department of Health, 2010) built on the 2004 report with new evidence and advanced techniques, focusing on the mechanisms by which smoking impacts health. Although attempts to designate which of the 4000 chemical constituents were the main

culprit(s) remained difficult given the different ways cigarettes can affect an individual, the scientific consensus placed the blame on a combination of several chemical compounds interacting during both emission and combustion of the cigarette as being toxic and carcinogenic. Some of these toxic effects, found even at acute levels of exposure, immediately generate endothelial dysfunction, increased platelet aggregation, increased inflammation while generating oxidative stress(Puranik & Celermajer, 2003), instantaneously impacting both the lungs and heart. While the report highlights that no amount of exposure was safe, particular importance was paid to the increased risk faced by prolonged, chronic abusers of cigarettes. The transition from experimentation and occasional smoking into chronic and persistent abuse was attributed to the addictive effects of nicotine. Although nicotine has been recognized as the main addictive component of cigarettes for decades, research into the exact mechanisms by which it causes addiction remains an important area of research. A recent review(Benowitz, 2010), summarizing our up-to-date understanding of nicotine and addiction, enforces the idea that nicotine addiction is similar to other forms of addiction, making use of not only pharmacologic pathways in the brain, but also through learning/conditioning, genetic susceptibility, social and environmental factors. Thus although many may begin to smoke sporadically, a percentage will make the transition to a strong multilevel habit that is difficult to break.

Given the wide-range of effects on the various organs of the body, it is little wonder that smoking remains the leading cause of premature death in both the United States(Danaei et al., 2009) and Canada(Janz, 2012). The pervasive use of cigarettes worldwide has also generated significant reports linking tobacco use and illness. In its report on non-communicable diseases (NCDs), the leading cause of death worldwide(World Health Organization, 2011), the WHO lists tobacco cessation as one of the 3 major behavioural changes required for prevention. Amongst the NCDs listed, many echo those diseases found in the aforementioned 2004 Surgeon General's report, including different types of cancers and cardiovascular diseases. One disorder missing from the 2004 report, Diabetes Mellitus, is projected to

reach epidemic rates worldwide in the near future, and its association with cigarette use is increasingly being recognized.

1.2 Diabetes Mellitus

Diabetes Mellitus is a non-communicable disease affecting 371 million people worldwide, with projections estimating that this number will reach 522 million by 2030(International Diabetes Federation, 2011). Diabetes is characterized by impairing the body's ability to produce or effectively use insulin. It is characterized by three main types: Type-1, Type-2 and Gestational Diabetes. The most prevalent form, Type-2 Diabetes Mellitus (T2DM), which we will focus on, makes up approximately 90% of worldwide cases. It was formerly known as adult-onset diabetes, as it was almost exclusively diagnosed in older adults, but is now beginning to be diagnosed in children, teenagers and young adults. T2DM(World Health Organization, 2013b) is a product of the body both not producing enough insulin, while simultaneously not being able to respond to its effects. This leads to a toxic buildup of glucose in the blood stream, which in turn leads to the development of macro and micro-vascular complications(Nolan, Damm, & Prentki, 2011). Highly prevalent worldwide, people who initially develop T2DM are often unaware that they have the illness because it may take years for meaningful symptoms to develop before they are formally tested. Unfortunately, this also means that the organs of the body have been under the stress of hyperglycaemia, and therefore these individuals may have already experienced years of damage before being formally diagnosed and treated.

1.21 Diabetes causes and complications

Although there are a number of hypotheses for antecedent causes of T2DM, major non-modifiable risk factors include age, gender, genetics and a family history of diabetes(Deshpande, Harris-Hayes, & Schootman, 2008). As discussed, the WHO maintains that modifiable and preventable risk factors are similar across all NCDs(World Health Organization, 2011), and include unhealthy diet, physical inactivity,

harmful use of alcohol, and tobacco. Both impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are two conditions(World Health Organization, 2013b) that have been recognized as intermediaries on the path from normally functioning individuals to the development of diabetes. Once the transition happens, in addition to behavioural changes targeting the aforementioned risk factors (controlled diet, increased physical activity and smoking cessation), pharmacologic interventions aimed at effectively producing and using insulin become required to properly control the illness. If uncontrolled, diabetes becomes one of the leading causes of disability, morbidity, and mortality worldwide(Beulens, Grobbee, & Nealb, 2010).

The most recognized complications(Fowler, 2008) include damage to the heart, the kidneys (nephropathy), the eyes (retinopathy), and the nervous system (neuropathy). People with diabetes are at increased risk of many macro-vascular complications, including coronary artery disease, stroke, and angina; in fact, heart disease is the leading cause of disability and death amongst those with diabetes, affecting approximately 50% of this population(Morrish, Wang, Stevens, Fuller, & Keen, 2001). Those with T2DM are also more likely to experience kidney failure as a vascular consequence of diabetes. Likewise, diabetes is also is a leading cause of eye-degeneration and leads to blindness, severely affecting the quality of life of those impacted. Finally, neuropathy is another common complication. Initial symptoms may include tingling sensations, numbness or weakness in the extremities; however, with progression comes increased pain, and if unchecked, development of foot ulcers and potential amputation.

Given the high and steadily increasing prevalence, it should not be surprising to find out that the costs associated with treating diabetes are similarly skyrocketing. The WHO estimates the health-care cost for an individual with diabetes is 2-3 times higher in the US than an individual without the illness(World Health Organization, 2013a). Factoring in the overall costs of treating diabetes, including hospital care,

physician services, lab tests and lab equipment are only the first part of the equation, in addition to the accrued costs of hospital fees required to treat the aforementioned complications. The Canadian Diabetes Association estimates that 9 million Canadians are living with diabetes today(Canadian Diabetes Association, 2013). A further 1 in 4 is currently pre-diabetic (IGT or IFG), a number projected to increase to 1 in 3 by 2020; furthermore, they estimate the annual cost of diabetes to be around $11.7 billion. Importantly, diabetes is recognized as an illness in which the application of successful lifestyle interventions, in addition to pharmacologic treatment, can be controlled. One such self-care behaviour is smoking cessation.

1.22 Diabetes and Smoking

Having established the dangers cigarette smoking pose to healthy individuals, one might assume a lower prevalence rate amongst those with type-2 diabetes given their increased risk. Unfortunately, estimates put the prevalence of smoking amongst those with this chronic illness on par with that of the general population, and subsequently reasonably stable over the last 2 decades(Ford, Mokdad, & Gregg, 2004). It appears that current cessation strategies may be underperforming or inadequate for this at risk population.

The association between smoking and T2DM has been studied from a variety of angles, including that of a causal relationship, increased mortality rates, and the increased risk of complications. There have been a number of prospective studies assessing the causal relationship between type-2 diabetes and smoking, well summarized by the review and meta-analysis conducted by Willi(Willi, Bodenmann, Ghali, Faris, & Cornuz, 2007). In the meta-analysis, smoking was significantly associated with the incidence of type-2 diabetes, specifically in a dose-response manner, with heavier smokers (20+ cigarettes per day; pooled RR= 1.61 95%CI 1.43-1.80) having an increased risk of developing type-2 diabetes. Moreover, any level of smoking was found to be dangerous, with slightly lower but still statistically significant risk (RR = 1.29,

95%CI 1.13-1.48 and RR = 1.23 95%CI 1.14-1.33) in light and former smokers, respectively. Although the exact mechanism isn't completely understood, smoking leads to both increased fasting glucose and impaired glucose metabolism through insulin resistance(Bergman et al., 2012) in otherwise normal individuals, which can lead to the development of the disorder(D. Haire-Joshu, Glasgow, & Tibbs, 1999; Rafalson et al., 2009). In terms of mortality, smoking plays an important mediating role in the strong association between cardiovascular disease and diabetes. Individuals with diabetes are 2-3 times more likely to die from cardiovascular disease than those within the general population(Morrish et al., 2001), making smoking that much more dangerous for this population. Studies conducted in both men(Stamler, Vaccaro, Neaton, Wentworth, & Group, 1993) and women(Al-Delaimy, Willett, Manson, Speizer, & Hu, 2001) indicate that the mortality rates were significantly higher for smokers with diabetes compared to those without; furthermore, recent research suggests that previous studies may have been underestimating the all-cause mortality attributed to smoking(Kenfield et al., 2010). A study looking at the relationship between years since quitting and mortality found that the increased risk of mortality remains high for several years after quitting, even when controlling for heart disease and blood pressure(Chaturvedi, Stevens, Fuller, & The World Health Organization Multinational Study, 1997).

Finally, it is important to consider the associations between smoking and diabetes related complications, which can severely impair individuals, reducing their quality of life. Smoking can affect health by impacting endothelial function, by increasing vascular problems and inflammation. These specific effects emulate many of the same complications associated with hyperglycaemia for those with diabetes; thus, smoking in conjunction with diabetes can accelerate the presentation of these complications(Deshpande et al., 2008; Eliasson, 2003). Macro-vascular complications are especially impacted by smoking, as the effects of cigarette abuse is responsible for a large portion of overlap between cardiovascular disease (CVD) and diabetes, given smoking is recognized as a major risk factors for many forms of CVD including ischemic heart disease, peripheral artery disease and stroke. Similarly,

micro-vascular complications including nephropathy and peripheral neuropathy have been independently associated with smoking, and are two of the largest contributors to disability in people with diabetes. Diabetic nephropathy specifically is particularly debilitating(Wolf & Ritz, 2003), and smoking is a major risk factor for kidney dysfunction(Chakkarwar, 2012).

The relationship between diabetes and smoking is therefore particularly dangerous, yet has remained high and stable despite these increased risks. One recent publication(Ding El, 2007), using recent smoking data from the US, estimated that smoking may be responsible for up to 12% of incident type-2 diabetes cases within the U.S. Strategies for promoting smoking cessation in those at risk for type-2 diabetes, as well as for those already diagnosed, are necessary, particularly those that attempt to integrate smoking cessation with current diabetes education programs. Unfortunately, in terms of smoking cessation interventions, there has been very little published for those with diabetes. Canga(Canga et al., 2000) examined the usefulness of incorporating a nurse trained in smoking cessation intervention for patients attending primary care facilities for diabetes, finding that this addition provided added cessation benefits over the usual care control group. Similarly, a study conducted in the United States(Hokanson, Anderson, Hennrikus, Lando, & Kendall, 2006) determined that it was possible to effectively integrate a structured tobacco cessation program into an established diabetes education program without detrimental effect to the program itself. Unfortunately, although there were short term (3-month abstinence gains compared to treatment as usual) benefits, this intervention did not impact cessation rates at 6 months. Tonstad(Tonstad, 2009) provides a more recent overview of the literature on smoking cessation and diabetes, highlighting specifically the overall lack of studies available, as well as the lack of evidence for efficacy and safety of current cessation pharmacologic interventions in those with diabetes. Another potential variable within this equation that may play an important role is the presence of a comorbid mental illness. Specifically, depression has been strongly and consistently linked with both smoking and diabetes in the literature.

1.3 Depression

Depression is a mental disorder characterized primarily by the presence of prolonged sad/depressed affect and a loss of pleasure. According to the WHO(Marcus, Yasamy, van Ommeren, Chisholm, & Saxena, 2012), over 350 million people worldwide are affected by depression, impacting those of all ages. In addition, depression is one of the leading causes of disability, leading to the increasing burden of disease worldwide. In Canada, estimates of prevalence of depression, according to a 2006 report using data from the Canadian Community Health Survey (CCHS)(Patten et al., 2006), were 12.8%, 4.8% and 1.8%, for lifetime, past year and past 30 day major depression, respectively. In addition to replicating other findings common in the literature (e.g. females had higher rates of depression than males), the report also highlighted the prevalence of depression amongst those with a chronic medical condition, including diabetes.

1.31 Depression and diabetes

Anderson(Anderson, Freedland, Clouse, & Lustman, 2001) and colleagues estimated the prevalence of comorbid depression and diabetes as 2-fold greater compared to the general population in their review of the literature. A number of studies on the association have since been conducted, including 2 more recent meta-analyses(Ali, Stone, Peters, Davies, & Khunti, 2006; Knol et al., 2006). Ali(Ali et al., 2006) documented the association between type-2 diabetes and depression, resulting in significant increased odds (Pooled ORs: 1.6, 95%CI 1.2-2.0) for depression in those with diabetes compared to those without, while Knol(Knol et al., 2006) found a pooled OR = 1.37 (95%CI 1.14-1.63) for risk of T2DM in those with depression compared to those without the disorder. While some studies have suggested the association to be causal, with depression as a risk factor for incident diabetes(Anne, 2007), the association today is generally believed to be bi-directional(Golden et al., 2008; Patrick J. Lustman & Clouse, 2007; Mezuk, Eaton, Albrecht, & Golden, 2008). In any case, comorbid depression presents very specific challenges for

those with diabetes. For example, Ciechanowski(Ciechanowski, Katon, & Russo, 2000) found that depression decreased diabetes regimen adherence (dietary and medication adherence), found that individuals had higher levels of functional disability, and significantly increased overall primary and ambulatory costs. Other studies have linked depression with poor glycemic control(P J Lustman et al., 2000), the development of both micro and macro-vascular complications(Lin et al., 2010), and higher overall health care use and expenditure for those affected(Egede, Zheng, & Simpson, 2002). In addition, studies have identified patients with comorbid depression and diabetes as having higher mortality rates than those without. A study by Katon(W. J. Katon et al., 2005) determined that both minor and major depression were significant predictors of mortality in patients with type-2 diabetes. The same authors then published a follow-up, linking comorbid diabetes/depression with an increased risk of all-cause mortality over a 2-year period(W. Katon et al., 2008). Similarly, results from the Fremantle Diabetes Study(Bruce, Davis, Starkstein, & Davis, 2005) found an increased risk of mortality for those with depression, although this risk was attenuated when including micro and macro-vascular complications in the model. Still, given that depression impacts on the development and severity of diabetes complications, its presence can be especially dangerous in this population. One self-care behaviour in diabetes regimens that may be negatively impacted by depression is smoking cessation, given the strong association between cigarette smoking and depression.

1.32 Depression and Smoking

While smoking is a common behaviour worldwide, it is particularly prevalent among those with mental disorders(Ziedonis et al., 2008). In fact, those with a mental illness are 2-3 times as likely to be smokers than those without(Annette K. McClave, McKnight-Eily, Davis, & Dube, 2010). Furthermore, they are also more likely to be heavier smokers, and subsequently experience increased illness morbidity and increased mortality compared to smokers without mental illness(Lawrence et al., 2009). Depression has

been a major research focus, and has been shown to be heavily linked with smoking, in a dose-dependent manner. Similar to depression and diabetes, some studies seem to point to smoking leading to incidence of depression(Boden, Fergusson, & Horwood, 2010; Pasco et al., 2008), including increasing levels of smoking being prospectively related to major depression(Flensborg-Madsen et al., 2011; Klungsoyr, NygÃrd, Sorensen, & Sandanger, 2006), with others reporting a bi-directional association(Chaiton, Cohen, O'Loughlin, & Rehm, 2009; Leung, Gartner, Hall, Lucke, & Dobson, 2012). Higher levels of smoking, and particularly nicotine dependence, also seem to be associated with worse depressive symptoms(Jamal, Willem Van der Does, Cuijpers, & Penninx), but once again, this finding appears to be reciprocated as high depressive symptoms are similarly related to increased tobacco smoking(Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Chaiton et al., 2009).

Though the etiology remains unclear, some possible explanations include common underlying shared vulnerabilities, such as genetics(Kendler, Neale, MacLean, Heath, & et al., 1993). Other possible explanations include the anti-depressant like effects of nicotine(Laje, Berman, & Glassman, 2001; Mineur & Picciotto, 2010), or the self-medication hypothesis (including self-efficacy and affect regulation)(Chaiton, Cohen, O'Loughlin, & Rehm, 2010; Minnix, Blalock, Marani, Prokhorov, & Cinciripini, 2011; Morrell, Cohen, & McChargue, 2010). Also unclear is the relationship between depression and smoking cessation. While some studies have found depression to negatively impact on cessation attempts(Fond et al., 2013; Glassman et al., 1990), others find that cessation may precipitate depression(Glassman, Covey, Stetner, & Rivelli, 2001); still others find there to be no association(Hitsman, Borrelli, McChargue, Spring, & Niaura, 2003).

1.4 Smoking and Depression in Diabetes: Previous research

Given the important associations between these 3 variables, a few studies have attempted to report on associations of all 3 variables simultaneously. For example, Haire-Joshu(Debra Haire-Joshu, Heady,

Thomas, Schechtman, & Fisher, 1994) found that depression was more prevalent in diabetic smokers than non-smokers, and that increasing cigarette consumption was independently associated with cognitive symptoms of depression, using a small clinical sample. More recently, larger studies assessing the relationship between chronic illness and depression(Egede, 2007; Gunn et al., 2012), as well as those specifically in those with diabetes(Egede & Zheng, 2003; W. Katon et al., 2004), have identified smoking as being strongly associated with depression in fully adjusted models. Unfortunately, beyond incorporating smoking as a binary variable amongst other lifestyle related characteristics, possible implications of this finding have been largely ignored. One study conducted by Solberg(Solberg, Desai, O'Connor, Bishop, & Devlin, 2004), compared smokers vs. non-smokers in an adult sample with diabetes by sampling adult health plan members. They found smokers to be more likely to report fair/poor self-rated health, to feel depressed, as well as to report being less likely to check the blood-glucose levels and less physically active. Here again, however, the authors simply dichotomized smoking behaviour (never vs. current).

1.41 Limitations and justification

Previous research highlights important differences across not only never and current smoking, but when comparing never/former, light/heavy and when looking at all categories simultaneously(Bondy et al., 2013; Fagan & Rigotti, 2009; Husten, 2009). Thus one major limitation to address is the treatment of the smoking status in previous studies conducted in those with diabetes. Using more descriptive categories adapted from the Canadian Tobacco Use Monitoring Survey(Health Canada, 2010) across both current smokers and cessation outcomes will allow us to look at meaningful differences in this heterogeneous behaviour. Similarly, many outcomes, including health problems, disease complications and disability, are common to both smoking and depression in people with diabetes. It is therefore important to assess the independent association of smoking and depression by carefully controlling for these potentially

confounding factors in order to gain a clear picture of the situation. By assessing the association between smoking and depression in a community sample with type-2 diabetes, and controlling for important demographic and clinical characteristics, we will be able to better understand the strength of this relationship. Smoking may importantly impact mental as well as physical health, an important consideration when developing interventions and treatment guidelines for diabetes. Moreover, depression may play a crucial role in determining not only the degree of an individual's smoking behaviour, but also in an individual's ability to attempt and ultimately successfully quit. It is therefore crucial to investigate the relationship between smoking, cessation and depression in this cohort with type-2 diabetes. This can provide a better theoretical framework in order for both researchers and clinicians to better provide integrated care across domains and ultimately benefit this at risk population.

1.42 Study Objectives

The objectives of the current study are the following: 1) To identify the sociodemographic, health and illness related characteristics of our sample, across smoking behaviour, categorized as never, former, light (<10 cigarettes per day) and moderate-heavy (11+ cigarettes per day) smokers; 2) To identify the association between smoking and depression within the sample, the stability of these 2 variables and their longitudinal associations while controlling for sociodemographic, health and illness related characteristics, as well as baseline levels of depression (longitudinal model); 3) To characterize our study sample according to their cessation status, categorized as successful quitters, unsuccessful quitters and non-attempters, across sociodemographic, health and illness related characteristics; 4) To identify those more likely to make quit attempts, those who were able to quit and those who relapsed according to both smoking cessation status and smoking status (light vs. heavy); 5) Finally, to ascertain the relationship between depression and smoking cessation status within our sample, while controlling for sociodemographic and illness related characteristi

Chapter 2 – Manuscript 1

Title: **The association between smoking and depression in a Canadian community- based sample with type-2 diabetes**

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Running title: Smoking, depression and diabetes

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2.1 ABSTRACT

Objective: To investigate the association between depression and smoking status within a community-based sample with type-2 diabetes, while controlling for socio-demographic, diabetes related characteristics and complications, disability, other chronic illness and other health-related variables.

Method: 1868 adults with type-2 diabetes were recruited via random digit dialing for the Montreal Health and Well Being Study (DHS). Smoking was classified as never, former, light (≤10 cigarettes a day) and heavy (11+ cigarettes a day). Depression was assessed using the Patient Health Questionnaire-9 and individuals were classified as no major depression vs. major depression syndrome. Logistic regression was used to test the association between major depression and smoking status, while controlling for other demographic and health related variables.

Results: Major depression was associated with an increased likelihood of being a light or heavy smoker, having 2 or more diabetes complications, moderate-severe disability, and having 2 or more other chronic illnesses. In the fully adjusted model, having major depression was associated with an increased likelihood of being a heavy smoker (OR = 2.62, 95% CI 1.43 – 4.81). The association between light smoking and major depression was not significant when adjusting for confounding variables.

Conclusions: Smoking and depression are strongly associated in patients with type-2 diabetes, and this association appears to be strongest for moderate/heavy smokers. This finding has important clinical implications given that smoking cessation is an important health recommendation, and potentially means depression status may be an important consideration when targeting clients with diabetes who continue to smoke.

