DIMENSIONS OF AGING: CHRONIC CONDITIONS, MULTIMORBIDITY AND SELF-RATED HEALTH: PREDICTORS AND TRENDS IN THE CONTEXT OF AN AGING POPULATION IN CANADA

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ABSTRACT

Mental illness and cognitive impairment are diseases that are of a substantial burden to Canada and the world at large. They are chronic and persistent conditions with considerable associated disability. The links between mental and physical health are well-established. Our main goal is to use population-based nationally representative datasets to establish both trends and risk factors for chronic conditions and multimorbidity in Canada. In order to develop effective public health intervention programs and policies there is the need to first of all generate the necessary evidence that will form the basis for intervention. This evidence can be generated through empirical research regarding predictors and trends in chronic diseases. Our current research is therefore grounded on the need to understand major determinants and trends in chronic diseases through the use of interdisciplinary population-based research which will provide evidence that will drive policy decision making and lead to better health and improved quality of life for Canadians.

In the first study, our systematic review and meta-analysis found that diabetes was a risk factor for incident depression. Population attributable fractions (PAFs) showed a reduction in depression that could result from reducing diabetes.

The second study examined the shared risk factors for diabetes and depression in a large-scale longitudinal cohort study. We found hypertension, daily smoking, physical inactivity and overweight or obesity were shared risk factors of major depressive disorder and diabetes. Sex differences existed in risk factors for the two debilitating conditions.

The third study examined both the prevalence of cognitive impairment and modifiable risk factors for such impairment. We found that cognitive impairment was on the decline despite the aging population in Canada and that the modifiable risk factors of cognitive impairment changed over time. Age and sex differences exist in the association between predictor variables and cognitive impairment. We found that different experiences shared by successive generations may predispose them to different disease risk.

Our final paper assessed prevalence and trends in chronic diseases and multimorbidity over a 36-year period. We found a significant decrease in the prevalence of chronic diseases in Canada. While at the same time there was an increase in the prevalence of multimorbidity. Our study

suggests that other contributory factors aside from the aging of the population are responsible for the contrasting trends in the prevalence of chronic diseases and multimorbidity in Canada.
The central message of our research findings is that to achieve an improved quality of life during old age there is a need for a better understanding of how individuals can age healthily without developing multiple chronic illnesses with substantial disability.

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LIST OF ABBREVIATIONS

BMI	Body mass index
CCHS	Canadian community health survey
CCHS-HA	Canadian community health survey-healthy aging
CHS	Canada health survey
CI	Confidence interval
CVD	Cardiovascular diseases
DALY	Disability adjusted life-years
HIC	High income countries
LE	Life expectancy
LMIC	Low- and middle-income countries
MDD	Major depressive disorder
NCD	Non-communicable diseases
NPHS	National population health survey
OR	Odds ratio
PAF	Population attributable fractions
PHAC	Public health agency of Canada
RR	Relative risk
WHO	World health organization
3MS	Modified mini-mental state examination

CHAPTER 1– INTRODUCTION

1.1 The epidemiological transition and the aging population

The epidemiological transition describes the shift from infectious or communicable diseases to non-communicable or chronic diseases (NCD) [1]. The changes in population structure from high birth and death rates to low births and death rates has adequately been described by the demographic transition model. Both transitions are occurring globally, albeit with somewhat different patterns, determinants, and rapidity.

The global life expectancy (LE) at birth has witnessed a substantial increase over the past decades, with a world-wide LE average of about 71.5 in 2017 (7 years longer than in 1990) [3]. Developed countries recorded an LE of around 80 in 2017 compared to about 50 years in those same countries in the early 20th century. Factors such as proper waste disposal, clean water, sanitation, temperature-controlled living, improvement in medical technology and improved working environments resulted in this achievement. The resultant effect of which was large reductions in communicable diseases [2]. Also, there has been significant progress made at reducing deaths from chronic diseases in the last quarter of the 20th century. This happened as a result of early treatments and advancement in new diagnostic technology as well as changes in behavioral risk factors (such as reductions in smoking), which has resulted in a continued improvement in life expectancy even though at a slower rate [2].

In the demographic and epidemiological transitions, rapid population aging or a “greying tsunami” is a global phenomenon. Both developed and less developed countries have witnessed their fair share of the consequences of population aging. Population aging is the increasing number of older persons in a population owing to a progressive lengthening of life expectancy [2].

Data from the World Health Organization (WHO) in 2010 show that 524 million (8%) of the world’s population were seniors aged 65 years or above. It is projected that this figure is expected to triple to about 1.5 billion or approximately 16% of the total population by the year 2050 [3]. In 2016, the global percentage of people aged 65+ years stood at 8.5 % with a world-wide breakdown as follows; 3.5 % for Africa’s senior’s population, 7.8 % of that of Asia, 15.2 % of that of North American, 17.9 % of that of Europe and the Oceania region (New Guinea and

other Pacific Ocean neighboring islands, New Zealand and Australia) with an estimated senior's population of 12.1% [4]. In absolute numbers, the world recorded approximately 634 million people aged 65+ years with Asia recording the highest number of 349 million, followed by Europe (133 million) and North America (54 million) [4]. It is projected that due to population aging and rising longevity the number of people aged 60 years is expected to double from the current 13% to nearly 25%, by 2050. Which means an estimated increase from about 962 million to 2.1 billion people is expected by 2050 [3].

While developed countries have higher life expectancy compared to less developed countries it is expected that less developed countries will increase their longevity in the short while [3]. Population aging and rising longevity are a testimony to the fact that the human race has been creative and ingenious in its fight against common diseases that threaten our existence and this increased longevity can be viewed as a great success of global public health efforts. On the other hand, global population aging can be viewed as one of the greatest challenges for global public health efforts in the future. That notwithstanding, there is the hope that further advances in public health efforts are possible despite population aging**.**

In the Canadian context, population aging has been accentuated by the "baby boom" of births after the Second World War, from 1946 to 1960, and the subsequent decrease in births from 1960 onwards. As of the year 2011, the leading edge of the baby boomers turned 65 years old. It is estimated that the proportion of seniors in the Canadian population will rise to about 25% in 2036 due to the aging of the baby boom generation [5]. Data released from Statistics Canada's 2016 census showed that for the first time in the country's history those 65+ years constituted 5.9 million of the Canadian population compared to a figure of 5.8 million for those 14 years or younger [6]. The number of Canadian seniors is expected to continue to grow because of the gains in life expectancy and the narrowing gap in life expectancy between men and women [6].

Policy makers are projecting that in the next 25 to 30 years, the aging Canadian population may have a negative impact on the health care system, economy and society at large [5]. The fact that aging is inevitable does not necessarily mean ill-health or disability, though the risk of both may increase as people age. In 2006, Statistics Canada reported a disability

prevalence of 33% among Canadians aged 65 or older and a disability prevalence of 44% among people aged 75 or older [7].

A concern expressed has been that as a result of the aging Canadian population there will be heavy health care demands for the care and treatment of seniors. It has been reported that as of 2011, 44% of both provincial and territorial health care budgets went into taking care of Canadian seniors (65+ years) and that overburdens governments financially [8]. Also, health care systems may not have the personnel or material resources to be able to provide quality services for seniors in the future [8].

1.2 The nature and burden of chronic diseases

Population aging is accompanied by a growing proportion of older individuals living with chronic conditions and that impacts on the health care systems of many countries. The number of people suffering from chronic non-communicable diseases over the world is expected to increase due to the aging of the population. It was reported that 36 million people globally were living with dementia as of 2011 [13]. Also, it is estimated that between 2030 to 2050, dementia is expected to increase from about 66 million to 115 million [13]. Seniors can be expected to experience multiple chronic conditions and this increased burden may be felt disproportionately among some vulnerable populations [10].

According to WHO data in 2018, an estimated 41 million or 71% of all annual deaths that occur globally, can be attributed to chronic non-communicable diseases [14]. In 2018 the reported annual world-wide cause-specific causes of deaths attributable to four major chronic diseases were as follows; “cardiovascular diseases” (17.9 million), “cancers” (9.0 million), “respiratory diseases” (3.9 million) and “diabetes” (1.6 million) [14]. These four major chronic diseases are also responsible for over 80% of premature chronic diseases deaths globally. For instance, the same WHO data report that each year, 85% of the 15 million premature deaths (30-69 years) occur in low- and middle-income countries due to chronic non-communicable diseases [14]. Out of the 57 million annual deaths recorded globally, over 60% of these deaths occur in the older population (60+ years), while nearly 50% of the deaths in the world occur among those 70+ years. This makes the health and care of older persons an urgent global health problem [14].

Those affected by chronic diseases require specialized care services that are expensive and prolong. Chronic diseases also impact negatively on the economies of countries globally owing to productivity losses, increase in social and health care cost as well as prolonged disability [32]. Although historically, the impact of chronic diseases was regarded as the preserve of high-income countries, due to population aging, economic growth and the epidemiological transition, low- and middle-income countries are not spared of their consequences in recent times. There has been a significant increase in the prevalence of chronic diseases in low- and middle-income countries as a result of improvement in life expectancy, high tobacco consumption, increase in sedentary and unhealthy lifestyles and increased alcohol intake [33]. Besides the years of life lost, the global economic impact of chronic diseases was estimated at $600 billion annually as at the year 2015 [34, 35].

In Canada, it was reported in the year 2011 that one in three of all Canadians lives with at least *one* major chronic disease [11]. In that same year, three-quarters of those 65+ years report at least one chronic disease [9]. Also, an estimated 62.7% of all annual deaths in the Canadian population for that same year was attributable to chronic conditions such as chronic respiratory diseases, heart disease, diabetes, cancers, and stroke [12]. As of the year 2013, three out of five Canadians aged twenty and above live with one of the majority chronic diseases (cardiovascular diseases, cancers, diabetes and chronic respiratory diseases) while 4 out of 5 were at risk [36]. An estimated 65% of all annual deaths in 2013 were attributable to these major chronic conditions and over 150,000 dies from them each year [37]. Apart from the healthy years of Canadians lives lost to chronic diseases, they are also a significant financial burden on the economy [38]. In the year 2000 about six major chronic diseases namely cardiovascular diseases, chronic respiratory diseases, cancer, mental illness, digestive and musculoskeletal diseases accounted for most health care cost in Canada (both direct and indirect). For example, an estimated $64 billion indirect cost and $31 billion direct healthcare costs was accrued primarily due to loss of productivity in that year [10]. The annual economic impact of chronic diseases and other illness is estimated at $190 billion comprising of $122 billion as productivity and indirect income losses and a direct health care cost of $68 billion in the year 2012 [38]. An estimated 58% of all annual health care spending in Canada goes into direct treatment and management of chronic diseases [39].

Despite all these challenges, the country has chalked huge successes in the prevention and control of some chronic diseases in the recent past. In its efforts to prevent and control chronic diseases the Public Health Agency of Canada (PHAC) was created in 2005 with the goal to protect and promote public health in Canada including chronic disease prevention [5]. Several specific initiatives under the guidance of PHAC have yielded some positive results. There has been a reduction in the prevalence and incidence of heart disease, stroke, lung cancer in males, motor vehicle accidents and tuberculosis over the last several decades [5].

In summary, in order to restrain the impact of chronic diseases globally and in Canada, effective public health prevention strategies and policies are necessary. Until these policies and preventive strategies are implemented, chronic diseases will continue to threaten societies and their health care systems.

1.3 The nature and burden of multimorbidity

Multimorbidity is the co-existence of multiple chronic diseases in one individual [15]. As the population age, people are more likely to report multiple chronic conditions [15]. The term multimorbidity has been interchangeably used wrongly to mean comorbidity. This distinction is necessary in order to direct health research. “Multimorbidity is the presence of two or more chronic diseases in an individual that is mostly caused by nonreversible pathologic alterations that require a permanent or long period of care” [40–43]. Similarly, the term “comorbidity is defined as the interactive or combined effect of an index disease and other additional conditions” [40–43]. A possible example of comorbidity can be the scenario where a person diagnosed with diabetes (index disease) who later develops cancer, depression or stroke. The striking difference is that whereas in “multimorbidity” no single condition holds priority over any of the co-occurring conditions, in “comorbidity” there is an index disease that precedes the occurrence of other conditions [40, 42].

The prevalence of multimorbidity has been on the rise over the past few decades across the world and may continue to increase. The worldwide prevalence of multimorbidity varies due to population and methodological differences. However, recent studies have provided a wide range of estimates between 13% and 72% for the prevalence of multimorbidity in the general population [17, 18]. Multimorbidity is an important risk concept because of its associated

dimensions such as high healthcare costs, decreased quality of life and ultimately increased mortality [19, 20].

Though multimorbidity is generally perceived to be the preserve of the elderly and people from high-income countries, some literature suggests otherwise. For example, a study by Barnett, et al [15] of high-income countries found that younger people were also likely to have multimorbidity even though it was more highly prevalent in older populations. In most high-income countries (HIC) such as the European Union (EU), multimorbidity has been accepted as the norm with at least 50 million people affected in that regional block [16].

Multimorbidity is an emerging problem in low-and-middle-income countries (LMICs), where already poorly equipped healthcare facilities struggle with the treatment of both infectious diseases and NCDs [21–23]. This increase in multimorbidity in low-and-middle-income countries is being driven by the growing burden of NCDs such as type 2 diabetes and hypertension, as well as urbanization and population aging [21–23].

In Canada, Agborsangaya et al [24] found a 36% multimorbidity prevalence in a cross-sectional study of Albertans. A study by Roberts et al [25] an analysis of the 2011/12 (CCHS) survey revealed a 12.9% prevalence in multimorbidity among participants with two or more chronic diseases as against a 3.9% multimorbidity prevalence reported among participants with three or more chronic diseases. A recent study using Canadian surveillance data also estimated a multimorbidity prevalence of 26.5% among 40+ years Canadians [26]. This is significantly lower than the 42.6% multimorbidity prevalence found in an earlier study of 18+ years Canadians [27].

From the foregoing, it can be stated that global population aging and rising longevity do not only come with challenges but also opportunities. It is evident that population aging poses grave and urgent challenges for global health and health systems in both developed and developing countries. Prominent among these challenges is that the presence of chronic diseases which are seen to have the potential of overstretching health care systems. However, population aging offers major opportunities to prevent and effectively treat diseases associated with aging.

1.4 Context of the thesis

The prevention of chronic diseases is deeply rooted in our ability to identify and address the risk factors and determinants of these chronic diseases [28]. In order to develop effective

public health intervention programs and policies, there is the need to, first of all, generate the necessary evidence that will form the basis for intervention. This evidence can be generated through empirical research in areas such as predictors and trends in chronic diseases [28]. Our current research is therefore grounded on the need to understand major determinants and trends in chronic diseases through the use of interdisciplinary population-based research which will provide evidence that will drive policy decision making and lead to better health and improved quality of life for Canadians.

The focus of this thesis is to assess predictors and trends of both mental and physical chronic health conditions. Chronic conditions are persistent with considerable associated disability and require a long period of care. The relationship between physical and mental health has been noted in the literature. This association has significant consequences for quality of life, health care delivery, other publicly funded services, and the society at large. Mental and physical health are closely linked in the following ways: 1) People with poor mental health status are more likely to develop other physical chronic conditions 2) major mental health problems are negatively associated with the development of physical health problems and, 3) poor physical health is also negatively associated with mental health problems [29, 30].

There are large research gaps that need to be filled if we are to reduce the prevalence and incidence of chronic diseases in the context of an aging population in Canada. Areas such as diabetes-depression relationship and the influence of population attributable fractions on risk factor reduction have not been fully explored. Also, not many studies have been conducted on shared risk factors for depression and diabetes in the Canadian context. Studies on estimates of cognitive impairment and dementia prevalence and/or incidence at the population level are scarce in Canada. Little is known about trends in the prevalence of chronic diseases and multimorbidity on a national scale over the last three decades. Our main goal is to use population-based nationally representative datasets to establish both trends and risk factors for chronic conditions and multimorbidity in Canada.

We also hope to establish how some chronic conditions cluster with others through common underlying risk factors or other associated factors. Whereas disability can be prevented and compressed, death can also be delayed although it is inevitable [31]. To achieve an improved

quality of life during old age a better understanding of how individuals can prevent the development of multiple chronic illnesses and disability is crucial. It is hoped that findings from the diverse studies in this thesis will provide useful information to help strengthen our health systems to meet the needs of the Canadian aging population.

This thesis is composed of four substantive chapters that aim to:

- Systematically review, including a meta-analysis, the existing literature on the relationship between diabetes and depression using longitudinal studies.
- Examine the shared and unique risk factors for depression and diabetes in a longitudinal study.
- Assess the prevalence of and modifiable risk factors for cognitive impairment among Canadian seniors in two national health surveys two decades apart, 1991–2009.
- Examine trends in chronic diseases and multimorbidity prevalence over a 36-year period in Canada.

What links the above distinct chapters includes the following; 1) the major chronic conditions assessed in this thesis are related to one another. Depression is related to diabetes as well as cognitive impairment 2) depression, diabetes, and cognitive impairment are some of the major chronic conditions in Canada impacting the health, economic and social fabric of society and also on the caregivers or people taking care of those with these conditions 3) majority of chronic conditions affect older populations and Canada has an aging population.

1.5 References

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CHAPTER 2– METHODS AND PROCEDURES

2.1 Study designs

This thesis uses three basic study designs and several epidemiological and statistical analysis techniques. A systematic review and meta-analysis are used in Chapter 3. A longitudinal population cohort design is used in Chapter 4. Two cross-sectional trend study designs are used in Chapters 5 and 6.

2.2 Chapter 3: Diabetes increases the risk of depression in longitudinal studies: A systematic review, meta-analysis and estimates of population attributable fractions.

For the systematic review and meta-analysis in Chapter 3, data were collected via a computerized and manual search with the goal to systematically review and conduct a meta-analysis of existing literature on the relationship between diabetes and depression in longitudinal studies. A computerized search was conducted in various databases, such as Medline/PubMed, Embase, PsycINFO, and Cochrane library for the period from January 1990 to December 2017. Article eligibility was determined using our inclusion and exclusion criteria. Gray literature and reference lists in eligible articles were screened to include the most comprehensive articles. Population attributable fractions were used to estimate the projected effect of reducing the prevalence of exposure would have on the incidence of an outcome.

2.3 Chapter 4: Examining shared and unique risk factors for incident depression and diabetes in a longitudinal study: An analysis of the Canadian National Population Health Survey.

We used the National Population Health Survey longitudinal component for this analysis. It is a national longitudinal survey involving 17, 276 participants who were examined at baseline in 1994/5 and were re-interviewed every two years to 2011. We assessed share and unique risk factors for incident depression and diabetes over a 10-year follow-up period in a sub-sample of the original sample.

2.4 Chapter 5: A comparison of prevalence of and modifiable risk factors for cognitive impairment among Canadian seniors over two decades, 1991-2009.

Two data sources were used in our analysis. The first was from the Canadian Study of Health and Aging 1991-92 (N=10,263). The community sample of 9008 respondents and a

sample of 1255 from long-term-care institutions were initially assessed. Our analysis was based on the representative community sample across Canada's 10 provinces.

The second source came from Statistics Canada's National Canadian Community Health Survey-Healthy Aging 2008-2009 (N=25864), which targeted those 45 years and older and was conducted from 2008-12-01 to 2009-11-30. A sub-sample of participants aged 65 years and over that measured cognition are included in our analysis.

Age-sex descriptive statistics were used to compare prevalence rates for cognitive impairment in 1991-92 to those reported in 2008-09. Logistic regression analysis was used to assess the modifiable and non-modifiable risk factors for cognitive impairment in the two time separated periods.

2.5 Chapter 6: Prevalence of chronic diseases and multimorbidity in Canada: contrasting trends.

Our trend in prevalence study was conducted using data from three different but similar sets of Canadian health surveys. Our first set of data came from the baseline study of the Canada Health Survey which was conducted in 1978/79. A total of 31668 participants responded to the survey.

The second source came from baseline data of the National Population Health Survey which was carried out by Statistics Canada. The study was conducted in 1994 among a representative sample of 17,276 household respondents using face-to-face interviews. This baseline survey was later used as a cohort panel for the longitudinal aspect of this survey.

The third source of data is a series of cross-sectional general health surveys called the Canadian Community Health Survey (CCHS) which replaced the NPHS. Its sampling methods and procedures were similar to those of CHS and NPHS. The first CCHS survey started in 2001 as CCHS 1.1 and repeated after every two years as CCHS 2.1 in 2003, the CCHS 3.1 in 2005, and CCHS 4.1 in 2007. Between the reference year of 2001 to 2007 large sample sizes of about 130, 000 respondents participated in the survey. The CCHS however made some changes in 2007 to the design of the survey and the study sample was reduced to about 65,000 participants annually.

2.6 Statistical Analysis

In our systematic review analysis, meta-analysis, (Chapter 3) and population attributable fractions were applied. We used the meta-analysis to pool earlier findings from two or more studies to answer a common question. This provides more power than separate studies, summarize numerous and inconsistent findings and measure the consistency of effect across different samples [1].

Descriptive analyses were applied to understand demographic and clinical characteristics of study populations, such as age, sex, smoking status, marital status, educational level, income level, and among others in Chapters 4 and 5.

We performed both univariate and multivariate Modified Poisson regression models for the outcome variables in Chapter 4. The Modified Poisson regression with a robust variance which was designed for estimating the relative risk and analyzing common events was also used.

In Chapter 5 both univariate and multivariate logistic regression models were fitted to measure predictor variables and the outcome in the two comparable time separated study samples.

In Chapter 6 age and sex, standardization was performed based on the population size and age and sex distributions in 2014. Prevalence estimates of the twelve common chronic conditions included in the study were also calculated using the standardized age and sex adjustments. Prevalence estimates were calculated by age, sex, the highest level of education, and the province of residence. We used the term “sex” here rather than gender as all the questionnaires in the datasets analyzed, asked respondents whether they were male or female. Therefore, sex was used to assess sex differences in this thesis.
Table 2-1 shows a summary of the various studies and study designs employed in this thesis.

Table 2- 1 Summary of studies in this thesis

Study design/ Level of evidence	**Title of study**	**Age category**	**Method & analysis**
Meta-analysis/ **High**	**Chapter 3** A systematic review and meta-analysis of existing literature assessing the relationship between Diabetes and Depression in Longitudinal Studies.	20+ years	Systematic review; Meta-analysis; Population Attributable Fractions
Prospective cohort **Moderate**	**Chapter 4** Examine the shared and unique risk factors of depression and diabetes in a longitudinal study: An analysis of the Canadian National Population Health Survey.	45+ years	Descriptive analysis; Modified Poisson regression
Cross-sectional **Low to medium depending on the specifics of the survey design**	**Chapter 5** A comparison of prevalence of and modifiable risk factors for cognitive impairment among Canadian seniors over two decades, 1991-2009.	65+ years	Descriptive analysis; Logistic regression
Time series	**Chapter 6** Prevalence of Chronic Diseases and Multimorbidity in Canada: contrasting trends using data from Canadian Health Surveys.	12+ years	Descriptive analysis; Trend analysis

2.7 References

1. Higgins J, and Green S. (Eds.). Cochrane Handbook for Systematic Reviews of Interventions. www.handbook.cochrane.org/, 2011 (accessed 28 June 2018).

CHAPTER 3– DIABETES INCREASES THE RISK OF DEPRESSION IN LONGITUDINAL STUDIES: A SYSTEMATIC REVIEW, META-ANALYSIS, AND ESTIMATES OF POPULATION ATTRIBUTABLE FRACTIONS

A version of this chapter has been published as: *"*B. Chireh, M. Li & C. D'Arcy (2019). Diabetes increases the risk of depression: A systematic review, meta-analysis and estimates of population attributable fractions based on prospective studies. *Preventive Medicine Reports*, 14: 100822. doi.org/10.1016/j.pmedr.2019.100822". My contributions to this study included contribution to study design, data collection, quality assessment, data synthesis, and manuscript writing and editing. This chapter also includes PAF estimates for Canada that were excluded in the published study.