2.12 INTRODUCTION

Diabetes is a progressive chronic illness currently affecting approximately 8% of Canadians(Canadian Diabetes Association, 2009), and its progression can lead to the development of both micro- and macro-vascular complications(Fowler, 2008). Two factors associated with diabetes are tobacco smoking and depression(Anderson, Freedland, Clouse, & Lustman, 2001; Eliasson, 2003). Studies in the general population find a consistent and strong bidirectional association between depression and smoking(Berlin, Covey, & Glassman, 2009); therefore, exploring these elements is important within this population, given both are linked with adverse outcomes in people with diabetes. Both smoking and depression are associated with acceleration of diabetes related complications(de Groot, Anderson, Freedland, Clouse, & Lustman, 2001; Eliasson, 2003), poor glycemic control(Fagard & Nilsson, 2009; Lustman et al., 2000) and overall increased risk of morbidity and mortality(Bruce, Davis, Starkstein, & Davis, 2005; Chaturvedi, Stevens, Fuller, & The World Health Organization Multinational Study, 1997). Furthermore, smoking cessation is a key goal in diabetes self-care guidelines, and depression has been linked with poor adherence to self-care regimens in people with diabetes(Ciechanowski, Katon, & Russo, 2000). Given the similar outcomes shared between smoking and depression, it is not surprising that previous studies often find a significant association between smoking and depression in people with diabetes; however these studies have several limitations. Many studies treat smoking as a binary variable(Engum, Mykletun, Midthjell, Holen, & Dahl, 2005; Katon et al., 2004), and thus may be missing crucial information with regards to this complex behaviour. One previous study was based on small clinical samples and may therefore not be generalizable(Haire-Joshu, Heady, Thomas, Schechtman, & Fisher, 1994); finally, a more recent study(Egede & Zheng, 2003) failed to control for potentially confounding factors related to the presence of diabetes. Therefore, in order to address these limitations, the current study aims to investigate the associations between multiple levels of smoking and depression in a community based sample of people with diabetes. The specific objectives of the

current study were to (1) report on prevalence and associations of smoking across socio-demographic, lifestyle and disease related factors and (2) determine whether smoking status was independently associated with major depression when controlling for a variety of potential confounding variables, using a community based sample with type-2 diabetes.

2.13 METHODS

This study is based on data from the Diabetes Health and Well Being Study (DHS); a population based telephone survey of the non-institutionalized adult population in Quebec, Canada. Participants were recruited between January and April 2008 through random selection of listed phone numbers in Quebec by a recognized polling firm, Bureau d'Intervieweurs Professionnels (Montreal, Quebec, Canada). Inclusion criteria were being aged 18 to 80 years of age, have a diagnosis of diabetes determined by a physician and the ability to respond to the interview in French or English. For those eligible for the study, we had a response rate of 62%. For the purpose of this report, only those with type-2 diabetes (n = 1868) were included in the analysis. The protocol was approved by the Research Ethics Committee of the Douglas Mental Health University Institute. All subjects voluntarily participated in the study and informed consent was obtained from each participant. Participants received a 20 CAD incentive. More details on the study have been published elsewhere (Schmitz et al., 2011).

Smoking

Smoking was assessed using questions from the Canadian Community Health Survey (Statistics Canada, 2009). Participants were asked if they had smoked 100 cigarettes in their lifetime, and were classified as never smokers (no) or ever smokers (yes). Ever smokers were then asked the follow-up question "At the present time, do you smoke cigarettes?". Those who answered no were classified as former smokers. Those who answered 'Occasionally' were asked to estimate the number of cigarettes they smoked per week. Those answering "daily" were asked to estimate the number of cigarettes per day (CPD). We

classified those who were occasional smokers and those who smoked ≤ 10 CPD as light smokers; those who smoked ≥ 11 CPD were classified as moderate/heavy smokers. Self-reported measures of smoking have been shown to be reliable estimates for current smokers(Kurt Kroenke, 2003); although there is no consensus for classifying light and heavy smokers(Fagan & Rigotti, 2009), in general rates of 5 – 15 CPD are commonly seen across studies. The cut-off and labels were chosen to be consistent with those used by Health Canada for the Canadian Tobacco Use Monitoring Survey(CTUMS) (Health Canada, 2010) and verified within our sample using sensitivity analysis. Sensitivity analyses were also conducted in order to determine if there were any differences between occasional and light daily smokers using different cut-offs for smoking categorisation; there were no significant differences.

Depression

Depression at baseline was assessed using the Patient Health Questionnaire (PHQ-9) (K. Kroenke, Spitzer, & Williams, 2001). The PHQ-9 is a highly sensitive screening tool, and provides a diagnosis of major depression according to Diagnostic and Statistical Manual, 4th Edition (DSM-IV) criteria as well as a continuous severity score. To be categorized as 'major depression' we used a scoring algorithm for the PHQ-9 that uses the criteria for *major depression disorder* (MDD) required the patient to have, for at least 2 weeks, five or more depressive symptoms present for more than half of the days (a score of 2 on the PHQ-9 item) with at least one of these symptoms being either depressed mood or anhedonia.

Socio-demographic and health related questions

The DHS collected data on socio-demographic characteristics: age at baseline, sex and marital status (married/common-law, single, divorced/separated/widowed), education level (less than high school graduation, high school graduation, post high school) and employment status (working full time or part time, retired, not working).

Lifestyle variables were assessed by questions from the Canadian Community Health Survey(Statistics Canada, 2009). Physical activity levels were measured by asking participants to rate the number of days they exercised or participated in sports activity for at least 15 minutes in the previous month. The response was collapsed into three categories: inactive (0 days), moderately active (1 to 12 days) and active (more than 12 days). Alcohol consumption was assessed from the first item of the Alcohol Use Disorders Identification Test (AUDIT): 'How often do you have a drink containing alcohol?'(Bush et al., 1998). Answers were categorized into never, less than twice a week and two or more times a week.

Disability, chronic illness and diabetes related characteristics and complications

Global disability was assessed using the 12-item version of the World Health Organization Disability Assessment Schedule II (WHO-DAS-II) which consists of both physical and non-physical dimensions (mobility, understanding and communication, interpersonal relations, etc), has been confirmed as a reliable and valid measure of global disability (Chwastiak & Von Korff, 2003) and has been validated and used in diabetes epidemiological studies (Von Korff et al., 2005). Based on available normative data, we classified a WHO-DAS-II score of 45 or greater as indicating substantial disability (Von Korff et al., 2005).

Diabetes complications were assessed using the Diabetes Complications Index (DCI) (Fincke et al., 2005). The DCI is a 17-item survey that assesses diabetes complications on the basis of patient self-report (retinopathy, neuropathy, large-vessel atherosclerotic disease, peripheral vascular disease, cerebrovascular disease and foot problems). A summary variable was computed counting the number of complications. Number of chronic conditions was assessed by asking participants whether they suffered from various health conditions diagnosed by a health professional at the time of the interview (asthma, high blood pressure, heart disease, stomach or intestinal ulcers, arthritis / rheumatism, migraine headaches, cancer, kidney disease, and back problems). Chronic conditions were summarized into 0 to 8 chronic conditions and categorized into 0, 1 or 2 and more chronic conditions. Duration of diabetes was

calculated in years based on the age at which participants were first diagnosed with diabetes. The duration was categorized into less than one year, one to 4.9 years and 5 or more years. Participants' treatment regimen was assessed by asking participants if they took insulin or if they took pills to control their diabetes in the past month.

Analyses

Data were analyzed using IBM SPSS Statistics 20 software version 20.0. Frequency tables and Chi-Square analyses were performed to test associations between categorical variables and smoking status. Binomial logistic regressions were performed to study the association between major depression syndrome (MDD vs. No MDD) as the dependent variable, and current smoking status as the independent variable of interest. Regression was performed in block entry in the following order: Block 1 – Smoking status; Block 2 – Socio-demographic variables; Block 3 – Diabetes and health related characteristics. In each block, all variables from the previous block were kept into the model.

2.14 RESULTS

In the present study, lifetime prevalence of smoking within the sample was 62.9%; current smoking prevalence of the population was 20.5%; among those currently smoking, 62.4% were moderate/heavy smokers.

Table 1 presents the socio-demographic variables and smoking status. Those in the 18 to 49 age bracket were more likely to be current smokers, while those 65 to 80 were more likely to be never smokers. Females were more likely to be never smokers (44.6% vs. 28.6%), while men were most likely to be former smokers (49.4% vs. 35.1%). Amongst those currently who were currently smoking, there was no difference between men and women. In the sample, moderate/heavy smokers were more likely to be single and be unemployed, and less likely to have achieved higher education.

Major depression, disability, diabetes related characteristics and complications, other chronic illness, physical activity level and alcohol use information is displayed in Table 2. Major depression status, diabetes complications, alcohol use and physical activity were all significantly different across smoking categories. Those with major depression were more likely to be smokers (17.5%); this finding was strongest in the moderate/heavy category, with 30.5% of moderate/heavy smokers having major depression compared to 12.1% of light smokers. Never smokers were more likely to have no diabetes complications (34.3%), while moderate/heavy smokers were more likely to have 2 or more complications (14.8%). Univariate analysis of variance was conducted using the PHQ-9 continuous severity score as the dependent variable, controlling for socio-demographic factors ($F_{3,1817} = 7.90$, $p < 0.001$). Smokers had significantly higher mean scores as compared to never smokers and former smokers; moderate/heavy smokers had higher mean scores compared to light smokers, but this difference was not statistically significant ($p = 0.267$). Finally, we tested for interaction effects between smoking and all covariates, there were no significant interaction effects.

Finally, table 3 displays results from the logistic regressions. Moderate/heavy smoking was significantly associated with major depression in all models; light smoking was only significantly associated in the first model, and this association did not remain significant after controlling for socio-demographic variables. In the fully-adjusted model, smoking status, number of diabetes complications, disability, number of chronic conditions and age were all significantly associated with major depression. Additionally, although not reported in table 3, for sensitivity purposes we entered the number of cigarettes smoked per day as a continuous variable; results remained significant in the fully adjusted model (OR = 1.034 (1.014-1.053), $p < 0.001$).

2.15 DISCUSSION

In the present Canadian community based study in people with type-2 diabetes, heavy smokers were over twice as likely to have major depression compared to never smokers. This association remained significant even when controlling for socio-demographic characteristics, diabetes characteristics and complications, disability, other chronic illness, alcohol use and physical activity. Our study adds to existing literature by demonstrating that a) smoking is strongly associated with major depression; b) this association remains robust even after controlling for both general and disease specific risk factors for depression; and c) this association is especially important for daily moderate/heavy smokers.

Studies in the general population have found a dose-dependent relationship between smoking and depression (Boden, Fergusson, & Horwood, 2010; Chaiton, Cohen, O'Loughlin, & Rehm, 2010; Flensborg-Madsen et al., 2011). Although light smoking was not associated with major depression in our adjusted models, given any level of smoking can be detrimental to health, our results simply highlight the impact of moderate/heavy smoking. To remain consistent with currently available literature and in order to make interpreting our results easier, we categorized smoking in accordance with the CTUMS(Health Canada, 2010).Additionally, the results of our sensitivity analyses suggest that our results remain robust even when using different cut-offs for light and moderate/heavy smokers, suggesting in all tested models that moderate/heavier smokers are significantly different compared to light smokers regardless of the cut-offs used. We found a 2.62-fold increased odds of major depression for moderate/heavy smokers, which is similar to other studies within the general population(Hämäläinen et al., 2001; Pasco et al., 2008), and can be considered especially robust considering the number of confounders controlled for in the regression model.

According to the recent Health Canada report on tobacco use, the prevalence of smoking in Quebec was 20.1% in 2006(Health Canada, 2010). The prevalence of current smoking reported in our sample is

20.5%. Given that smoking cessation is an important recommendation and self-care behaviour for people with diabetes, targeting persistent smokers remains an important goal. This specific population is already at increased risk of disability, morbidity and mortality, and so our reported prevalence remains substantially high. These results suggest that current public health initiatives and programs for smoking cessation are not optimal for people with diabetes. People with diabetes might have more problems with smoking cessation than people without diabetes due to the physical and emotional burden associated with diabetes. Additionally, they might continue smoking in order to cope with their condition or as a reaction to diabetes related stress. These factors should be taken into account when developing smoking cessation programs in diabetes. Those who continue to smoke despite strong guidelines advising against continuation need to be assessed, as they may differ on key variables compared to never smokers and successful quitters. One study(Solberg, Desai, O'Connor, Bishop, & Devlin, 2004) conducted via questionnaires sent to health plan members with diabetes showed that smokers as compared to non-smokers reported feeling depressed more often and were less likely to adhere to self-care behaviours such as blood-glucose monitoring and regular diabetes complications check-ups, even when controlling for depression. Similarly, another study (Weinberger, George, & McKee, 2010) found that smokers with a history of major depression endorsed more positive beliefs about smoking compared to those without a history of major depression. In a previous study, we used latent analysis to identify groups of smokers amongst people with type-2 diabetes (Gariepy et al., 2012). We found 3 distinct groups that displayed different demographic and clinical characteristics, who may benefit from different interventions to aid in cessation.

Regardless, cessation strategies that neglect to account for comorbid depression, even those targeted to patients with diabetes, may have limited success. New intervention strategies might take a similar stance as those who treat co-morbid substance abuse and mental disorders when devising interventions. In this approach, the issue of which problem developed first and thus what is considered

the primary condition is irrelevant. Instead treatment is integrated across domains so that assessments focus on how each problem/illness affects the presentation and characteristics of the other. Studies in the UK(Davies et al., 2008) and the U.S.(MacAller, Brown, Black, & Greenwood, 2011) have found that immediate education for newly diagnosed type-2 diabetes patients, as well as promoting smoking intervention resources amongst diabetes educators can lead to some gains in cessation. Finally, from the point of view of clinicians, offering advice and strategies for smoking cessation in this population can be difficult. Smoking cessation has been linked with weight gain (Yeh, Duncan, Schmidt, Wang, & Brancati, 2010), and clinicians may be reluctant to push cessation when in the presence of co-morbid mood disorders. However, both weight gain and worsened mood are short-term consequences and are far outweighed by the long-term gain of patients (Sherman, 2005).

Smoking and depression may also be linked through disability in people with type 2 diabetes. A previous report using data from the Canadian Community Health Survey (Schmitz, Kruse, & Kugler, 2007), found that smoking was associated with elevated disability and disability days in subjects with a variety of chronic conditions. Although disability and other chronic conditions were significantly associated with major depression in our fully adjusted model, smoking remained a significant independent predictor of major depression when controlling for these variables. Smoking might be directly associated with depression in people with diabetes or indirectly through functioning and disability. Conversely, depression has been linked with poorer self-care behaviours in people with diabetes(Ciechanowski et al., 2000; Lin et al., 2004), and in the general population, specifically with troubles initiating and maintaining smoking cessation(Berlin et al., 2009; Glassman, Covey, Stetner, & Rivelli, 2001). Thus this association in people with diabetes may be mediated through a bi-directional pathway, in which depression maintains smoking behaviour, which leads to increases in disability and disease related complications, further increasing burden and feeding back into depression. Given that we controlled for

disability and our model remained significant, more research into these potential pathways should be pursued.

There are several limitations to the current study. Firstly, the data are cross-sectional and therefore causality and directionality of relationships cannot be inferred. Due to the nature and design of the study, a number of potentially important clinical characteristics could not be assessed, including lifetime history of major depression, smoking variables such as life years spent smoking, time since quitting and assessment of nicotine dependence. The data, including diabetes related characteristics and complications, were self-reported and were not validated via clinical assessment; depression was assessed via a symptom screening tool and not through a structured clinical interview which may have over-estimated the prevalence of major depression in our study. . Despite these limitations, our study also had a number of strong points. We used a population-based design to capture a representative sample of the population with diabetes. We collected information on a large sample of people with type-2 diabetes. Finally, we controlled for a large number of potential confounders in our analysis that may have biased the estimated association between smoking and depression in previous studies.

Smoking is a leading cause and also one of the largest modifiable health behaviours associated with disability, morbidity and mortality in the world. It has been associated with the development and maintenance of depression, and also with the worsening of diabetes related complications. Our results indicate that smoking, even when controlling for known associations, is associated with major depression in a population already at increased risk. Clinical implications of this association include further development of smoking cessation guidelines for those with diabetes; conversely, the co-presence of major depression might negatively impact current cessation interventions and therefore becomes an important assessment consideration in this population. Future research should look at

longitudinal data on individuals who are smokers and attempt to better understand the progression to both depression and diabetes.

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2.16 REFERENCES

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The Prevalence of Comorbid Depression in Adults With Diabetes. *Diabetes Care, 24*(6), 1069-1078.

Berlin, I., Covey, L. S., & Glassman, A. H. (2009). Smoking and Depression: A Co-morbidity. [Article]. *Journal of Dual Diagnosis, 5*(2), 149-158. doi: 10.1080/15504260902870129

Boden, J. M., Fergusson, D. M., & Horwood, L. J. (2010). Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. *The British Journal of Psychiatry, 196*(6), 440-446.

Bruce, D., Davis, W., Starkstein, S., & Davis, T. (2005). A prospective study of depression and mortality in patients with type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia, 48*(12), 2532-2539-2539. doi: 10.1007/s00125-005-0024-3

Bush, K., Kivlahan, D. R., McDonell, M. B., Fihn, S. D., Bradley, K. A., & for the Ambulatory Care Quality Improvement Project. (1998). The AUDIT Alcohol Consumption Questions (AUDIT-C): An Effective Brief Screening Test for Problem Drinking. *Arch Intern Med, 158*(16), 1789-1795. doi: 10.1001/archinte.158.16.1789

Canadian Diabetes Association. (2009). An Economic Tsunami: The Cost of Diabetes in Canada Retrieved 2012-03-26, from http://www.diabetes.ca/advocacy/reports-and-information/federal-provincial-cost-model-reports/

Chaiton, M., Cohen, J., O'Loughlin, J., & Rehm, J. (2010). Use of cigarettes to improve affect and depressive symptoms in a longitudinal study of adolescents. *Addictive Behaviors, 35*(12), 1054-1060.

Chaturvedi, N., Stevens, L., Fuller, J. H., & The World Health Organization Multinational Study, G. (1997). Which Features of Smoking Determine Mortality Risk in Former Cigarette Smokers With Diabetes? The World Health Organization Multinational Study Group. *Diabetes Care, 20*(8), 1266-1272.

Chwastiak, L. A., & Von Korff, M. (2003). Disability in depression and back pain: Evaluation of the World Health Organization Disability Assessment Schedule (WHO DAS II) in a primary care setting. *Journal of Clinical Epidemiology, 56*(6), 507-514.

Ciechanowski, P. S., Katon, W. J., & Russo, J. E. (2000). Depression and Diabetes: Impact of Depressive Symptoms on Adherence, Function, and Costs. *Arch Intern Med, 160*(21), 3278-3285. doi: 10.1001/archinte.160.21.3278

Davies, M. J., Heller, S., Skinner, T. C., Campbell, M. J., Carey, M. E., Cradock, S., . . . Khunti, K. (2008). Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: Cluster randomised controlled trial. *BMJ, 336*(7642), 491-495.

de Groot, M., Anderson, R., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). Association of Depression and Diabetes Complications: A Meta-Analysis. *Psychosomatic Medicine, 63*(4), 619-630.

Egede, L. E., & Zheng, D. (2003). Independent Factors Associated With Major Depressive Disorder in a National Sample of Individuals With Diabetes. *Diabetes Care, 26*(1), 104-111. doi: 10.2337/diacare.26.1.104

Eliasson, B. (2003). Cigarette smoking and diabetes. *Progress in Cardiovascular Diseases, 45*(5), 405-413.

Engum, A., Mykletun, A., Midthjell, K., Holen, A., & Dahl, A. A. (2005). Depression and Diabetes. *Diabetes Care, 28*(8), 1904-1909. doi: 10.2337/diacare.28.8.1904

Fagan, P., & Rigotti, N. A. (2009). Light and intermittent smoking: The road less traveled. *Nicotine & Tobacco Research, 11*(2), 107-110. doi: 10.1093/ntr/ntn015

Fagard, R. H., & Nilsson, P. M. (2009). Smoking and diabetes—The double health hazard! *Primary Care Diabetes, 3*(4), 205-209. doi: 10.1016/j.pcd.2009.09.003

Fincke, B. G., Clark, J. A., Linzer, M., Spiro, A., III, Miller, D. R., Lee, A., & Kazis, L. E. (2005). Assessment of Long-term Complications due to Type 2 Diabetes Using Patient Self-report: The Diabetes Complications Index. *The Journal of Ambulatory Care Management, 28*(3), 262-273.

Flensborg-Madsen, T., Bay von Scholten, M., Flachs, E. M., Mortensen, E. L., Prescott, E., & Tolstrup, J. S. (2011). Tobacco smoking as a risk factor for depression. A 26-year population-based follow-up study. *Journal of Psychiatric Research, 45*(2), 143-149.

Fowler, M. J. (2008). Microvascular and Macrovascular Complications of Diabetes. *Clinical Diabetes, 26*(2), 77-82. doi: 10.2337/diaclin.26.2.77

Gariepy, G., Malla, A., Wang, J., Messier, L., Strychar, I., Lesage, A., & Schmitz, N. (2012). Types of smokers in a community sample of individuals with Type 2 diabetes: a latent class analysis. *Diabetic Medicine, 29*(5), 586-592. doi: 10.1111/j.1464-5491.2011.03493.x

Glassman, A. H., Covey, L. S., Stetner, F., & Rivelli, S. (2001). Smoking cessation and the course of major depression: a follow-up study. *The Lancet, 357*(9272), 1929-1932.

Haire-Joshu, D., Heady, S., Thomas, L., Schechtman, K., & Fisher, E. B. (1994). Depressive symptomatology and smoking among persons with diabetes. *Research in Nursing & Health, 17*(4), 273-282. doi: 10.1002/nur.4770170406

Hämäläinen, J., Kaprio, J., Isometsä, E., Heikkinen, M., Poikolainen, K., Lindeman, S., & Aro, H. (2001). Cigarette smoking, alcohol intoxication and major depressive episode in a representative population sample. *Journal of Epidemiology and Community Health, 55*(8), 573-576. doi: 10.1136/jech.55.8.573

Health Canada. (2010). *Canadian Tobacco Use Monitoring Survey*. Ottawa, Ontario: Retrieved from http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/_ctums-esutc_prevalence/prevalence-eng.php#annual_06.

Katon, W., Von Korff, M., Ciechanowski, P., Russo, J., Lin, E., Simon, G., . . . Young, B. (2004). Behavioral and Clinical Factors Associated With Depression Among Individuals With Diabetes. *Diabetes Care, 27*(4), 914-920. doi: 10.2337/diacare.27.4.914

Kroenke, K. (2003). Patients presenting with somatic complaints: epidemiology, psychiatric co-morbidity and management. *International Journal of Methods in Psychiatric Research, 12*(1), 34-43. doi: 10.1002/mpr.140

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9 - Validity of a brief depression severity measure. [Article]. *Journal of General Internal Medicine, 16*(9), 606-613.

Lin, E. H. B., Katon, W., Von Korff, M., Rutter, C., Simon, G. E., Oliver, M., . . . Young, B. (2004). Relationship of Depression and Diabetes Self-Care, Medication Adherence, and Preventive Care. *Diabetes Care, 27*(9), 2154-2160. doi: 10.2337/diacare.27.9.2154

Lustman, P. J., Anderson, R. J., Freedland, K. E., de Groot, M., Carney, R. M., & Clouse, R. E. (2000). Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care, 23*(7), 934-942. doi: 10.2337/diacare.23.7.934

MacAller, T., Brown, M., Black, K., & Greenwood, D. (2011). Collaborating With Diabetes Educators to Promote Smoking Cessation for People With Diabetes. *The Diabetes Educator, 37*(5), 625-632. doi: 10.1177/0145721711416010

Pasco, J. A., Williams, L. J., Jacka, F. N., Ng, F., Henry, M. J., Nicholson, G. C., . . . Berk, M. (2008). Tobacco smoking as a risk factor for major depressive disorder: population-based study. *The British Journal of Psychiatry, 193*(4), 322-326. doi: 10.1192/bjp.bp.107.046706

Schmitz, N., Kruse, J., & Kugler, J. (2007). Smoking and its Association with Disability in Chronic Conditions: Results from the Canadian Community and Health Survey 2.1. *Nicotine & Tobacco Research, 9*(9), 959-964. doi: 10.1080/14622200701540846

Schmitz, N., Messier, L., Nitka, D., Ivanova, A., Gariepy, G., Wang, J., . . . Strychar, I. (2011). Factors Associated with Disability and Depressive Symptoms Among Individuals with Diabetes: A Community Study in Quebec. *Psychosomatics, 52*(2), 167-177. doi: 10.1016/j.psym.2010.11.020

Sherman, J. J. (2005). The Impact of Smoking and Quitting Smoking on Patients With Diabetes. *Diabetes Spectrum, 18*(4), 202-208. doi: 10.2337/diaspect.18.4.202

Solberg, L. I., Desai, J. R., O'Connor, P. J., Bishop, D. B., & Devlin, H. M. (2004). Diabetic Patients Who Smoke: Are They Different? *Ann Fam Med, 2*(1), 26-32. doi: 10.1370/afm.36

Statistics Canada. (2009). *Canadian Community Health Survey 2.1*. Ottawa, Ontario: Retrieved from http://www23.statcan.gc.ca:81/imdb/p2SV.pl?Function=getSurvey&SDDS=3226&lang=en&db=imdb&adm=8&dis=2#b8.

Von Korff, M., Katon, W., Lin, E. H. B., Simon, G., Ludman, E., Ciechanowski, P., . . . Bush, T. (2005). Potentially modifiable factors associated with disability among people with diabetes. [Article]. *Psychosomatic Medicine, 67*(2), 233-240. doi: 10.1097/01.psy.0000155662.82621.50

Weinberger, A. H., George, T. P., & McKee, S. A. (2010). Differences in smoking expectancies in smokers with and without a history of major depression. *Addictive Behaviors, 36*(4), 434-437.

Yeh, H.-C., Duncan, B. B., Schmidt, M. I., Wang, N.-Y., & Brancati, F. L. (2010). Smoking, Smoking Cessation, and Risk for Type 2 Diabetes Mellitus. *Annals of Internal Medicine, 152*(1), 10-17. doi: 10.1059/0003-4819-152-1-201001050-00005

2.17 Table 1

Table 1 - Socio-demographic characteristics	Never Smoker (n=688)	Former smoker (n=794)	Current Smokers		
			All (n=383)	Light (n=141)	Heavy (n=238)
Age					
18-49 (n=324)	110 (16.0)	107 (13.5)	107 (27.9)	64 (27.0)	43 (29.0)
50-64 (n=837)	288 (41.9)	366 (46.1)	185 (48.3)	106 (48.2)	79 (48.3)
65-80 (n=700)	290 (42.2)	321 (40.4)	91 (23.8)	54 (24.8)	37 (22.7)
Sex					
Female (n=1021)	457 (66.4)	360 (45.3)	208 (54.3)	130 (58.9)	78 (50.8)
Marital Status					
Married/Partner (n=1153)	419 (61.2)	538 (67.8)	192 (51.7)	124 (53.2)	74 (50.8)
Widowed/divorced/separated (n=482)	191 (27.9)	179 (22.6)	114 (29.8)	66 (29.8)	48 (29.4)
Single (n=222)	75 (10.9)	76 (9.6)	71 (18.5)	34 (17.0)	37 (19.7)
Education level					
Less than high school (n=796)	289 (42.7)	325 (41.6)	185 (48.9)	102 (45.7)	83 (50.4)
Secondary school graduation (n=520)	189 (27.9)	221 (28.3)	111 (29.4)	65 (29.0)	46 (29.7)
Some post-secondary (n=517)	199 (29.4)	236 (30.2)	82 (21.7)	53 (25.4)	29 (19.9)
Employment status					
Not Working (n=345)	125 (18.2)	113 (14.2)	109 (28.6)	51 (22.9)	58 (31.6)
Working (n=626)	217 (31.5)	262 (33.0)	147 (38.6)	96 (43.6)	51 (36.3)
Retired (n=887)	346 (50.3)	418 (52.7)	125 (32.8)	76 (33.6)	49 (32.1)
Note: Values are frequencies with percentages, n (%)					

2.18 Table 2

Table 2 – Depression, disease and health related characteristics					
			Smoking Status		
Category	Never	Former	All	Light	Heavy
Major Depression (PHQ-9)***					
No major depression (n=1687)	93.1	93.7	82.5	85.8	80.3
Major Depression (n=163)	6.9	6.3	17.5	14.2	19.7
PHQ-9 Score***					
Mean (s.d.)	4.7 (5.0)	4.8 (4.9)	6.7 (6.4)	6.3 (6.1)	7.0 (6.5)
Diabetes Duration					
Less than 1 year (n=76)	3.8	3.8	5.3	5.0	5.5
1 to 4.9 years (n=526)	26.5	28.1	33.1	34.3	32.3
5 or more years (n=1239)	69.6	68.1	61.6	60.7	62.1
Diabetes Treatment**					
None (n=143)	7.1	6.7	10.7	12.1	10.1
Pills (n=1279)	69.4	69.8	66.5	56.4	71.8
Insulin (n=434)	23.5	23.5	22.8	31.4	18.1
Diabetes Complications*					
0 complications (n=527)	34.4	28.7	26.0	26.9	25.3
1 complication (n=494)	29.6	27.4	28.0	28.4	28.1
2 or more complications (n=720)	36.0	43.9	46.0	44.8	46.5
WHO-DAS II Disability					
No – Low disability (n=1722)	94.0	92.9	90.6	89.3	91.1
Mild to Substantial disability (n=133)	6.0	17.1	9.4	10.7	8.9
Chronic Conditions					
No Chronic Conditions (n=346)	19.9	17.9	22.1	21.6	22.3
1 Chronic condition (n=479)	27.4	28.1	23.5	23.1	24.1
2 or more chronic conditions (n=952)	52.7	54.0	54.5	55.2	53.6
Alcohol Consumption***					
Never (n=804)	52.3	36.2	43.4	37.1	46.2

Less than twice a week (n=750)	34.4	44.4	43.4	47.1	41.9
More than twice a week (n=295)	13.4	19.4	13.2	15.7	12.0
Physical Activity level***					
Inactive (n=565)	27.1	30.2	40.4	34.8	44.0
Moderately active (n=649)	37.8	35.3	33.4	36.2	31.5
Active (n=599)	35.1	34.5	26.2	29.0	24.6

Note: Chi-square analysis conducted for all categorical variables. Values are percentages.
Major Depression $\chi2(3) = 48.58$; Diabetes Duration $\chi2\ (6) = 7.82$; Diabetes Treatment $\chi2\ (6) = 12.9$; Diabetes Complications $\chi2\ (6) = 17.1$; Disability $\chi2\ (3) = 5.05$; Chronic Conditions $\chi2\ (6) = 11.11$; Alcohol Consumption $\chi2\ (6) = 46.87$; Physical Activity $\chi2\ (6) = 35.55$
* $p < 0.05$; ** $p < 0.01$; ***$p < 0.001$
Univariate Analysis of Variance performed for PHQ-9 Summary Score, controlling for Age, Sex, Marital Status, Education level and Employment.

2.19 Table 3

Table 3 - Association between Major Depression status and Status, Socio-demographic characteristics and diabetes and health characteristics in individuals with diabetes				
		Model 1 COR (95% CI)	Model 2 AOR (95% CI)	Model 3 AOR (95% CI)
Smoking Status (Ref: Never Smoker)	Former Smoker Light Smoker Heavy Smoker	0.90 (0.56 - 1.45) 1.96 (1.00 - 3.84)* 3.20 (1.92 - 5.34) ‡	0.99 (0.61 - 1.63) 1.71 (0.85 - 3.45) 2.58 (1.52 - 4.39) ‡	0.83 (0.47 - 1.46) 1.42 (0.63 - 3.21) 2.62 (1.43 - 4.81) †
Demographics				
Age (*Ref: 18 -49*)	50 - 64 65 - 80		0.68 (0.40 - 1.14) 0.26 (0.13 - 0.54) ‡	0.43 - (0.23 - 0.80) † 0.15 (0.06 - 0.36) ‡
Sex (*Ref: Female*)	Male		0.82 (0.54 - 1.24)	0.86 (0.53 -1.39)
Marital Status (*Ref: Single*)	Widowed/Divorced/ Separated Married / Partner		0.64 (0.37 - 1.10) 0.84 (0.46 - 1.53)	0.74 (0.40 - 1.36) 0.68 (0.34 - 1.35)
Education Level (*Ref: Less than high school*)	High School Diploma More than High School		0.94 (0.60 - 1.46) 0.56 (0.33 - 0.96)*	1.13 (0.68 - 1.88) 0.54 (0.29 - 1.01)
Working Status (*Ref: Unemployed*)	Employed (Full + Part time) Retired		0.35 (0.20 - 0.59)‡ 0.88 (0.51 - 1.52)	0.69 (0.37 - 1.29) 1.48 (0.77 - 2.84)
Diabetes and health characteristics				
Diabetes baseline treatment (Ref: None)	Pills Insulin			0.88 (0.51 - 1.53) 1.19 (0.49 - 2.88)
Diabetes Duration at baseline (Ref: Less than 1 year)	1 - 4.9 years 5 or more years			0.71 (0.25 - 2.11) 0.69 (0.24 - 1.96)
Diabetes Complications (*Ref: 0 complications*)	1 Complication 2 + complications			2.46 (1.04 - 5.79)* 5.12 (2.29 - 11.48) ‡
WHO DAS II Disability Scale (*Ref: No-Low Disability*)	Mild - Substantial Disability			10.58 (6.01 - 18.61) ‡

Number of Chronic Conditions (*Ref: 0*)	1 Chronic condition 2 or more chronic conditions	2.13 (0.81 - 5.65) 3.62 (1.51 - 8.67) †
Alcohol usage (Ref: Never)	< twice a week > twice a week	0.73 (0.44 - 1.20) 0.53 (0.24 - 1.19)
Physical Activity (Ref: Inactive)	Moderately Active Active	0.67 (0.38 - 1.16) 0.82 (0.48 - 1.42)

Note. * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$. WHO-DAS II scores dichotomized into No-Low Disability and Mild-Substantial disability due to skewness; COR = Crude Odds Ratio; AOR = Adjusted Odds Ratio

2.20 Connecting text

In our first manuscript, we demonstrated important sociodemographic, diabetes and health characteristic differences across smokers in a community sample with type-2 diabetes. Importantly, we also established a strong and independent association between moderate-heavy smoking and major depression. Depression is twice as prevalent amongst those with diabetes, and is commonly associated with smoking in previous studies. In our study, we included a robust model, controlling for potentially important sociodemographic, diabetes and health related characteristics that may confound the association between smoking and depression. Our results therefore reflect those found in the general population in a population suffering from a chronic illness, indicating that current cessation interventions may be inadequate for this population. Moreover, given smoking is associated with increased complications, morbidity and mortality in diabetes, that smoking may also negatively impact the mental health of users is an important consideration. By increasing levels of depression, smoking may contribute to the poor outcomes associated with depression and diabetes. The main limitation was that our results were based on cross-sectional analyses. Determining how smoking behaviour evolves over time in this at risk population, and equally investigating any potential longitudinal association between smoking and depression is an important next step. Having established an independent and strong association between smoking and depression, we next investigated smoking's effect on elevated symptoms over time (major and minor depression status combined) in individuals with type-2 diabetes while exploring the stability of this assocation.

Chapter 3 – Manuscript 2

Title: **Assessing the longitudinal associations and stability of smoking and depression syndrome over 4 year period in a community sample with type-2 diabetes**

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Running title: Smoking, Depression and Diabetes

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3.1 ABSTRACT

Objective: To investigate the stability and longitudinal association between depression and smoking status within a community sample with type-2 diabetes, while controlling for socio-demographic and disease related variables.

Method: 1618 adults with type-2 diabetes were recruited and agreed to be followed-up via random digit dialing for the Montreal Diabetes Health Study (DHS). Individuals were classified as never, former, light (≤10 cigarettes a day) and moderate-heavy (11+ cigarettes a day); Depression was assessed using the Patient Health Questionnaire-9 and individuals were classified as none vs. depression syndrome. Generalized Estimating Equations were used to test the association between depression syndrome and current smoking status, while controlling for other demographic and health related variables.

Results: Prevalence rates of smoking and depression showed mild-substantial agreement over time; Depression syndrome was significantly associated with moderate-heavy smoking in the fully adjusted model using cross-sectional (all 4 waves, OR = 1.46, 95% CI 1.08-1.99, $p < 0.05$) and longitudinal (controlling for depression at baseline; OR = 1.54, 95% CI 1.02-2.31, $p < 0.05$) data.

Conclusions: Smoking and depression prevalence rates appear to be stable over time in our community sample with type-2 diabetes. Moderate-heavy smoking is strongly associated with elevated depression, both in cross-sectional and longitudinal models; persistent moderate-heavy smokers may are at increased risk of both physical and mental health complications. This burden is even greater for those with type-2 diabetes.

3.12 INTRODUCTION

Diabetes mellitus is a disease of increasing prevalence projected to reach epidemic proportions worldwide in the near future(Wild, Roglic, Green, Sicree, & King, 2004). Smoking is an important behaviour to consider in people with diabetes, as it has been linked with the progression of complications(Eliasson, 2003), increased morbidity(Fagard & Nilsson, 2009) and mortality(Chaturvedi, Stevens, Fuller, & The World Health Organization Multinational Study, 1997). Smoking is also associated with increased depression(Berlin, Covey, & Glassman, 2009). Given that depression is 2 times as prevalent in those with diabetes compared to those without(Anderson, Freedland, Clouse, & Lustman, 2001), assessing the potential impact of smoking on depression in this population might have important research and clinical implications. Recently(Clyde, Smith, Gariépy, & Schmitz, 2013), we showed that the prevalence of smoking within our community sample with diabetes was comparable to that of the general population, at 20.5% We also reported that moderate-heavy smokers had a greater than 2-fold increased odds of having major depression as compared to never smokers. Our results extended previous investigations which have identified current smoking as being associated with depression amongst people with diabetes(Egede & Zheng, 2003; Katon et al., 2004). Depression itself has been linked with poorer outcomes for those with comorbid type-2 diabetes, including poor regimen adherence, lower overall functioning and increased total health care expenditure(Ciechanowski, Katon, & Russo, 2000). Smoking cessation is already an important self-care recommendation in diabetes, given the adverse physical health consequences it can elicit. That smoking might also lead to poor mental health, and specifically depression, would underline the need for interventions targeting cessation in this population. Unfortunately, our results and others investigating this relationship have been based on cross-sectional analyses, and therefore were unable to make inferences of causality. It is therefore important to investigate this relationship with longitudinal data. Moreover, using longitudinal data would also enable us to characterize the stability of both behaviours over time in this population. Thus,

the current study seeks to: 1) Report the 4 year prevalence of both smoking and depression, with a focus on the stability of this relationship; and 2) Assess the association between smoking and depression over the 4 year period, while also taking into account a potential temporal association by controlling for baseline depression syndrome, socio-demographic and health related characteristics.

3.13 METHODS

The data comes from the Montreal Diabetes Health Study (DHS); a random digit dialed population based survey of the non-institutionalized adult population in the province of Quebec, Canada. Participants were recruited between January and April 2008 through random selection of listed phone numbers in Quebec by a recognized polling firm, and were asked post baseline interview if they would like to take part in follow-up. Only those who answered yes were contacted for follow-up interviews, conducted 12, 24 and 36 months from baseline. Participants needed to be aged between 18-80, able to answer in English or French and have diabetes diagnosed by a physician. The protocol was approved by the Research Ethics Committee of the Douglas Mental Health University Institute. All subjects voluntarily participated in the study and informed consent was obtained from each participant. Participants received a 20 CAD incentive. More details on the study have been published elsewhere(Schmitz et al., 2011).

Smoking

To assess smoking status, participants were asked if they had smoked a total of 100 cigarettes in their lifetime, to be classified as never vs. ever smokers. Ever smokers were then asked “At the present time, do you smoke cigarettes?” – participants who said no were classified as former smokers. Those answering yes were then asked to estimate the number of cigarettes smoked per day (CPD). These responses were categorized into light smokers (<10 CPD) and moderate-heavy smokers (11+ CPD). Self-

reported cigarette smoking has been shown to be reliable estimates for current smokers(Rebagliato, 2002).

Depression

Depression Syndrome at each time point was assessed using the Patient Health Questionnaire (PHQ-9)(Kroenke, Spitzer, & Williams, 2001). The PHQ-9 is a highly sensitive screening tool, and provides a diagnosis of major and minor depression according to Diagnostic and Statistical Manual, 4th Edition (DSM-IV) criteria. For major depression, individuals had to have 5 or more symptoms over the past 2 weeks, including depressed mood or anhedonia. For minor depression, individuals needed between 2-4 symptoms, one of which being depressed mood or anhedonia. Those meeting criteria for either major or minor depression were categorized as having depression syndrome category.

Socio-demographic and health related questions

The DHS collected data on socio-demographic characteristics: age, gender, marital status (Married/Common Law, Divorced/Widowed, Single), education level (Less than secondary school, secondary school diploma, some post-secondary) and employment status (retired, working part-time / full-time, unemployed). Lifestyle variables were also based on self report; physical activity levels were categorized into inactive (0 days), moderately active (1-12 days) or active (12+ days) by asking the question “How many days did you exercise or participate in a sports activity for at least 15 minutes in the past month”; Alcohol consumption was assessed from the first item of the Alcohol Use Disorders Identification Test (AUDIT)(Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998): and were categorized into never, less than twice a week and two or more times a week.

Disability, chronic illness and diabetes related characteristics and complications

Global disability was assessed using the 12-item version of the World Health Organization Disability Assessment Schedule II (WHO-DAS-II)(Chwastiak & Von Korff, 2003) which consists of both physical and non-physical dimensions and categorized based on available normative data (score of ≥45 was classified as mild-substantial disability).

Diabetes complications were assessed using the Diabetes Complications Index (DCI)(Fincke et al., 2005). The DCI assesses diabetes complications via patient self-report (e.g. retinopathy, neuropathy, foot problems). A summary variable was computed counting the number of complications, and categorized into 0, 1 and 2 or more. Diagnosis of chronic conditions was similarly assessed by self-report (e.g. asthma, high blood pressure, heart disease, kidney disease) and responses were categorized to 0, 1 or 2 or more.

Analyses

Data were analyzed using IBM PASW version 20.0. Chi-Square analyses were performed to look at proportions of smokers with depression syndrome for each interview, with Cohen's Kappa(Carletta, 1996) coefficient used to estimate agreement across both smoking and depression syndrome across intervals. Generalized Estimating Equations (GEE)(Hanley, Negassa, Edwardes, & Forrester, 2003), a technique for analyzing sets of correlated data, was fit for both cross-sectional and longitudinal associations. Smoking status (never (reference), former, light and moderate-heavy smoker) was entered with depression syndrome as the outcome. We tested 3 models: Model 1 - Smoking status; Model 2 – Adjusting for Socio-demographic characteristics (Age, Gender, Marital Status, Occupation Status, Education level); Model 3 – Adjusting for model 2 as well as Health (Physical Activity levels, Alcohol consumption) and Disease characteristics (Diabetes complications, Disability, other Chronic illness). For longitudinal associations we entered smoking status (at Baseline, F1 and F2) as the predictor, and

depression syndrome (at F1, F2 and F3) as the outcome. We used the same models as above, with the exception that we also adjusted for baseline depression syndrome in model 3.

3.14 RESULTS

There were a total of 2003 completed interviews at baseline. We removed those with type-1 diabetes (n = 125), those with undetermined diabetes (n = 4), those who declined follow-up interview (n = 246) and finally those with missing baseline lifetime smoking data (n = 14) for a total of 1618 eligible participants. In sensitivity analyses those who dropped out or missed one or more follow-up interviews were older, had higher levels of disability, higher rates of depression syndrome and were more likely to be moderate-heavy smokers. At baseline, the mean age of the sample was 59.7 years old (SD = 11.2), and was 53.4% female.

Table 1 displays the breakdown of smoking status, along with corresponding prevalence of depression syndrome for each category for all 4 periods of the study. Current smoking prevalence was 20.5%, 19.4%, 16.6% and 16.4%, while depression syndrome prevalence was 19.8%, 21.4%, 19.5% and 21.5%, for each period respectively. For smoking, the Kappa measurements of agreement were 0.721, 0.747 and 0.805 across each interval (all $p < 0.000$; classified as high-substantial), while depression syndrome's coefficients of agreement were 0.374, 0.292 and 0.268 (all $p < 0.000$; classified moderate). At Baseline ($\chi2(3)=25.42$, $p < 0.000$), F1 ($\chi2(3)=13.58$, $p < 0.004$) and F3 ($\chi2(3) =9.80$, $p < 0.02$), moderate-heavy smokers were significantly more likely to experience depression syndrome; at F2 ($\chi2(3)=5.92$, $p=0.118$) this association was not significant for moderate-heavy smokers, but was significant for current smokers overall ($\chi2(2)=9.75$, $p <0.008$).