3.1 Abstract

Background: Earlier empirical evidence suggests an association between diabetes and depression. However, most previous studies used cross-sectional designs to assess this relationship and thus limiting evidence of causality. In this current study, we aim to: (1) systematically examine the relationship between diabetes and the risk of developing depression using systematic review and meta-analysis in longitudinal cohort studies and (2) provide estimates of how much the incidence of depression in a population would be reduced if diabetes was reduced.

Methods: Medline/PubMed, EMBASE, PsycINFO, and Cochrane Library databases were searched for English-language published literature from January 1990 to December 2017. Longitudinal studies with criteria for depression and either self-report doctors' diagnoses or diagnostic blood test measurement of diabetes were assessed. Study results were synthesized using systematic review with meta-analysis of published literature. Publication bias, heterogeneity, and quality of the individual studies were examined. Pooled odds ratios were calculated using random effects models. The preventive impact of diabetes reduction on depression incidence was estimated using population attributable fractions (PAFs).

Results: Twenty high-quality articles met inclusion criteria and were used in the analyses. The pooled odds ratio (OR) between diabetes and incident depression was 1.33 [95% confidence interval (CI) 1.18–1.51]. For the type of study design and method of diabetes diagnoses and their relationship with depression, the ORs were: prospective studies (OR 1.34, 95% CI 1.14–1.57), retrospective studies (OR 1.30, 95% CI 1.05–1.62), self-reported diagnosis of diabetes (OR 1.37, 95% CI 1.17–1.60), and diagnostic blood test for diabetes (OR 1.25, 95% CI 1.04–1.52). We found that diabetes prevalence potentially accounted for over 9.5 million global cases of depression in our PAFs estimates. A 10–25% reduction in diabetes could potentially prevent 930,000–2.34 million depression cases worldwide.

Conclusions: Our systematic review provides fairly strong evidence to support the hypothesis that diabetes is a risk factor for the subsequent development of depression. At the same time, it shows the impact of risk factor reduction, study design, and diagnostic measurement of exposure. The review provides evidence of the need to adopt multisectoral approaches, programs, and

policies aimed at combating diabetes and reducing its prevalence. Well-managed diabetes could weaken the association between the two fellow travelers of depression and diabetes.
Keywords: epidemiology, diabetes, depression, population attributable fractions, projected effects.

3.2 Introduction

Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced [1]. There is a steady rise in the global prevalence of diabetes. A recent trend analysis of worldwide diabetes prevalence reported that the number of adults aged 18 years and over living with diabetes substantially increased from 108 million in 1980 to 422 million as of the year 2014, almost a 400% increase in prevalence [1]. The interaction between the rise in diabetes incidence and population growth and population aging has also contributed to the number of diabetes cases worldwide [1]. Diabetes is also recognized as an important determinant of premature death, disability, morbidity and increased health-system costs in the world [2, 3]. People without diabetes are less likely to report major depressive disorder (MDD) or depressive symptoms compared to those with diabetes. Recent studies revealed that depression is twice as prevalent in individuals with Type 2 diabetes compared to controls [4, 5]. Some researchers have argued that diabetes precedes depression and increases the risk of developing depression due to the psychological trauma following diagnoses of diabetes and its burdens such as hyperglycemia leading to altered glucose transport or treatment of the disease itself or both combined. The disease combination poses a significant challenge for clinical practice [4, 52]. This line of argument was challenged by recent longitudinal studies that found that depression may be a risk factor for diabetes [4, 42] but others found that diabetes may not necessarily predict depression or diabetes may just be modestly associated with depression [52]. As was reported in a recent WHO study, individuals with both conditions are more likely to rate their health as poor in comparison to individuals with asthma, arthritis or angina and other chronic conditions or depression only [6].

Available literature suggests that diabetes with co-morbid depression is associated with lower quality of life [7], poorer diabetes self-care [8], impaired glycemic control [9], and an increased risk of developing diabetes-related complications [10]. Depression is also reported to be a large health care burden on most economies [11] and is a major determinant of increased mortality [12, 13]. This has led to the recommendation by most clinical guidelines that patients with diabetes undergo regular screening for depression [14, 15].

Most studies in this diabetes and depression subject have utilized cross-sectional study designs, this limits causal inferences, making recommendations for practice problematic [4, 5]. Research regarding the diabetes-depression relationship has been mixed. While depression was found to be associated with an increased risk in diabetes in some systematic reviews and meta-analyses [16–18, 66, 67] other reviews found diabetes to be moderately associated with the risk of developing depression [18–21, 68]. The possibility of a bidirectional relationship has gained much attention in recent years become the focus of a number of systematic reviews, as well as meta-analysis and longitudinal prospective studies [49, 69–72].

There are a variety of biological pathways that have been mooted as being shared biological origins for depression and diabetes including innate immunity and inflammation, the hypothalamic-pituitary-adrenal axis (HPA axis), insulin resistance and secretion, circadian rhythms, and anti-depressant medications. In-utero and early childhood experiences are also posited and a common pathway linking depression and diabetes, particularly Type 2 diabetes [64, 65].

This study is different from other reviews to the extent that, it emphasized on the diagnostic criteria for measuring diabetes (self-report vs blood test) which was lacking in previous reviews. This distinction is important as studies using self-report of diabetes might underestimate diabetes prevalence in contrast to studies that use diagnostic blood tests [22].

In addition, little can be found with respect to the potential impact of reducing diabetes prevalence in decreasing the incidence of depressive symptoms or depressive disorders in a population or vice versa. Our study used the Population attributable fractions (PAFs) to estimate the number of depression cases that could be reduced if the prevalence of diabetes is reduced by a particular margin [23].The literature recognizes the role of PAFs as an effective instrument for measuring the potential effects of risk factors reduction on disease occurrence [24–28]. In this vein, Northridge [29] is of the opinion that PAFs can assist policy-makers in judging priorities for public health action, intervention planning, and decision-making.

In this current study we aim to:

1) Systematically examine the relationship between diabetes and the risk of developing depression using systematic review and meta-analysis of longitudinal cohort studies.

2) Provide estimates of by how much the incidence of depression in a population would be reduced if diabetes was reduced.

While a previous study [19] sub-analyzed their results according to the outcome (depression), our analysis is based on sub-analyses according to the method of diagnoses of the exposure of interest (diabetes). What our analysis adds new is the use of only longitudinal studies, separate analysis of studies that used diagnostic blood tests versus self-report of doctor's diagnoses as measures of diabetes, and the calculation of the potential population's health effects of reducing diabetes would have on depression incidence.

3.3 Methods – Systematic review and meta-analysis

The current systematic review and meta-analysis follow the PRISMA guidelines, 2009 revision [30], and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations [31]. Using the Newcastle–Ottawa Scale criteria, the quality of this study was assessed [34]. All the included studies rated highly in terms of quality.

3.3.1 Search strategy

A computerized search for published articles was conducted in Medline/PubMed, EMBASE, PsycINFO, and Cochrane Library databases for the period from January 1990 to December 2017. Also, a manual search was done on other resources for additional relevant studies. We finally scanned through the reference lists of the selected articles, as well as review articles on the topic, and also screened for grey literature.

3.3.2 Inclusion and exclusion criteria

All suitable articles were evaluated for inclusion in this review using the following inclusion and exclusion criteria: 1) be published between (January 1990 and December 2017); 2) written in English language; 3) have cohort study designs; 4) depression measured by the use of Centre for Epidemiologic Studies Depression Scale Questionnaire (CES-D), a structured diagnostic interview, Hospital Anxiety and Depression Scale Questionnaire (HADS), Beck Depression Inventory (BDI) or other measurements such as antidepressants use [32, 33]; 5) explicit exclusion of patients that had depression at baseline; 6) give clear information on the diagnosis of diabetes used either a self-report of a doctor's diagnosis or a diagnostic blood test to

measure diabetes; 7) provided a statistical indicator (relative risk, odds ratio, hazard ratio) or original data to estimate the relationship between diabetes and depression; 8) controlled for potential confounders by using statistical adjustment in the analysis or matching in the study design; and we excluded studies that were: 1) case reports, cross-sectional, case-control, a chart review, or 2) did not provide enough information on key inclusion criteria.

3.3.3 Data collection and quality assessment

We retrieved full-text of all articles for studies that initially met our inclusion criteria for further examination. Articles eligibility was independently conducted by authors B.C. and M.L. In instances where disagreements emerged, reviewers consulted each other, and they were resolved through discussion. Two authors [B.C. and M.L.] used indicators such as outcomes, adjustments, methods, publication year, sample size, comorbidities, study design and names of first authors to independently extract data for subsequent analysis. One author of a selected article was contacted for a full-text article after it could not be retrieved online, and it was directly sent to us via email.

3.3.4 Statistical analyses

3.3.4.1 Meta-analysis

The analyses generated pooled estimates of the effects of diabetes in general and according to study design and method of diabetes diagnosis on depression incidence. We examined heterogeneity in our main and sub-analyses using DerSimonian and Laird I^2 statistics [35]. To provide a visual assessment of publication bias, funnel plots and Egger's tests were used to generate a standard error for each study and ORs [36]. Funnel plots are visual aids that are used purposely to detect bias or systematic heterogeneity in meta-analysis. We computed both funnel plot and Egger's test even though the latter provides a more objective way to estimate the reliability of the results. A Begg-adjusted rank correlation test was also conducted to check for publication bias. If these tests show non-significant heterogeneity, we used a fixed-effects model, whereas a more conservative random-effects model was used if we saw the possibility of heterogeneity. Furthermore, the influence of each individual study on the main estimates was assessed using sensitivity analysis which recalculates the odds ratios of all the eligible studies. Study quality was also assessed using the Newcastle–Ottawa Scale. Finally, the influence of each

study design and method of diabetes diagnosis on depression incidence and the impact of study quality on results was investigated using meta-regression analyses. Stata v. 14.2 statistical software (StataCorp., USA) was used for the analyses.

3.3.4.2 Calculation of projected effects – Population Attributable Fractions (PAFs)

PAF represents the proportional reduction in disease average risk that would be achieved by removing an exposure of interest or its reduction to a specified level. It shows how a risk factor is potentially attributable to a disease on the assumption that a causal relationship exists between the risk factor and the disease of interest [37]. We calculated the current PAF using a formula derived from the literature [23, 24, 26].

$$PAF = \frac{p(OR - 1)}{p(OR - 1) + 1}$$

where p represents the population prevalence of the exposure and OR is the pooled odds ratio of outcomes given different categories of diabetes diagnosis and the different study designs. We retrieved the present worldwide prevalence estimates of diabetes from the most recent review of trend analysis of diabetes prevalence study [1]. We used the worldwide prevalence estimates of diabetes to generate PAFs for prospective and retrospective studies as well as self-reported doctor's diagnosis and diagnostic blood test for diabetes.

Finally, we estimated the total number of depression cases attributable to diabetes by multiplying PAF estimates and the present number of cases worldwide. We estimated that if the global prevalence of diabetes were to be reduced between 10 and 25 percentage points, it would subsequently translate into a substantial reduction in depression cases. Pooled OR estimates and 95% confidence intervals (CIs) were used to generate the number of cases that could potentially be prevented, the number of attributable cases and confidence ranges for the PAF estimates.

3.4 Results

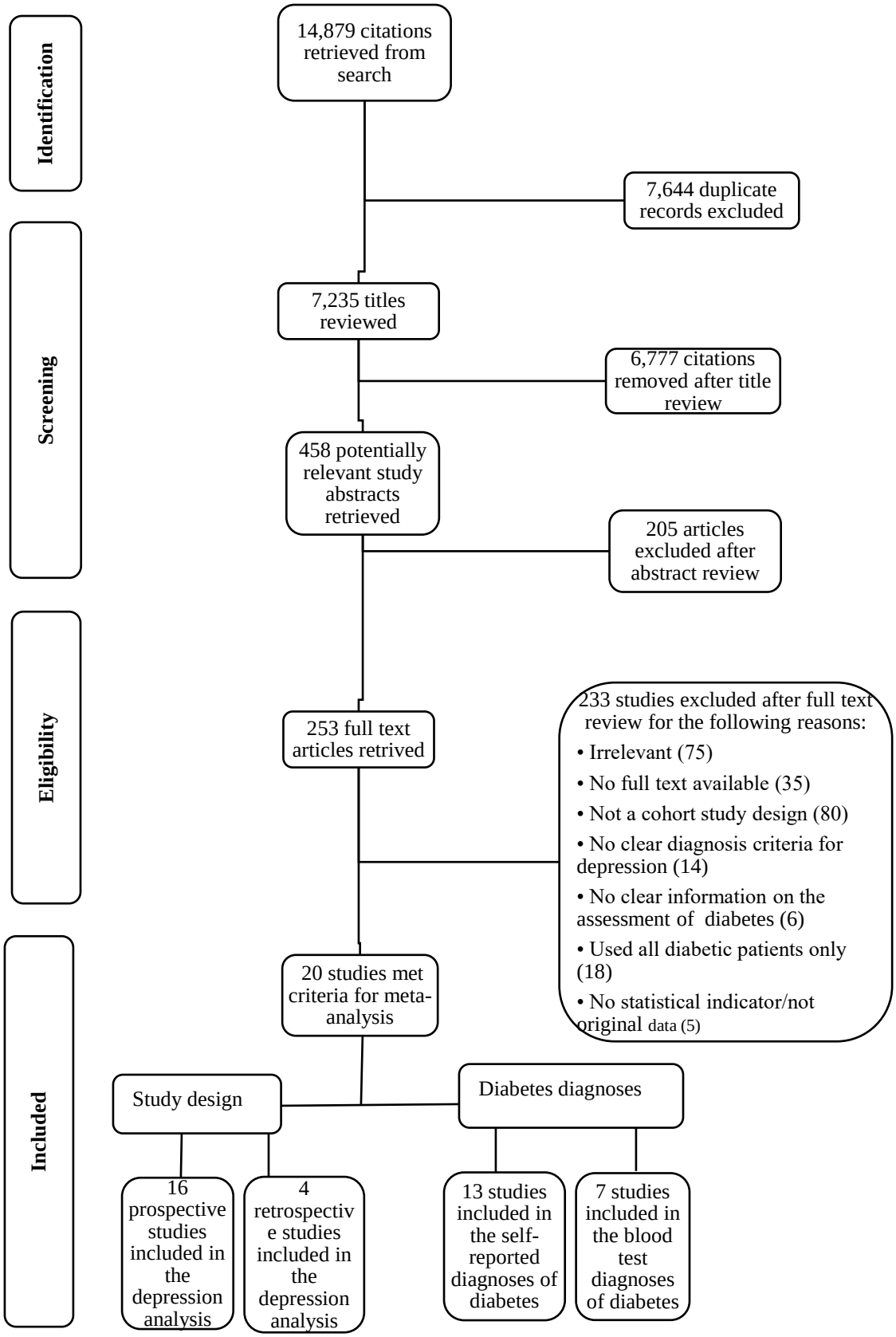
3.4.1 Meta-analysis

3.4.1.1 Selection of articles

To get a maximum number of relevant citations, we conducted three steps search process under the MeSH terms using relevant keywords or title search. In step I, depression was searched as follows; “depression OR major depressive disorder OR MDD OR depressive disorders OR depression symptoms OR depressive symptoms”. At step II, diabetes was also searched as “diabetes mellitus OR diabetes OR type 2 diabetes OR diabetes symptoms”. In step III, we combined step I AND step II AND (cohort studies OR prospective OR retrospective OR follow up OR follow-up OR longitudinal OR panel OR incident OR concurrent OR incidence) for study literature retrieval.

Figure 3-1 shows the search process. We retrieved 14,879 citations in our initial search which later reduced to 7,235 titles after duplicates were excluded. Another 6,777 articles were removed after the title review which resulted in 458 potentially relevant articles remaining. A little over half of the articles (253) remained after the abstract screening. A final list of 20 articles that met the criteria for meta-analysis after full-text screening were included in the study. Figure 3-1 provides reasons for exclusion as a result of full-text screening.

Figure 3- 1 PRISMA flow diagram – Diabetes and incidence of depression in later life



Twenty articles met our inclusion and exclusion criteria. Data from the selected articles were extracted and saved in an Excel spreadsheet for further analysis. The extracted data included study design, exposure, and outcome of interest, sample size, measurement of exposure and outcome, confounding, estimated prevalence of exposure of interest, authors, year of publication and other relevant information (Table 3-1).

Table 3-1 shows a detailed summary of the study attributes and data on the characteristics of the reviewed articles. Included articles were assess based on the following parameters; representative of the population, accuracy in selecting non-exposed groups, absence of depression before the start of the study, proper assessment of both exposure and outcome, adequate follow-up period for outcome to occur, appropriate statistical analysis, control for confounding and other related information(see Supplementary Appendix 3). This study quality is evident in the fact that none of the study characteristics examined had any impact on observed odds ratios in any of the analyses reported. This was also supported by the absence of any publication bias.

Table 3- 1 Summary of studies' attributes

First Author	Year	Setting	Study Design	Sample/Data Source	Sample Size	Age of Exposure	Follow–up (years)	Ascertainment of Exposure	Assessment of Health Outcome
Asamsama et al.[39]	2015	USA	Prospective	Biopsychosocial Religion and Health Study of Adventist Adults	4152	≥61	3	Self-report of doctor's diagnosis	Centre for Epidemiologic Study Depression Scale Questionnaire (CES-D>11)
Bisschop et al.[38]	2004	Netherlands	Prospective	Longitudinal Aging Study Amsterdam	1839	55-85	6	Self-report of doctor's diagnosis	Centre for Epidemiologic Study Depression Scale Questionnaire (CES-D>16)
Chen et al.[40]	2013	Taiwan	Prospective	National Health Insurance claims of the General population	33914	≥35	7	Self-report of doctor's diagnosis	Medical Reports
de Jonge et al.[41]	2006	Spain	Prospective	Community based study of the elderly	4757	≥55	5	Self-report of doctor's diagnosis	Structured Interview
Engum[52]	2007	Norway	Prospective	Nord-Trøndelag Health Study	37291	≥30	10	Self-report of doctor's diagnosis	Hospital Anxiety and Depression Scale Questionnaire (HADS-D>8)
Garcia et al.[50]	2016	USA	Prospective	Sacramento Latino Study on Aging	1583	≥60	10	Fasting blood glucose	Centre for Epidemiologic Study Depression Scale Questionnaire (CES-D>16)
Golden et al.[42]	2008	USA	Prospective	Multi-Ethnic Study of Atherosclerosis	3488	45-84	3	Fasting Plasma Glucose(FPG)	Centre for Epidemiologic Study Depression Scale Questionnaire (CES-D>16)
Hamer et al.[43]	2011	England	Prospective	English Longitudinal Study of Ageing(ELSA)	2545	≥62	2	Fasting Plasma Glucose(FPG)	Centre for Epidemiologic Study Depression Scale Questionnaire(CES-D>4)

Hasan et al.[44]	2015	Australia	Prospective	Australian Pregnancy and Birth Cohort Study	2791	≥20	6	Self-report of doctor's diagnosis	Delusions-Symptoms-States-Inventory (DSSI-depression)
Icks et al.[45]	2013	Germany	Prospective	Population-based Heinz Nixdorf Recall Study	3439	45-75	5	Fasting blood glucose	Centre for Epidemiologic Study Depression Scale Questionnaire (CES-D>16)
Kim et al.[46]	2006	South Korea	Prospective	Community Residents aged 65+	521	≥65	2	Self-report of doctor's diagnosis	Structured Diagnostic Interview
Luijendijk et al.[47]	2008	Netherlands	Prospective	Rotterdam Study of Community dwelling elderly	2876	≥61	5	Fasting Plasma Glucose	Centre for Epidemiologic Study Depression Scale Questionnaire (CES-D>16) or DSM-IV
Maraldi et al.[51]	2007	USA	Prospective	Health, Aging & body composition study	2522	70-79	5.9	Self-report of doctor's diagnosis	Centre for Epidemiologic Study Depression Scale Questionnaire (CES-D10>10)
Pan et al.[49]	2010	USA	Prospective	Nurses' Health Study Cohort	56857	50-75	10	Self-report of doctor's diagnosis	Antidepressant medications(drugs)
Palinkas et al.[53]	2004	USA	Prospective	Adult population of Rancho Bernardo	971	≥50	8	Oral Glucose Tolerance Test(OGTT)	Beck Depression Inventory (BDI>11)
Polsky et al.[48]	2005	USA	Prospective	Health & Retirement Study of elderly	8387	51-61	8	Self-report of doctor's diagnosis	Centre for Epidemiologic Study Depression Scale Questionnaire CES-D8>5)
Aarts et al.[55]	2009	Netherlands	Retrospective	Registration Network Family Practice Study	24556	≥40	7.8	Fasting Plasma Glucose(FPG)	Diagnostic interview by a specialist
Brown et al.[54]	2006	Canada	Retrospective	Population-based Saskatchewan Residents	88776	≥20	4.5	Self-report of doctor's diagnosis	Antidepressant medications(drugs)

Finkelstein et al.[56]	2003	USA	Retrospective	Medicare Standard Analytic Files	237864	≥65	6	Self-report of doctor's diagnosis	Medical reports
O'Connor et al.[57]	2009	USA	Retrospective	Health Partners Medical Group(HPMG)	28288	≥40	2	Self-report of doctor's diagnosis	Antidepressant medications(drugs)

The reviewed articles were categorized into four groups for the analyses: (1) prospective studies and incidence of depression; (2) retrospective studies and incidence of depression; (3) self-reported doctor's diagnosis of diabetes and incidence of depression; (4) blood test diagnosis of diabetes and depression incidence. We report on these studies first looking at prospective studies and retrospective studies, then diagnostic blood test studies and self-report studies, then prospective studies with diagnostic blood test measures and retrospective studies with diagnostic blood test measures, and then prospective studies with self-report measures and retrospective studies with self-report measures. Some studies are involved in multiple separate analyses as their available data permitted.

3.4.1.2 Relationship between prospective studies and depression

Sixteen articles [38-53] used prospective study designs in examining the relationship between diabetes and depression incidence. Most of these studies used the Epidemiologic Studies Depression Scale Questionnaire (CES-D) to measure depression. They had a median follow-up period of 5.95 years. Eight studies[40,41,43,44,47,49-51] with a median follow-up of 5.95 years reported a significant association between diabetes and depression incidence, the other eight studies[38,39,42,45,46,48,52,53] with a median follow-up of 5.5 years reported no association.

Figure 3-2a presents the individual study, pooled estimates, and funnel plots for this group of studies. A random-effects model was used. The pooled OR for incident depression among respondents with diabetes in these prospective studies was 1.34 (95% CI 1.14–1.57, χ^2 = 76.65, I^2 = 80.4%, p<0.001) clearly indicating that diabetes was a risk factor for depression. Figure 3-2a shows all the studies were within the domain which represents 95% CI limits. No evidence of asymmetry or publication bias was found (Egger's test, p = 0.053). Sensitivity analysis yielded ORs ranging from 1.29 (95% CI 1.14–1.47) to 1.39 (95% CI 1.19–1.62) in these prospective studies.

3.4.1.3 Relationship between retrospective studies and depression

Four articles [54-57] used retrospective study designs to examine diabetes and incident depression relationship. Depression was assessed through antidepressants use, medical reports or structured interviews by a specialist. The median follow-up time was 5.25 years. Two studies

[55, 56] with a median follow-up of 6.9 years reported an association while the two other studies [54, 57] with a median follow-up of 3.25 years did not find an association. Figure 3-2b shows the individual study and pooled estimates, and funnel plots. A random-effects model was used. The pooled OR for these studies was 1.30 (95% CI 1.05–1.62, $\chi^2 = 46.71$, $I^2 = 93.6\%$, $p<0.000$). No asymmetry or publication bias was found (Egger's test, $p = 0.85$). Sensitivity analyses for the retrospective studies reported ORs ranging from 1.23 (95% CI 0.95–1.60) to 1.46 (95% CI 1.34–1.59).

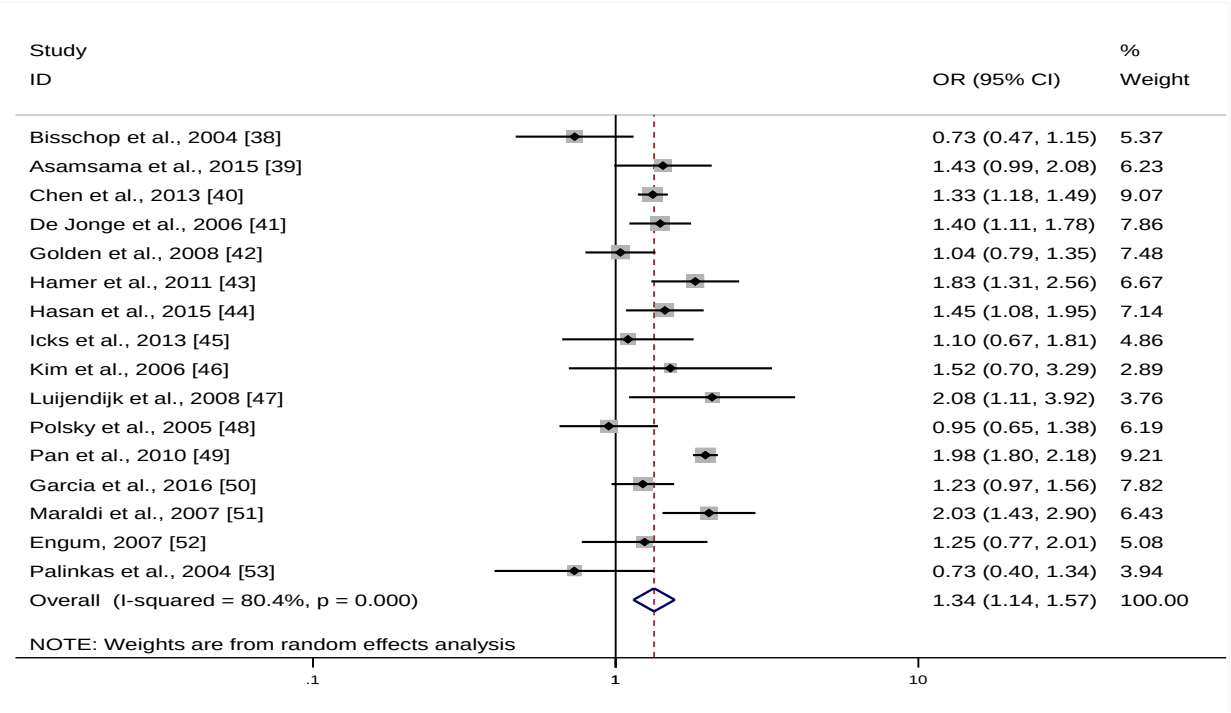
3.4.1.4 Relationship between self-report of doctors' diagnosis of diabetes and depression

Thirteen articles [38-41, 44, 46, 48, 49, 51, 52, 54, 56, 57] measured diabetes using self-reported doctor's diagnosis of diabetes. Figure 3-2c presents the individual study ORs, pooled estimates, and funnel plots. A random-effects model was used. The pooled OR for incident depression for these studies was 1.37 (95% CI 1.17–1.160, $\chi^2 = 127.51$, $I^2 = 90.6\%$, $p<0.001$). No asymmetry or publication bias was found (Egger's test, $p = 0.848$). Sensitivity analysis produced ORs ranging from 1.32 (95% CI 1.15–1.51) to 1.43 (95% CI 1.26–1.63).

3.4.1.5 Relationship between a diagnostic blood test diagnosis of diabetes and depression

Seven articles [42, 43, 45, 47, 50, 53, 55] were included in this analysis of the relationship between blood test diagnosis of diabetes and depression. Pooled estimates and funnel plots of the respective individual studies are presented in figure 3-2d. We used the random-effects model to assess this association. The pooled OR for depression for people with diabetes assessed using diagnostic blood tests was 1.25 (95% CI 1.04–1.52, $\chi^2 = 12.76$, $I^2 = 53.0\%$, $p = 0.047$), indicating that depression was likely in diabetic patients who were diagnosed through any form of a blood test. As shown in figure 3-2d, the funnel plot indicated that all the studies were within the 95% CI domain. No asymmetry was found in the funnel plot. No evidence of publication bias was found (Egger's test = 0. 896). Sensitivity analysis yielded ORs ranging from 1.17 (95% CI 1.0–1.38) to 1.31 (95% CI 1.06–1.62) with/without diabetes as a result of blood test diagnosis. The combined OR was 1.25 (95% CI 1.04–1.52), again showing an increased risk of depression among those with diabetes when a diagnostic blood test was used to ascertain diabetes.

Figure 3- 2a Prospective studies of diabetes and the risk of incident depression–odds ratios



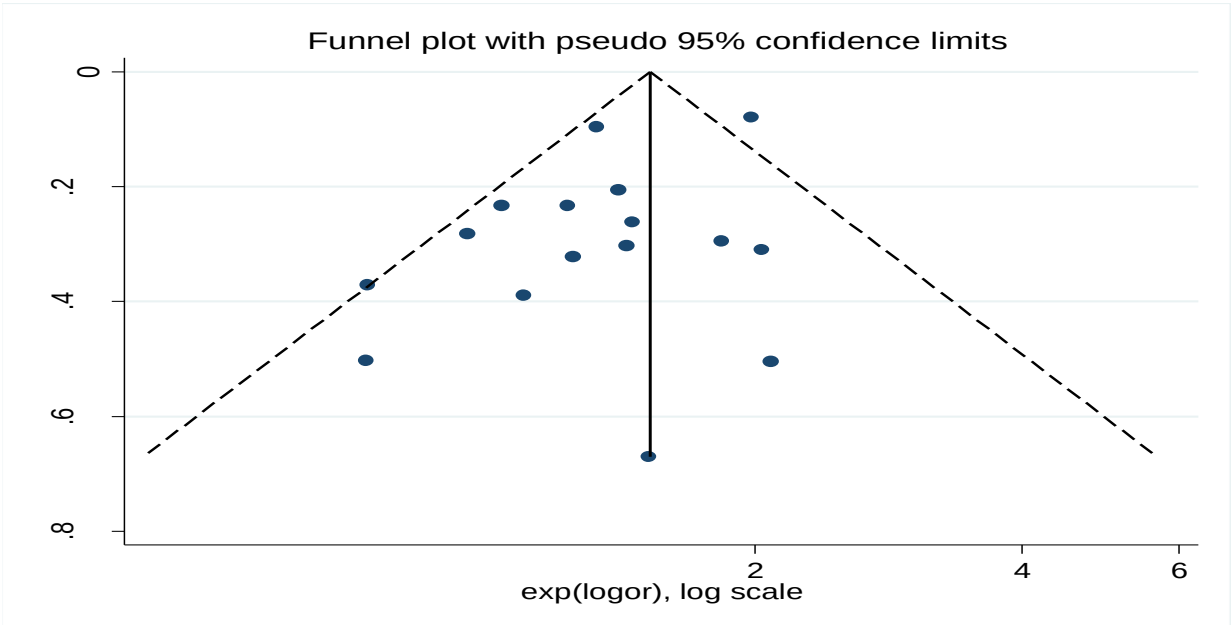
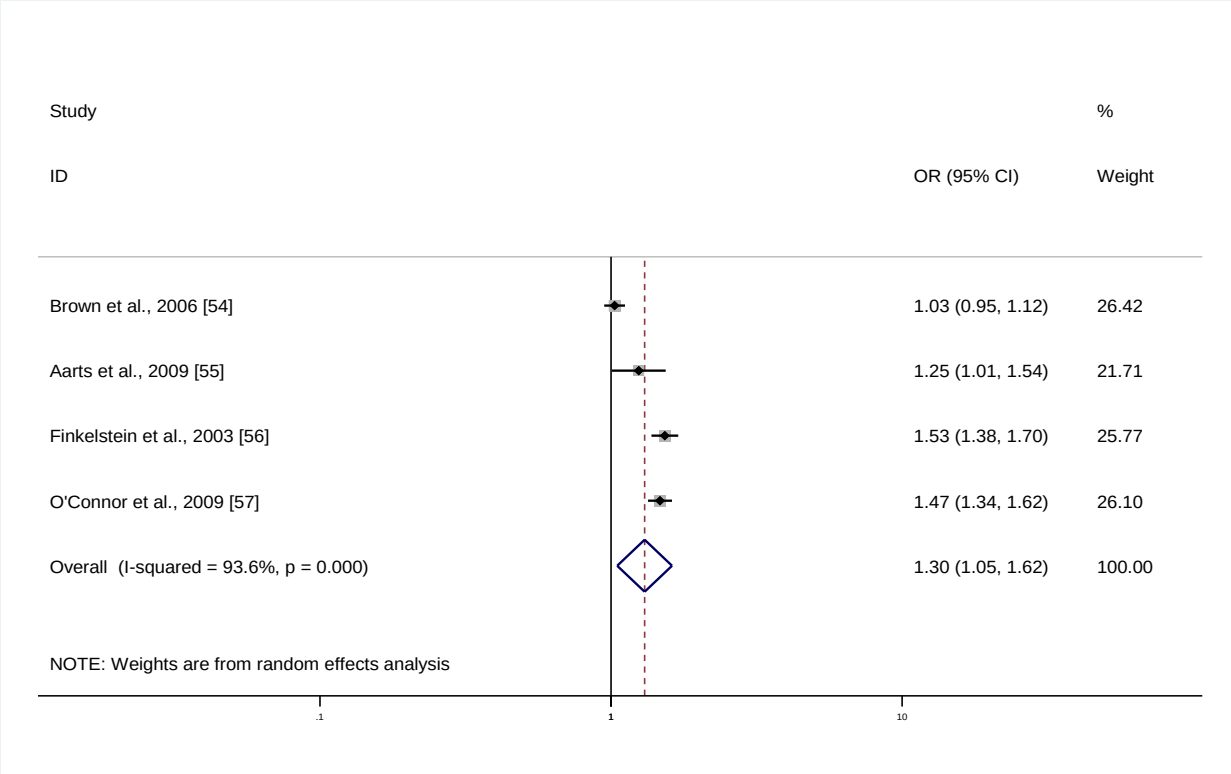


Figure 3- 2b Retrospective studies of diabetes and the risk of incident depression–odds ratios



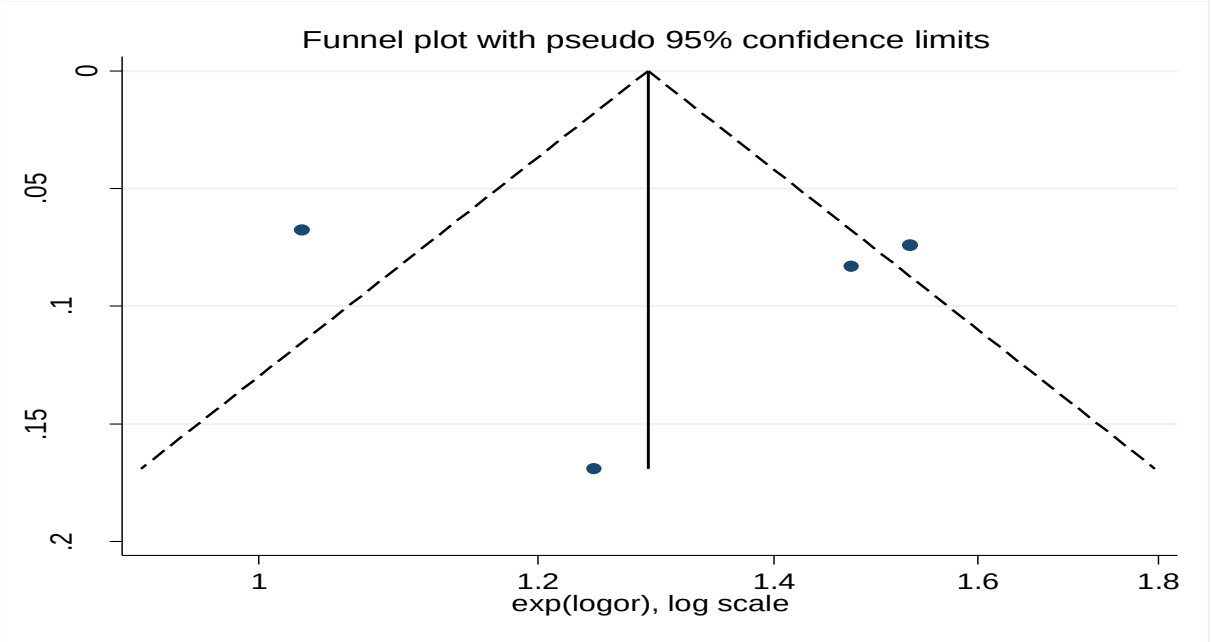
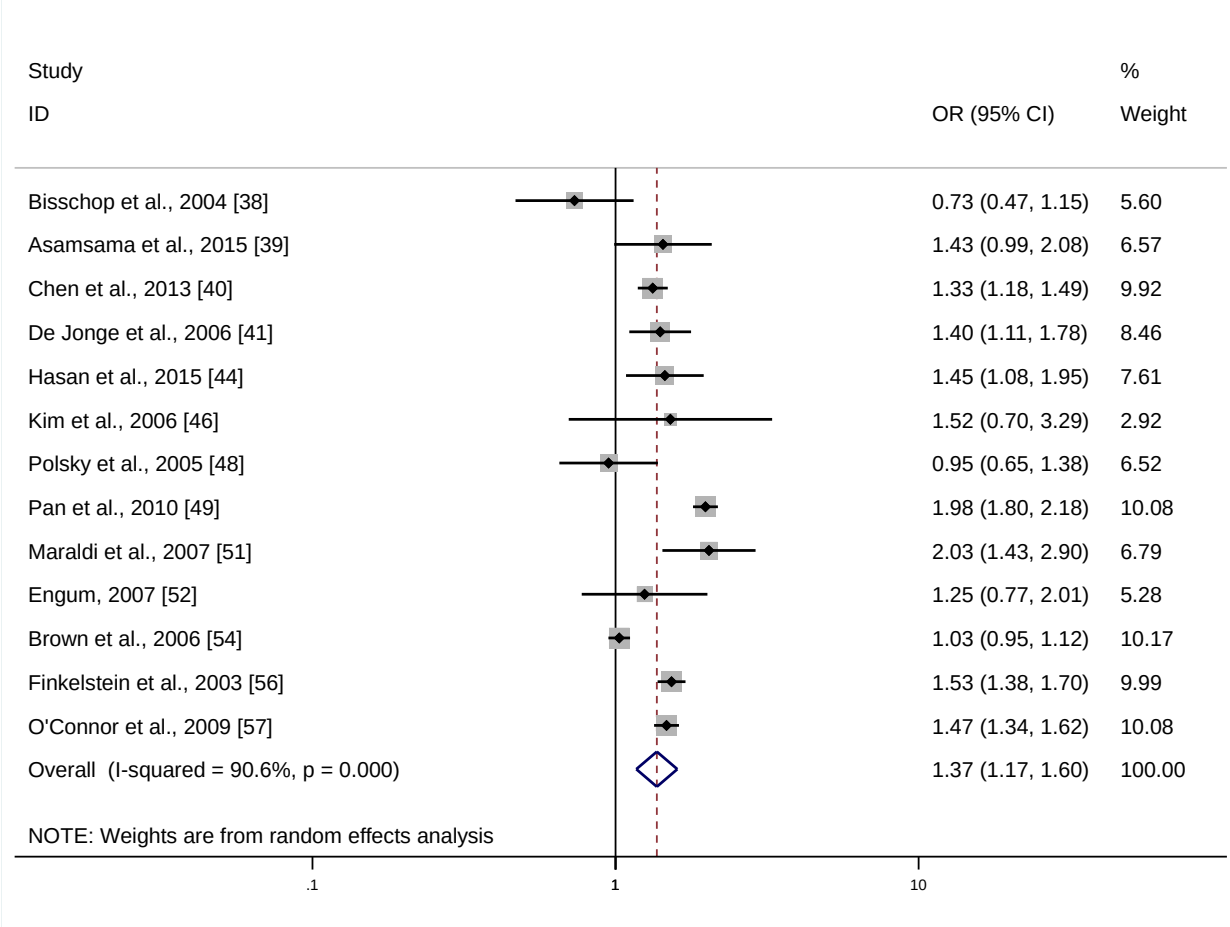


Figure 3-2c Self-report doctors' diagnoses of diabetes and the risk of incident depression–odds ratios



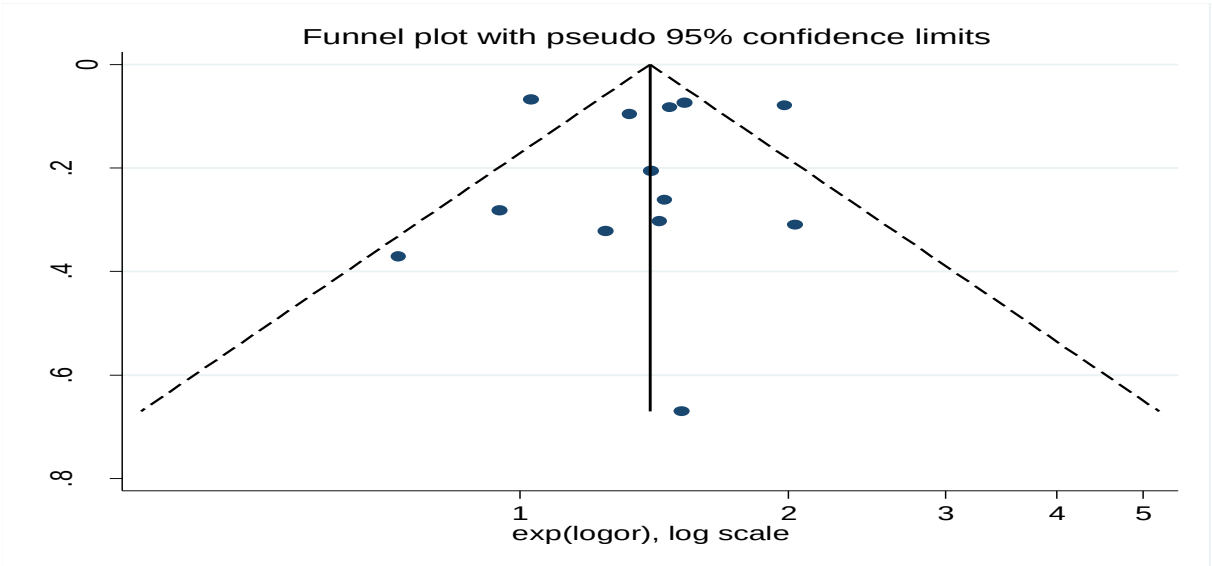
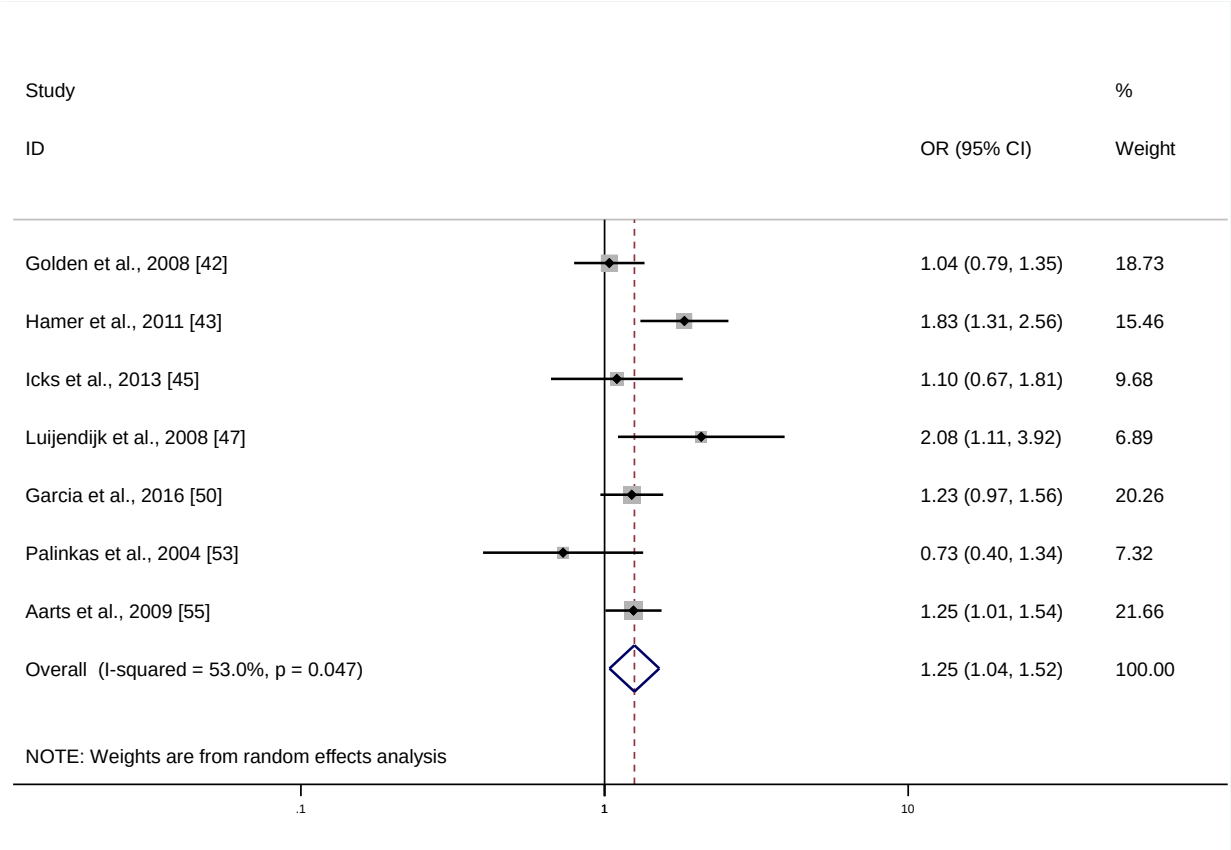


Figure 3-2d Blood test diagnoses of diabetes and the risk of depression–odds ratios



3.4.1.6 Prospective studies and Self-report of doctors' diagnoses measure of diabetes

Ten prospective studies [38–41, 44, 46, 48, 51, 52] used self-report of a doctors' diagnoses of diabetes. Figure 3a shows that in prospective studies that used self-report diagnoses of diabetes were 1.39 times (95% CI 1.14–1.68, $\chi^2 = 54.28$, $I^2 = 83.4\%$, $p<0.001$) more likely to report incident depression compared to those without diabetes. There was some marginal evidence of asymmetry and publication bias (see Table 3- 2).