Table 2 shows the cross-sectional and longitudinal odds ratios obtained using GEE to compute binary logistic regressions for overall smoking status and depression syndrome. In both cross-sectional and longitudinal analyses, as compared to the never smokers, moderate-heavy smoking was significantly

associated with depression syndrome for every model (Fully adjusted models: Cross-Sectional OR = 1.46, 95% CI 1.08-1.99; Longitudinal OR = 1.54, 95% CI 1.02-2.31).

3.15 DISCUSSION

We found a strong association between smoking and depression within our longitudinal study in a community based sample with type-2 diabetes. Firstly, agreement across study intervals ranged from moderate (depression syndrome) to substantial (smoking), indicating stability across the study interval reported here (4 years total). Furthermore, both prevalence of smoking, depression syndrome and smoking x depression syndrome was stable for each period. Current smokers has higher prevalence of depression syndrome for each interval, and with the exception of follow-up 2, moderate-heavy smokers having the highest prevalence as compared to never, former and light smokers. Moreover, moderate-heavy smoking was significantly associated with depression syndrome in cross-sectional analyses, controlling for socio-demographic and disease related characteristics, extending our previous findings across a 4-year interval. Finally, moderate-heavy smoking remained associated with depression syndrome in the longitudinal model, after controlling for depression syndrome baseline.

In both cross-sectional and longitudinal models, the fully adjusted Odds Ratio (OR) for moderate-heavy smokers was significantly associated with depression syndrome. Smoking status is therefore not only strongly associated with concurrent depressive symptoms but also with increased prevalence of poor mental health at subsequent waves. Many studies favour a bi-directional relationship in which smoking and depression appear to feed off each other, in both adults(Berlin et al., 2009) and adolescents(Chaiton, Cohen, O'Loughlin, & Rehm, 2009). Still, other longitudinal investigations have found smoking to predict incident depression(Boden, Fergusson, & Horwood, 2010; Flensborg-Madsen et al., 2011), where a dose dependent response for smoking is often observed. The question of causality was recently tested using Canadian data(Khaled et al., 2012), in which the authors categorized people

according to both type (never, light, heavy) and the degree of smoking persistence (current or former). They found a greater than 3-fold increase in the risk of a major depressive episode (MDE) for persistent-heavy smokers as compared to former-heavy smokers, former/current light smokers and never smokers. Moreover, the risk appeared to decrease as abstinence periods increased. The authors interpreted these results against a purely vulnerability factors hypothesis between heavy smoking and major depression (e.g. genetics(Kendler, Neale, MacLean, Heath, & et al., 1993)), in which the impact persistent heavy smoking can have on incident depression.

That smoking may itself lead to increased negative affect has been investigated. Parrott(Andy C. Parrott, 2000; A. C. Parrott, 2004) has previously described this relationship, indicating that heavy smokers (and particularly those with nicotine dependence) experienced fluctuating moods, and greater negative affect. This finding has since been replicated in other studies, including one looking at natural mood fluctuations during the day in smokers(Chandra, Scharf, & Shiffman, 2011). Heavy smokers, and those with nicotine dependence, may therefore be entering a particular cycle after each cigarette, in which mood increases immediately post consumption but falls quickly in the aftermath, causing mood disturbances until the next opportunity to smoke arises. This chronic effect might therefore precipitate depression, by lowering mood and inhibiting these individuals.

This idea may be related to the notion that cigarette use is a form of self-medication, a popular hypothesis to explain smoking behaviours in individuals who have mental illness(Markou, Kosten, & Koob, 1998). These individuals have higher prevalence rates of smoking, while simultaneously smoking in heavier amounts than individuals without(McClave, McKnight-Eily, Davis, & Dube, 2010). Additionally, this hypothesis may be shared by both smokers with a mental illness as well as their health care providers(Ziedonis et al., 2008). Smokers with a history of major depression, for example, endorse the idea that smoking can improve affect(Weinberger, George, & McKee, 2010). Likewise, given that

patients with mental illness(Ziedonis et al., 2008) and those with diabetes(Fisher, Hessler, Polonsky, & Mullan, 2012) encounter high levels of distress thanks to their illness and accompanying treatment regimens, health care providers might be unmotivated to push cessation and increase the load on their patients. However, considering the elevated rates of morbidity and mortality associated with smoking(World Health Organization, 2013), as well as its ability to influence drug metabolism(Prochaska, 2011), a health care provider's reluctance may be impacting the health of their patients. That our results show the association smoking has on both current and future instances of elevated depression in those with diabetes further highlights this point, given the important and reciprocal associations between these 3 variables. Given the high rates of depression amongst smokers, depression might also play an important role in cessation outcomes, although current evidence remains mixed. Indeed, a history of depression has been associated with lower abstinence rates(Wilhelm, Wedgwood, Niven, & Kay-Lambkin, 2006), while cessation attempts have also been shown to precipitate depression(Glassman, Covey, Stetner, & Rivelli, 2001); still others find no concrete association(Hitsman, Borrelli, McChargue, Spring, & Niaura, 2003). Providers who do offer cessation advice may therefore want to assess concurrent depression before offering specific recommendations.

The main limitation of our study was the use of self-reported data. Depression was assessed via a screening questionnaire, and we were unable to assess lifetime history of depression. It is possible that previous depressive episodes could have impacted smoking behaviour in our sample. We did not assess for nicotine dependence, which may be an important mediating factor for the impact of cigarette smoking on mood. Our strengths include the use of a large community based sample, 4 years of follow-up data and the use of a robust model controlling for potential confounders.

We found smoking and depression to be relatively stable across over a 4 year period in a Canadian community sample with type-2 diabetes. Furthermore, moderate-heavy smoking was found to be

strongly associated with elevated symptoms of depression over the 4-year period. This association remained significant even after controlling for many potential confounders. In addition, using longitudinal data we showed that moderate-heavy smoking was associated with elevated symptoms of depression at the following assessment point after controlling for baseline depression syndrome. Moderate-heavy smoking may therefore impact the mental health of users, leading to elevated levels of depression. Smokers should be encouraged to quit, given the elevated risk of health complications, including that of depression.

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3.16 REFERENCES

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The Prevalence of Comorbid Depression in Adults With Diabetes. *Diabetes Care, 24*(6), 1069-1078.

Berlin, I., Covey, L. S., & Glassman, A. H. (2009). Smoking and Depression: A Co-morbidity. [Article]. *Journal of Dual Diagnosis, 5*(2), 149-158. doi: 10.1080/15504260902870129

Boden, J. M., Fergusson, D. M., & Horwood, L. J. (2010). Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. *The British Journal of Psychiatry, 196*(6), 440-446.

Bush, K., Kivlahan, D. R., McDonell, M. B., Fihn, S. D., & Bradley, K. A. (1998). The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med., 158*(16), 1789-1795.

Carletta, J. (1996). Assessing agreement on classification tasks: the kappa statistic. *Computational linguistics, 22*(2), 249-254.

Chaiton, M., Cohen, J., O'Loughlin, J., & Rehm, J. (2009). A systematic review of longitudinal studies on the association between depression and smoking in adolescents. *BMC Public Health, 9*(1), 356.

Chandra, S., Scharf, D., & Shiffman, S. (2011). Within-day temporal patterns of smoking, withdrawal symptoms, and craving. *Drug and Alcohol Dependence, 117*(2–3), 118-125. doi: http://dx.doi.org/10.1016/j.drugalcdep.2010.12.027

Chaturvedi, N., Stevens, L., Fuller, J. H., & The World Health Organization Multinational Study, G. (1997). Which Features of Smoking Determine Mortality Risk in Former Cigarette Smokers With Diabetes? The World Health Organization Multinational Study Group. *Diabetes Care, 20*(8), 1266-1272.

Chwastiak, L. A., & Von Korff, M. (2003). Disability in depression and back pain: evaluation of the World Health Organization Disability Assessment Schedule (WHO DAS II) in a primary care setting. *Journal of Clinical Epidemiology, 56*(6), 507-514.

Ciechanowski, P. S., Katon, W. J., & Russo, J. E. (2000). Depression and Diabetes: Impact of Depressive Symptoms on Adherence, Function, and Costs. *Arch Intern Med, 160*(21), 3278-3285. doi: 10.1001/archinte.160.21.3278

Clyde, M., Smith, K. J., Gariépy, G., & Schmitz, N. (2013). The Association between Smoking and Depression in a Canadian Community-Based Sample with Type 2 Diabetes. *Canadian Journal of Diabetes, 37*(3), 150-155.

Egede, L. E., & Zheng, D. (2003). Independent Factors Associated With Major Depressive Disorder in a National Sample of Individuals With Diabetes. *Diabetes Care, 26*(1), 104-111. doi: 10.2337/diacare.26.1.104

Eliasson, B. (2003). Cigarette smoking and diabetes. *Progress in Cardiovascular Diseases, 45*(5), 405-413.

Fagard, R. H., & Nilsson, P. M. (2009). Smoking and diabetes—The double health hazard! *Primary Care Diabetes, 3*(4), 205-209. doi: 10.1016/j.pcd.2009.09.003

Fincke, B. G., Clark, J. A., Linzer, M., Spiro III, A., Miller, D. R., Lee, A., & Kazis, L. E. (2005). Assessment of long-term complications due to type 2 diabetes using patient self-report: the diabetes complications index. *The Journal of Ambulatory Care Management, 28*(3), 262-273.

Fisher, L., Hessler, D. M., Polonsky, W. H., & Mullan, J. (2012). When Is Diabetes Distress Clinically Meaningful?: Establishing cut points for the Diabetes Distress Scale. *Diabetes Care, 35*(2), 259-264. doi: 10.2337/dc11-1572

Flensborg-Madsen, T., Bay von Scholten, M., Flachs, E. M., Mortensen, E. L., Prescott, E., & Tolstrup, J. S. (2011). Tobacco smoking as a risk factor for depression. A 26-year population-based follow-up study. *Journal of Psychiatric Research, 45*(2), 143-149.

Glassman, A. H., Covey, L. S., Stetner, F., & Rivelli, S. (2001). Smoking cessation and the course of major depression: a follow-up study. *The Lancet, 357*(9272), 1929-1932.

Hanley, J. A., Negassa, A., Edwardes, M. D. d., & Forrester, J. E. (2003). Statistical Analysis of Correlated Data Using Generalized Estimating Equations: An Orientation. *American Journal of Epidemiology, 157*(4), 364-375. doi: 10.1093/aje/kwf215

Hitsman, B., Borrelli, B., McChargue, D. E., Spring, B., & Niaura, R. (2003). History of depression and smoking cessation outcome: A meta-analysis. *Journal of Consulting and Clinical Psychology, 71*(4), 657-663. doi: 10.1037/0022-006x.71.4.657

Katon, W., Von Korff, M., Ciechanowski, P., Russo, J., Lin, E., Simon, G., . . . Young, B. (2004). Behavioral and Clinical Factors Associated With Depression Among Individuals With Diabetes. *Diabetes Care, 27*(4), 914-920. doi: 10.2337/diacare.27.4.914

Kendler, K. S., Neale, M. C., MacLean, C. J., Heath, A. C., & et al. (1993). Smoking and major depression: A causal analysis. *Archives of General Psychiatry, 50*(1), 36-43.

Khaled, S. M., Bulloch, A. G., Williams, J. V. A., Hill, J. C., Lavorato, D. H., & Patten, S. B. (2012). Persistent heavy smoking as risk factor for major depression (MD) incidence – Evidence from a longitudinal Canadian cohort of the National Population Health Survey. *Journal of Psychiatric Research, 46*(4), 436-443. doi: 10.1016/j.jpsychires.2011.11.011

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9. *Journal of General Internal Medicine, 16*(9), 606-613.

Markou, A., Kosten, T. R., & Koob, G. F. (1998). Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. *Neuropsychopharmacology, 18*(3), 135-174.

McClave, A. K., McKnight-Eily, L. R., Davis, S. P., & Dube, S. R. (2010). Smoking Characteristics of Adults With Selected Lifetime Mental Illnesses: Results From the 2007 National Health Interview Survey. *American Journal of Public Health, 100*(12), 2464-2472. doi: 10.2105/ajph.2009.188136

Parrott, A. C. (2000). Cigarette smoking does cause distress. *American Psychologist, 55*(10), 1159-1160. doi: 10.1037/0003-066x.55.10.1159

Parrott, A. C. (2004). Heightened stress and depression follow cigarette smoking. *Psychol Rep, 94*(1), 33-34.

Prochaska, J. J. (2011). Smoking and Mental Illness — Breaking the Link. *New England Journal of Medicine, 365*(3), 196-198. doi: doi:10.1056/NEJMp1105248

Rebagliato, M. (2002). Validation of self reported smoking. *Journal of Epidemiology and Community Health, 56*(3), 163-164. doi: 10.1136/jech.56.3.163

Schmitz, N., Messier, L., Nitka, D., Ivanova, A., Gariepy, G., Wang, J., . . . Strychar, I. (2011). Factors Associated with Disability and Depressive Symptoms Among Individuals with Diabetes: A Community Study in Quebec. *Psychosomatics, 52*(2), 167-177. doi: 10.1016/j.psym.2010.11.020

Weinberger, A. H., George, T. P., & McKee, S. A. (2010). Differences in smoking expectancies in smokers with and without a history of major depression. *Addictive Behaviors, 36*(4), 434-437.

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global Prevalence of Diabetes. *Diabetes Care, 27*(5), 1047-1053. doi: 10.2337/diacare.27.5.1047

Wilhelm, K., Wedgwood, L., Niven, H., & Kay-Lambkin, F. (2006). Smoking cessation and depression: current knowledge and future directions. *Drug and Alcohol Review, 25*(1), 97-107. doi: 10.1080/09595230500459560

World Health Organization. (2013). Fact Sheet: Tobacco. *Fact Sheet no. 339* Retrieved 15/07/2013, from http://www.who.int/mediacentre/factsheets/fs339/en/

Ziedonis, D., Hitsman, B., Beckham, J. C., Zvolensky, M., Adler, L. E., Audrain-McGovern, J., . . . Riley, W. T. (2008). Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob Res, 10*(12), 1691-1715. doi: 10.1080/14622200802443569

3.17 Table 1

Table 1 – Smoking and Depression Syndrome prevalence				
	Smoking Prevalence (%)	95% CI	% with Depression Syndrome	95% CI
Baseline (n=1614)				
Never	36.7	(34.3-39.1)	18.1	(15.2-21.4)
Former	42.6	(40.2-45.1)	16.2	(13.6-19.2)
Light	7.9	(6.7-9.9)	22.5	(15.8-30.8)
Moderate/Heavy	12.6	(11.0-14.3)	30.9	(24.7-37.8)
All Current	20.5		**p-value**	**0.000**
Follow-up 1 (n=1181)				
Never	37.3	(34.6-40.1)	19.3	(15.8-23.4)
Former	43.3	(40.5-46.2)	19.3	(16.1-23.1)
Light	7.7	(6.3-9.9)	25.3	(17.0-35.7)
Moderate/Heavy	11.7	(10.0-13.6)	32.6	(25.0-41.2)
All Current	19.4		**p-value**	**0.004**
Follow-up 2 (n=1062)				
Never	42.8	(39.9-45.8)	17.7	(14.3-21.6)
Former	40.6	(37.7-43.5)	18.8	(15.2-22.8)
Light	7.0	(5.7-8.7)	26.7	(17.4-38.3)
Moderate/Heavy	9.6	(8.0-11.5)	25.5	(17.6-35.3)
All Current	16.6		p-value	0.116 (n.s.)
Follow-up 3 (n=1060)				
Never	42.5	(39.5-45.5)	20.6	(17.0-24.8)
Former	40.7	(37.8-43.7)	20.1	(16.5-24.2)
Light	6.5	(5.10-8.10)	17.4	(9.7-28.8)
Moderate/Heavy	9.9	(8.30-11.9)	33.0	(24.4-42.9)
All Current	16.4		**p-value**	**0.02**
Note: P-values for Chi-square analysis, Baseline ($\chi2(3)=25.42$, $p < 0.000$), follow-up 1 ($\chi2(3)=13.58$, $p < 0.004$), Follow-up 2 ($\chi2(3)=5.92$, $p=0.118$) and follow-up 3 ($\chi2(3) =9.80$, $p < 0.02$) Cohen's Kappa coefficient of agreement: Smoking: BL-F1 = 0.721, F1-F2 = 0.778, F2-F3 = 0.761 (all $p < 0.000$, substantial) Depression Syndrome: BL-F1 = 0.374; F1-F2 = 0.375; F2-F3 = 0.413 (all $p < 0.000$, fair-moderate)				

3.18 Table 2

Table 2 - Logistic Regression using Generalized Estimating Equations						
Cross-Sectional Results: Smoking and Depression Syndrome						
Model:	I		II		III	
Smoking Status	OR	95% CI	OR	95% CI	OR	95% CI
Never Smoker	*1.00*	*REF*	*1.00*	*REF*	*1.00*	*REF*
Former Smoker	0.88	(0.81-1.20)	1.12	(0.92-1.38)	1.06	(0.85-1.33)
Light Smoker	1.34	(0.98-1.82)	1.29	(0.93-1.79)	1.14	(0.79-1.64)
Moderate-Heavy Smoker	**1.92**	**(1.47-2.52)**	**1.77**	**(1.34-2.34)**	**1.46**	**(1.08-1.99)**
Longitudinal Results: Smoking and Depression Syndrome						
Never Smoker	*1.00*	*REF*	*1.00*	*REF*	*1.00*	*REF*
Former	1.10	(0.86-1.40)	1.29	(0.98-1.66)	1.24	(0.93-1.64)
Light Smoker	1.12	(0.75-1.67)	1.07	(0.71-1.62)	1.00	(0.64-1.57)
Moderate-Heavy Smoker	**2.10**	**(1.49-2.96)**	**1.99**	**(1.39-2.86)**	**1.54**	**(1.02-2.31)**

Note: OR = Odds Ratio; CI = Confidence interval.
Model I – Unadjusted (Smoking Status only)
Model II - Adjusting for Age, Gender, Marital Status, Employment and Education
Model III - Adjust for Model I + Disability, Diabetes Complications, Chronic Conditions, Physical Activity, Alcohol use.

3.19 Connecting text

Manuscript 2 importantly extends the findings from our first manuscript, while providing additional important information. Similar to findings reported from a U.S. sample, smoking prevalence remains high and stable in this at risk population over time. This was also true of depression syndrome (minor and major depression), with approximately 20% of our study population experiencing elevated symptoms of depression at each time point. At all 4 assessments, current smokers also had higher prevalence of depression syndrome – with highest prevalence rates found in moderate-heavy smokers (nearly 1/3 of moderate-heavy smokers had depression syndrome at each wave). We tested cross-sectional and longitudinal models, resulting in significant odds of depression syndrome in moderate-heavy smokers in both cases. For both analyses, we again controlled for important sociodemographic and health characteristics in the fully adjusted model. Furthermore, the fully adjusted longitudinal model controlled for baseline depression syndrome. Our results highlight the important association between smoking and poor mental health – including implicating smoking with not only current elevated symptoms of depression but also the development of elevated future ones. One important limitation in this study is the lack of information on depression history, preventing us from concluding that smoking caused *incident* depression in the sample. Regardless, we demonstrated a strong association between current heavy smoking and poor mental health, which was stable over a 4 year period. Moreover, this stability also underlines the apparent ineffectiveness of current cessation strategies and guidelines. One important explanation for this may be the strong association between smoking and depression. In the following chapter, we present the results from our third manuscript, in which we describe in detail the characteristics of smoking cessation within this sample over a 4 year period. Moreover, we assess the association between cessation, cessation attempts and cessation failures with depression syndrome.

Chapter 4 Manuscript 3

Title**: Smoking cessation, depression and type-2 diabetes: Characteristics and associations successful, unsuccessful and non-attempting quitters in a community sample with type-2 diabetes.**

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4.1 Abstract

Objective: To describe the characteristics of successful smoking quitters, unsuccessful quitters and non-attempters in adults with type-2 diabetes and to assess the association between smoking cessation success and attempts with depression syndrome in this population. .

Method: 1871 adults with type-2 diabetes were recruited via random digit dialing for the Montreal Health and Well Being Study (DHS). Ever smokers were classified as Successful Quitters, Unsuccessful Quitters and Non-Attempters. Depression was assessed using the Patient Health Questionnaire-9 and categorized as no vs. depression syndrome. Generalized Estimating Equations were used to test the association between depression syndrome and smoking cessation status, while controlling for other demographic and health related variables.

Results: At baseline, we categorized 794 ever smokers as successful quitters, 189 as unsuccessful quitters and 188 as quitting non-attempters. Across subsequent waves, we recorded 68 cases of quitting, and 50 cases of relapse to smoking. In the fully adjusted model, depression syndrome was significantly associated with being an unsuccessful quitters (AOR = 1.53 (95% CI 1.12 – 2.08), but not non-attempters, compared to successful quitters (reference group).

Conclusions: Those making unsuccessful quitting attempts were more likely to have depression syndrome compared to successful quitters. Depression may therefore have impacted their ability to successfully quit. Addressing depression may be an important clinical goal for those attempting to successfully quit smoking.

4.2 INTRODUCTION

Cigarette smoking remains a prevalent behaviour worldwide, in spite of the numerous health risks it imposes on both users and non-users alike(Health & Services, 2004). The WHO recognizes that smoking an important modifiable risk factor for disease, as well as associating smoking with the increased morbidity of numerous illnesses, including diabetes(World Health Organization, 2011). Furthermore, smoking is associated with adverse outcomes in people with diabetes including the accelerated development of diabetes-related micro and macro-vascular complications(Eliasson, 2003) and increased mortality(Al-Delaimy, Willett, Manson, Speizer, & Hu, 2001).

Along with dietary changes and increased physical activity, smoking cessation is a key component of diabetes self-care guidelines (Haire-Joshu, 2004; Jones, Berard, MacNeill, Whitham, & Yu, 2013; Stone, Fitchett, Grover, Lewanczuk, & Lin, 2013). The literature on smoking and diabetes(Beziaud, Halimi, Lecomte, Vol, & Tichet, 2004; Gariepy et al., 2012; Solberg, Desai, O'Connor, Bishop, & Devlin, 2004), and smoking cessation within the general population(Hyland et al., 2006; Hymowitz et al., 1997; Lee & Kahende, 2007) is well characterised. However, little evidence exists specifically for those attempting to quit with diabetes and data suggests that prevalence rates of smoking remain high for those with diabetes despite guidelines that encourage cessation. We previously characterized smoking status in a Canadian community sample with type-2 diabetes (Clyde, Smith, Gariépy, & Schmitz, 2013) and found a current smoking prevalence of 20.5%, similar to that found in a similar US population recently(Ford, Mokdad, & Gregg, 2004). This figure is also on a par with that of the general population of Canada(Health Canada, 2010). Taken together these findings indicate that smoking cessation efforts may not be optimal for people with diabetes. It is therefore important to determine the impact of diabetes and illness related complications may have on quitting, while simultaneously using our longitudinal data to describe the quitting behaviours and attempts over time of our smokers.

Characterizing differences between successful and unsuccessful quitters, as well as those who did not attempt to quit might allow for better targeted cessation strategies for people with diabetes.

One potentially important factor which may impact on smoking cessation attempts in people with diabetes is depression. Studies conducted in the general population have found bidirectional association between smoking and depression(Berlin, Covey, & Glassman, 2009), and have reported that the presence of depression may negatively impact smoking cessation success rates(Fond et al., 2013). Importantly, depression is 2-3 times more prevalent in those with diabetes compared to the general population(Anderson, Freedland, Clouse, & Lustman, 2001), and therefore may play an even larger role in cessation within this population. In our previous study, we found that current heavy smokers were over 2-times more likely to have major depression, and determining whether this association extends to smoking cessation as well as for current smokers in people with diabetes is an important topic.

To address current limitations within diabetes and smoking cessation literature, we analysed data from a community sample with type-2 diabetes in order to: 1) Describe the sociodemographic and health related characteristics of successful quitters, unsuccessful quitters and non-attempters; 2) Characterize the cessation attempts of this sample over a 4-year period according to their smoking status (light vs. heavy); and 3) Assess the association between depression and smoking cessation.

4.13 METHODS

The data comes from the Montreal Diabetes Health Study (DHS), a population based random-digit dialed telephone survey of the non-institutionalized adult population in the province of Quebec, Canada. Recruitment took place between January and April 2008 and was conducted by a recognized polling firm, Bureau d'Intervieweurs Professionnels (Montreal, Quebec, Canada). To be included in the study, individuals needed to be between the ages of 18 and 80, have diabetes as previously diagnosed by a physician, and be capable of responding to interview questions in either English or French. After

baseline interview, participants were asked if they would be willing to participate in follow-up interviews; those who agreed were contacted at 12, 24 and 36 months after their baseline assessment. The protocol was approved by the Research Ethics Committee of the Douglas Mental Health University Institute. All subjects voluntarily participated in the study and informed consent was obtained from each participant. Participants received a 20 CAD incentive. Results reported in this paper are for individuals with type 2 diabetes; participants who were diagnosed prior to the age of 30 and used insulin immediately after diagnosis were epidemiologically classified as having type 1 diabetes and excluded from this analysis. More details on the study have been published elsewhere(Schmitz et al., 2011).

Smoking

Smoking status was obtained using questions adapted from the Canadian Community Health Survey (CCHS)(Statistics Canada, 2009). Participants were asked if they had smoked a total of 100 cigarettes in their lifetime; those answering no were classified as never smokers, while those answering yes were classified as ever smokers. Ever smokers were asked the follow-up question "At the present time, do you smoke cigarettes?". – Those answering no were classified as former smokers and those answering yes were classified as smokers. Current smokers were dichotomized based on the number of reported cigarettes smoked per day (CPD) into light smokers (≤10 CPD) or heavy smokers (11+ CPD)(Health Canada, 2010). Current smokers were also asked "In the last 6 months, did you stop smoking for at least 24 hours with the goal of quitting?". Former smokers were considered 'Successful Quitters'; smokers who answered 'Yes' to the cessation question but continued to smoke were considered "Unsuccessful Quitters'; smokers answering no to the cessation question were considered to be 'Non-Attempters'. This approach has been used with previous surveys(Annette K. McClave et al., 2009) to contrast and compare the heterogeneous group of ever smokers.

Depression Syndrome

Depression syndrome at each time point was evaluated using the Patient Health Questionnaire (PHQ-9), a highly sensitive screening tool(Kroenke, Spitzer, & Williams, 2001), to assess for major and minor depression according to Diagnostic and Statistical Manual, 4th Edition (DSM-IV) criteria. The criteria for *major depression disorder* (MDD) required the patient to have, for at least 2 weeks, five or more depressive symptoms present for more than half of the days with at least one of these symptoms being either depressed mood or anhedonia. For minor depression, the patient needed to have between 2 – 4 symptoms of depression for at least 2 weeks, with at least one of these symptoms being either depressed mood or anhedonia. Individuals who met the criteria for major or minor depression were categorized as having depression syndrome.

Socio-demographic and health related questions

The DHS collected data on socio-demographic characteristics, including age, sex and marital status (married/common-law, single, divorced/separated/widowed), education level (less than high school graduation, high school graduation, post high school) and employment status (working full or part time, retired, not working).

Lifestyle variables were assessed using questions adapted from the CCHS(Statistics Canada, 2009). Alcohol consumption was assessed using the first item of the Alcohol Use Disorders Identification Test (AUDIT)(Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998): 'How often do you have a drink containing alcohol?'; answers were categorized into never, less than twice a week and two or more times a week.

Physical activity levels were assessed via self-report by asking participants to rate the number of days they exercised or participated in sports for at least 15 minutes in the previous month. Responses were

categorized into three groups: inactive (0 days), moderately active (1 to 12 days) and active (more than 12 days).

Disability, chronic illness and diabetes related characteristics and complications

Diabetes complications were assessed using the Diabetes Complications Index (DCI)(Fincke et al., 2005). The DCI is a 17-item survey that assesses the presence of diabetes complications (retinopathy, neuropathy, large-vessel atherosclerotic disease, peripheral vascular disease, cerebrovascular disease and foot problems) on the basis of patient self-report. A summary variable was computed for number of complications, and individuals were categorized into 0 diabetes complications and 1 or more diabetes complications

Participants were also asked whether they suffered from various health conditions diagnosed by a health professional at the time of the interview (asthma, high blood pressure, heart disease, stomach or intestinal ulcers, arthritis / rheumatism, migraine headaches, cancer, kidney disease, and back problems). Chronic conditions were then summarized into 0 to 8 chronic conditions and categorized into 0 and 1 or more chronic conditions.

Diabetes related characteristics were also assessed. Duration of diabetes was calculated in years based on the age at which participants were first diagnosed with diabetes. The participant's diabetes treatment regimen was assessed by asking if they took insulin or pills to control their diabetes in the past month.

Self-rated health was ascertained by asking the question: "In general, would you consider your health to be excellent, very good, good, fair or poor?", with responses dichotomized into excellent/very good/good and fair/poor.

Activity limitation, characterized by the number of reported disability days, was assessed by asking "During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation?" This question is part of the standard 4-item set of the Centers for Disease Control and Prevention's (CDC)(Moriarty, Zack, & Kobau, 2003) health related quality of life instrument, and self-reported disability days have been shown to be reliable estimates of disease burden and disability across a variety of demographics(REVICKI, IRWIN, REBLANDO, & SIMON, 1994).

Analyses

Data were analyzed using IBM SPSS Statistics 20 software version 20.0. Frequency tables and Chi-Square analyses were performed to assess socio-demographic (Age, Gender, Marital Status, Employment Status, Education) and illness-related variables (Duration of diabetes, Diabetes treatment, Diabetes complications, Other chronic conditions, Alcohol use, Physical activity levels, Depression syndrome, Self-rated health and Activity Disability Limited Days), across smoking cessation groups (Successful Quitters, Unsuccessful Quitters and Non-Attempters) at baseline.

To assess the association between smoking cessation and depression syndrome, we used Generalized Estimating Equations (GEE), to fit a logistic regression for all 4 waves (cross-sectional association). GEE is a tool used with longitudinal data of correlated response data that accounts for the correlation of responses made by individuals across time points(Hanley, Negassa, Edwardes, & Forrester, 2003). For our analysis, we used smoking cessation status (Reference: Successful Quitters) as the independent variable, with depression syndrome as the outcome variable. We tested 3 models for the analysis: Model 1 - unadjusted (cessation status alone); Model 2 – Adjusting for Socio-demographic characteristics (Age, Gender, Marital Status, Occupation Status, Education level); Model 3 – Adjusting for Socio-demographic characteristics as well as health (physical activity levels, alcohol consumption) and

disease characteristics (diabetes duration, diabetes treatment, diabetes complications, disability, other chronic illness).

4.14 RESULTS

There were a total of 2003 completed interviews at baseline. For this report, after removing those with type-1 diabetes (n = 125), we were left with 1878 eligible participants for baseline assessment. For longitudinal assessment, we excluded individuals who refused at baseline to take part in follow-up interviews (n=246) and those with undetermined diabetes (n = 4) for a total of 1618 eligible participants. Sensitivity analyses conducted for missing responses at one or more follow-up interviews indicated that missing individuals were older, had more self-reported diabetes complications, had higher rates of depression and were more likely to be current smokers.

The mean age of the sample was 59.7 years old (SD = 11.2), was 53.4% female, with 37.0% of participants being classified as never smokers. Prevalence rates of current smoking were 20.5%, 19.4%, 16.6% and 16.4% for each assessment, respectively. The average age for current smokers was significantly lower than never and former smokers (mean 55.5 vs. 60.7 respectively, $p < 0.05$), with the average age of first cigarette smoked being 16.3 years old (SD = 5.7; n.s. across ever smokers). As for depression syndrome, we found prevalence rates of 19.8%, 21.4%, 19.5% and 21.5% for each of the 4 interview periods, respectively.

Table 1 presents the demographic characteristics across cessation categories at baseline. Successful quitters were more likely to be older, male, married, have higher levels of education and be retired. Unsuccessful quitters were more likely to be younger, be female, single, unemployed, and have less than high-school diploma. By contrast, non-attempters followed many of the same trends as unsuccessful quitters, being significantly more often younger, female, single and unemployed, as compared to successful quitters. The bottom of table 1 displays the prevalence of depression syndrome for the 4

points of the study. At all 4 times, unsuccessful quitters had higher prevalence of depression syndrome, as compared to both successful quitters and non-attempters.

Table 2 shows the health-related characteristics of our sample across cessation groups. Successful quitters had experienced diabetes longer, were more likely to be physically active, reported a higher level of alcohol consumption, were more likely to report good/very good/excellent self rated health and were more likely to report 0 disability days. Unsuccessful quitters and Non-attempters had diabetes for slightly shorter periods, and were more likely to self-report fair/poor self-rated health and having 1 or more disability days over the last 30 days compared to be successful quitters and non-attempters. Interestingly, there were no differences amongst the 3 groups for current diabetes treatment (although non-attempters reported the use of insulin less often), number of diabetes complications or number of chronic conditions

Table 3 displays the longitudinal characteristics for the cessation attempts for ever smokers (n = 1171, 685, 522, 452, respectively). The number of smokers attempting to quit in the previous 6 months remained fixed around 50% of all current smokers at each period; however, stratification revealed that light smokers were more likely to attempt to quit in the last 6 months compared to heavy smokers (64.7 vs. 41.6 at baseline; 58.0 vs. 41.5 at follow-up 3). We also looked at quit attempts made for subsequent waves: those making an unsuccessful quit attempt were more likely to make another attempt by the next wave for all intervals. Over the 3 years of follow-up, we recorded 68 cases where a smoker was able to quit by follow-up assessment. Light smokers were also more likely than heavy smokers to have successfully quit compared to heavy smokers at follow-up 1(19.8 vs. 9.7, $p < 0.05$) and follow-up 3 (19.0 vs. 5.3, $p < 0.05$). Although not statistically significant, a larger portion of light smokers successfully quit at follow-up 2 (14.8 vs. 11.5, $p = 0.411$ n.s.) as well. Finally, we recorded a total of 50 cases of relapse to

smoking throughout our study. Amongst those who did relapse, they were more likely to relapse into light smoking as compared to heavy smoking.

Table 4 shows the GEE binary logistic regression models for smoking cessation status and depression syndrome. As compared to successful quitters (reference), unsuccessful quitters were more likely to have depression syndrome, even after adjusting for all sociodemographic and health variables (Fully adjusted model: OR = 1.53, 95% CI 1.12-2.08). Non-attempters were significantly more likely to have depression syndrome in the un-adjusted model (OR = 1.35, 95% CI 1.01-1.80), but this was attenuated after controlling for socio-demographic and disease characteristics (Fully adjusted Model: OR = 1.01, 95% CI 0.72-1.42).

4.15 DISCUSSION

In our community sample with type-2 diabetes, we found that unsuccessful quitters were more likely to suffer from the depression syndrome than successful quitters, even after adjusting for socio-demographic and health related characteristics. Unsuccessful quitters were more often younger, single, unemployed and had lower education than individuals who had successfully quit in the past. In terms of diabetes characteristics, unsuccessful quitters and non-attempters both had slightly shorter duration of diabetes diagnosis compared to successful quitters. Unsuccessful quitters were more likely to report fair/poor self-rated health, and were also more likely to report 1 or more disability affected day within the past month compared to both successful quitters and non-attempters.

We recorded a total of 68 cases of quitting and 50 cases of relapse within the course of our study. Light smokers were more likely than heavy smokers to make a quit attempt in the last 6 months, and to successfully quit as compared to moderate-heavy smokers. These findings mirror results from general population surveys(Hyland et al., 2006; Hymowitz et al., 1997; Lee & Kahende, 2007) . In our study, however, previous unsuccessful quitters did not appear to be more likely to quit at subsequent waves

compared to those who did not attempt to quit. Taken in conjunction with our previous baseline characterization of this samples smoking habits(Clyde et al., 2013), we find that those who make attempts and fail are more likely to have elevated symptoms of depression as compared to those who were successful at quitting. One explanation for this may be that while the presence of elevated depression does not seem to affect an individual's motivation to attempt cessation, it may impact their ability to successfully quit. Alternatively, unsuccessful attempts may impact the mental health of an individual, as it is possible that the (unsuccessful) attempt lead to increased symptoms of depression.

Although there is a large body of evidence linking smoking and depression(Berlin et al., 2009), the role depression plays in cessation is less well understood. Some studies conducted in the general population indicate that a history of depression may lowers abstinence rates(Fond et al., 2013), others report no apparent effect(Hitsman, Borrelli, McChargue, Spring, & Niaura, 2003), and still others report on the impact cessation attempts may have on precipitating depression(Glassman, Covey, Stetner, & Rivelli, 2001). McClave(Annette K. McClave et al., 2009; McClave, Dube, Strine, & Mokdad, 2009) reported that unsuccessful quitters have higher rates of both lifetime and current depression, in addition to having poorer self-perceived health-related quality of life, which may itself impact mental health. Subjective measures, such as self-rated health, may therefore be particularly important for cessation, with depression again strongly implicated in this association. Hayes(Hayes, Dunsiger, & Borrelli, 2010) found that the odds of quitting smoking increased for every unit decrease in physical quality of life, but only in individuals with little/no depression. Within our study, we found that unsuccessful quitters were more likely to report fair/poor self rated health and to report more disability days than successful quitters. Their cessation attempt may therefore reflect their poor health perceptions, while ultimately being negatively impacted by the presence of depression.

While we unfortunately do not have detailed information on when our successful quitters quit, recent evidence points at the importance of diagnosis as a potential motivator to quit. Twardella(Twardella et al., 2006) showed that the diagnosis of a smoking related disease was related to initiating cessation, and two recent studies(Agborsangaya et al., 2013; Newson et al., 2012) on chronic conditions in Canada also reported increased cessation post-diabetes diagnosis. However, both studies also noted that the majority of attempters failed, with the bulk of smokers continuing to smoke. Furthermore, Newson(Newson et al., 2012) reported that cessation attempts and outcomes were not affected by Health Care provider recommendations, indicating a need for stronger intervention methods. Given that the majority of our study population has had diabetes for several years, it is unclear how disease progression may impact on future cessation attempts. Within our study, there was no difference in prevalence of diabetes complications or in number of other chronic illnesses across cessation groups, indicating that these more objective measures may not be motivators.

Current smoking cessation best practices have been extensively reviewed and studied(Fiore & Jaen, 2008), and can include a variety of behavioral, psychosocial and pharmacological interventions, employed alone or in tandem with one another. Unfortunately, studies assessing efficacy and integration of this evidence base into current diabetes education programs are lacking. One study from the U.S.(Hokanson, Anderson, Hennrikus, Lando, & Kendall, 2006) determined that while feasible to incorporate motivational interviewing for cessation into diabetes education, 6 month abstinence rates showed no gains over treatment as usual. Other studies, including multi-center studies from Sweden(Persson & Hjalmarson, 2006) and the U.K.(Davies et al., 2008), have however reported improved rates of cessation. The DESMOND(Davies et al., 2008) trial focused on improving education, and also found higher weight loss and improved mood in the treatment group. Improved efforts from primary health care providers are needed, which might seek to increase awareness and education vis-à-vis the specific increased risks posed by continual smoking. Likewise, we have demonstrated important

associations between current smoking and depression, as well as between depression and smoking cessation, clinical characteristics which primary care providers should assess and take into account when making treatment decisions and recommendations. The burden must equally falls on researchers to study treatment modalities and approaches in order to properly derive and integrate these new programs for cessation. A recent review(Weinberger, Mazure, Morlett, & McKee, 2013) on cessation and depression highlights both the abundance of published evidence on this topic, along with the lack of information on *how* specific treatment approaches actually work.

There are a number of limitations to our study. The data presented are based on self-report, and as such misclassification may have occurred. For smoking, we do not know how long individuals have been abstinent, when they quit, how many previous attempts they made or their reason for quitting (former smokers). Without a detailed history, we also are unable to determine how long and at what level they have persistently smoked (current smokers). Depressive symptoms were assessed using a screening questionnaire, which may lead to an over or under estimation of the prevalence of depression. We do not have a history of depressive disorder and therefore cannot account for chronic past episodes or the effect of lifetime depression. Our study also has a number of strengths. We have a large, representative community based sample of Canadians with type-2 diabetes. We observed the longitudinal prevalence and associations between smoking cessation and depressive symptoms. Our regression models were fully adjusted for demographic and health related characteristics and thus robust to some potential confounding.

In our survey of a Canadian Community sample with type-2 diabetes, we found prevalence rates of current smoking to be similar to that of the general population, in spite of the increased risk of these individuals. Our findings show that successful and unsuccessful quitters differ across sociodemographic, physical and mental health characteristics. Clinicians should tailor their cessation interventions

according to these characteristics in order to increase abstinence rates amongst smokers. Given the increased prevalence of depression in people with diabetes, our findings also highlight the importance of cessation interventions which address depression, which may be a particularly important outcome in those who unsuccessfully quit.

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4.16 REFERENCES

Agborsangaya, C. B., Gee, M. E., Johnson, S. T., Dunbar, P., Langlois, M. F., Leiter, L. A., . . . Johnson, J. A. (2013). Determinants of lifestyle behavior in type 2 diabetes: results of the 2011 cross-sectional survey on living with chronic diseases in Canada. [Article]. *BMC Public Health, 13*. doi: 10.1186/1471-2458-13-451

Al-Delaimy, W. K., Willett, W. C., Manson, J. E., Speizer, F. E., & Hu, F. B. (2001). Smoking and Mortality Among Women With Type 2 Diabetes The Nurses' Health Study cohort. *Diabetes Care, 24*(12), 2043-2048.

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The Prevalence of Comorbid Depression in Adults With Diabetes. *Diabetes Care, 24*(6), 1069-1078.

Berlin, I., Covey, L. S., & Glassman, A. H. (2009). Smoking and Depression: A Co-morbidity. [Article]. *Journal of Dual Diagnosis, 5*(2), 149-158. doi: 10.1080/15504260902870129

Beziaud, F., Halimi, J. M., Lecomte, P., Vol, S., & Tichet, J. (2004). Cigarette smoking and diabetes mellitus. *Diabetes & Metabolism, 30*(2), 161-166. doi: http://dx.doi.org/10.1016/S1262-3636(07)70102-7

Bush, K., Kivlahan, D. R., McDonell, M. B., Fihn, S. D., & Bradley, K. A. (1998). The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med., 158*(16), 1789-1795.

Clyde, M., Smith, K. J., Gariépy, G., & Schmitz, N. (2013). The Association between Smoking and Depression in a Canadian Community-Based Sample with Type 2 Diabetes. *Canadian Journal of Diabetes, 37*(3), 150-155.

Davies, M. J., Heller, S., Skinner, T. C., Campbell, M. J., Carey, M. E., Cradock, S., . . . Khunti, K. (2008). Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: Cluster randomised controlled trial. *BMJ, 336*(7642), 491-495.

Eliasson, B. (2003). Cigarette smoking and diabetes. *Progress in Cardiovascular Diseases, 45*(5), 405-413.

Fincke, B. G., Clark, J. A., Linzer, M., Spiro III, A., Miller, D. R., Lee, A., & Kazis, L. E. (2005). Assessment of long-term complications due to type 2 diabetes using patient self-report: the diabetes complications index. *The Journal of Ambulatory Care Management, 28*(3), 262-273.

Fiore, M. C., & Jaen, C. R. (2008). A clinical blueprint to accelerate the elimination of tobacco use. *Jama., 299*(17), 2083-2085. doi: 2010.1001/jama.2299.2017.2083.

Fond, G., Guillaume, S., Artero, S., Bernard, P., Ninot, G., Courtet, P., & Quantin, X. (2013). Self-reported major depressive symptoms at baseline impact abstinence prognosis in smoking cessation program. A one-year prospective study. *J Affect Disord., 149*(1-3), 418-421. doi: 410.1016/j.jad.2012.1011.1066. Epub 2012 Dec 1023.

Ford, E. S., Mokdad, A. H., & Gregg, E. W. (2004). Trends in cigarette smoking among US adults with diabetes: findings from the Behavioral Risk Factor Surveillance System. *Preventive Medicine, 39*(6), 1238-1242. doi: 10.1016/j.ypmed.2004.04.039

Gariepy, G., Malla, A., Wang, J., Messier, L., Strychar, I., Lesage, A., & Schmitz, N. (2012). Types of smokers in a community sample of individuals with Type 2 diabetes: a latent class analysis. *Diabetic Medicine, 29*(5), 586-592. doi: 10.1111/j.1464-5491.2011.03493.x

Glassman, A. H., Covey, L. S., Stetner, F., & Rivelli, S. (2001). Smoking cessation and the course of major depression: a follow-up study. *The Lancet, 357*(9272), 1929-1932.