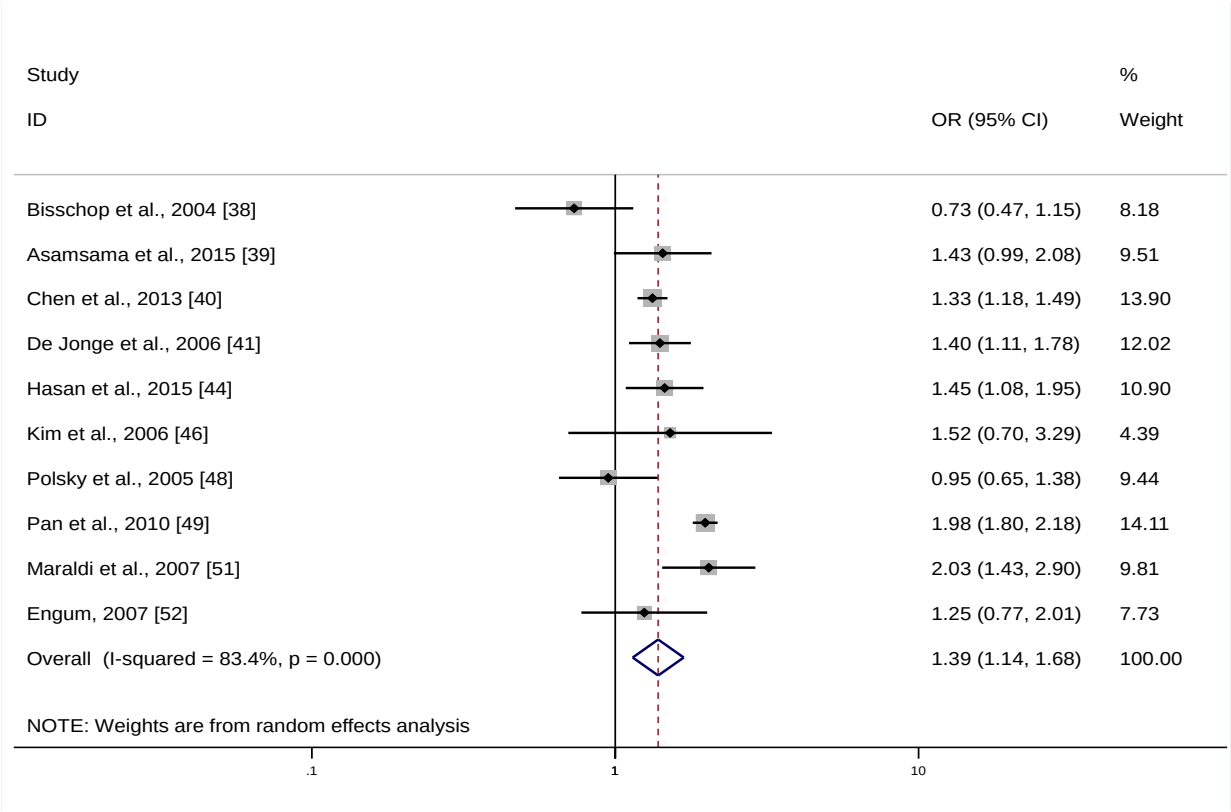
3.4.1.7 Prospective studies and blood test measures of diabetes

Six out of the 16 prospective studies measured the diabetes-depression relationship using diagnostic blood tests [42, 43, 45, 47, 50, 53]. In comparison to the results from the prospective self-report studies, these studies collectively report non-significant results (OR=1.26, 95% CI 0.98–1.61, $\chi^2 = 12.78$, $I^2 = 60.9\%$, $p=0.026$), for diabetes increases the risk of incident depression as reported in Figure 3-3b. A possible explanation for this finding could be the small sample size of 14,908 recorded for blood test studies ranging from 971 to 3488.

3.4.1.8 Retrospective studies and Self-report of doctors' diagnoses measures of diabetes

Three of these four retrospective studies [54, 56, 57] used self-report diagnoses of diabetes to examine the diabetes-depression relationship. The pooled odds for these studies showed that individuals with diabetes were 1.32 times (95% CI 1.02–1.72, $\chi^2 = 46.66$, $I^2 = 95.7\%$, $p<0.001$) more likely to report incident depression (see Figure 3c). Asymmetry and publication bias were evident. The one study [55] that used a diagnostic blood test measure reported an OR of 1.25 (CI 1.01-1.54).

Figure 3- 3a Prospective study designs of self-report diabetes diagnoses and risk of incident depression–odds ratios



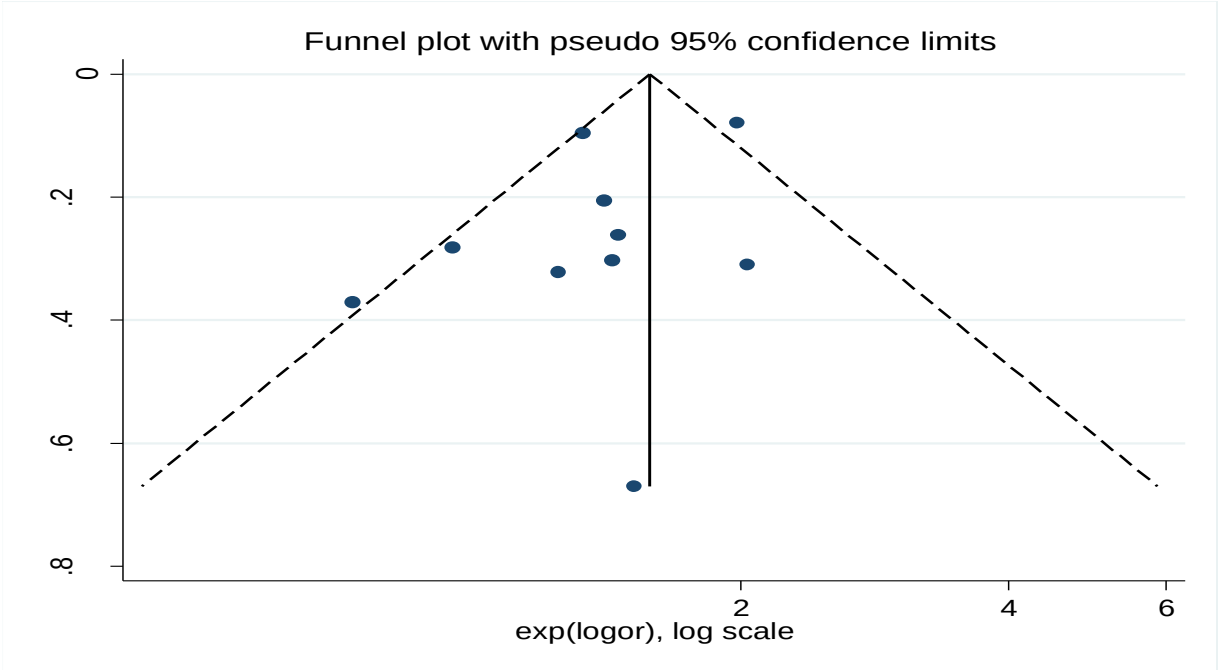
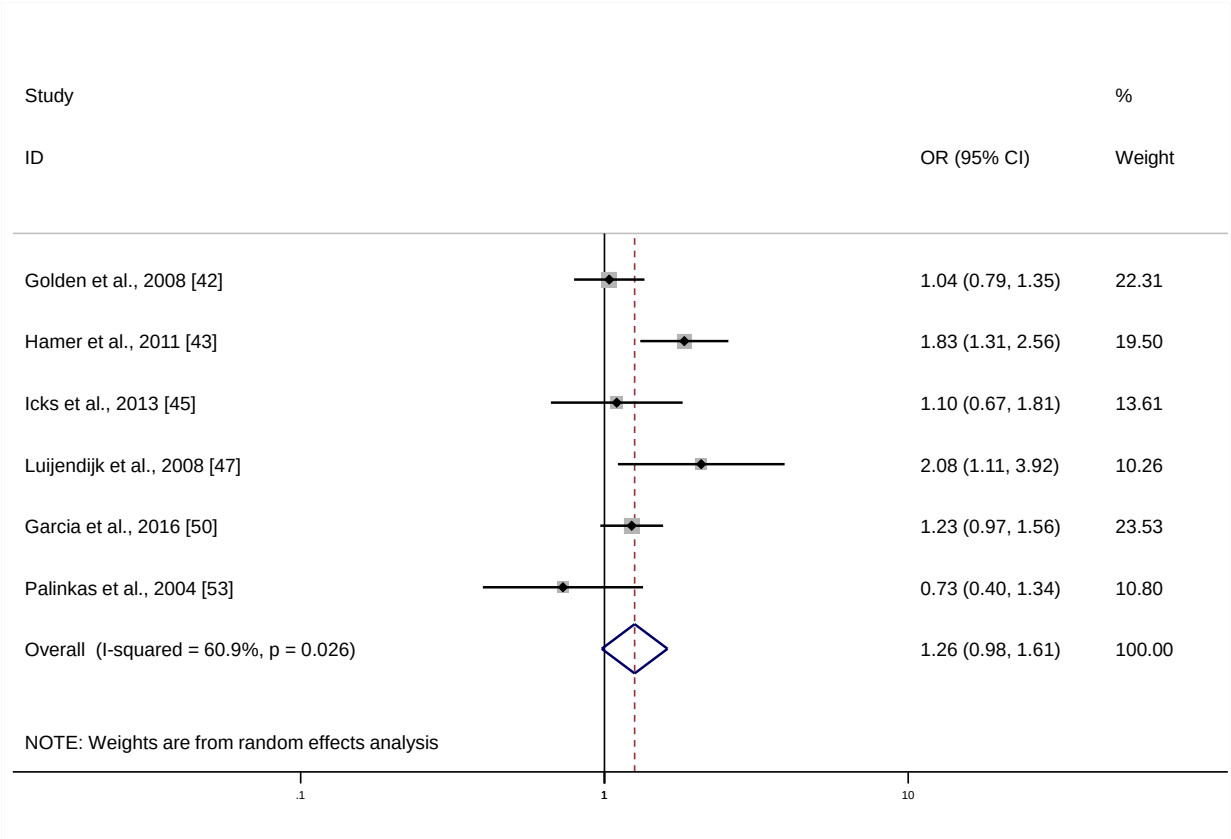


Figure 3-3b Prospective studies of blood test measures of diabetes and risk of incident depression– odds ratios



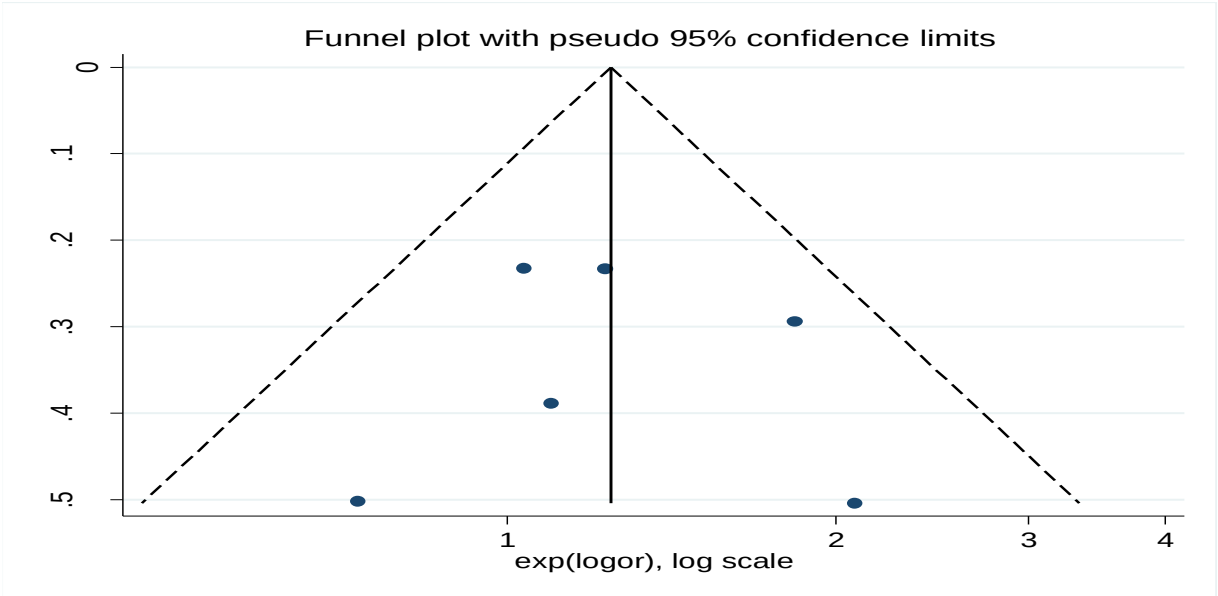
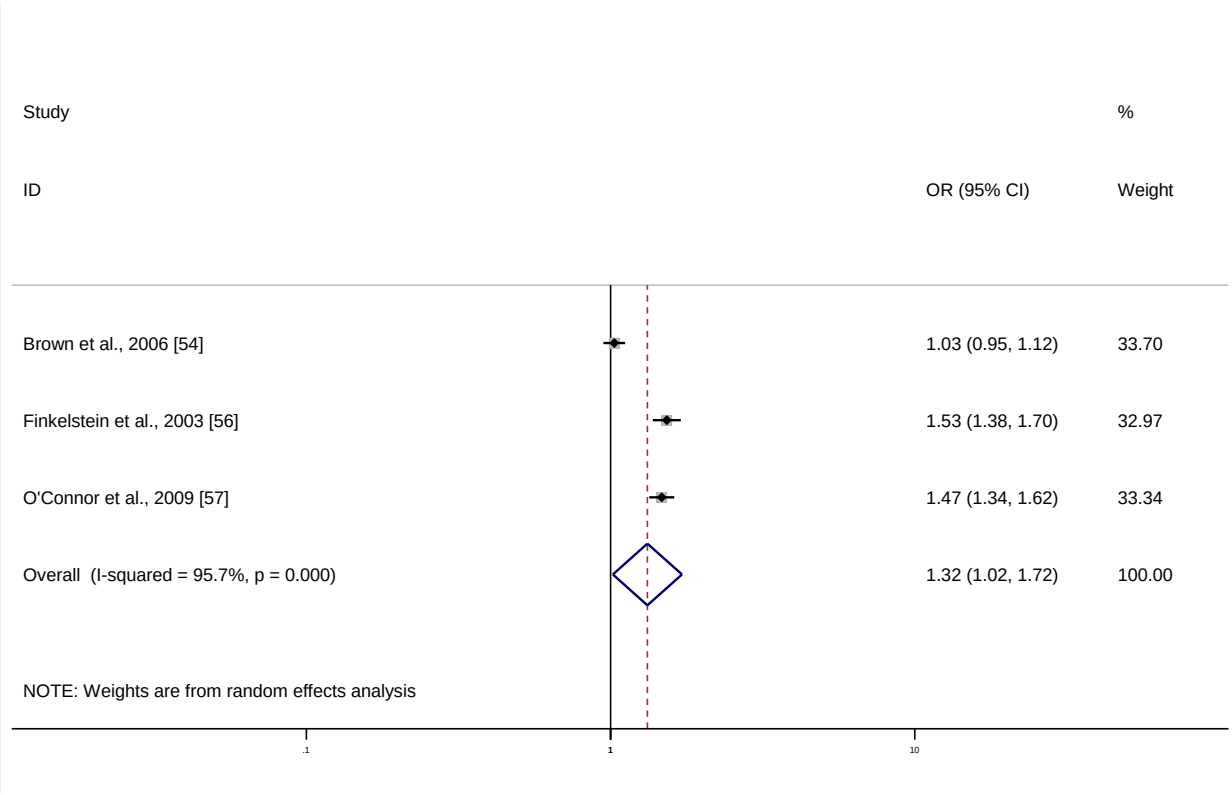
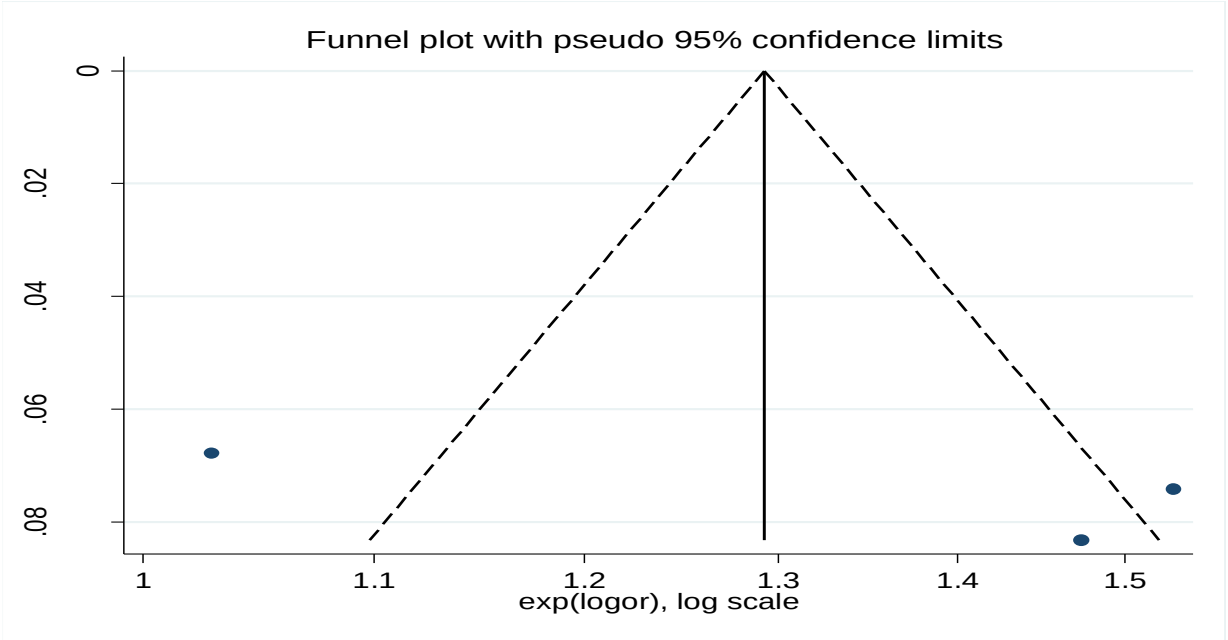


Figure 3-3c Retrospective studies of self-report doctors' diagnoses measures of diabetes and incident depression–odds ratios





The major finding to emerge from our analyses is that although there is some variability in findings by study method the pooled ORs emerging from this group of studies are essentially similar generally supporting diabetes as a risk factor for increasing the risk of depression (Table 3-2).

Table 3- 2 Summary of the results of our meta-analysis

Study group	Odds ratios (OR)	95% Confidence interval (CI)	P-value
Prospective studies	1.34	1.14-1.57	<0.001
Retrospective studies	1.30	1.05-1.62	<0.001
Studies using self-report	1.37	1.17-1.60	<0.001
Studies using blood tests	1.25	1.04-1.52	0.047
Prospective studies using self-report measure	1.39	1.14-1.68	<0.001
Prospective studies using blood test measure	1.26	0.98-1.61	0.026
Retrospective studies using self-report measure	1.32	1.02-1.72	<0.001

3.4.2 Projected effects (PAFs) of risk reduction

3.4.2.1 World wide

3.4.2.1.1 Prevalence of diabetes and PAFs

As of 2016, the worldwide estimated prevalence of diabetes was 8.5 % (422 million) [1] whilst that of depression was estimated to affect 350 million [58]. The PAF estimates used here for the effect of diabetes on the incidence of depression was 2.73%, which indicates that over 9.55 million depression cases are potentially attributable to diabetes globally (Table 3-3). If the global prevalence of diabetes was reduced by 10%, we estimated that there would be 930,000 fewer depression cases worldwide, whereas a 25% reduction could reduce incidence by 2.34 million cases (Figure 3-4). It should be noted that the number of cases attributable to diabetes may be overestimated as a result of co-morbidity with other chronic diseases. Using prospective study values, it is estimated that 2.81% over 9.83 million depression cases in the world are potentially attributable to diabetes. If the prevalence of diabetes was reduced by 10%, 960,000 cases of depression could potentially be reduced; whilst a 25% reduction in the prevalence of diabetes would result in reducing the incidence of depression by 2.41 million cases worldwide. Using retrospective study values yields slightly lower estimates of reduction in the incidence of depression. Estimates from studies using self-report and blood test measure again yield sizeable reductions in depression incidence (see Figure 3-4).

Table 3- 3 Estimated depression cases attributable to diabetes worldwide by type of study design

	Pooled OR (95%CI)	Population prevalence of Diabetes	PAF (confidence range)	Number of cases attributable-millions (Confidence range)
Worldwide	1.33(1.18–1.51)	8.50%	2.73% (1.51–4.15)	9.55 (5.27–14.54)
Prospective *and* depression	1.34(1.14–1.57)	8.50%	2.81% (1.18–4.62)	9.83 (4.12–16.17)
Retrospective *and* depression	1.30(1.05–1.62)	8.50%	2.49% (0.42–5.01)	8.70 (1.48–17.52)
Self-reported diabetes measure *and* depression	1.37(1.17–1.60)	8.50%	3.05% (1.42–4.85)	10.67 (4.99–16.98)
Blood test diabetes measure *and* depression	1.25(1.04–1.52)	8.50%	2.08% (0.34–4.23)	7.28 (1.19–14.82)

OR, odds ratio; PAF, Population Attributable Fraction

Figure 3- 4 Potential depression cases that could be prevented through diabetes reduction worldwide: estimates based on various study designs

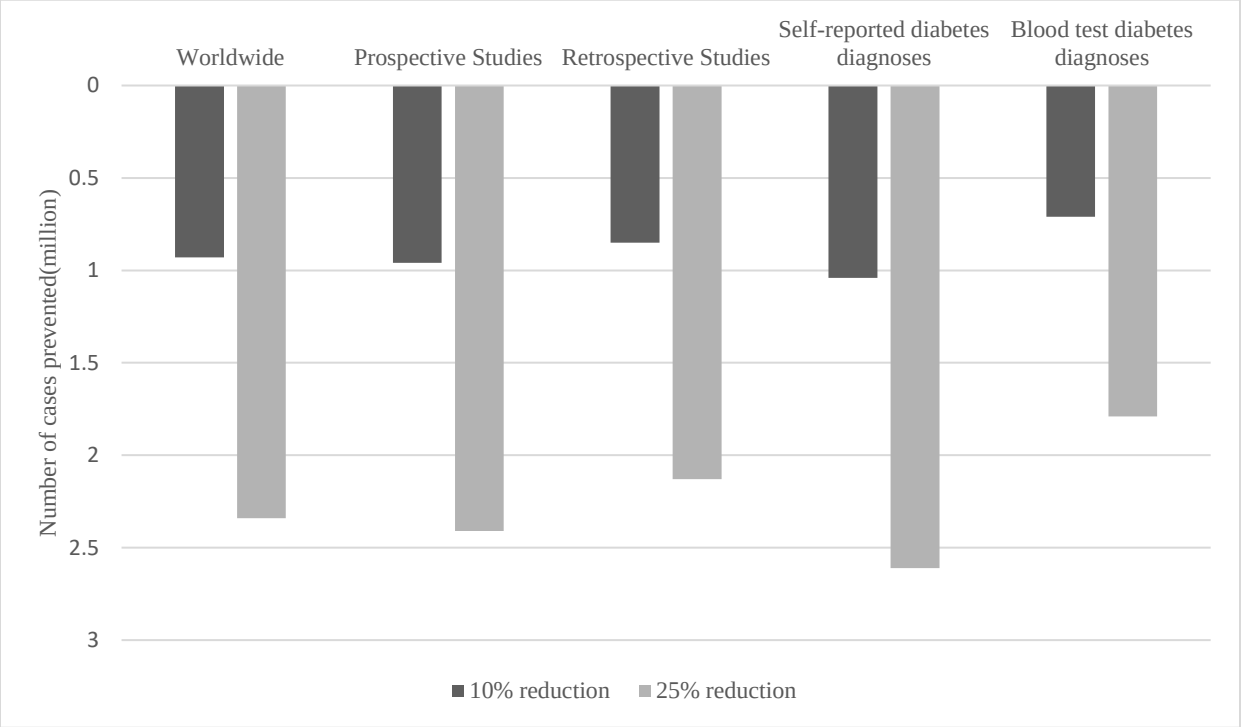
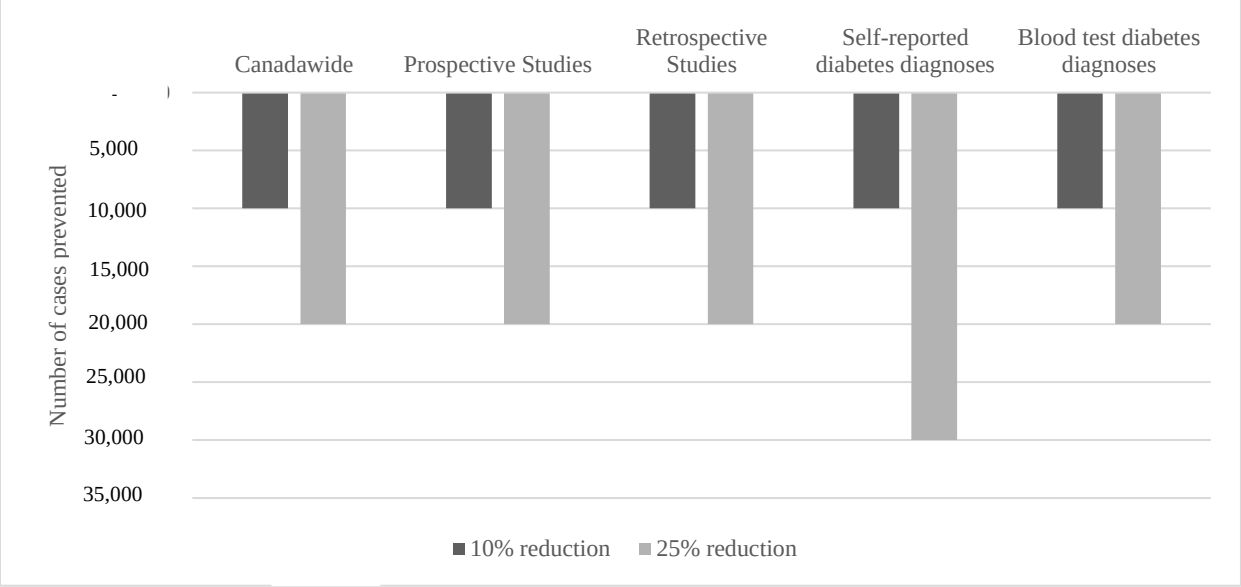


Figure 3- 5 Potential depression cases that could be prevented through diabetes reduction in Canada: estimates based on various study designs



3.4.2.2 Canada

As of 2014, the Canadian prevalence of diabetes, in general, was estimated at 9.41% [66] while an estimated 3.2 million people aged 15 years and above were reported in 2012 to have been suffering from depression in Canada [67].