Haire-Joshu, D. (2004). Smoking and Diabetes. *Diabetes Care, 27*(suppl 1), s74-s75. doi: 10.2337/diacare.27.2007.S74

Hanley, J. A., Negassa, A., Edwardes, M. D. d., & Forrester, J. E. (2003). Statistical Analysis of Correlated Data Using Generalized Estimating Equations: An Orientation. *American Journal of Epidemiology, 157*(4), 364-375. doi: 10.1093/aje/kwf215

Hayes, R., Dunsiger, S., & Borrelli, B. (2010). The influence of quality of life and depressed mood on smoking cessation among medically ill smokers. *Journal of Behavioral Medicine, 33*(3), 209-218. doi: 10.1007/s10865-010-9254-z

Health Canada. (2010). *Canadian Tobacco Use Monitoring Survey*. Ottawa, Ontario: Retrieved from http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/_ctums-esutc_prevalence/prevalence-eng.php#annual_06.

Health, U. D. o., & Services, H. (2004). The health consequences of smoking: a report of the surgeon general: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health Atlanta^ eGeorgia Georgia.

Hitsman, B., Borrelli, B., McChargue, D. E., Spring, B., & Niaura, R. (2003). History of depression and smoking cessation outcome: A meta-analysis. *Journal of Consulting and Clinical Psychology, 71*(4), 657-663. doi: 10.1037/0022-006x.71.4.657

Hokanson, J. M., Anderson, R. L., Hennrikus, D. J., Lando, H. A., & Kendall, D. M. (2006). Integrated tobacco cessation counseling in a diabetes self-management training program: a randomized trial of diabetes and reduction of tobacco. *Diabetes Educ., 32*(4), 562-570.

Hyland, A., Borland, R., Li, Q., Yong, H.-H., McNeill, A., Fong, G. T., . . . Cummings, K. M. (2006). Individual-level predictors of cessation behaviours among participants in the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control, 15*(suppl 3), iii83-iii94. doi: 10.1136/tc.2005.013516

Hymowitz, N., Cummings, K. M., Hyland, A., Lynn, W. R., Pechacek, T. F., & Hartwell, T. D. (1997). Predictors of smoking cessation in a cohort of adult smokers followed for five years. *Tobacco Control, 6*(suppl 2), S57. doi: 10.1136/tc.6.suppl_2.S57

Jones, H., Berard, L. D., MacNeill, G., Whitham, D., & Yu, C. (2013). Self-Management Education. *Canadian Journal of Diabetes, 37, Supplement 1*(0), S26-S30. doi: http://dx.doi.org/10.1016/j.jcjd.2013.01.015

Kroenke, K., Spitzer, R., & Williams, J. (2001). The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med, 16*, 606 - 613.

Lee, C.-w., & Kahende, J. (2007). Factors Associated With Successful Smoking Cessation in the United States, 2000. *American Journal of Public Health, 97*(8), 1503-1509. doi: 10.2105/ajph.2005.083527

McClave, A. K., Dube, S. R., Strine, T. W., Kroenke, K., Caraballo, R. S., & Mokdad, A. H. (2009). Associations between smoking cessation and anxiety and depression among U.S. adults. *Addictive Behaviors, 34*(6–7), 491-497. doi: 10.1016/j.addbeh.2009.01.005

McClave, A. K., Dube, S. R., Strine, T. W., & Mokdad, A. H. (2009). Associations between health-related quality of life and smoking status among a large sample of U.S. adults. *Preventive medicine, 48*(2), 173-179.

Moriarty, D., Zack, M., & Kobau, R. (2003). The Centers for Disease Control and Prevention's Healthy Days Measures–Population tracking of perceived physical and mental health over time. *Health and Quality of Life Outcomes, 1*(1), 37.

Newson, J. T., Huguet, N., Ramage-Morin, P. L., McCarthy, M. J., Bernier, J., Kaplan, M. S., & McFarland, B. H. (2012). *Health behaviour changes after diagnosis of chronic illness among Canadians aged 50 or older*. Statistics Canada Retrieved from http://www.statcan.gc.ca/pub/82-003-x/2012004/article/11740-eng.htm.

Persson, L.-G., & Hjalmarson, A. (2006). Smoking cessation in patients with diabetes mellitus: Results from a controlled study of an intervention programme in primary healthcare in Sweden. *Scandinavian Journal of Primary Health Care, 24*(2), 75-80. doi: 10.1080/02813430500439395

REVICKI, D. A., IRWIN, D., REBLANDO, J., & SIMON, G. E. (1994). The Accuracy of Self-Reported Disability Days. *Medical Care, 32*(4), 401-404.

Schmitz, N., Messier, L., Nitka, D., Ivanova, A., Gariepy, G., Wang, J., . . . Strychar, I. (2011). Factors Associated with Disability and Depressive Symptoms Among Individuals with Diabetes: A Community Study in Quebec. *Psychosomatics, 52*(2), 167-177. doi: 10.1016/j.psym.2010.11.020

Solberg, L. I., Desai, J. R., O'Connor, P. J., Bishop, D. B., & Devlin, H. M. (2004). Diabetic Patients Who Smoke: Are They Different? *Ann Fam Med, 2*(1), 26-32. doi: 10.1370/afm.36

Statistics Canada. (2009). *Canadian Community Health Survey 2.1*. Ottawa, Ontario: Retrieved from http://www23.statcan.gc.ca:81/imdb/p2SV.pl?Function=getSurvey&SDDS=3226&lang=en&db=imdb&adm=8&dis=2#b8.

Stone, J. A., Fitchett, D., Grover, S., Lewanczuk, R., & Lin, P. (2013). Vascular Protection in People with Diabetes. *Canadian Journal of Diabetes, 37, Supplement 1*(0), S100-S104. doi: http://dx.doi.org/10.1016/j.jcjd.2013.01.030

Twardella, D., Loew, M., Rothenbacher, D., Stegmaier, C., Ziegler, H., & Brenner, H. (2006). The diagnosis of a smoking-related disease is a prominent trigger for smoking cessation in a retrospective cohort study. *Journal of Clinical Epidemiology, 59*(1), 82-89.

Weinberger, A. H., Mazure, C. M., Morlett, A., & McKee, S. A. (2013). Two Decades of Smoking Cessation Treatment Research on Smokers with Depression: 1990–2010. *Nicotine & Tobacco Research, 15*(6), 1014-1031. doi: 10.1093/ntr/nts213

World Health Organization. (2011). Global status report on noncommunicable diseases 2010. In WHO (Ed.). Geneva, Switzerland.

4.17 Table 1

Table 1 – Socio-demographic and depression syndrome across Smoking Cessation				
Smoking Cessation Status	Successful Quitter (n = 794)	Unsuccessful Quitter (n = 189)	Non Attempter (n = 188)	p-value
Age (mean)	61.3	56.6	55.5	**0.000**
Gender				**0.024**
Female	45.3	53.4	54.3	
Marital Status				**0.000**
Single	9.6	20.1	17.6	
Widowed/Divorced/Separated	22.6	31.7	27.1	
Married	67.8	48.1	55.3	
Education				**0.049**
Less than High School	41.6	48.9	48.8	
High School Diploma	28.3	29.3	29.9	
Post-Secondary	30.2	21.8	21.7	
Employment				**0.000**
Retired	53.0	29.9	35.5	
Employed	32.6	40.1	37.6	
Unemployed	14.3	29.9	26.9	
Depression Syndrome				
Baseline	17.2	32.3	25.0	**0.000**
Follow-up 1	19.3	35.8	22.9	**0.001**
Follow-up 2	18.8	31.1	24.5	**0.025**
Follow-up 3	20.0	33.3	20.4	**0.025**

Note: P-values for Chi-square analysis, ANOVA for mean difference.

4.18 Table 2

Table 2 – Diabetes and illness characteristics across Smoking Cessation				
Smoking Cessation Status	Successful Quitter (n = 794)	Unsuccessful Quitter (n = 189)	Non Attempter (n = 188)	p-value
Years Diabetes diagnosis (mean)	11.50	9.80	8.98	**0.005**
Diabetes Treatment				0.059
Insulin	23.5	26.6	19.1	
Pills	69.8	62.8	69.7	
Neither	6.7	10.6	11.2	
Physical Activity				**0.004**
Inactive	30.2	36.4	44.0	
Moderately Active	35.3	35.3	31.5	
Active	34.5	28.3	24.5	
Alcohol Consumption				0.053
Never	36.2	42.8	42.7	
Less than twice a week	44.4	41.7	45.9	
Twice or more a week	19.4	15.5	11.4	
Diabetes complications				0.501
None	28.7	27.8	24.3	
1 or more	71.3	72.2	75.7	
Other chronic conditions				0.126
None	17.9	19.8	24.6	
1 or more	82.1	80.2	75.4	
Self Rated Health				**0.015**
Excellent/Very Good/Good	79.0	69.8	73.4	
Fair/Poor	21.0	30.2	26.5	
Disability Days (past month)				**0.001**
None	77.8	64.1	72.5	
1 or more	22.2	35.9	27.5	

Note: Note: P-values for Chi-square analysis, ANOVA for mean difference.

4.19 Table 3

Table 3 – Ever smoking quitting attempts, success and relapse				
	Baseline	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**
Made cessation attempt in previous 6 months				
All current smokers	189 (50.4)	120 (52.4)	87 (48.6)	84 (46.7)
Light Smokers	90 (64.7)	61 (67.0)	43 (58.1)	40 (58.0)
Heavy Smokers	99 (41.6)	59 (42.8)	44 (43.1)	44 (41.5)
p-value	**0.000**	**0.000**	**0.050**	**0.033**
Made quit attempt at subsequent wave				
All current smokers		64 (69.6)	47 (59.5)	42 (67.7)
Light Smokers		32 (72.7)	21 (56.8)	24 (82.8)
Heavy Smokers		32 (68.1)	26 (61.9)	18 (56.2)
p-value		**0.000**	**0.001**	**0.000**
Successfully Quit at next wave				
Unsuccessful attempt at previous wave				
Yes		19 (17.1)	14 (15.1)	7 (10.3)
No		11 (9.2)	8 (11.0)	9 (11.8)
p-value		n.s.	n.s.	n.s.
All current smokers		31 (13.5)	21 (12.7)	16 (11.5)
Light Smokers		17 (19.8)	9 (14.8)	12 (19.0)
Heavy Smokers		14 (9.7)	12 (11.5)	4 (5.3)
p-value		**0.013**	n.s.	**0.004**
Relapsed at subsequent wave				
Total		25 (5.5)	16 (4.4)	9 (2.9)
Light Smokers		15 (3.3)	12 (3.3)	8 (2.6)
Heavy Smokers		10 (2.2)	4 (1.1)	1 (0.3)
p-value		**0.001**	**0.006**	**0.003**

Note: Frequency n (% of category) presented; p-values are for chi-square analysis.
N.S. = non significant.

4.20 Table 4

Table 4	**Smoking cessation and Depression Syndrome 3 models**					
Model:	I		II		III	
Smoking cessation status	OR	95% CI	OR	95% CI	OR	95% CI
Successful Quitter	**1.00**	**REF**	**1.00**	**REF**	**1.00**	**REF**
Unsuccessful Quitter	2.17	(1.68-2.81)	1.73	(1.33-2.26)	1.53	(1.12-2.08)
Non-Attempter / Current Smoker	1.35	(1.01-1.80)	1.12	(0.83-1.53)	1.01	(0.72-1.42)

OR = Odds Ratio; CI = Confidence interval.
Model I – Smoking Cessation alone (unadjusted)
Model II - Adjusting for Age, Gender, Marital Status, Employment and Education
Model III - Adjust for Model I + Disability, Diabetes Complications, Chronic Conditions, Physical Activity, Alcohol use.

Chapter 5 - Conclusion

5.1 Restating objectives and findings summary

Smoking is a major modifiable risk factor for a number of non-communicable diseases, including diabetes(World Health Organization, 2011). In addition to the risk of developing diabetes(Xie, Liu, Wu, & Wakui, 2009), smoking is associated with all-cause mortality(Al-Delaimy et al., 2001; Chaturvedi et al., 1997) and the progression of diabetes related complications(D. Haire-Joshu et al., 1999). Despite these important clinical associations, smoking prevalence rates amongst those with diabetes appear to be similar to those within the general population, and appears to be stable over time(Clair, Meigs, & Rigotti, 2013). An overall better understanding and characterization of this sub-population is required to address this.

Cigarette smoking is also associated with depression(Berlin, Covey, & Glassman, 2009). This association is often characterized in a bi-directional manner(Chaiton et al., 2009), in which heavy cigarette use is related to higher levels of depression and higher levels of depressive symptoms leading to increased cigarette consumption(Breslau et al., 1998). Importantly, depression is twice as prevalent in those diagnosed with diabetes compared to those without(Anderson et al., 2001), and has been shown to equally influence the progression of complications(de Groot, Anderson, Freedland, Clouse, & Lustman, 2001) and all-cause mortality(W. Katon et al., 2008) within this population. Depression is also associated with poorer adherence to the self-care guidelines, which play a crucial role in controlling diabetes(Ciechanowski et al., 2000) and preventing disability(Schmitz, Wang, Malla, & Lesage, 2007). Smoking cessation is one such self-care behaviour that may be impacted by depression, although the exact relationship between quitting and depression remains complex(Wilhelm, Wedgwood, Niven, & Kay-Lambkin, 2006). Thus, the present studies' aims were to characterize the socio-demographic, lifestyle, diabetes and illness related characteristics of a community based sample with type-2 diabetes

according to their smoking behaviour. In addition to this, we also wanted to investigate the potential independent association between cigarette smoking and depression within this sample, while carefully controlling for potential confounders such as gender, education, alcohol consumption, disability, and the presence of other chronic medical illnesses. Finally, we wanted to characterize the sample across the same demographic and illness domains, this time by comparing individuals according to their smoking cessation class. Our results provide valuable information with regards to important differences between light and heavy smokers, current vs. former smokers, and never vs. ever smokers. We were also able to contrast data for those successful quitters to those who tried to quit but failed, and to those who did not make any cessation effort. Our studies' results highlight the important connection between depression and smoking behaviour. Both smoking and depression were highly associated at all points of our study, remained relatively stable over time, with smoking subsequently being associated with depression at follow-up, after controlling for baseline depression. These findings were extended to including smoking cessation, as compared to both successful quitters and non-attempters, unsuccessful quitters were more likely to have depression syndrome.

5.12 Implications of findings

Having reported smoking prevalence rates on par with those found in surveys conducted for the general population, and additionally observing a high degree of stability over time, efforts made to reduce smoking amongst those with diabetes appear to be inadequate, and thus need to be re-examined and strengthened. Given that those with diabetes are at increased risk of disability, morbidity, and mortality, any and all efforts to control modifiable factors, be they targeted at behaviour changes or improving the individual's mental health, can have important treatment implications.

In our first manuscript, we reported on a number of factors, including socio-demographic, diabetes, and illness related characteristics. Consistent with findings in those with other chronic conditions(Schmitz,

Kruse, & Kugler, 2007), current smokers had poorer overall profiles. They were more likely to be single, unemployed, and have lower levels of education compared to never and former smokers. They also were less likely to be physically active, another important self-care recommendation for those with diabetes. Moderate-heavy smokers were also more likely to have 2 or more diabetes related complications, while current smokers had increased levels of comorbid chronic illness. In people with diabetes, current smokers, and particularly current heavy smokers, should be made aware of the increased risk they face, especially in relation to complications of the diseases. Furthermore, health professionals should be keenly aware of the increased prevalence of major depression in this population, and how it may negatively affect diabetes outcomes in addition to self-care behaviours, including smoking. In fact, in our fully adjusted model, diabetes complications, other chronic illness, and mild-substantial disability were all associated with major depression. That smoking may serve as not only a source of poor physical health complications, but also adversely impact the mental health of individuals with diabetes independent of their disease characteristics is an important finding. Thus we concluded that smokers with diabetes were not only at increased risk of poor physical outcomes, but also potentially poor mental health outcomes.

In order to extend these conclusions, we conducted the longitudinal assessments of manuscript 2, in which we found a stability of smoking behaviours in this sample over a 4 year period. This stability in smoking behaviour was mirrored, although not quite as strongly, with a high and stable prevalence of depression syndrome over time in the cohort. Furthermore, the association between smoking and depression was further strengthened by the longitudinal association, in which moderate-heavy smoking was associated with depression syndrome at follow-up, after controlling for demographic and illness confounders, in addition to controlling for baseline depression syndrome in the fully adjusted model. Current smoking thus adversely affects both physical and mental health, which our findings extended to include both elevated current and future depression. Smoking has been shown to produce increased

negative affect, and chronic heavy smokers may be particularly at risk for mood fluctuations. Long term and persistent heavy smoking was thus implicated in both poor physical and mental health, especially dangerous for those with diabetes given they are already at increased risk. Individuals with diabetes thus require improved efforts aimed at promoting cessation.

In order to assess the impact of this association on cessation and quitting behaviour, our third manuscript characterized our study sample according to their cessation status. We compared those successful quitters (former smokers) to those who had attempted to quit (previous 6 months) but failed (unsuccessful quitters) and to those current smokers who did not attempt to quit (non-attempters). Our results highlighted the impact of depression, which was more strongly associated with unsuccessful quitters compared to both other groups at all 4 time points. Moreover, the odds of having depression syndrome were significant for unsuccessful quitters compared to successful quitters, a finding not replicated for non-attempters. Two possible explanations for this association include: 1) That depression does not impact motivation to quit, but impacts the individual's ability to do so; or 2) that those who are unsuccessful experience increases in depression syndrome relative to those who were successful and to those who did not make such an attempt. Either way, the implication that depression is associated with failure to quit in this population makes it imperative that health care providers address depression before and during a cessation attempt to maximize the likelihood of success.

5.13 Limitations

There are a number of limitations that need to be considered for the studies presented. Firstly, all individuals in our study were from the province of Quebec, and therefore may not be generalizable to the Canadian context in general or to other provinces. Due to our methodology, only those with landline telephones could be contacted, and therefore those without telephone access or with cell-phone access only were not eligible for our study. The variables used in the analyses of our studies were assessed via

self-report, including the primary variables of interest, smoking status and depression syndrome. Smoking status was assessed using questions taken from the Canadian Community Health Survey(Statistics Canada, 2009) and in general, self-reported smoking status is believed to be an accurate indicator of smoking behaviours(Rebagliato, 2002). Depression status was assessed using the Patient Health Questionnaire-9 (PHQ-9)(Kroenke, Spitzer, & Williams, 2001), which is a sensitive symptom screening tool which through the use of a scoring algorithm can provide a DSM-IV-TR diagnosis of major and minor depression. Despite the sensitivity and accuracy of the above mentioned methodology, there remain a number of issues to consider. For smoking status, and specifically ever smokers, we did not assess other potentially important factors, including smoking life years (cumulative years of persistent smoking), and conversely the time since quitting. Former smokers may be a particularly heterogeneous subsample, as we did not ascertain when individuals quit and for how long they had remained abstinent. Although we asked at each time point about cessation attempts in the previous 6 months, we did not ask about frequency or number of previous attempts individuals may have taken prior to the baseline survey, nor did we assess methods employed for cessation. We did not assess nicotine dependence, which may be a better indicator of problematic smoking than number of cigarettes consumed per day. Similarly, for depression, the PHQ-9 assesses symptoms experienced in the past 2 weeks. Although the PHQ-9 was been reported to have likelihood ratios greater than 4 when compared to the SCID(Phelan et al., 2010), the PHQ-9 is not a structured clinical interview and may have over-estimated of the prevalence of depression in our study sample.

In manuscript 1, our results were based on cross-sectional data only, and therefore no causal relationship between any of the variables assessed could be drawn. Manuscript 2 used longitudinal assessment, controlling for baseline depression syndrome – however given we did not assess for a history of depression, this may impact our results. Manuscript 3 classified smokers according to their cessation status. Again, we did not have detailed information for these categories, including how long a

successful quitter had been abstinent, or the number of previous cessation attempts. In addition, we did not have enough power to assess the impact of depression on subsequent cases of quitting or relapse, nor were we able to assess other potential variables of interest, such as the individuals current readiness to change (i.e. stages of change model(J. O. Prochaska & Norcross, 2001)).

5.14 Smoking and depression – A double hazard for type-2 diabetes

The presence of current smoking and/or current depression is of serious concern for those with type-2 diabetes. Not only a risk factor for the transition to impaired glucose tolerance and ultimately to type-2 diabetes, continued smoking equally accentuates the negative prognosis for those with diabetes by accelerating the development of illness complications. While efforts over the last few decades have included targeted messaging about the dangers posed by cigarettes for the general population(Friend & Levy, 2002; Goel & Nelson, 2006), current smoking trends amongst those with concurrent diabetes may underline an important missing element: the need for health care professionals to specifically emphasize the increased risk posed by smoking with the disease. Diabetes educators should aim to not only introduce the notion of quitting by highlighting the overall benefits, but should stress the advantages specific to diabetes self-care and diabetes outcomes. Twardella(Twardella et al., 2006) reported on the importance of being diagnosed with a smoking related disease as a trigger for cessation. Increasing awareness amongst those with newly diagnosed type-2 diabetes on the dangers of smoking, which they may not be completely aware of, should be a key area for diabetes educators to further improve. While the risk factors for the development of type-2 diabetes are numerous and include both non-modifiable (age, gender, genetics, family history) and modifiable (obesity, physical activity, smoking)(Deshpande et al., 2008) factors, integrating current smoking education, prevention, and cessation strategies with current diabetes education programs appears to be a viable option(Hokanson et al., 2006). In a study conducted in Sweden(Persson & Hjalmarson, 2006), smokers were identified

using computerized records and were invited to participate in a smoking cessation group. This group was implemented by diabetes nurses who were given half-day training in motivational interviewing and smoking cessation. Ultimately, this group produced higher abstinence rates 1 year later compared to the treatment as usual group. Similarly, a controlled trial for smokers with diabetes at primary health centers in Spain(Canga et al., 2000) featured an intervention group who received a 40-minute meeting with a nurse (providing counselling, education, and a negotiated cessation date) along with follow-up telephone calls and letters. The treatment group displayed both increased incidence of cessation, as well as a decrease in the amount of daily cigarette consumption compared to the treatment as usual group. These initial results thus indicate that integrated cessation counseling (i.e. trained nurse) into currently existing diabetes education and treatment paradigms can be effective strategies. In addition to these controlled trials, MacAller(MacAller, Brown, Black, & Greenwood, 2011) reported on the effects of a statewide campaign conducted in California to help inform diabetes educators on available smoking cessation interventions, along with the development of a smoking cessation toolkit they could use. The intervention was determined to be both sustainable and an effective strategy for increasing the use of currently available cessation programs (e.g. cessation hotline), and is a strong example of the kind of cross-promotion and integration needed to maximize the use of services already available to the community. Still, despite these positive findings, more studies are needed to investigate which cessation interventions are best suited for those with type-2 diabetes. Tonstad(Tonstad, 2009) specifically highlights the lack of information on the safety and efficacy of smoking cessation pharmacological interventions in those with diabetes, a major gap in current knowledge. A combination of behavioural and pharmacological interventions are currently considered to be the most efficacious for producing abstinence in smokers(Stead & Lancaster, 2012). Again, a basic integration of services may provide additional benefits, and thus research into evidence based practices designed to integrate services would also aid in determining the most effective and successful combinations.

Unfortunately, the lack of education and poor integration of treatment strategies are not the only important gaps in the literature. Cessation interventions that neglect to account for past or concurrent depression may find it difficult to provide the desired outcomes. The association we observed between smoking and depression within our sample was robust, given we investigated both the cross-sectional and longitudinal link while controlling for socio-demographic and disease characteristics. While this association appears to be bi-directional within the literature(Berlin et al., 2009), others including recent longitudinal evidence seems to implicate heavy smoking with the incidence of major depression(Boden et al., 2010; Flensborg-Madsen et al., 2011; Klungsoyr et al., 2006). A recent study using data from the National Population Health Survey (NPHS)(Khaled et al., 2012) focused specifically on persistent heavy smoking and incidence of major depression, finding that the risk was greater for current-heavy smokers compared to former-heavy smokers. Given the results from our second manuscript where smoking behaviour appeared stable over time, in conjunction with the age of smoking initiation approximately 16 for ever smokers in our sample (reported in manuscript 3), it is possible that a portion of our sample have been persistently smoking for several decades. This consistent smoking may have caused significant cumulative damage to both their physical and mental health, increasing their risk of depression on top of other adverse health outcomes. The authors of the study(Khaled et al., 2012) also found that the risk of major depression episode was inversely related to years of abstinence, highlighting the need to not only quit as soon as possible, but remain abstinent.

That smoking produces negative affect is not itself a novel finding(A. C. Parrott, 2004); unfortunately, many smokers hold the misguided belief that smoking serves as an affect modifier, positively affecting their mood(Heinz, Kassel, Berbaum, & Mermelstein, 2010). Even more unfortunate, this belief may also lead to decreased enthusiasm on the part of health care providers to push for cessation(J. J. Prochaska, 2011). Regrettably, given the dangers of smoking, this unwillingness to increase the burden on their patients by pushing cessation means that health care providers may be indirectly contributing to

morbidity and mortality rates in this population. Although many individuals are aware of the addictive properties of nicotine, the deprivation reversal model(A. Parrott, 1995) thought to be responsible for nicotine's effect on mood is less well understood. Parrott(Andrew C. Parrott & Murphy, 2012) recently conducted a study using an information leaflet designed to address this. He found that knowledge and understanding levels increased, and that these gains appeared stable after 1 week. Emphasizing this information to both health care providers and consumers may therefore be beneficial in addressing maladaptive beliefs held about smoking.

On the other hand, depression itself may impact the ability of individuals to quit. A recent study(Fond et al., 2013) highlighted the negative impact of self-reported depressive symptoms on 1-year abstinence rates of smokers; others(Hitsman et al., 2003), however, have found no relationship. Our study found a strong association between unsuccessful quitters and depression syndrome at all 4 time points, providing evidence for this association in those with diabetes. Possible explanations for this association include: 1) that depression negatively impacted the ability of the individual to quit (but not their motivation to attempt to quit); or 2) that the inability to quit produced increased symptoms of depression. Either possibility might be mediated by the effects of increasing symptoms of withdrawal. For example, individuals with lifetime depression may experience stronger symptoms of withdrawal; conversely, symptoms of withdrawal may serve as a stressor, precipitating depression. Findings supporting both possibilities exist. In one study(Bolam, West, & Gunnell, 2010), symptoms of depression and anxiety were not more likely following smoking cessation when those symptoms were not present at baseline. In another, unsuccessful quitters experienced poorer self-perceived health related quality of life (HRQoL) leading to mental distress, as was the case in a study using data from the 2006 BRFSS(A. K. McClave, Dube, Strine, & Mokdad, 2009). Depression may therefore be an important mediator for smoking cessation in those motivated to attempt to quit. Among those with a chronic medical illness, the odds of smoking cessation increased for every unit decrease in perceived Physical Quality of Life

(PQoL), but only in those individuals without a depressed mood(Hayes, Dunsiger, & Borrelli, 2010). In our study, unsuccessful quitters were not only more likely to have depression syndrome, but were also more likely to report poor/fair self rated health. It is therefore possible that while motivated to quit, their failure produced negative health perceptions, leading to elevated symptoms of depression.

Assessing the patient's beliefs about smoking and cessation may also be important for health care providers to consider. Smoking expectancies may similarly impact the ability to quit, and appear to be affected by the presence of comorbid depression. Weinberger(Weinberger, George, & McKee, 2010) found that those with a history of major depression endorsed beliefs that smoking decreased negative affect, boredom, and cravings, while also endorsing in the belief that cigarette smoking help manage weight gain. Weight gain as a consequence of smoking cessation might be a potential barrier(Sherman, 2005), which health care providers should target by providing education emphasizing the long-term gains, while closely monitoring any short term changes accompanying cessation. Smokers should also be made aware that any impact on mood is likewise short-term, as overall mood does appear to increase post cessation in a study following successful quitters(Shahab & West, 2009).

Those who do not quit as a consequence of their diagnosis may be particularly difficult cases with poorer prognoses: a recent Canadian study(Agborsangaya et al., 2013) found that those diagnosed for more than 6 years with type-2 diabetes had difficulty following treatment regimens, including remaining abstinent from smoking. It becomes clear that addressing all of these issues individually could severely increase the burden on the individual. An integrated approach, using diabetes education while specifically targeting both smoking cessation and depression needs to be developed to maximize effectiveness. One such study undertaken in the U.K., the DESMOND trial(Davies et al., 2008) conducted a structured group interview for newly diagnosed individuals with type-2 diabetes. The group intervention was implemented in primary care facilities around the country, using a 6-hour education

program delivered by 2 trained health professions. This group intervention focused on a number of outcomes, including biomedical (HbA1c levels), psychosocial (illness-related beliefs, depression) and lifestyle measures (smoking cessation, weight loss). At 12-months, those in the integrated intervention group showed increased illness belief scores, lost more weight, had lower levels of depression, and displayed a 3-fold increased odds of successfully quitting smoking.

5.15 Future Directions and Conclusion

There are a number of directions that future research should seek to address with regards to smoking and depression within diabetes. Many studies that currently assess smoking in those with concurrent diabetes dichotomize it, potentially missing valuable information about the subject's history of abuse and risk profile associated with their current level of smoking. Although any level of smoking is potentially harmful, in our studies we found the worst outcomes to be associated with heavy smokers. In some previous studies specifically assessing smoking behaviour in those with diabetes, smokers as opposed to non-smokers engaged in poorer self-care behaviours overall(Gucciardi, Mathew, Demelo, & Bondy, 2011; Solberg et al., 2004). Understanding how smoking may affect an individual's desire to partake in or continue to practice self-care behaviours would be of value to health care providers as they attempt to tailor their treatments. Moreover, the impact which a failed cessation attempt has on self-efficacy, as well as perceived physical and mental health, may be another avenue of investigation. Increasing support to those who have made attempts and failed may help mitigate the psychological impact of failing to quit.

Studies in smoking and depression have highlighted how self-efficacy(Minnix et al., 2011) and beliefs about smoking(Weinberger et al., 2010) may differ across groups. These ideas need to be addressed, with improved dissemination of evidence needed to educate and help clarify misconceptions related to smoking. Studies assessing those with newly diagnosed type-2 diabetes and their current beliefs about

smoking, especially with regards to smoking's impact on their diabetes are needed. These may help diabetes educators target and clarify gaps in knowledge or potentially dangerous patient perceptions. The use of a qualitative study assessing individual's beliefs about their smoking, how it may have affected their diagnosis, and how they feel it can affect the progression of their illness going forward could be an important first step.

The relationship between smoking, smoking cessation and depression must also be further investigated. As Weinberger(Weinberger, Mazure, Morlett, & McKee, 2013) points out, although the literature studying this phenomenon has continued to grow over the past 2 decades, there is a almost no evidence for a specific treatment approach tailored to those with major or minor depression. The relationship between cessation and depression may be bidirectional in nature, such that those with depression experience worse symptoms of withdrawal, which may feed back onto their mood and increase symptoms of depression. Addressing the disproportionate number of smokers who currently have depression may be necessary before we see any meaningful declines in smoking prevalence.

The term integration has appeared numerous times in the studies presented above, as well as in the convening discussion. The DESMOND trial(Davies et al., 2008) demonstrates some of the clinical advantage of integrating education and interventions targeting different domains. The need for an integrated approach for this population echoes research in other related areas. For example, new clinical approaches for substance abusers with concurrent mental illnesses are currently tailoring integrated interventions that address both issues simultaneously. These could be extending to the treatment of those with nicotine dependence and concurrent depression, providing extra cessation support while closely monitoring symptoms of depression. Consequently, the idea that the diagnosis of an illness represents a 'teachable moment'(McBride, Emmons, & Lipkus, 2003) should also be

considered. Newly diagnosed individuals could be referred to different programs with different modules (i.e. one for cessation should they be a smoker) depending on their clinical needs and characteristics.

In conclusion, both smoking and depression are associated with a number of adverse health outcomes in a community based sample with type-2 diabetes, including disability and diabetes related complications. Furthermore, smoking and depression displayed strong independent association with each other, even after controlling for important socio-demographic and illness related characteristics. Moreover, moderate-heavy smoking was associated with higher depression at follow-up, linking current heavy smoking with poorer mental health outcomes. In terms of diabetes treatment regimes, smoking cessation is recognized as an important self-care behaviour, but smoking prevalence rates within this population continue to remain dangerously high. Furthermore, both smoking and depression appears to be relatively stable over time in this population, increasing individuals affected by this co-morbidity's risk of disability, morbidity and mortality. In our sample, depression was associated with unsuccessful quitters, compared to successful quitters and non-attempters, and therefore may play a crucial role in cessation outcomes. Identifying cessation treatments that address depression, and which can be integrated into current diabetes education programs, is an key area going forward in order to minimize disability, morbidity and mortality in this at risk population. Integration of health services, including improved knowledge dissemination aimed at increasing awareness and education of individuals should be encouraged at the level of primary health care providers.

REFERENCES

Agborsangaya, C. B., Gee, M. E., Johnson, S. T., Dunbar, P., Langlois, M. F., Leiter, L. A., . . . Johnson, J. A. (2013). Determinants of lifestyle behavior in type 2 diabetes: results of the 2011 cross-sectional survey on living with chronic diseases in Canada. *BMC Public Health., 13:451.*(doi), 10.1186/1471-2458-1113-1451.

Al-Delaimy, W. K., Willett, W. C., Manson, J. E., Speizer, F. E., & Hu, F. B. (2001). Smoking and Mortality Among Women With Type 2 Diabetes The Nurses' Health Study cohort. *Diabetes Care, 24*(12), 2043-2048.

Ali, S., Stone, M. A., Peters, J. L., Davies, M. J., & Khunti, K. (2006). The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabetic Medicine, 23*(11), 1165-1173.

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The Prevalence of Comorbid Depression in Adults With Diabetes. *Diabetes Care, 24*(6), 1069-1078.

Anne, E. (2007). The role of depression and anxiety in onset of diabetes in a large population-based study. *Journal of Psychosomatic Research, 62*(1), 31-38. doi: 10.1016/j.jpsychores.2006.07.009

Bala, M., Strzeszynski, L., & Cahill, K. (2008). Mass media interventions for smoking cessation in adults. *Cochrane Database Syst Rev, 1*.

Benowitz, N. L. (2010). Nicotine addiction. *The New England journal of medicine, 362*(24), 2295.

Bergman, B. C., Perreault, L., Hunerdosse, D., Kerege, A., Playdon, M., Samek, A. M., & Eckel, R. H. (2012). Novel and reversible mechanisms of smoking-induced insulin resistance in humans. *Diabetes, 61*(12), 3156-3166.

Berlin, I., Covey, L. S., & Glassman, A. H. (2009). Smoking and Depression: A Co-morbidity. [Article]. *Journal of Dual Diagnosis, 5*(2), 149-158. doi: 10.1080/15504260902870129

Beulens, J. W., Grobbee, D. E., & Nealb, B. (2010). The global burden of diabetes and its complications: an emerging pandemic. *European Journal of Cardiovascular Prevention & Rehabilitation, 17*(1 suppl), s3-s8.

Boden, J. M., Fergusson, D. M., & Horwood, L. J. (2010). Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. *The British Journal of Psychiatry, 196*(6), 440-446.

Bolam, B., West, R., & Gunnell, D. (2010). Does Smoking Cessation Cause Depression and Anxiety? Findings from the ATTEMPT Cohort. *Nicotine & Tobacco Research, 13*(3), 209-214.

Bondy, S. J., Victor, J. C., Diemert, L. M., Mecredy, G. C., Chaiton, M., Brown, K. S., . . . Schwartz, R. (2013). Transitions in Smoking Status Over Time in a Population-Based Panel Study of Smokers. *Nicotine & Tobacco Research, 15*(7), 1201-1210. doi: 10.1093/ntr/nts259

Breslau, N., Peterson, E. L., Schultz, L. R., Chilcoat, H. D., & Andreski, P. (1998). Major depression and stages of smoking: A longitudinal investigation. *Archives of General Psychiatry, 55*(2), 161-166. doi: 10.1001/archpsyc.55.2.161

Bruce, D., Davis, W., Starkstein, S., & Davis, T. (2005). A prospective study of depression and mortality in patients with type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia, 48*(12), 2532-2539-2539. doi: 10.1007/s00125-005-0024-3

Canadian Diabetes Association. (2013). Diabetes facts. Retrieved 2013-07-02, from CDA http://www.diabetes.ca/documents/about-diabetes/114001_08-358-diabetes_0413_lc_final.pdf

Canga, N., De Irala, J., Vara, E., Duaso, M. J., Ferrer, A., & Martinez-Gonzalez, M. A. (2000). Intervention study for smoking cessation in diabetic patients: a randomized controlled trial in both clinical and primary care settings. *Diabetes Care., 23*(10), 1455-1460.

Chaiton, M., Cohen, J., O'Loughlin, J., & Rehm, J. (2009). A systematic review of longitudinal studies on the association between depression and smoking in adolescents. *BMC Public Health, 9*(1), 356.

Chaiton, M., Cohen, J., O'Loughlin, J., & Rehm, J. (2010). Use of cigarettes to improve affect and depressive symptoms in a longitudinal study of adolescents. *Addictive Behaviors, 35*(12), 1054-1060.

Chakkarwar, V. A. (2012). Smoking in diabetic nephropathy: sparks in the fuel tank? *World journal of diabetes, 3*(12), 186.

Chaturvedi, N., Stevens, L., Fuller, J. H., & The World Health Organization Multinational Study, G. (1997). Which Features of Smoking Determine Mortality Risk in Former Cigarette Smokers With Diabetes? The World Health Organization Multinational Study Group. *Diabetes Care, 20*(8), 1266-1272.

Ciechanowski, P. S., Katon, W. J., & Russo, J. E. (2000). Depression and Diabetes: Impact of Depressive Symptoms on Adherence, Function, and Costs. *Arch Intern Med, 160*(21), 3278-3285. doi: 10.1001/archinte.160.21.3278

Clair, C., Meigs, J. B., & Rigotti, N. A. (2013). Smoking behavior among US adults with diabetes or impaired fasting glucose. *Am J Med., 126*(6), 541.e515-548. doi: 510.1016/j.amjmed.2012.1011.1029. Epub 2013 Apr 1015.

Danaei, G., Ding, E. L., Mozaffarian, D., Taylor, B., Rehm, J., Murray, C. J. L., & Ezzati, M. (2009). The Preventable Causes of Death in the United States: Comparative Risk Assessment of Dietary, Lifestyle, and Metabolic Risk Factors. *PLoS Med, 6*(4), e1000058. doi: 10.1371/journal.pmed.1000058

Davies, M. J., Heller, S., Skinner, T. C., Campbell, M. J., Carey, M. E., Cradock, S., . . . Khunti, K. (2008). Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: Cluster randomised controlled trial. *BMJ, 336*(7642), 491-495.

de Groot, M., Anderson, R., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). Association of Depression and Diabetes Complications: A Meta-Analysis. *Psychosomatic Medicine, 63*(4), 619-630.

Deshpande, A. D., Harris-Hayes, M., & Schootman, M. (2008). Epidemiology of Diabetes and Diabetes-Related Complications. *Physical Therapy, 88*(11), 1254-1264. doi: 10.2522/ptj.20080020

Ding El, H. F. B. (2007). Smoking and type 2 diabetes: Underrecognized risks and disease burden. *JAMA, 298*(22), 2675-2676. doi: 10.1001/jama.298.22.2675

Egede, L. E. (2007). Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *General Hospital Psychiatry, 29*(5), 409-416. doi: 10.1016/j.genhosppsych.2007.06.002

Egede, L. E., & Zheng, D. (2003). Independent Factors Associated With Major Depressive Disorder in a National Sample of Individuals With Diabetes. *Diabetes Care, 26*(1), 104-111. doi: 10.2337/diacare.26.1.104

Egede, L. E., Zheng, D., & Simpson, K. (2002). Comorbid Depression is Associated With Increased Health Care Use and Expenditures in Individuals With Diabetes. *Diabetes Care, 25*(3), 464-470. doi: 10.2337/diacare.25.3.464

Eliasson, B. (2003). Cigarette smoking and diabetes. *Progress in Cardiovascular Diseases, 45*(5), 405-413.

Fagan, P., & Rigotti, N. A. (2009). Light and intermittent smoking: The road less traveled. *Nicotine & Tobacco Research, 11*(2), 107-110. doi: 10.1093/ntr/ntn015

Flensborg-Madsen, T., Bay von Scholten, M., Flachs, E. M., Mortensen, E. L., Prescott, E., & Tolstrup, J. S. (2011). Tobacco smoking as a risk factor for depression. A 26-year population-based follow-up study. *Journal of Psychiatric Research, 45*(2), 143-149.

Fond, G., Guillaume, S., Artero, S., Bernard, P., Ninot, G., Courtet, P., & Quantin, X. (2013). Self-reported major depressive symptoms at baseline impact abstinence prognosis in smoking cessation program. A one-year prospective study. *J Affect Disord., 149*(1-3), 418-421. doi: 410.1016/j.jad.2012.1011.1066. Epub 2012 Dec 1023.

Ford, E. S., Mokdad, A. H., & Gregg, E. W. (2004). Trends in cigarette smoking among US adults with diabetes: findings from the Behavioral Risk Factor Surveillance System. *Preventive Medicine, 39*(6), 1238-1242. doi: 10.1016/j.ypmed.2004.04.039

Fowler, M. J. (2008). Microvascular and Macrovascular Complications of Diabetes. *Clinical Diabetes, 26*(2), 77-82. doi: 10.2337/diaclin.26.2.77

Fowles, J., Bates, M., & Noiton, D. (2000). The chemical constituents in cigarettes and cigarette smoke: priorities for harm reduction. *A report of the New Zealand Ministry of Health. New Zealand Ministry of Health, Porirua*.

Friend, K., & Levy, D. T. (2002). Reductions in smoking prevalence and cigarette consumption associated with mass-media campaigns. *Health Education Research, 17*(1), 85-98.

Glassman, A. H., Covey, L. S., Stetner, F., & Rivelli, S. (2001). Smoking cessation and the course of major depression: a follow-up study. *The Lancet, 357*(9272), 1929-1932.

Glassman, A. H., Helzer, J. E., Covey, L. S., Cottler, L. B., Stetner, F., Tipp, J. E., & Johnson, J. (1990). Smoking, Smoking Cessation, and Major Depression. *JAMA: The Journal of the American Medical Association, 264*(12), 1546-1549.

Goel, R. K., & Nelson, M. A. (2006). The effectiveness of Anti-Smoking legislation: A review. *Journal of Economic Surveys, 20*(3), 325-355.

Golden, S. H., Lazo, M., Carnethon, M., Bertoni, A. G., Schreiner, P. J., Roux, A. V. D., . . . Lyketsos, C. (2008). Examining a Bidirectional Association Between Depressive Symptoms and Diabetes. *JAMA, 299*(23), 2751-2759. doi: 10.1001/jama.299.23.2751

Gucciardi, E., Mathew, R., Demelo, M., & Bondy, S. J. (2011). Profiles of smokers and non-smokers with type 2 diabetes: initial visit at a diabetes education centers. *Prim Care Diabetes, 5*(3), 185-194. doi: 10.1016/j.pcd.2011.03.001

Gunn, J., Ayton, D., Densley, K., Pallant, J., Chondros, P., Herrman, H., & Dowrick, C. (2012). The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort. *Social Psychiatry and Psychiatric Epidemiology, 47*(2), 175-184. doi: 10.1007/s00127-010-0330-z

Haire-Joshu, D., Glasgow, R. E., & Tibbs, T. L. (1999). Smoking and diabetes. *Diabetes Care, 22*(11), 1887-1898.