The PAF estimate for diabetes using prospective studies leading to depression was about 3.10%, corresponding to over 100,000 depression cases potentially attributable to diabetes (Table 3-4). If the prevalence of diabetes was 10% lower than at present, we estimated that there would be 10,000 fewer depression cases across Canada, whereas a 25% reduction could result in 20,000 fewer cases (Figure 3-5).

We calculated that studies using retrospective studies to measure diabetes showed that 2.75% (90,000) of depression cases are attributable to diabetes (Table 3-4). If the prevalence of diabetes was 10% lower than at present, we estimated that there would be 10,000 fewer depression cases across Canada, whereas a 25% reduction could result in 20,000 fewer cases (Figure 3-5).

In the case of studies using self-report studies to measure diabetes, we estimated that 3.36% (110,000) of depression cases are as a result of diabetes prevalence (Table 3-4). Therefore, if the prevalence of diabetes was 10% lower than at present, we estimated that there would be 10,000 fewer depression cases across Canada, whereas a 25% reduction could result in 30,000 fewer cases (Figure 3-5).

In studies where doctor's diagnoses of diabetes were used to measure diabetes, we calculated that about 2.3 %(70,000) cases of depression are potentially attributable to diabetes (Table 3-4). If the prevalence of diabetes was reduced by 10%, we estimated that there would be 10,000 fewer depression cases across Canada, whilst a 25% reduction in diabetes prevalence could result in 20,000 fewer cases (Figure 3-5).

Table 3- 4 Estimated depression cases attributable to diabetes in Canada by type of study design

	Pooled OR (95%CI)	Population prevalence of Diabetes	PAF (confidence range)	Number of cases attributable-millions (Confidence range)
Canada wide	1.33(1.18–1.51)	9.41%	3.01% (1.67–4.58)	0.10 (0.05–0.15)
Prospective *and* depression	1.34(1.14–1.57)	9.41%	3.10% (1.30–5.09)	0.10 (0.04–0.16)
Retrospective *and* depression	1.30(1.05–1.62)	9.41%	2.75% (0.47–5.51)	0.09 (0.01–0.18)
Self-reported diabetes measure *and* depression	1.37(1.17–1.60)	9.41%	3.36% (1.57–5.34)	0.11 (0.05–0.17)
Blood test diabetes measure *and* depression	1.25(1.04–1.52)	9.41%	2.30% (0.37–4.66)	0.07 (0.01–0.15)

OR, odds ratio; PAF, Population Attributable Fraction

3.5 Discussion

This meta-analysis generally showed that people with diabetes had a greater risk of developing depression compared to those without. Out of the 20 studies involving 547,417 participants, half of them (10 studies) constituting 67.6% of the participant population suggested increased depression risk. The pooled OR between diabetes and depression for all the studies included in this analysis was 1.33 (95% CI 1.18–1.51). The ORs for various study types were: prospective studies OR 1.34 (95% CI 1.14–1.57); retrospective OR 1.30 (95% CI 1.05–1.62); self-reported doctor's diagnosis OR 1.37 (95% CI 1.17–1.60) and blood test diagnosis OR 1.25 (95% CI 1.04–1.52). Specific studies that did not find an increased risk of depression generally had smaller sample sizes, had a shorter follow-up period and had an earlier publication date. Conversely, studies that found a relationship between the two conditions had a longer follow-up period, larger sample size and published more recently.

Our results are consistent with previous reviews that reported diabetes was a risk factor for depression. The pooled OR of 1.33 reported in this systematic review is higher than the ORs reported in previous meta-analyses of 1.15 (95% CI 1.02–1.30) , 1.24 (95% CI 1.09–1.40) and 1.29 (95% CI 1.03–1.63) respectively [18, 19, 68] but fell short of a two-fold increased risk of depression in diabetes found in one previous meta-analysis [4]. Also, our current finding is in keeping with recent bidirectional reviews measuring the relationship between diabetes and depression where a moderate association was found [69, 71, 72]. Our review is however at odds with a small meta-analysis that involved 3 longitudinal studies which found those with diabetes to have had an insignificant higher risk of developing incident depression compared to controls, RR 1.50 (95% CI 0.92–2.44) [59].

Overall prospective studies using both diabetic diagnoses methods reviewed here found that respondents with diabetes were 34% more likely to develop depression compared to controls (OR 1.34, 95% CI 1.14–1.57) while retrospective study designs found those with diabetes were 1.30 times more likely to develop depression. These findings are consistent with an earlier meta-analysis of seven longitudinal studies where the pooled OR for risk of depression was 1.15 (95% CI 1.02–1.30) [18].

A previous meta-analysis of studies using clinical measures of diabetes reported smaller effects (RR1.11) compared to self-reported studies (RR 1.16) [18]. We found that studies using self-report of doctor's diagnoses showed a slightly larger effect (OR 1.37, 95% CI 1.17–1.60) than studies which used clinical measures or diagnostic blood tests. Our study is consistent with what has been earlier reported [18]. Among the seven studies analyzed here that examined the relationship between diabetes and depression using diagnostic blood tests, we found a pooled OR=1.25 (95% CI 1.04–1.52). Four of the studies largely from the USA reported a negative relationship between diabetes and depression while three of the studies, from two European countries, reported a significant relationship. The literature suggests that while the overall prevalence of obesity among adults has increased in the US, there are significant ethnic or racial disparities with the highest prevalence among the African-American populations [63]. We suggest that the sample variations in these studies, oversampling of white or Latino populations, could possibly explain the non-significant results reported.

In our review heterogeneity was large compared to previous reviews [18, 19]. This could probably be due to the fact that earlier studies did not report a more increased risk of depression in people with diabetes is currently being reported by later studies. We cannot authoritatively state why recent studies report an increased risk of depression in people with diabetes. However, a plausible explanation could be that health care professionals and patients with diabetes are increasingly becoming knowledgeable about depression or depressive symptoms in people with diabetes and this could possibly influence responses during follow-up periods. But the results of this study should be interpreted with caution since it is possible that the incident depression reported in this study can be due to recurrence of depressive disorder among those with a history of depression or as a result of diabetes-related complications.

To the authors' knowledge, this is the first study to provide quantitative estimates on the projected reduction of depression cases that could result from a reduction in the worldwide prevalence of diabetes. The PAFs estimates show a significant number (9.55 million) of worldwide depression cases could be due to diabetes prevalence. Measures used to reduce the prevalence of diabetes will eventually lead to a reduction in depression and that should be the focus of public health prevention efforts. This study projects that a 10–25% reduction in diabetes prevalence could potentially prevent 930,000–2.34 million depression cases worldwide.

3.5.1 Strength and limitations of the current study

The major strength of this study comes from the pooled findings of longitudinal cohort studies and the relatively large number of studies involved. The reviewed studies were of high quality. We also provided PAF estimates to show the potential impact of substantially reducing diabetes prevalence on the global incidence of depression. However, the current study has limitations that may affect generalizability. First and foremost, we reviewed only English-language databases and journals which may lead to publication bias giving the fact that studies in other languages were not retrieved. Secondly, our reviewed studies were not geographically representative of the world's population. Majority of the studies reviewed emanated from the US, Europe, and other developed countries. There were no studies from Africa, South America, and other developing countries. However, a 2013 diabetes report by the International Diabetes Federation revealed that about 80% of all those with diabetes reside in low and middle-income countries [61].

In addition, some of our studies failed to adequately adjust for strong moderating factors such as sex, smoking, alcohol abuse, and the presence of other chronic diseases [62]. Confounding is possible. Another limitation is the high values of heterogeneity that were recorded in 3 out of the 4 analyses performed in our meta-analysis. This shows substantial variation in the degree of association between diabetes and depression in the studies reviewed. We reported on studies using self-report of doctor's diagnosis of diabetes and diagnostic blood tests (fasting plasma glucose or oral glucose tolerance test). Both measures have their respective strengths and limitations. A major drawback of self-reported diagnosis is that it may be an underestimate of the real prevalence of diabetes. On the other hand, others have argued that people who are unaware of their diabetes blood tests diagnosis (fasting glucose or oral glucose tolerance test) may avoid the psychological trauma associated with this diagnosis [22].

It is not clear cut that all self-reported diagnosis lead to over or underestimate of diabetes prevalence. We assume that the source of the recorded heterogeneity is either clinical or methodological which suggests the need to adjust for known moderators in future studies of the diabetes-depression relationship.

Finally, in estimating PAF values, the worldwide prevalence of diabetes was not broken down by the severity of complications, we used crude overall prevalence rate to calculate PAFs.

Our PAF estimates did not take into account diabetes severity and its effects on complications and their combined effect on depression incidence. Diabetes in itself does not usually cause death directly but rather it is the complications that arise from the disease that has a substantial impact on an individual's health.

3.6 Conclusion

Despite the limitations, our systematic review provides fairly robust evidence to support the hypothesis that diabetes is a risk factor in the development of depression. This increased risk reported may be due to recurrence of depressive symptoms among people with a history of depression or as a result of diabetes-related complications. We also note some of the impacts of risk factor reduction, study design, and diagnostic measurements of exposure of interest. More and better-designed cohort studies are still needed to corroborate our study and to also firmly establish the relationship between diabetes and depression. The calculated PAFs showed that a large reduction in the worldwide prevalence of diabetes could translate into a significant reduction in the incidence of depression. However, this impact is not limited to the incidence of depression but has a larger effect because of the clinical and economic repercussions that come with the long-term management and treatment of both conditions globally. Interventions and services for diabetes prevention such as healthy diet, physical activity, and weight loss also improve the mental health of general populations. We are of the view that there is the need to adopt a more holistic and multisectoral approach as well as programs and policies aimed at combating diabetes and reducing its prevalence since a reduced diabetes prevalence will eventually translate into a reduction in depression cases worldwide.

3.7 References

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Appendix A: Search Strategy

To get a maximum number of relevant citations, we used the following search strings: “depression OR major depressive disorder OR MDD OR depressive disorders OR depression symptoms OR depressive symptoms” AND “diabetes mellitus OR diabetes OR type 2 diabetes OR diabetes symptoms” AND (cohort studies OR prospective OR retrospective OR follow up OR follow-up OR longitudinal OR panel OR incident OR concurrent OR incidence) as the keywords for study retrieval.

Appendix B: Data References

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Appendix C: Assessment of Studies' Quality Characteristics

First Author	Year	Represen-tativeness[1]	Selection of control[2]	Ascertainment of exposure to Diabetes [3]	Assessment of exposure[4]	Assessment of outcome[5]	Temporality[6]	Adequacy of follow-up of cohorts or response rate[7]	Was follow-up long enough[8]	Appropriate analysis[9]	Appropriate confounding control[10]	TOTAL
Bisschop et al.	2004	1	1	1	0	1	1	1	1	1	0	8
Asamsama et al.	2015	0	1	1	0	1	1	1	1	1	1	8
Chen et al.	2013	1	1	1	2	0	1	1	1	1	1	10
De Jong et al.	2006	1	1	1	1	1	1	1	1	1	1	10
Golden et al.	2008	1	1	1	2	1	1	1	1	1	1	11
Hamer et al.	2011	1	1	1	2	1	1	1	1	1	1	11
Hasan et al.	2015	0	1	1	1	1	0	1	1	1	1	8
Icks et al.	2013	1	1	1	1	1	1	1	1	1	1	10
Kim et al.	2006	1	1	1	0	0	1	1	1	1	1	8
Luijendijk et al.	2008	1	1	1	2	1	1	1	1	1	1	11
Polsky et al.	2005	1	1	1	0	1	1	1	1	1	1	9
Pan et al.	2010	0	1	1	0	0	1	1	1	1	1	7
Garcia et al.	2016	0	1	1	2	1	1	1	1	1	1	10
Maraldi et al.	2007	1	1	1	0	1	1	1	1	1	1	9
Engum et al.	2007	1	1	1	0	1	1	1	1	1	1	9
Palinkas et al.	2004	1	1	1	2	1	1	1	1	1	1	11
Brown et al.	2006	1	1	0	2	1	1	1	1	1	1	10
Aarts et al.	2009	0	1	0	2	1	1	1	1	1	1	9
Finkelstein et al.	2003	0	1	0	2	1	0	1	1	1	0	7
O' Connor et al.	2009	0	1	0	2	1	1	1	1	1	1	9

[1]Representativeness of the population: population-based representative = 1; Not representative, selected group, volunteers, or no description = 0.
[2]Selection of the non-exposed cohort/control drawn from the same population =1; drawn from a different source or no description =0.
[3]Assertainment of exposure to diabetes: data on diabetes collected prospectively = 1; data on diabetes collected retrospectively = 0.
[4]Assessment of exposure: all cases from secure official record (FPG, OGTT, ICD) = 2; cases partially from secure official record = 1; self-reported or structured interview or self-administered questionnaire or no description = 0.
[5]Assessment of outcome: use of structured clinical interview for DSM-III/IV (CES-D, CIDI, HADS, BDI, ICD) = 1; questions from published health surveys/screening instruments, own system, symptoms described, no system, not specified, or self-reported = 0.
[6]Demonstration that outcome of interest was not present at start of study: yes = 1; no = 0.
[7]Adequacy of follow-up of cohorts or response rate: completeness good (>= 80%), with description of those lost to follow-up = 1; completeness poor (< 80%) or no statement = 0.
[8]Was follow-up long enough for outcomes to occur: yes = 1; no = 0.
[9]Appropriate statistical analysis: yes = 1; no = 0.
[10]Appropriate methods to control confounding: yes (multivariable adjusted OR including SES, education, or family dysfunction in models) = 1; no (univariate analysis or controls for age/sex only) = 0.

CID, Composite International Diagnostic Interview; DIS, Diagnostic Interview Schedule; DISC, Diagnostic Interview Schedule for Adults; SES, socioeconomic status.

Doi:10.1371/journal.pmed.1991349.t002

CHAPTER 4 – EXAMINING SHARED AND UNIQUE RISK FACTORS OF DEPRESSION AND DIABETES IN A LONGITUDINAL STUDY: AN ANALYSIS OF THE CANADIAN NATIONAL POPULATION HEALTH SURVEY

A version of this chapter has been submitted to Therapeutic Advances in Endocrinology and Metabolism Journal for publication review.

4.1 Abstract

Background: Although both cross-sectional and longitudinal studies have consistently reported the risk factors for depression and Type 2 diabetes separately, almost no studies have investigated the two disorders together in the same national population sample. Literature is non-existent regarding shared risk factors for depression and diabetes at a national level in Canada. This study explores the shared risk factors for both incident depression and incident type 2 diabetes separately using data from a national longitudinal population-based survey study over a *10-year follow-up*. Sex differences in these shared risk factors for depression and diabetes are also assessed.

Methods: A secondary analysis of data from the Canadian National Population Health longitudinal Survey (NPHS) was conducted in this study. A subsample (N=4845) subjects of the entire sample of the NPHS was analyzed over a 10-year period. The modified Poisson regression was used to estimate the relative risk (RR) for the association between shared or unique risk factors and incident depression and diabetes. Stratified analyses by sex were also conducted to measure its moderating role in this relationship. We tested the goodness-of-fit for the various models.

Results: We found the cumulative incidence rates of major depressive disorder and incident diabetes at the 10-year follow-up to be 4.1% and 10.1% respectively. We found hypertension, smoking status, physical inactivity, and overweight or obesity as the four shared risk factors between major depressive disorder and diabetes. In our stratified analysis, being underweight, having family stress, having a chronic disease and heart disease were all shared risk factors for major depressive disorder in both sexes. Shared risk factors for incident diabetes in men and women were six namely; age, race or ethnicity, high blood pressure, smoking status, physical inactivity, and body mass index. Our results show risk factors for major depressive disorder and diabetes were not generally different in both sexes, except that their respective effects on major depressive disorder and diabetes incident were more prominent in females compared to males.

Conclusions: We conclude that both conditions can be potentially prevented through healthier lifestyles such as eating healthy, quitting or reducing smoking, having adequate rest, being physically active and having enough social support and that should be the focus of public depression and diabetes prevention programs. These programs should take into consideration sex

differences in risk factors for the two conditions. Cigarette smoking specifically stood out as the significant risk factor for both conditions and merit specific policy interventions regarding smoking cessation, especially programs geared towards individuals with depression or diabetes.

Keywords: Major depressive disorder, diabetes, cohort study, longitudinal study, risk factors, implications for prevention

4.2 Introduction

The relationship between depression and diabetes is of interest to health care providers since both conditions contribute significantly to the global burden of disease. Depression is one of the major public health problems globally as reported by the Global Burden of Disease Study 2010 [1]. The increasing burden of depression has a huge financial impact on the healthcare systems of many nations as they struggle to meet the needs of those affected [2, 3].

Most of the cross-sectional and longitudinal studies conducted in the past have consistently shown an association between depressive disorder and mostly psychosocial factors. These include, body mass index [4], female sex, younger adults, having a chronic disease [5] low birth weight [6], unhealthy eating styles [7], low income [8] unemployment [9], family or maternal stress [10, 11] the use of alcohol, tobacco and drugs during pregnancy, [12] child abuse and adverse childhood experience [13, 14] smoking, [5, 15], physical inactivity [16] and among others. In a nutshell, the prevalence and incidence of depression are rapidly rising globally [17, 18].

Type 2 diabetes mellitus, a progressive chronic disease continues to increase in prevalence and is viewed as a threat to global economies. Recent reports by the International Diabetes Federation suggest that as of 2017 about 425 million people globally were living with Type 2 diabetes and this number is expected to increase to almost 642 million by the year 2040 [19]. These estimates, therefore, mean that one in 11 adults had diabetes as of the year 2017. Diabetes is also projected to become the 7th cause of global deaths by 2030 [20].

The commonly reported risk factors for diabetes include rapid increases in overweight, obesity, physical inactivity, sedentary lifestyles and certain dietary behaviors, such as high fat intake [21]. Other risk factors such as smoking status, age, abdominal obesity, high blood pressure or hypertension, urban residence, family history of diabetes, high triglycerides and low HDL cholesterols have also been reported as strong predictors of Type 2 diabetes [22]. A recent Lancet study revealed that depression and diabetes respectively accounted for 34 and 57 millions of all-age disability adjusted life-years (DALYs) globally [23].

Aside from the known traditional risk factors for the two conditions, evidence suggests that depression and diabetes are closely linked [24, 25]. For instance, Ducat et al [26] reported

that mental health problems often co-occur in people with Type 2 diabetes. Also, people with depression are more likely to report poor health outcomes and is also common in people with Type 1 or Type 2 diabetes compared to the general population [27]. In three meta-analyses it was reported that individuals with depressive symptoms had a 37–60% greater risk of incident diabetes compared to those without depressive symptoms [28–30]. In addition, Chireh et al [52] found a 33% increased risk of depression in patients with diabetes in their recent review of longitudinal studies. Other studies have suggested a reciprocal relationship between these diseases [27, 29, 30].

Researchers have tried in diverse ways to unravel the link between depression and diabetes in time past. Some researchers are of the view that the psychological trauma associated with the diagnosis of a chronic disease predisposes patients to depression. Others report that Type 2 diabetes patients are predisposed to poor self-care behaviors leading to depression [27, 31].

Another explanation is that both conditions share the same or similar lifestyle and environmental risk factors such as reduced physical activity, socioeconomic deprivation, smoking, and social adversity. For example, research shows that work-related stress is a risk factor for both depression and diabetes in adulthood [32, 33].

In addition, it is believed that depression is prominent in early adult life rather than in older age and is linked to self-neglect and low self-esteem resulting in unhealthy lifestyle which in turn, increases the risk of diabetes. Katon et al [34] reported that depressed people are more likely to have a high body-mass index, poor diet, physically inactive and smoke daily. All of which are known risk factors for diabetes and other cardiovascular diseases.

There is enough evidence to show that depression and diabetes are closely related. It has also been established that a bidirectional and/or a comorbid relationship exist between the two conditions [27, 29, 30]. What is not well understood are the mechanisms linking depression and type 2 diabetes though it is likely that behavioral and biological factors both contribute.

Research regarding shared biological mechanisms or origins of depression and diabetes have been the focus of some recent studies. A recent Lancet study has used the hypothalamic-pituitary-adrenal axis of humans in an attempt to explain why depression and diabetes may have

shared origins. They argued that the overactivation of the human innate immunity can lead to dysregulation of the hypothalamic-pituitary-adrenal axis which in turn leads to cytokine-mediated inflammatory response. The resultant effect therefore is that, these intertwined pathways can lead to several chronic diseases including depression and Type 2 diabetes and even mortality [35].

Although both cross-sectional and longitudinal studies have consistently reported the risk factors for depression and Type 2 diabetes separately, however, few studies have investigated the two disorders together. It is acknowledged that the four major groups of chronic diseases of "cardiovascular", "cancers", "chronic respiratory diseases" and "diabetes" have well-established common risk factors [23]. Factors such as high alcohol consumption, sedentary lifestyle, unhealthy diet and obesity have been noted in the literature as shared risk factors for these four major chronic diseases [23]. This enables policymakers to target public health interventions towards these conditions together simultaneously. However, in the Canadian context, literature is non-existent regarding shared risk factors of depression and diabetes at the national level. There is, therefore, the need to conduct a well-characterized longitudinal cohort study to determine whether shared origins of depression and type 2 diabetes exist on a national scale. To our knowledge, this study is the first of its kind in Canada to simultaneously examine the two conditions longitudinally over a 10-year period.

What this study adds new is the concurrent measure of shared risk factors of depression and type 2 diabetes over a 10-year follow-up period among middle age and older Canadians. We hope to identify the temporal relationships between the risk factors for depression and type 2 diabetes as well as their shared or unique risk factors. These shared origins could provide joint avenues for public health prevention strategies and treatment for both conditions [35]. Our current study explores the common and unique risk factors of the two debilitating conditions in a 10-year longitudinal study of Canadians age 45 years and older.

The study has two major objectives:

1) To explore shared and unique risk factors of depression and diabetes in the same population over a 10-year follow-up period.
2) To assess sex differences in the shared or unique risk factor identification between depression and diabetes.

4.3 Method

4.3.1 Data Sources

A secondary analysis of data from the Canadian National Population Health longitudinal Survey (NPHS) was conducted in this study [36–38]. It is a representative longitudinal community sample study of 17, 276 participants of the Canadian population initialized in 1994–1995 and followed up until 2010–2011 [36–38]. This longitudinal study can establish the temporal relationship between predictor variables and incident depression and diabetes. A major limitation of this survey is the significant number of participant's loss to follow-up.

The NPHS was conducted by Statistics Canada with the sole purpose of collecting longitudinal information on population health. A multistage stratification method was used to select respondents whilst taking into consideration the geographic and socioeconomic characteristics and clustering in the various Census Enumeration Areas [36–38]. Baseline interviews were conducted in the first cycle (1994–1995). Interviewers had face-to-face interviews with respondents at baseline and after which respondents were re-interviewed every second year through telephone and followed prospectively [36]. Our study used data collected up to the 6th data collection cycle (2004–2005) for our analysis. The initial sample of the NPHS longitudinal study was 17, 726 participants (ages 12 years and over) with an overall response rate of 69.7% after a successful follow-up to the Cycle 9 in the entire study [36]. Our analysis stopped at cycle 6 to limit loss to follow-up issues. After the 6th cycle, over fifty percent of respondents were lost to follow-up. We recorded a lower response rate after cycle 6 because we excluded respondents who were less than 45 years of age and that affected our sample size. The significant loss to follow-up recorded after cycle 6 could also be due to deaths and migration. Statistics Canada received informed consent from all respondents as well as ethics review approval before the NPHS study started. A more detailed description and information on how NPHS was conducted have been described elsewhere [36–38].

4.3.2 Study sample

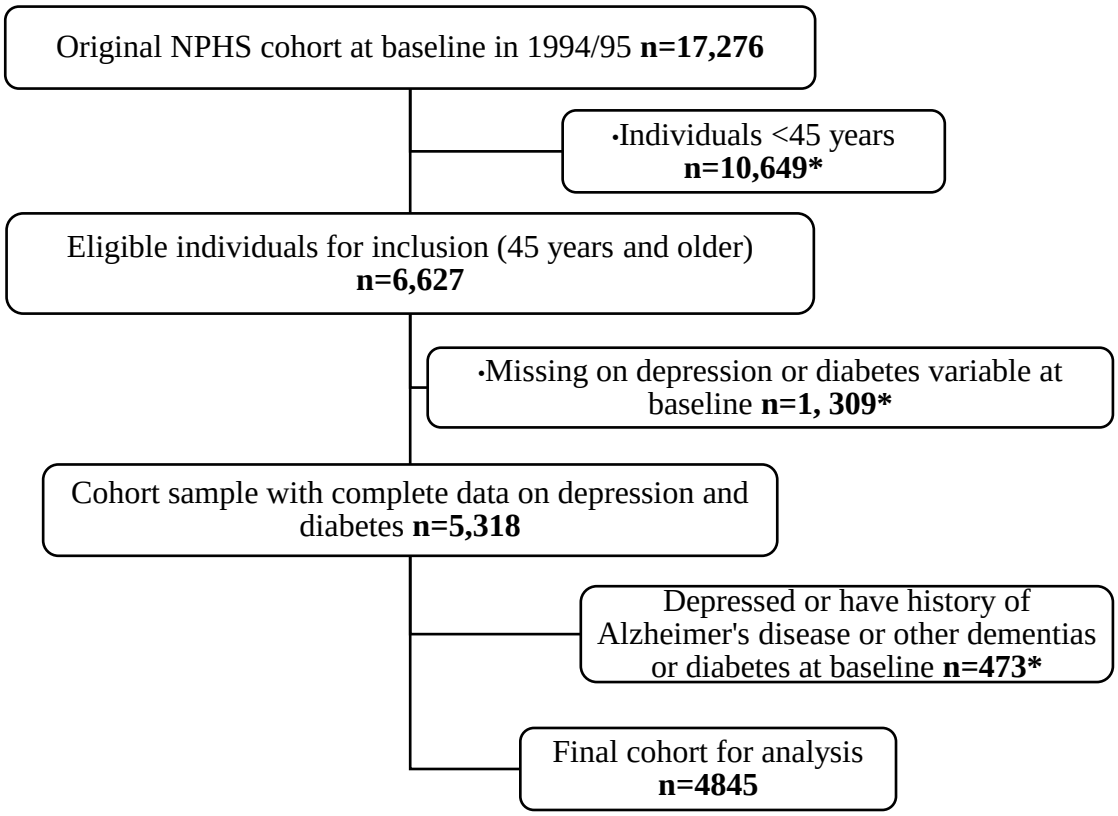
Our study was limited to 4,845 participants who at the baseline were over the age of 45 years and were followed-up to 2004–2005. We included only participants aged 45+ years in order to effectively measure Type 2 diabetes incidence, even though NPHS did not distinguish between Type 1 and 2 diabetes. Five exclusion criteria were used to exclude participants at

baseline. We excluded participants who at baseline (1994–1995) were: (1) depressed (2) self-reported positively to having a doctor diagnosis of diabetes (3) reported a history of Alzheimer's disease or other dementias (4) had missing values on diabetes at baseline or at follow-up and (5) had missing values on depression at baseline or at follow-up.

Figure 4-1 shows a detailed description of the restriction criteria used to obtain the sub-sample of the NPHS cohort (45 years and above). Final analyses were conducted with the sample that met the objectives of this study. Figure 4-2 also presents a follow-up chart of subjects who responded to depression questions in the various cycles. Figure 4-3 represents a follow-up chart of respondents who responded to diabetes questions in the various cycles.

As shown in figures 4-2 and 4-3, at cycle 6, only 56.6%% of depression sample respondents and 62.7% of diabetes sample respondents remained in the study. After cycle 6, the loss to follow-up was more than 50% for depression sample and a little over fifty percent for diabetes sample. Therefore, for purposes of uniformity and comparison, our sub-sample stopped at the 6^{th} cycle.

Figure 4- 1 Restriction criteria employed to obtain the sub-sample of NPHS cohort in this study



***Excluded from the analysis**

Figure 4- 2 Follow-up chart for participants who responded to depression questions

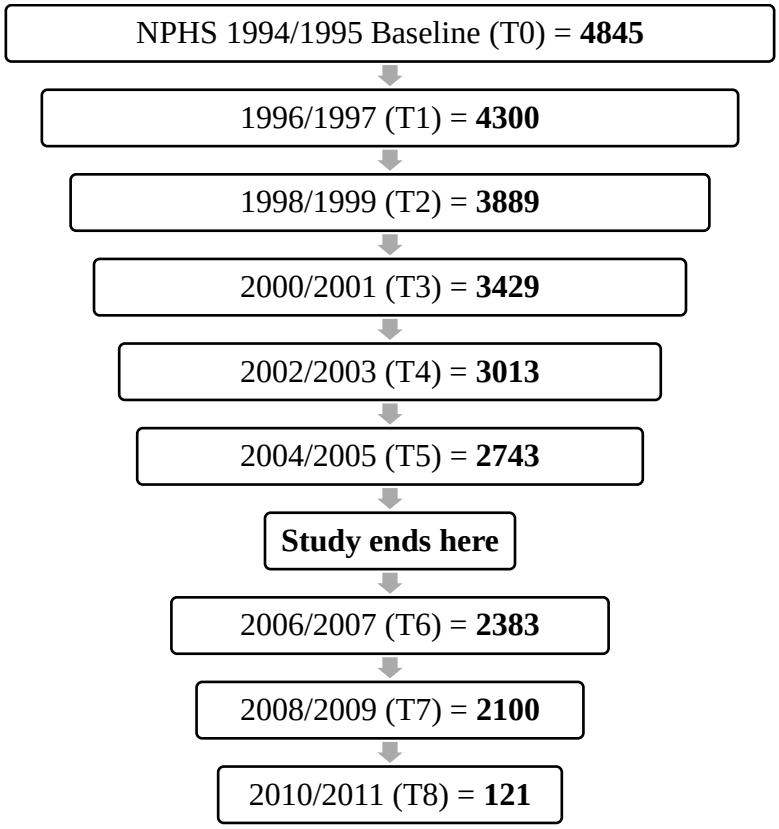
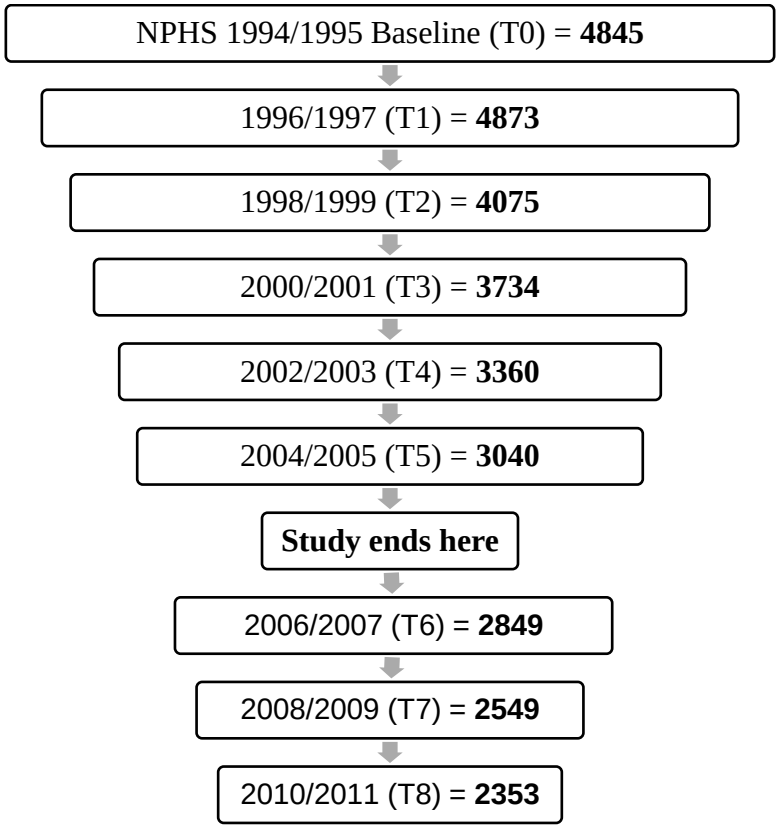


Figure 4- 3 Follow-up chart for participants who responded to diabetes questions



4.3.3 Measures

4.3.3.1 Assessment of depression incidence (outcome variable)

In the NPHS study, "the Composite International Diagnostic Interview Short Form (CIDI-SF) was used to measure major depressive episode" (MDE) [40]. The CIDI-MDE-SF is a short version of the CIDI-MDE long form. The CIDI is a major standardized diagnostic instrument for detecting psychiatric disorders and has been used in epidemiological studies. This measure has been validated by Statistic Canada and also used in other research [59]. Participant's major depressive episode status was measured prior to being interviewed and the presence or absence of a major depressive episode in a participant was determined by trained personnel. Also, to avoid depression recurrence in our follow-up study, we selected a pure sample and excluded all participants with recorded cases of major depressive episode at or prior to baseline (1994–1995). We also excluded both baseline depression and diabetes to avoid the bidirectional influence of depression-diabetes relationship in our study. In the NPHS study, a major depressive episode was defined by a cut-point of 90% predictive probability for the CIDI-SF [40]. In this study, respondents who recorded predictive probability above 90% were regarded as incident major depressive episode cases while those who recorded below the 90% cut-point were reported as not depressed. Incident cases for the major depressive episode were determined for the five cycles followed-up in our study [cycle 2 (1996–1997), cycle 3 (1998–1999), cycle 4 (2000–2001), cycle 5 (2002–2003), and cycle 6 (2004–2005)]. In this study, we used the first incidence case of the major depressive episode for our analysis.

4.3.3.2 Assessment of diabetes incidence (outcome variable)

Diabetes incidence was measured through self-report. We excluded both baseline depression and diabetes to avoid the bidirectional influence of depression-diabetes relationship in our study. In this study, we used the first incidence case of diabetes for our analysis. We determined incident diabetes cases based on a self-reported doctor or a health professional diagnosed diabetes at cycle 2 (1996–1997), cycle 3 (1998–1999), cycle 4 (2000–2001), cycle 5 (2002–2003), and cycle 6 (2004–2005). Our exclusion criteria were a positive response to having been diagnosed with diabetes by a doctor or any trained health professional prior to or at baseline (1994–1995).

4.3.3.3 Predictors/covariates

We are interested in the shared and unique predictors of both depression and diabetes over a period. Guided by previous literature, several lifestyles or behavioral, socio-demographic, and physiological predictors or covariates were assessed in this study at baseline. Heart disease is included here as a separate variable from chronic diseases because of the links reported in the literature between heart disease and both diabetes and depression and also because it was reported separately from chronic diseases in the survey. The term "white" is used in the NPHS dataset to represent ethnicity or racial origin.

The variables included in this analysis were:
Waves/cycles (1994/95, 1996/97, 1998/99, 2000/01, 2002/03, 2004/05)

Sex (male *vs* female)

Age (45–54, 55–64, 65+ years)

Household annual income (<= $15,000, $15,000–$29,999, $30,000–$49,999, $50,000–$79,999, $80,000 or more)

Body mass index-BMI (underweight 16–18.5 kg/m^2, normal weight 18.5–25 kg/m^2, overweight 25–29 kg/m^2 and obese > 30 kg/m^2)

Type of smoker ("occasional/former/never smoked"=0 and "daily smoker"=1)

Race or ethnicity ("Caucasian/white"=0 and "all other race/non-white"=1)

High blood pressure ("yes"=1 and "no"=0)

Family stress index ("some stress/stress overload/yes"=1 and "no stress/no"=0)

Traumatic life events ("less than three traumatic life events/ three or more traumatic life events/ yes"=1 and "no traumatic life events/no"=0)

Chronic disease ("yes"=1 and "no"=0)

Heart disease ("yes"=1 and "no"=0)

Physical activity ("inactive"=1 and "active=0")

Marital status ("married/common law"=1, "divorced/separate/widowed"=2 and "never married/single"=3)

4.3.4 Statistical analysis

This secondary analysis of the NPHS longitudinal 1994 dataset was done using Statistics Canada confidential microdata files (Master data files) which are accessible through Research Data Centers only (https://crdcn.org). We are limited on the details on the data that can be released. Descriptive frequencies and cross-tabulations were generated by socio-demographic factors such as age, race or ethnicity, body mass index (BMI), sex, marital status, income (household), and educational level. Unweighted analyses were conducted because models could not converge and were giving error messages.

The modified Poisson regression was used to estimate the relative risk (RR) for the association between shared or unique risk factors and incident depression and diabetes because of its ability to consistently and effectively estimate RR with a robust error variance in prospective studies as has been reported elsewhere [39].

We conducted univariate modified Poisson regressions to assess the unadjusted relationship between shared or unique risk factors and incident depression and diabetes. Unadjusted measures could not be reported in the stratified analysis because most variables did not meet the minimum required the number of cases in a cell necessary for vetting. Predictor variables with unadjusted p-values less than 0.20 were maintained for subsequent analyses in the multivariate Poisson regression. At the multivariate analysis stage, a modified Poisson regression was used to measure the association between shared or unique risk factors and incident depression and diabetes.

In total, three modified Poisson regression models were fitted: (1) Shared or unique risk factors and incident depression and diabetes; (2) Sex differences in characteristics associated with an incident major depressive disorder; and (3) Sex differences in the association between shared or unique risk factors and diabetes incidence. The goodness-of-fit was also tested for the various models. We reported unadjusted and adjusted relative risk (RR) and 95% confidence intervals at a significance level of $p < 0.05$. STATA version 14 [41] was used to complete all statistical analyses.

4.4 Results

4.4.1 Characteristics of the study population

Participants below the age of 45 years were excluded from our analysis. Therefore we found that in a final sub-sample of 4,845 (unweighted) adults aged 45 years and above at baseline (1994–1995), majority of the respondents were females (56.8%), the majority of the study population fell within the age groups 55–64 years (40.8%), many had less than secondary graduation education (43%), many were still married or in common law relationships (60%), were whites (96.5%), 29.8% fell within the household income bracket $15,000–$29,999 and 56.5% were overweight or obese. Table 4-1 below shows the demographic characteristics of respondents at baseline.

Table 4- 1 Baseline demographic characteristics of respondents (aged 45+) covered in the 1994/95 cycle

Characteristics	Frequency	Percentage (%)
Sex		
Male	2,095	43.2
Female	2,750	56.8
Total	4,845	100
Age categories, years		
45 - 54	896	18.5
55 - 64	1,976	40.8
65 and above	1,973	40.7
Total	4,845	100
Educational level		
Post-secondary graduation	1,205	24.9
Some post-secondary graduation	955	19.7
Secondary graduation	602	12.4
Less than secondary graduation	2,083	43.0
Total	4,845	100
Marital Status		
Married/common law	2,909	60.0
Divorced/separate/widowed	1,547	31.9
Never married/single	389	8.0
Total	4,845	100
Ethnic background		
White	4,673	96.5
Non-white	172	3.6
Total	4,845	100

Household income, CAD		
<= $15,000	1,118	23.1
$15,000-$29,999	1,444	29.8
$30,000-$49,999	1,121	23.1
$50,000-$79,999	762	15.7
$80,000 or more	400	8.3
Total	4,845	100
Self-reported BMI		
Normal weight	1,985	41.0
Underweight	122	2.5
Overweight	1,995	41.2
Obese	743	15.3
Total	4,845	100

4.4.2 Characteristics associated with incident depression and diabetes during follow-up (univariate analysis)

At cycle 6, participants who remained in the study and responded to depression questions (N=2,743) and diabetes questions ((N=3,040) were used in the univariate as well as multivariate analyses. Sex (female) was a risk factor for depression but not for to males whilst sex was not a risk factor for diabetes. The unadjusted risk of reporting depression decreases as participant's aged. On the other hand, the risk of diabetes was 1.74 (95%CI =1.26–2.42) times higher in the age group (55–64 years) and 1.83 (95%CI = 1.30–2.57) times higher in the senior's age group (aged 65+ years). Meaning that diabetes is more prominent in people over the age of fifty-five years compared to younger age groups (see Table 4-2).

Also, those with an annual household income of $80,000 or more were 0.35 (95%CI = 0.15–0.79) and 0.60 (0.40–0.90) times *less likely* to report depression and diabetes respectively compared to less than $15,000 annual household income category. In addition, being non-white was a protective factor for depression but a risk factor for diabetes.

We found seven shared risk factors for depression and diabetes at this stage of our analysis. Firstly, those who were hypertensive were 1.53 (95%CI = 1.01–2.32) and 2.04 (1.63–2.54) times *more likely* to develop depression and diabetes respectively compared to those who were not. Also, daily smokers were at 1.91 increased risk of depression (95%CI=1.30–2.81) and 1.14 risk of diabetes (95%CI=0.89–1.48) compared to the reference group. Furthermore, physical inactivity was a risk factor for both depression (RR=1.33, 95%CI =0.91–1.96) and diabetes

(RR=1.34, 95%CI =1.07–1.69). In addition, depression recorded a U-shape relationship with body mass index (BMI) while diabetes was positively associated with BMI. Indicating that underweight persons were 3.52 times at risk of depression (95%CI=1.49–8.33) whilst obese persons were 1.12 times (95%CI=0.67–1.86) more likely to report depression.

Similarly, diabetes was positively associated with BMI. Those who were obese, had 3.50 times (95%CI=2.61–4.69) *higher* risk of reporting diabetes compared to normal weight persons. Those who experienced traumatic life events at childhood, adolescence or adulthood 1.90 (95%CI = 1.32–2.73) times were more likely to report depression compared to those with who did not. It was also an insignificant risk factor for diabetes.

Those living with one or more chronic diseases were 2.7 times more at risk of reporting depression (95%CI = 1.64–4.45) and 1.31 times at risk of reporting diabetes (95%CI = 1.03–1.67) compared to those without. History of heart disease was also found to be a significant risk factor for depression 2.42 (95%CI = 1.44–4.07) and diabetes 1.57 (95%CI = 1.12–2.22) respectively. Our study revealed family stress as a significant risk factor for depression but not diabetes. Those with family-related stress were 1.82 times (95%CI = 1.44–4.07) more at risk of depression and 0.83 times (95%CI =0.64–1.09) less at risk of diabetes compared to those without family stress.

In summary, household income was the only shared protective factor for both incident depression and diabetes. While age and race or ethnicity were unique protective factors for depression, sex and family stress were unique insignificant protective factors for diabetes (see Table 4-2).

Table 4- 2 Univariate analysis of shared and unique risk factors of depression and diabetes during the 10-year follow-up (Cycle 6)

	Depression n=2743		Diabetes n=3040	
Characteristics	**RR, 95% CI**	**p-Value**	**RR, 95% CI**	**p-Value**
Sex				
Male	Reference		Reference	
Female	2.15 (1.41–3.27)	<0.001	0.95 (0.76–1.17)	0.621
Age categories, years				
45 - 54	Reference		Reference	
55 - 64	0.72 (0.48–1.07)	0.11	1.74 (1.26–2.42)	0.001
65 and above	0.51 (0.30–0.87)	0.013	1.83 (1.30-2.57)	0.001
Household income, CAD				
<= $15,000	Reference		Reference	
$15,000-$29,999	0.58 (0.35–0.97)	0.038	0.81 (0.61–1.06)	0.131
$30,000-$49,999	0.66 (0.40–1.09)	0.102	0.54 (0.40–0.75)	<0.001
$50,000-$79,999	0.57 (0.33–0.99)	0.047	0.53 (0.37–0.75)	<0.001
$80,000 or more	0.35 (0.15–0.79)	0.011	0.60 (0.40–0.90)	0.013
Ethnic background				
White	Reference		Reference	
Non-white	0.95 (0.36–2.53)	<0.001	1.42 (0.89–2.26)	0.142
High blood pressure				
No	Reference		Reference	
Yes	**1.53** (1.01–2.32)	0.045	**2.04** (1.63–2.54)	<0.001
Type of smoker				
Abstainer/never smoke	Reference		Reference	
Daily smoker	**1.91** (1.30–2.81)	0.001	**1.14** (0.89–1.48)	0.303
Physical activity				
Active	Reference		Reference	
Inactive	**1.33** (0.91–1.96)	0.145	**1.34** (1.07–1.69)	0.012
Self-reported BMI				
Normal weight	Reference		Reference	
Underweight	**3.52** (1.49–8.33)	0.004	0.45 (0.064–3.14)	0.418
Overweight	0.86 (0.57–1.29)	0.465	**1.83** (1.38–2.43)	<0.001
Obese	**1.12** (0.67–1.86)	0.669	**3.50** (2.61–4.69)	<0.001
Family stress				
No	Reference		Reference	
Yes	1.82 (1.25–2.64)	0.002	0.83 (0.64–1.09)	0.191
Traumatic events				
No	Reference		Reference	
Yes	1.90 (1.32–2.73)	0.001	1.08 (0.84–1.37)	0.514
Chronic disease				

Without	Reference		Reference	
With	**2.70** (1.64–4.45)	<0.001	**1.31** (1.03–1.67)	0.026
Heart disease				
No	Reference		Reference	
Yes	**2.42** (1.44–4.07)	0.001	**1.57** (1.12–2.22)	0.010

Note: **BOLD** RR represents shared risk factors for both depression and diabetes

4.4.3 Characteristics associated with incident depression and diabetes during follow-up (multivariate analysis)

All the variables with a *(p <0 .20)* in the initial univariable analyses were forwarded for multivariate modified Poisson regression modeling. Table 4-3 represents the final multivariate modified Poisson regression model for incident depression and diabetes among those aged 45 years and over after adjusting for covariates and/or predictor variables. The present study produced relative risks for depression and diabetes incidence over a 10-year follow-up period. Our interpretation of the final results is based on unique, shared or common risk factors as well as protective factors for depression and diabetes.