Haire-Joshu, D., Heady, S., Thomas, L., Schechtman, K., & Fisher, E. B. (1994). Depressive symptomatology and smoking among persons with diabetes. *Research in Nursing & Health, 17*(4), 273-282. doi: 10.1002/nur.4770170406

Hayes, R., Dunsiger, S., & Borrelli, B. (2010). The influence of quality of life and depressed mood on smoking cessation among medically ill smokers. *Journal of Behavioral Medicine, 33*(3), 209-218. doi: 10.1007/s10865-010-9254-z

Health Canada. (2010). *Canadian Tobacco Use Monitoring Survey*. Ottawa, Ontario: Retrieved from http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/_ctums-esutc_prevalence/prevalence-eng.php#annual_06.

Heinz, A. J., Kassel, J. D., Berbaum, M., & Mermelstein, R. (2010). Adolescents' expectancies for smoking to regulate affect predict smoking behavior and nicotine dependence over time. *Drug and Alcohol Dependence, 111*(1–2), 128-135. doi: http://dx.doi.org/10.1016/j.drugalcdep.2010.04.001

Hitsman, B., Borrelli, B., McChargue, D. E., Spring, B., & Niaura, R. (2003). History of depression and smoking cessation outcome: A meta-analysis. *Journal of Consulting and Clinical Psychology, 71*(4), 657-663. doi: 10.1037/0022-006x.71.4.657

Hokanson, J. M., Anderson, R. L., Hennrikus, D. J., Lando, H. A., & Kendall, D. M. (2006). Integrated tobacco cessation counseling in a diabetes self-management training program: a randomized trial of diabetes and reduction of tobacco. *Diabetes Educ., 32*(4), 562-570.

Husten, C. G. (2009). How should we define light or intermittent smoking? Does it matter? *Nicotine & Tobacco Research, 11*(2), 111-121. doi: 10.1093/ntr/ntp010

Hyland, A., Borland, R., Li, Q., Yong, H.-H., McNeill, A., Fong, G. T., . . . Cummings, K. M. (2006). Individual-level predictors of cessation behaviours among participants in the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control, 15*(suppl 3), iii83-iii94. doi: 10.1136/tc.2005.013516

International Diabetes Federation. (2011). IDF Diabetes Atlas, 5th edn. In I. D. Federation (Ed.), (Vol. 2012). Brussels, Belgium: International Diabetes Federation.

Jamal, M., Willem Van der Does, A. J., Cuijpers, P., & Penninx, B. W. J. H. Association of smoking and nicotine dependence with severity and course of symptoms in patients with depressive or anxiety disorder. *Drug and Alcohol Dependence*(0). doi: 10.1016/j.drugalcdep.2012.05.001

Janz, T. (2012). *Health at a glance: Current Smoking Trends*. Ottawa, Ontario: Retrieved from http://www.statcan.gc.ca/pub/82-624-x/2012001/article/11676-eng.htm.

Katon, W., Fan, M.-Y., Unützer, J., Taylor, J., Pincus, H., & Schoenbaum, M. (2008). Depression and Diabetes: A Potentially Lethal Combination. *Journal of General Internal Medicine, 23*(10), 1571-1575-1575. doi: 10.1007/s11606-008-0731-9

Katon, W., Von Korff, M., Ciechanowski, P., Russo, J., Lin, E., Simon, G., . . . Young, B. (2004). Behavioral and Clinical Factors Associated With Depression Among Individuals With Diabetes. *Diabetes Care, 27*(4), 914-920. doi: 10.2337/diacare.27.4.914

Katon, W. J., Rutter, C., Simon, G., Lin, E. H. B., Ludman, E., Ciechanowski, P., . . . Von Korff, M. (2005). The Association of Comorbid Depression With Mortality in Patients With Type 2 Diabetes. *Diabetes Care, 28*(11), 2668-2672.

Kendler, K. S., Neale, M. C., MacLean, C. J., Heath, A. C., & et al. (1993). Smoking and major depression: A causal analysis. *Archives of General Psychiatry, 50*(1), 36-43.

Kenfield, S. A., Wei, E. K., Rosner, B. A., Glynn, R. J., Stampfer, M. J., & Colditz, G. A. (2010). Burden of smoking on cause-specific mortality: application to the Nurses' Health Study. *Tobacco Control, 19*(3), 248-254. doi: 10.1136/tc.2009.032839

Khaled, S. M., Bulloch, A. G., Williams, J. V. A., Hill, J. C., Lavorato, D. H., & Patten, S. B. (2012). Persistent heavy smoking as risk factor for major depression (MD) incidence – Evidence from a longitudinal Canadian cohort of the National Population Health Survey. *Journal of Psychiatric Research, 46*(4), 436-443. doi: 10.1016/j.jpsychires.2011.11.011

Klungsoyr, O., NygÃrd, J. F., Sorensen, T., & Sandanger, I. (2006). Cigarette Smoking and Incidence of First Depressive Episode: An 11-Year, Population-based Follow-up Study. *American Journal of Epidemiology, 163*(5), 421-432.

Knol, M., Twisk, J., Beekman, A., Heine, R., Snoek, F., & Pouwer, F. (2006). Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia, 49*(5), 837-845. doi: 10.1007/s00125-006-0159-x

Kroenke, K., Spitzer, R., & Williams, J. (2001). The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med, 16*, 606 - 613.

Laje, R., Berman, J., & Glassman, A. (2001). Depression and nicotine: Preclinical and clinical evidence for common mechanisms. *Current Psychiatry Reports, 3*(6), 470-474-474. doi: 10.1007/s11920-001-0040-z

Lawrence, D., Mitrou, F., & Zubrick, S. (2009). Smoking and mental illness: results from population surveys in Australia and the United States. *BMC Public Health, 9*(1), 285.

Lee, C.-w., & Kahende, J. (2007). Factors Associated With Successful Smoking Cessation in the United States, 2000. *American Journal of Public Health, 97*(8), 1503-1509. doi: 10.2105/ajph.2005.083527

Leung, J., Gartner, C., Hall, W., Lucke, J., & Dobson, A. (2012). A longitudinal study of the bi-directional relationship between tobacco smoking and psychological distress in a community sample of young Australian women. *Psychological medicine, 42*(6), 1273.

Lin, E. H. B., Rutter, C. M., Katon, W., Heckbert, S. R., Ciechanowski, P., Oliver, M. M., . . . Von Korff, M. (2010). Depression and Advanced Complications of Diabetes. *Diabetes Care, 33*(2), 264-269. doi: 10.2337/dc09-1068

Lustman, P. J., Anderson, R. J., Freedland, K. E., de Groot, M., Carney, R. M., & Clouse, R. E. (2000). Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care, 23*(7), 934-942. doi: 10.2337/diacare.23.7.934

Lustman, P. J., & Clouse, R. E. (2007). Depression in Diabetes: The Chicken or the Egg? *Psychosomatic Medicine, 69*(4), 297-299. doi: 10.1097/PSY.0b013e318060cc2d

MacAller, T., Brown, M., Black, K., & Greenwood, D. (2011). Collaborating With Diabetes Educators to Promote Smoking Cessation for People With Diabetes. *The Diabetes Educator, 37*(5), 625-632. doi: 10.1177/0145721711416010

Marcus, M., Yasamy, M., van Ommeren, M., Chisholm, D., & Saxena, S. (2012). Depression: A global public health concern. WHO Department of Mental Health and Substance Abuse. *World Health Organization. Accessed on http://www. who. int/mental_health/management/depression/who_paper_depression_wfmh_2012. pdf*.

Mathers, C. D., & Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS medicine, 3*(11), e442.

McBride, C., Emmons, K., & Lipkus, I. (2003). Understanding the potential of teachable moments: the case of smoking cessation. *Health Education Research, 18*(2), 156-170.

McClave, A. K., Dube, S. R., Strine, T. W., & Mokdad, A. H. (2009). Associations between health-related quality of life and smoking status among a large sample of U.S. adults. *Preventive medicine, 48*(2), 173-179.

McClave, A. K., McKnight-Eily, L. R., Davis, S. P., & Dube, S. R. (2010). Smoking Characteristics of Adults With Selected Lifetime Mental Illnesses: Results From the 2007 National Health Interview Survey. *American Journal of Public Health, 100*(12), 2464-2472. doi: 10.2105/ajph.2009.188136

Mezuk, B., Eaton, W. W., Albrecht, S., & Golden, S. H. (2008). Depression and Type 2 Diabetes Over the Lifespan. *Diabetes Care, 31*(12), 2383-2390. doi: 10.2337/dc08-0985

Mineur, Y. S., & Picciotto, M. R. (2010). Nicotine receptors and depression: revisiting and revising the cholinergic hypothesis. *Trends in Pharmacological Sciences, 31*(12), 580-586. doi: 10.1016/j.tips.2010.09.004

Minnix, J. A., Blalock, J. A., Marani, S., Prokhorov, A. V., & Cinciripini, P. M. (2011). Self-Efficacy Mediates the Effect of Depression on Smoking Susceptibility in Adolescents. *Nicotine & Tobacco Research, 13*(8), 699-705.

Morrell, H. E. R., Cohen, L. M., & McChargue, D. E. (2010). Depression vulnerability predicts cigarette smoking among college students: Gender and negative reinforcement expectancies as contributing factors. *Addictive Behaviors, 35*(6), 607-611.

Morrish, N., Wang, S.-L., Stevens, L., Fuller, J., & Keen, H. (2001). Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia, 44*(2), S14-S21.

Nolan, C. J., Damm, P., & Prentki, M. (2011). Type 2 diabetes across generations: from pathophysiology to prevention and management. *The Lancet, 378*(9786), 169-181.

Parrott, A. (1995). Smoking cessation leads to reduced stress, but why? *Substance Use & Misuse, 30*(11), 1509-1516.

Parrott, A. C. (2004). Heightened stress and depression follow cigarette smoking. *Psychol Rep, 94*(1), 33-34.

Parrott, A. C., & Murphy, R. S. (2012). Explaining the stress-inducing effects of nicotine to cigarette smokers. *Human Psychopharmacology: Clinical and Experimental, 27*(2), 150-155. doi: 10.1002/hup.1247

Pasco, J. A., Williams, L. J., Jacka, F. N., Ng, F., Henry, M. J., Nicholson, G. C., . . . Berk, M. (2008). Tobacco smoking as a risk factor for major depressive disorder: population-based study. *The British Journal of Psychiatry, 193*(4), 322-326. doi: 10.1192/bjp.bp.107.046706

Patten, S. B., Li Wang, J., Williams, J. V., Currie, S., Beck, C. A., Maxwell, C. J., & el-Guebaly, N. (2006). Descriptive epidemiology of major depression in Canada. *Canadian Journal of Psychiatry, 51*(2), 84.

Persson, L.-G., & Hjalmarson, A. (2006). Smoking cessation in patients with diabetes mellitus: Results from a controlled study of an intervention programme in primary healthcare in Sweden. *Scandinavian Journal of Primary Health Care, 24*(2), 75-80. doi: 10.1080/02813430500439395

Phelan, E., Williams, B., Meeker, K., Bonn, K., Frederick, J., LoGerfo, J., & Snowden, M. (2010). A study of the diagnostic accuracy of the PHQ-9 in primary care elderly. *BMC Family Practice, 11*(1), 63.

Prochaska, J. J. (2011). Smoking and Mental Illness — Breaking the Link. *New England Journal of Medicine, 365*(3), 196-198. doi: doi:10.1056/NEJMp1105248

Prochaska, J. O., & Norcross, J. C. (2001). Stages of change. *Psychotherapy: Theory, Research, Practice, Training, 38*(4), 443.

Puranik, R., & Celermajer, D. S. (2003). Smoking and endothelial function. *Progress in Cardiovascular Diseases, 45*(6), 443-458.

Rafalson, L., Donahue, R. P., Dmochowski, J., Rejman, K., Dorn, J., & Trevisan, M. (2009). Cigarette smoking is associated with conversion from normoglycemia to impaired fasting glucose: the Western New York Health Study. *Annals of epidemiology, 19*(6), 365-371.

Rebagliato, M. (2002). Validation of self reported smoking. *Journal of Epidemiology and Community Health, 56*(3), 163-164. doi: 10.1136/jech.56.3.163

Reid, J., & Hammond, D. (2009). Tobacco Use in Canada: Patterns and Trends, 2009 Edition (v2). *Waterloo, ON: Propel Centre for Population Health Impact, University of Waterloo*.

Schmitz, N., Kruse, J., & Kugler, J. (2007). Smoking and its Association with Disability in Chronic Conditions: Results from the Canadian Community and Health Survey 2.1. *Nicotine & Tobacco Research, 9*(9), 959-964. doi: 10.1080/14622200701540846

Schmitz, N., Wang, J., Malla, A., & Lesage, A. (2007). Joint effect of depression and chronic conditions on disability: results from a population-based study. *Psychosomatic Medicine, 69*(4), 332-338.

Shahab, L., & West, R. (2009). Do ex-smokers report feeling happier following cessation? Evidence from a cross-sectional survey. *Nicotine & Tobacco Research, 11*(5), 553-557.

Sherman, J. J. (2005). The Impact of Smoking and Quitting Smoking on Patients With Diabetes. *Diabetes Spectrum, 18*(4), 202-208. doi: 10.2337/diaspect.18.4.202

Solberg, L. I., Desai, J. R., O'Connor, P. J., Bishop, D. B., & Devlin, H. M. (2004). Diabetic Patients Who Smoke: Are They Different? *Ann Fam Med, 2*(1), 26-32. doi: 10.1370/afm.36

Stamler, J., Vaccaro, O., Neaton, J. D., Wentworth, D., & Group, T. M. R. F. I. T. R. (1993). Diabetes, Other Risk Factors, and 12-Yr Cardiovascular Mortality for Men Screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care, 16*(2), 434-444. doi: 10.2337/diacare.16.2.434

Statistics Canada. (2009). *Canadian Community Health Survey 2.1*. Ottawa, Ontario: Retrieved from http://www23.statcan.gc.ca:81/imdb/p2SV.pl?Function=getSurvey&SDDS=3226&lang=en&db=imdb&adm=8&dis=2#b8.

Statistics Canada. (2012). Smoking. Retrieved 25/07/2013 http://www.statcan.gc.ca/pub/82-625-x/2013001/article/11844-eng.htm

Stead, L. F., & Lancaster, T. (2012). Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst. Rev, 10*.

Tonstad, S. (2009). Cigarette smoking, smoking cessation, and diabetes. *Diabetes Research and Clinical Practice, 85*(1), 4-13. doi: 10.1016/j.diabres.2009.04.013

Twardella, D., Loew, M., Rothenbacher, D., Stegmaier, C., Ziegler, H., & Brenner, H. (2006). The diagnosis of a smoking-related disease is a prominent trigger for smoking cessation in a retrospective cohort study. *Journal of Clinical Epidemiology, 59*(1), 82-89.

US Department of Health. (2010). *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*. Atlanta, Georgia: Retrieved from http://www.cdc.gov/tobacco/data_statistics/sgr/2010/index.htm.

US Department of Health, & Human Services. (2004). The health consequences of smoking: a report of the surgeon general. In Centers for Disease Control and Prevention (Ed.). Atlanta, Georgia.

US Department of Health and Human Services. (1964). *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*.

Weinberger, A. H., George, T. P., & McKee, S. A. (2010). Differences in smoking expectancies in smokers with and without a history of major depression. *Addictive Behaviors, 36*(4), 434-437.

Weinberger, A. H., Mazure, C. M., Morlett, A., & McKee, S. A. (2013). Two Decades of Smoking Cessation Treatment Research on Smokers with Depression: 1990–2010. *Nicotine & Tobacco Research, 15*(6), 1014-1031. doi: 10.1093/ntr/nts213

Wetter, D. W., Cofta-Gunn, L., Irvin, J. E., Fouladi, R. T., Wright, K., Daza, P., . . . Gritz, E. R. (2005). What accounts for the association of education and smoking cessation? *Preventive medicine, 40*(4), 452-460.

Wilhelm, K., Wedgwood, L., Niven, H., & Kay-Lambkin, F. (2006). Smoking cessation and depression: current knowledge and future directions. *Drug and Alcohol Review, 25*(1), 97-107. doi: 10.1080/09595230500459560

Willi, C., Bodenmann, P., Ghali, W. A., Faris, P. D., & Cornuz, J. (2007). Active Smoking and the Risk of Type 2 Diabetes. *JAMA: The Journal of the American Medical Association, 298*(22), 2654-2664. doi: 10.1001/jama.298.22.2654

Wolf, G., & Ritz, E. (2003). Diabetic Nephropathy in Type 2 Diabetes Prevention and Patient Management. *Journal of the American Society of Nephrology, 14*(5), 1396-1405. doi: 10.1097/01.asn.0000065639.19190.cf

World Health Organization. (2011). Global status report on noncommunicable diseases 2010. In WHO (Ed.). Geneva, Switzerland.

World Health Organization. (2013a). Diabetes: The cost of diabetes. *Fact Sheet* Retrieved 2012-03-26, 2012, from http://www.who.int/mediacentre/factsheets/fs236/en/

World Health Organization. (2013b). Fact Sheet: Diabetes. from WHO http://www.who.int/mediacentre/factsheets/fs312/en/index.html

World Health Organization. (2013c). Fact Sheet: Tobacco. *Fact Sheet no. 339* Retrieved 15/07/2013, from http://www.who.int/mediacentre/factsheets/fs339/en/

Xie, X.-t., Liu, Q., Wu, J., & Wakui, M. (2009). Impact of cigarette smoking in type 2 diabetes development. *Acta Pharmacol Sin, 30*(6), 784-787.

Ziedonis, D., Hitsman, B., Beckham, J. C., Zvolensky, M., Adler, L. E., Audrain-McGovern, J., . . . Riley, W. T. (2008). Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob Res, 10*(12), 1691-1715. doi: 10.1080/14622200802443569

Appendix A

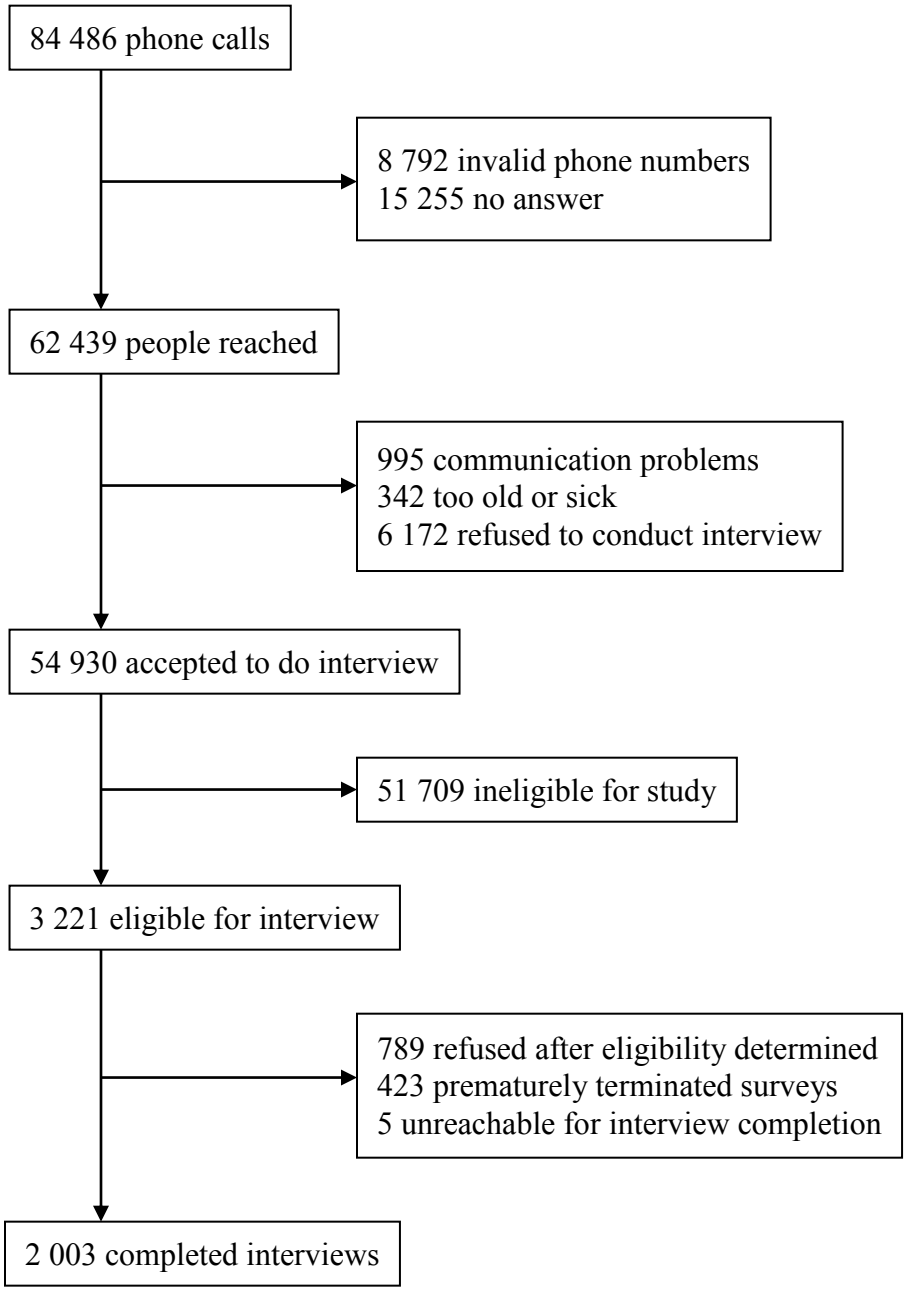
Additional details on data source:

Telephone interviews were conducted by the trained professional interviewing firm Bureau d'Intervieweurs Professionnels (BIP). Interviews took approximately 30 minutes, and were assisted through use of a computer telephone interviewing system. A flow-chart of initial recruitment can be seen in *Appendix* B. Throughout data collection, lab members conducted regular telephone monitoring to ensure quality and consistency across interviews. Informed consent was obtained from all study participants.

Study participants received a cheque for $20 CAD after completion of each interview. The protocol was approved by the Research Ethics Committee of the Douglas Mental Health University Institute, McGill University, Montreal, Canada.

Appendix B

Participant recruitment – Flow Chart



Appendix C

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

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