Depression was uniquely associated with five risk factors. These include female sex, family stress, traumatic life events, the presence of one or more chronic diseases and heart diseases. We found that females were 2.13 times (95%CI = 1.40–3.24) at risk of developing depression compared to males whilst sex was not a risk factor for diabetes. Respondents with family stress were 1.48 times (95%CI =1.02–2.15) at risk of developing depression compared to those without. Also, compared to the reference group, people with any history of traumatic experiences during childhood, adolescence or adulthood were at a 46% (95%CI =1.00–2.13) increased risk of depression. In addition, participants with one or more chronic health conditions diagnosed by a health professional were 2.47 times (95%CI =1.47–4.15) at a higher risk of depression compared to those without any chronic disease. Having a heart disease was also a significant unique risk factor for the development of depression (p=0.002).

Secondly, we recorded only two unique risk factors for incident diabetes after follow-up. We found a positive association between age and diabetes. Respondents aged, (55–64 years) and those above 65 years were 1.66 times (95%CI = 1.22–2.28) and 1.63 times (95%CI = 1.16–2.29) at risk of developing diabetes respectively. Indicating that diabetes increases with age. The second unique risk factor for diabetes incidence was race or ethnicity. Non-white participants

were almost twice as likely to report diabetes compared to whites (RR=1.73, 95%CI =1.09–2.75).

Additionally, we found four shared or common risk factors of incident depression and diabetes in our study. These include high blood pressure or hypertension, type of smoker, physical inactivity and body mass index (BMI). Compared to non-hypertensive participants, those who were hypertensive were 1.34 times (95%CI = 0.87–2.07) and 1.62 times (95%CI = 1.28–2.06) more likely to report incident depression and diabetes respectively. Daily smoking was significantly associated with the risk of depression (RR=1.72, 95%CI =1.16–2.56) and diabetes (RR=1.36, 95%CI =1.04–1.77) compared to non-smokers. Physically inactive participants were at equal risk of developing both conditions; 1.24 times (95%CI = 0.85–1.80) and 1.24 times (95%CI = 0.99–1.56) at risk of developing depression and diabetes respectively. As reported in the univariate analysis we found a U-shape relationship between body mass index (BMI) and depression and a positive relationship between BMI and diabetes. Underweight participants were 3.34 times at risk of depression (95%CI=1.40–7.97) whilst obese persons were 1.01 times (95%CI=0.61–1.69) more likely to report depression. Similarly, diabetes was positively associated with BMI such that those who were overweight or obese, had 1.81 and 3.24 times (p <0.001) *higher* risk of reporting diabetes compared to the reference group (normal weight). Overall, this study did not find a common protective factor for both conditions. Age was protective for depression (p =0.018), while, income was protective for diabetes (p =0.037).

Table 4- 3 Multivariate analysis of shared and unique risk factors of depression and diabetes during the 10-year follow-up (Cycle 6)

	Depression n=2743		Diabetes n=3040	
Characteristics	**RR, 95% CI**	**p-Value**	**RR, 95% CI**	**p-Value**
Sex				
Male	Reference		Reference	
Female	2.13 (1.40–3.24)	<0.001	N/A	N/A
Age categories, years				
45 - 54	Reference		Reference	
55 - 64	0.65 (0.43–0.98)	0.040	1.66 (1.22–2.28)	0.002
65 and above	0.43 (0.24–0.78)	0.005	1.63 (1.16–2.29)	0.005
Household income, CAD				
<= $15,000	Reference		Reference	
$15,000-$29,999	N/A	N/A	0.83 (0.63–1.09)	0.188
$30,000-$49,999	N/A	N/A	0.62 (0.45–0.85)	0.003
$50,000-$79,999	N/A	N/A	0.66 (0.46–0.94)	0.023
$80,000 or more	N/A	N/A	0.76 (0.50–1.16)	0.204
Ethnic background				
White	Reference		Reference	
Non-white	N/A	N/A	1.73 (1.09–2.75)	0.021
High blood pressure				
No	Reference		Reference	
Yes	1.34 (0.87–2.07)	0.183	1.62 (1.28–2.06)	<0.001
Type of smoker				
Abstainer/never smoke	Reference		Reference	
Daily smoker	1.72 (1.16–2.56)	0.007	1.36 (1.04–1.77)	0.022
Physical activity				
Active	Reference		Reference	
Inactive	1.24 (0.85–1.80)	0.275	1.24 (0.99–1.56)	0.066
Self-reported BMI				
Normal weight	Reference		Reference	
Underweight	3.34 (1.40–7.97)	0.007	0.39 (0.06–2.72)	0.345
Overweight	0.94 (0.63–1.42)	0.772	1.81 (1.36–2.40)	<0.001
Obese	1.01 (0.61–1.69)	0.960	3.24 (2.39–4.41)	<0.001
Family stress				
No	Reference		Reference	
Yes	1.48 (1.02–2.15)	0.049	N/A	N/A
Traumatic events				
No	Reference		Reference	
Yes	1.46 (1.00–2.13)	0.001	N/A	N/A
Chronic disease				

Without	Reference		Reference	
With	2.47 (1.47–4.15)	0.001	N/A	N/A
Heart disease				
No	Reference		Reference	
Yes	2.21 (1.33–3.69)	0.002	N/A	N/A

Note: **BOLD** RR represents shared risk factors for both depression and diabetes

4.4.4 Characteristics associated with incident depression during follow-up (cycles 6) by sex

Different regression models were run for males and females. We found four common risk factors of depression among males and females. Table 4-4 presents shared and unique risk or protective factors for depression by sex differences. Factors including underweight, having family stress, one or more chronic diseases, and heart disease were risk factors for incident depression in both males and females. Underweight males were 9.09 times (95%CI = 1.95–42.5) more at risk of depression compared to 2.92 times (95%CI = 1.09–7.84) for females. Males who experience family stress were 1.82 times (95%CI = 0.85–3.90) at risk of depression compared 1.47 times (95%CI = 0.96–2.27) for females. Females were more likely to report depression (RR=2.45, 95%CI =1.33–4.51) due to chronic diseases compared to males (RR=2.14, 95%CI =0.78–5.89). However, males with heart diseases were 3.29 times (95%CI = 1.34–8.07) more likely to report depression compared to 1.94 times (95%CI = 1.02–3.69) for females.

We found that females reported two unique risk factors of depression. Compared to their non-hypertensive colleagues, hypertensive females were 1.61 times (95%CI = 1.00–2.62) more at risk of depression. Also, female daily smokers were more at risk of depression compared non-smokers (RR=1.82, 95%CI =1.16–2.86).

Our study found increasing age as a shared protective factor for depression for both males (p =0.251) and females (p =0.003) even though the effect was more prominent among females than males. We found that while females did not have a unique protective factor for depression, income was a significant protective factor for males only (p <0.001).

Table 4- 4 Characteristics associated with incident major depressive disorder during the 10-year follow-up by sex

	Males n=1136		Females n=1607	
Characteristics	**RR, 95% CI**	**p-Value**	**RR, 95% CI**	**p-Value**
Age categories, years				
45–54	Reference		Reference	
55–64	0.53 (0.23–1.21)	0.130	0.62 (0.38–0.99)	0.048
65 and above	0.46 (0.15–1.39)	0.170	0.33 (0.17–0.62)	0.001
Household income, CAD				
<= $15,000	Reference		Reference	
$15,000–$29,999	0.38 (0.16–0.94)	0.037	N/A	N/A
$30,000–$49,999	0.26(0.089–0.76)	0.013	N/A	N/A
$50,000–$79,999	0.34 (0.13–0.90)	0.030	N/A	N/A
$80,000 or more	0.21(0.006–0.45)	<0.001	N/A	N/A
High blood pressure				
No	Reference		Reference	
Yes	N/A	N/A	1.61 (1.00–2.62)	0.052
Type of smoker				
Abstainer/never smoke	Reference		Reference	
Daily smoker	N/A	N/A	1.82 (1.16–2.86)	0.010
Self-reported BMI				
Normal weight	Reference		Reference	
Underweight	**9.09** (1.95–42.5)	0.005	**2.92** (1.09–7.84)	0.033
Overweight	1.61 (0.66–3.91)	0.294	0.84 (0.52–1.35)	0.471
Obese	1.35 (0.43–4.22)	0.601	0.96 (0.54–1.71)	0.888
Family stress				
No	Reference		Reference	
Yes	**1.82** (0.85–3.90)	0.124	**1.47** (0.96–2.27)	0.079
Chronic disease				
Without	Reference		Reference	
With	**2.14** (0.78–5.89)	0.141	**2.45** (1.33–4.51)	0.004
Heart disease				
No	Reference		Reference	
Yes	**3.29** (1.34–8.07)	0.009	**1.94** (1.02–3.69)	0.044

Note: **BOLD** RR represents shared risk factors of depression by males and females

4.4.5 Characteristics associated with incident diabetes during follow-up (cycles 6) by sex

The same methods that were used to analyze the depression sample were used for the diabetes sample. Table 4-5 shows characteristics associated with incident diabetes at the 10-year follow-up by sex. We found six common risk factors of diabetes among males and females in our diabetes sample analyses.

Factors such as age, race or ethnicity, hypertension, smoking status, physical inactivity, and body mass index were risk factors for incident diabetes in both males and females. Female seniors were 2.72 times (95%CI = 1.54–4.79) more at risk of diabetes compared to 1.44 times (95%CI = 0.92-2.28) for male seniors. Female non-whites were also at risk of diabetes (RR=1.91, 95%CI =1.02–3.58). In addition, hypertensive males were 1.71 times (95%CI = 1.18–2.47) at a greater risk of diabetes compared to 1.59 times (95%CI = 1.17–2.16) for hypertensive females. Male daily smokers (RR=1.49, 95%CI =1.03–2.15) were significantly more at risk of incident diabetes compared to female daily smokers (RR=1.30, 95%CI =0.89–1.90). Males who were physically inactive had a 32% (95%CI = 0.93–1.87) increased risk of reporting diabetes compared to 19% (95%CI = 0.93–1.87) increased risk among physically inactive females. Our study also found a positive association between diabetes and body mass index between both sexes. Obese male respondents were 3.73 times (95%CI = 2.24–6.18) at risk of diabetes compared to 3.09 times (95%CI = 2.09–4.58) increased the risk of diabetes in females.

The only unique risk factor we found in our study was the association between heart disease and incident diabetes among females. Females with heart disease were 1.66 times (95%CI = 1.08–2.56) at risk of incident diabetes compared to those without heart disease. This was not true of males. The data analyzed did not reveal any protective factors for diabetes for males or females (see Table 4-5).

Table 4- 5 Characteristics associated with diabetes incidence during the 10-year follow-up by sex

	Males n=1253		Females n=1787	
Characteristics	**RR, 95% CI**	**p-Value**	**RR, 95% CI**	**p-Value**
Age categories, years				
45–54	Reference		Reference	
55–64	**1.25** (0.84–1.87)	0.270	**2.72** (1.57–4.73)	<0.001
65 and above	**1.44** (0.92–2.28)	0.110	**2.72** (1.54–4.79)	0.001
Ethnic background				
White	Reference		Reference	
Non-white	**1.59** (0.80–3.17)	0.185	**1.91** (1.02–3.58)	0.044
High blood pressure				
No	Reference		Reference	
Yes	**1.71** (1.18–2.47)	0.005	**1.59** (1.17–2.16)	0.003
Type of smoker				
Abstainer/never smoke	Reference		Reference	
Daily smoker	**1.49** (1.03–2.15)	0.036	**1.30** (0.89–1.90)	0.179
Physical activity				
Active	Reference		Reference	
Inactive	**1.32** (0.93–1.87)	0.119	**1.19** (0.88–1.61)	0.270
Self-reported BMI				
Normal weight	Reference		Reference	
Underweight	0.33 (1.33–8.33)	<0.001	0.53 (0.08–3.66)	0.521
Overweight	**1.73** (1.08–2.79)	0.023	**1.77** (1.23–2.55)	0.002
Obese	**3.73** (2.24–6.18)	<0.001	**3.09** (2.09–4.58)	<0.001
Heart disease				
No	Reference		Reference	
Yes	N/A	N/A	1.66 (1.08–2.56)	0.021

Note: **BOLD** RR represents shared risk factors of diabetes by males and females

4.4.6 Number of risk factors and probability of having incident depression and diabetes during follow-up (cycles 6)

Our study categorized the study sample into a healthy group (without any major depressive disorder) and a group with depression (having major depressive disorder). The risk factors included in the depression group were high blood pressure, having a chronic disease, physical inactivity, family stress, traumatic life events, heart disease, type of smoker and sex. Figure 4.4 shows the relationship between the number of risk factors and the possibility of having depression during the 10-year follow-up. Similarly, we divided the study population into

a healthy group (without any diabetes) and a group with diabetes (having incident diabetes). We included the following risk factors: body mass index, high blood pressure, physical inactivity, age, race and type of smoker. Figure 4.5 shows the relationship between the number of risk factors and the possibility of having diabetes during the 10-year follow-up.

In our study, we found those with an increased number of risk factors also have an increased probability of having a major depressive disorder. As shown in figure 4-4 in the depression sample, people with 1, 2, 3 or 4 risk factors have a low (less than 10%) probability of having major depressive disorder. In contrast, however, those with 5, 6 or 7 risk factors have a 10% to 40% possibility of reporting major depressive disorder.

Also, in the diabetes sample population, we found that an increasing number of risk factors for diabetes positively correlates with an increased probability of having diabetes. Figure 4-5 reveals that people with 1or 2 risk factors have a much lower (less than 10%) probability of having diabetes. On the other hand, those with 3, 4 or 5 risk factors have a 12% to 32% possibility of having diabetes. Our findings show that a number of risk factors in the same individual have an additive effect in increasing the probability of having either mental health disorder (depression) and metabolic disorder (diabetes).

Table 4.6 summarizes the common and unique risk factors for depression and diabetes for both the overall and stratified analysis. As can be found in Table 4-6, high blood pressure, cigarette smoking, physical inactivity and Body mass index (BMI) were common risk factors for both depression and diabetes. Unique risk factors for depression include; female sex, family stress, traumatic events, chronic disease, and heart disease. Factors unique to diabetes incidence include; increasing age and race or ethnicity (non-white).

In our stratified analysis, Table 4-6 shows that four risk factors were common in the incidence of depression in both men and women. These include; body mass index (BMI) family stress, chronic disease, and heart disease. Diabetes incidence was more likely in both men and women who were old, in the minority (non-white), have high blood pressure, smoke daily, physically inactive and were either overweight or obese. Heart disease was uniquely associated with the risk of developing diabetes in females only. However, just as in the case of depression, the male sex did not report any unique risk factors for diabetes.

Table 4- 6 Summary table of common and unique risk factors for depression and diabetes in general and by sex

	Overall analysis			Stratified by Gender					
Risk factors	**Common factors**	**Uniq.-depression**	**Uniq.-diabetes**	**Risk factors for depression for both sexes**	**Uniq.-Male**	**Uniq.-Female**	**Risk factors for Diabetes for both sexes**	**Uniq.-Male**	**Uniq.-Female**
Sex		✓		N/A	N/A	N/A	N/A	N/A	N/A
Age			✓				✓		
Income									
Race			✓				✓		
High blood pressure	✓					✓	✓		
Smoking status	✓					✓	✓		
Physical activity	✓						✓		
BMI	✓			✓			✓		
Family stress		✓		✓					
Traumatic events		✓							
Chronic disease		✓		✓					
Heart disease		✓		✓					✓

Note: The symbol (✓) risk factor presences and N/A means not applicable

Figure 4- 4 Relationship between number of risk factors of depression and the possibility of having depression during the 10-year follow-up.

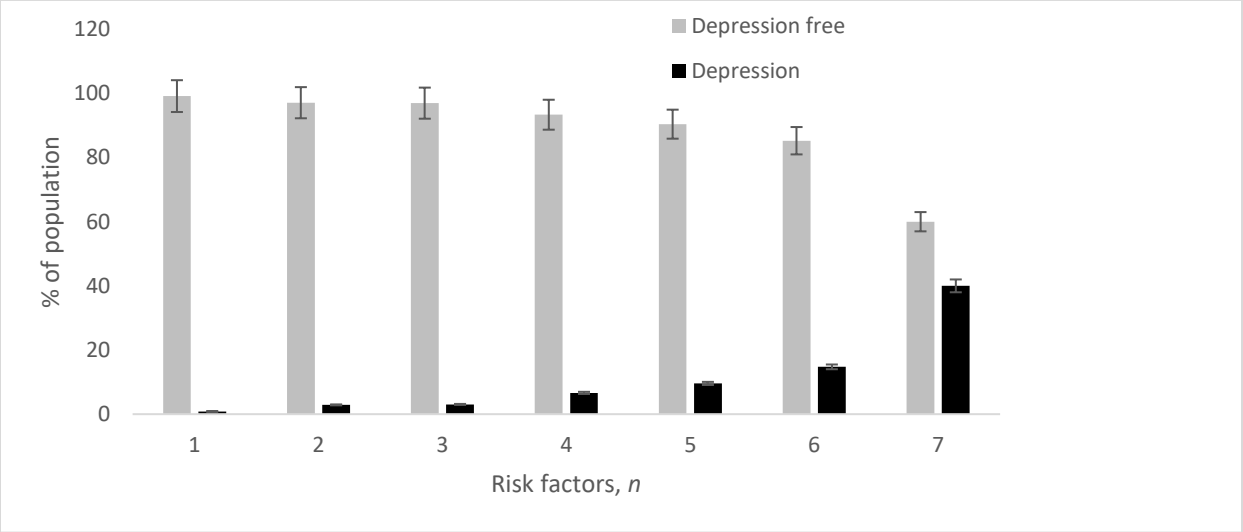
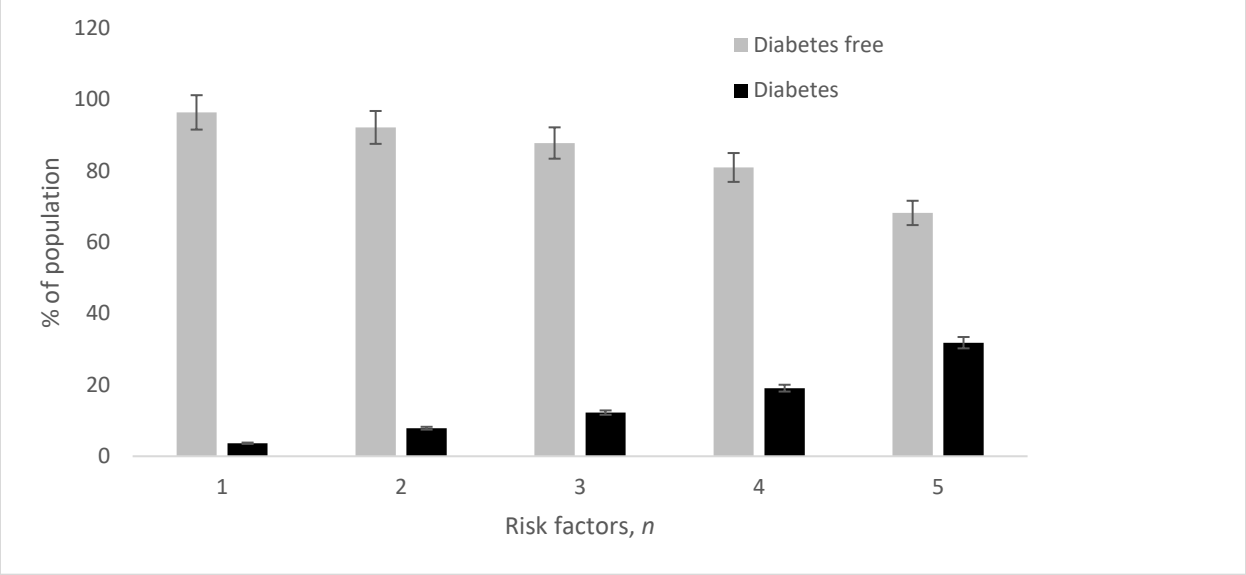


Figure 4- 5 Relationship between number of risk factors of diabetes and the possibility of having diabetes during the 10-year follow-up.



4.5 Discussion

This study concurrently assessed the incidence, shared and unique risk factors of depression and diabetes in a representative community longitudinal sample of the Canadian population. We also examined sex differences in the shared and unique risk factors of depression and diabetes. We found that the cumulative incidence of depression and diabetes during the 10-year follow-up were 4.1% and 10.1% respectively. Our cumulative incidence of major depressive disorder reported is much lower than the 12.1% cumulative incidence previously reported in a 16-year Canadian longitudinal study [5]. However, these differences may be due to differences in age restrictions in our study sample and follow-up periods. As expected, we found that sociodemographic, biological, physiological and physical risk factors were associated with the incidence of depression and diabetes.

First and foremost, we found four shared mechanisms of both depression and diabetes. Respondents who were hypertensive, daily smokers, physically inactive and overweight or obese had a higher risk of developing depression and diabetes. Our finding is in keeping with that of Katon et al [34] who reported that depressed people are more likely to have a high body-mass index, poor diet, physically inactive and smoke daily. All of which are known risk factors for diabetes and other cardiovascular diseases.

In comparison to other previous studies [5, 33], we found that five risk factors were uniquely associated with incident depression. These include female sex, family stress, traumatic life events, the presence of one or more chronic diseases and heart disease.

In our study, we also found age and race or ethnicity (non-white) as the only two unique risk factors for diabetes. It shows that after age fifty-five years the risk of developing diabetes was almost twice as likely compared to those below fifty-five. It also shows that the risk of diabetes increases with advancement in age. Our finding is similar to an earlier study [22]. Our finding on ethnic background and diabetes relationship is consistent with a previous study in the United States where a high prevalence of diabetes was found among non-Hispanic black and those of Mexican origin had highest prevalence rates [42].

Furthermore, we did not find a common protective factor for both conditions. They both have different protective factors. We found that whereas age was a protective factor for

depression, income was the only significant protective factor for diabetes. Our finding that major depressive disorder decreases as people age has been reported in the literature [54, 57, 58]. Kessler et al [57] for instance argue that the low estimated prevalence of major depressive disorder among the elderly could be due to increased confounding with physical disorders. A possible explanation could also be that older adults have a lot of life experiences and are more accepting of difficult situations and better-coping strategies than younger populations.

Also, we found a U-shape relationship between body mass index and depression as earlier reported [4]. Our findings also show the relationship between diabetes and body mass index was positive. Those who were overweight or obese were at a higher risk of diabetes compared to normal weight people. This is in keeping with a similar finding in a Chinese longitudinal population [43].

This study stratified our analyses into major depressive disorder and diabetes incidence groups by sex. Significant sex differences in the determinants of the major depressive disorder have been previously reported in the literature [50, 51]. Our results depict the same phenomenon. We found four shared risk factors for depression between males and females. Being underweight, having family stress, having a chronic disease and heart disease were all shared risk factors for depression in both sexes. Our study confirms similar results in the literature [4, 5, 10, 11].

Our study found that while males were more likely to be depressed due to underweight and heart disease, females were more likely to report depression as a result of the presence of chronic disease or family stress. This NPHS study also found two unique risk factors for incident major depressive disorder for females. Females that were hypertensive and smoke daily were at a significant risk of depression while the finding did not apply to their male counterparts.

We found age as a protective factor for major depressive disorder in both sexes. Age was not a risk for major depressive disorder in both males and females. Our finding confirms earlier results that shows age as a significant risk factor for incident major depression in younger participants but not for older ones [5, 51]. In our study, we also found that household income status was a protective factor and that the relationship between household income and major depressive disorder was linear among males. However, table 4-4 does not include data on household income for women due to insignificant odds ratios at the univariate stage.

Our current findings give credence to the fact that sex differences exist in major depressive disorder incidence. What is particularly striking is the sex differences in the magnitude of the effect of these risk factors on depression incidence. Our study revealed that incident major depression was more prominent in females compared to males. This is consistent with the general literature that finds women to be more likely to report depression than men [55, 56]. Although difficult to explain why these differences in mechanisms exist due to the complex nature of the domains involved, such as sociocultural, psychological and biological influences, our finding reinforces the need to recognize sex disparities in incident major depressive disorder and calls for sex-specific public health prevention programs for major depressive disorder.

Our study demonstrated a strong positive association between six shared or common risk factors and incident diabetes in both sexes. The six shared risk factors identified in both sexes include age, race or ethnicity, high blood pressure, smoking status, physical inactivity, and body mass index. The only unique risk factor for diabetes was heart disease which was only significantly associated with only females and not for males.

We found a positive association between daily cigarette smoking and incident depression risk among women but not for men. This is in keeping with what has been reported previously [53]. At the same time, our results contradict findings from the Faenza study in Italy [54] where no association between smoking and depression incidence was found either among men or women.

In our study, we demonstrated body mass index as a strong positive risk factor for incident diabetes in both sexes. However, our finding shows that BMI effect was much stronger in men than in women. This is in keeping with previous literature [48, 49]. We also found that high blood pressure or hypertension was positively associated with incident diabetes in both males and females even though the effect is higher in women than men. Our finding contradicts earlier results where high blood pressure was associated with diabetes in men only but not for women [49].

Our study revealed that physical inactivity was an insignificant risk factor for diabetes for both men and women. This finding is at variance to that reported by the MONICA Augsburg Cohort Study that found physical inactivity during leisure time to be significantly associated with (80%) increased risk of diabetes incidence in only females but not males [49].

We found that non-white females but not males were at a higher risk of incident diabetes compared to their white counterparts. Our finding is consistent with earlier results [44–46] especially those from the Atherosclerosis Risk in Communities (ARIC) study of adults aged 45 to 64 years, whereby diabetes risk factors were associated with the greatest disparity in diabetes incidence between non-white and white individuals. They also found diabetes incidence to be more pronounced in women than men. Earlier findings [46, 47] also suggest that sex-specific mechanisms are more likely to contribute to a greater risk in diabetes incidence among non-white females than white males which coincides with what we found in our study.

In our present study, age was an independent risk factor for diabetes. Older adults in both sexes were at a higher risk of diabetes compared to younger adults. It is, however, more prominent in older females compared to their male colleagues. This confirms what was reported earlier in the literature [49]. In summary, our results show that although risk factors for diabetes were not generally different in both sexes, their respective effects on diabetes incident were more pronounced in females compared to males and warrants sex-specific actions and public health prevention programs in incident diabetes.

4.5.1 Strengths and limitations of the study

The major strength of this study is the use of a nationally representative relatively large longitudinal population-based study with a long follow-up period of 10 years to concurrently measure the shared risk factors for major depressive disorder and diabetes incidence. We also examined sex disparities in the shared risk factors for major depressive disorder and diabetes in the same population. Shared and unique risk factors for the two debilitating conditions were longitudinally and simultaneously examined. Although we aim to produce reliable results, this study is not devoid of limitations. These include but not limited to the following;

First and foremost, in the depression sample, the attrition rate of about 43.4% at cycle 6 was on the high side and could underestimate the cumulative incidence of major depressive disorder incidence and not representative of the original study population. In addition, some other potential risk factors for major depressive disorder such as childhood maltreatment could not be assessed in the NPHS study because they were not included in the original design of this study.

Furthermore, another limitation of this study is the absence of a distinction between Type 1 and Type 2 diabetes incident cases in the NPHS study. Therefore the current study only assessed Type 2 diabetes on the assumption that majority of the cases reported were Type 2 diabetes cases since our study sample was among those 45 years and over and literature also supports the view that Type 2 diabetes is more prominent among adults over the age of 45 years [46].

Also, our study used self-reported information to identify diabetes cases. There is the possibility that undetected type 2 diabetes cases were included in the non-diabetic group thereby underestimating the relative risk estimated in this study as well as the real effects of the various risk factors for incident diabetes.

Moreover, our study could not include other important risk factors for diabetes such as waist-to-hip ratio, cholesterol level, and low-density lipoprotein cholesterol level. This is because these risk factors were not part of the panel data in all the 6 cycles. Therefore, our analysis was based on only the available risk factors.

4.6 Conclusion

This study using a nationally representative longitudinal sample of the Canadian population provides robust evidence of a positive relationship between many shared and unique risk factors and the development of depression and diabetes. After 10 years of follow-up, our study shows that shared risk factors such as high blood pressure, daily smoking, physical inactivity, and self-reported BMI appear to be responsible for incident depression and diabetes risk. This, therefore, means that both depression and diabetes may be linked by psychological, lifestyle and biological influences.

The findings also reflect the influence of sex differences in both incident major depressive disorder and diabetes. We found in our stratified analyses that although risk factors for incident major depressive disorder and diabetes were not majorly different, the effects or the magnitude of these risk factors were more prominent in female sex compared to males in both depression and diabetes samples and warrants sex-specific actions and public health prevention programs in incident major depressive disorder and diabetes.

We recommend that future research should concentrate on population-based interventions to reduce common or shared risk factors for depression and diabetes we found in this study. Cigarette smoking specifically stood out as the significant risk factor for both conditions and merit specific policy interventions on smoking cessation, especially programs geared towards individuals with depression or diabetes. Also, research is necessary for the identification and modification of common biomarkers of the two debilitating conditions with the aim of preventing their development. Primary public health prevention should also be the focus of depression and diabetes prevention programs. Public health policy interventions should take into cognizance sex differences in their quest to reducing risk factors for these two conditions. It is our belief that through primary public health prevention strategies both conditions can be prevented by encouraging healthier lifestyles such as eating healthy, quitting or reducing smoking, having adequate rest, engaging in physical activities and having enough social support so as to interrupt the cycle of mental and metabolic diseases.

In summary, the results of this study strengthened the importance of targeting general risk behaviors that are not specific to a particular disease but are in fact common to a variety of chronic conditions.

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CHAPTER 5 – A COMPARISON OF THE PREVALENCE OF AND MODIFIABLE RISK FACTORS FOR COGNITIVE IMPAIRMENT AMONG CANADIAN SENIORS OVER TWO DECADES, 1991–2009.

A version of this chapter will be submitted for journal publication review.

5.1 Abstract

Background: The prevalence of cognitive impairment or dementia is of public health concern globally especially in light of aging populations. Accurate estimates of this debilitating condition are needed for future public health policy planning. However, research regarding trends in the prevalence of cognitive impairment is scarce in the Canadian context. We investigated whether the prevalence of cognitive impairment changed over an 18-year period as well as measuring sex differences in modifiable risk factors for cognitive impairment between two-time separated cohorts.

Method: We used baseline data of the Canadian Study of Health and Aging which was conducted between 1991 and 1992 to measure the prevalence of cognitive impairment and dementia among seniors (65+ years). The Modified Mini-Mental State Examination (3MS) was used for the screening test in the identification of cognitive impairment and dementia for the CSHA data. We compared the CSHA data with the Canadian Community Health Survey–Healthy Aging (cognition module) which also measured cognitive impairment using computer-assisted questionnaire and interviews conducted between 2008 and 2009. The community sample of 9008 respondents in the CSHA sample and a sub-sample of 13,306 respondents (65+ years) in the CCHS– HA sample were analyzed. Final subsamples of (N=8504) for the CSHA sample and (N=7764) for CCHS– HA sample were used for analysis. In the first phase of our data analysis, prevalence estimates were calculated using age–sex standardization to the 2001 population census of Canada to generate proportions and confidence intervals for this study. In the second phase of the analysis, logistic regression analyses were performed between predictor variables and the outcome. Stratified analyses by sex were also conducted between predictor variables and the outcome.

Results: The CSHA age and sex-specific estimates of the prevalence of cognitive impairment among respondents aged 65+ years standardized to the 2001 Canadian population census was 15.5% in 1991. However, in the CCHS– HA sample in 2009, it shows that 10.8% of the population reported cognitive impairment, a 4.7% reduction [15.5 % (CI=14.8–16.3), CSHA *vs* 10.8 % (CI=10.1–11.5), CCHS– HA]. Whereas men had a higher prevalence of cognitive impairment in CSHA study, women had a higher prevalence of cognitive impairment in CCHS–HA (with a prevalence of 16.0% in 1991 for men *vs* 11.6% for women in 2009). In the

multivariate analyses, risk factors such as age, poor self-rated health, stroke, Parkinson disease and hearing problems were common to both cohorts. Also, reported protective factors were female sex, race, an area of residence, high blood pressure, heart disease, and educational level. Sex differences in modifiable risk factors were also recorded.

Conclusion: Consistent with two recent European studies, our results suggest that cognitive impairment may have declined among the elderly despite population aging in Canada. It reinforces the suggestion that although the increased prevalence of cognitive impairment could have been influenced by many factors such as survival after stroke, vascular incidents and diabetes, the decreased prevalence recorded in our study may be as a result of improvement in the prevention and treatment of vascular morbidity as well as higher educational attainment or a general decline in the prevalence of chronic diseases. Our results provide suggestive evidence regarding how different experiences shared by successive generations predispose them to different disease risk.

Key words: Cognitive impairment, chronic diseases, risk factors, prevalence

5.2 Introduction

The aging Canadian population is more likely to negatively influence the prevalence of cognitive impairment among older adults though its prevalence is not absolutely due to population aging [1]. In 2016, an estimated 5.9 million senior's population (65 or older) outnumbered 5.8 million children (0–14 years) for the first in time in the country's history [2]. Also, among the seniors, the percentage aged 80 or older continues to grow, as does the number of centenarians suggesting a potential increase in the prevalence of cognitive impairment [2].

Cognitive impairment which is a precursor to dementia is described as a chronic condition that is in between normal aging and dementia [3–5]. Cognitive impairment is when a person has trouble remembering, learning new things, concentrating, or making decisions that affect their everyday life. Cognitive impairment ranges from mild to severe. With mild impairment, people may begin to notice changes in cognitive function, but still be able to do their everyday activities. Severe levels of impairment can lead to losing the ability to understand the meaning or importance of something and the ability to talk or write, resulting in the inability to live independently [50]. Dementia is an overall term for a set of symptoms that are caused by disorders affecting the brain. Symptoms may include memory loss and difficulties with thinking, problem-solving or language, severe enough to reduce a person's ability to perform everyday activities. A person with dementia may also experience changes in mood or behavior. Dementia is progressive, which means the symptoms will gradually get worse as more brain cells become damaged and eventually die [51]. As a transitional zone between normal aging and dementia, people with cognitive impairment, have a less severe cognitive deficit than those with dementia and their normal daily function and independence are generally maintained [3–5]. Many researchers have different criteria for defining cognitive impairment except that the idea is similar with regards to the aim and framework of these studies. Two central aims are common in most studies regarding cognitive impairment; 1) "individuals are non-demented but are with cognitive deficits that are measurable in some form or the other"; 2) "signifies a clinical syndrome that can be used to classify persons who do not fulfill the diagnostic criteria for dementia, but who have a high risk of progressing to a dementia disorder" [3–5].

Research regarding the incidence and prevalence of cognitive impairment and dementia are mixed. While some studies are of the view that dementia is stable or on the decline, others

report an increasing incidence and prevalence due to the increase in life expectancy. An earlier study reported in the Lancet journal had projected that dementia prevalence in North America will increase from 3.4 million in 2001 to 5.1 million whilst that of Europe will increase from 4.9 million in 2001 to 6.9 million in the year 2020 [36]. Also, a Canadian report entitled "The Rising Tide" by the Alzheimer society, Canada [6] which measures the impact of dementia on population health and economic burden among Canadians reported that dementia was on the increase. This study indicated that among seniors (65+ years), 103, 728 new cases of dementia per year were reported as of 2008 and it is estimated to increase to 257,811 new cases per year by the year 2038. This means a 2.5 times increase in prevalence from that of 2008 [6]. The same report also estimated the prevalence of dementia to be 1.5% or 480,618 prevalent cases in the entire Canadian population as of 2008 and is projected to increase to 1,125,184 or 2.8% of prevalent cases in 2038 [6]. The annual total economic burden of dementia was reported to rise from between $15 billion dollars in 2008 to $153 billion dollars by the year 2038 in the same study [6]. Also, a study conducted in the Canadian province of Alberta revealed increasing trends in dementia [48]. Another recent Canadian study reported a simultaneous decreasing trend in incidence and increasing trend in the prevalence of dementia [49].

In other Western countries, it has been reported that despite a declining trend in the age-specific incidence of dementia in those countries, the prevalence of cognitive impairment and dementia continue to grow along with the increase of life expectancy, as well as the associated burden in financial and social domains to the healthcare system [7–11]. On the other hand, two recent studies published in Lancet found that dementia prevalence had stabilized and was on the decline in Western Europe despite the aging population [12, 47]. These authors are of the opinion that the reported reduction in dementia is a result of improved educational attainment, better prevention, and treatment of vascular and general decline in chronic conditions prevalence. Other modifiable risk factors such as tobacco smoking, alcohol consumption, exercise, fruit, and vegetable consumption that are considered to prevent against cognitive impairment have been the focus of recent research on cognitive health [13, 14].

Dementia has no cure at the moment despite efforts made to find curative treatment for it. However, researchers have consistently identified both modifiable and non-modifiable risk factors for dementia. Factors such as apolipoprotein E-epsilon 4 allele (ApoE4), sex, and age are

regarded as non-modifiable risk factors for dementia [15]. Modifiable risk factors include health behavior and lifestyle, high vegetable and fruit intake, educational attainment, diabetes mellitus, high blood pressure, an anti-hypertensive medication, psychological health, emotion health, and among others [15].

The consequences of cognitive impairment have been reported in the literature. A U.S. study found that within 3 years of cognitive impairment diagnosis about 46% of the participants were more likely to progress to dementia compared to those with no prior cognitive problems who had a 3% risk [16]. It has also been reported that seniors with cognitive impairment have a higher risk of hospitalization and mortality following an emergency department visit [17, 18]. Other studies suggest that older adults with cognitive impairment are more likely to be exposed to avoidable injuries whiles performing their daily activities [19, 20, 22].

A Canadian study also found that young adults (20–64 years) were less likely to seek cognitive health care in an emergency department (ED) compared to seniors (65+ years) [21]. In the United States, it was also reported that cognitive impairment related incidents represent over 20% of emergency department consultations by seniors [23]. With the advent of the global aging population, senior-friendly initiatives such as fall prevention programs and driving classes have been put in place to help reduce these avoidable accidents in some jurisdictions [24–26]. But it is however not known whether such preventive measures are specifically tailored to the needs of older adults with cognitive impairment as a vulnerable population of target [24–26].

The worrying trend, however, is that many people who have cognitive impairment do not receive diagnosis. A study found that an estimated 40 percent of cognitively impaired patients were undiagnosed by their physicians [27]. Also, Chodosh et al [28] found that most physicians failed to clinically evaluate over half of the patients with cognitive impairment. This failure in clinical evaluation may lead to a delay in treatment of associated predictors and can pose safety challenges to patients with cognitive problems and their caregivers [29].

Risk reduction is paramount in the prevention and control of chronic diseases of which cognitive impairment is no exception. Even in instances where treatment is available, risk reduction still plays an important role in disease prevention and control. For example, although chronic conditions such as heart disease, diabetes, and cancer are treatable, risk reduction still forms an integral part of public health prevention efforts and strategies [31].

The relationship between behavioral and lifestyle factors and the prevalence or incidence of cognitive impairment has been well-established. What is not well known is whether modifiable risk factors of cognitive impairment changed over the years in the context of an increasingly aging population in Canada. To be able to appreciate and understand the magnitude of this problem, better knowledge about the changing prevalence of cognitive impairment among different cohorts and changes in risk factors over time is required. It will also offer us the opportunity to unearth areas where risk factor modification has been effective. It will further help to identify targeted preventive measures that should be implemented upstream to reduce its occurrence.

The objectives of this study are to:

1) Estimate differences in the prevalence of cognitive impairment between two cohorts of seniors.
2) Determine whether modifiable risk factors of cognitive impairment changed over time by sex.

5.3 Method

5.3.1 Data Sources

5.3.1.1 The 1990-91 population sample- Canadian Study of Health and Aging (10,263)

The data analyzed in this study were part of the Canadian Study of Health and Aging (CSHA) study, a national, multicenter epidemiological study of dementia among seniors (65+ years) [32]. The first wave (CSHA-1) of this study drew a representative sample of people (65+ years) across Canada and was conducted between 1991 and 1992. A total sample of 10,263 participants made up of a community sample of 9,008 people and 1,255 participants as an institutional sample (long-term-care participants) took part in the CSHA study in 1991[32]. After baseline, participants were reassessed after every five years. Participants of this study (CSHA-1) were personally interviewed in their homes which broadly covered areas such as socio-demographics, health and well-being, disability, frailty, caregiving, dementia and cognitive impairment [32]. Clinical evaluation of the subset of the larger sample also occurred. Samples were excluded from Yukon and Northwest Territories, due to low numbers of elderly people living in those areas and the dispersed nature of the population making clinical examinations

very difficult to undertake [32]. Sample weights were used to adjust data analyses for these features of the sample design, ensuring that the results are representative of the Canadian population [32].

5.3.1.2 The 2008-09 population sample- Canadian Community Health Survey–Healthy Aging (n =25,864)

We analyzed the second release of cross-sectional data from Statistics Canada's National Canadian Community Health Survey—Healthy Aging, the cognitive component which consisted of (N = 25,864) participants [30]. The study targeted people aged 45 years and older and data collection was conducted from 2008-12-01 to 2009-11-30 using Computer-Assisted Personal Interviewing. The response rate was 62.3%. A subsample of 13, 306 participants (65+ years) were included in the analysis [30]. The main purpose of the cognitive component was to measure cognitive function across the lifespan. Major areas of interest assessed in this study were mainly on chronic diseases, cognitive impairment, well-being, and socio-demographic characteristics [30]. The study excluded participants who were in Indian reserves, from the three northern territories, those in some remote or hard to reach areas and full-time service men and women [30]. Sampling weights were also applied to the study sample (45+ years) to represent the Canadian population across the ten provinces of the country [30].

5.3.2 Study samples

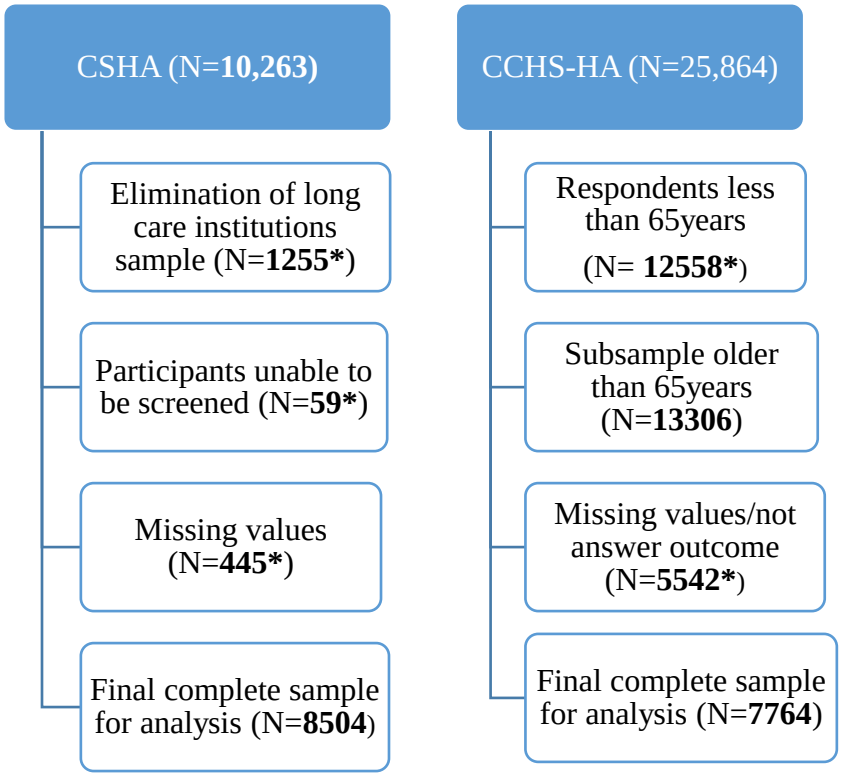
We analyzed two national survey datasets that measured cognitive impairment among respondents (65+ years). In the CSHA-1 1991 sample, analyses were limited to the 9008 community sample who at baseline were 65 years of age or over. The original CSHA sample included only people aged 65 years and over since its main aim was to measure dementia. Our second study sample was from CCHS—HA 2009 cognitive component. It included those aged 45 years and over. It was conducted separately from the main CCHS—HA 2009 component to measure cognitive function across the lifespan. For purposes of comparison to the 1990-91 CSHA-1 sample, we selected a subsample of 13,306 respondents aged 65 years and over who participated in the cognition module to compare the prevalence of cognitive impairment.

In both samples, the following exclusion criteria were used to exclude participants. These include the following :(1) those who were less than 65 years ;(2) participants who were not screened or did not respond to the outcome of interest (3) those who had missing values.

Figure 5-1 shows a detailed description of the restriction criteria used to obtain the subsamples of the CSHA-1cohort and CCHS—HA cohort of respondents 65 years and above. Figure 5-1 also shows the screening process of the two samples using our inclusion and exclusion criteria. In the CSHA-1 sample, 1,225 of the participants who were resident in institutional care settings were eliminated from the sample. An additional 59 respondents who were not screened were also excluded from this analysis. Another 445 respondents with missing values were also left out in this analysis. Finally, we arrived at a CSHA-1 subsample of 8,504 which was used in our analyses (see Figure 5-1).

In the CCHS—HA sample, a total of 12,558 respondents who were younger than 65 years were excluded from our analysis. This gave us a total eligible subsample of 13,306. Of this figure 38.7% or 5152 of the respondents did not state or answer the outcome variable (cognitive impairment) and were eliminated as missing values. Also, 390 of the respondents had missing values. A final figure of 7764 was used for the analyses after all the missing values and not stated were excluded (see Figure 5-1).

Figure 5- 1 Cohorts sample derivation



***Excluded from the analysis**

5.3.3 Measures

5.3.3.1 Assessment of cognitive impairment (outcome variable) in CSHA and CCHS-HA

In the (CSHA-1 1991) sample, the Modified Mini-Mental State Examination (3MS) [33] was administered to the community sample of (n=9008) as a cognitive screen by a trained interviewer to identify respondents who appeared to have cognitive impairments that will merit a detailed clinical examination. The 3MS is a widely used screening test for dementia and has a scoring system that ranges between (0–100) as the response scale for the participants. In the CSHA-1 sample, cognitive impairment was assessed using a cut-off point of ≤ 77 [33]. Those scoring below 77 were considered cognitively impaired whilst those scoring above 77 were regarded as cognitively intact. The outcome variable was derived by recoding all those participants with 3MS scores from 0 to 77 as ("yes"=1) and those with 3MS scores from 78 to 100 as ("no"=0). Our current study used the community sample to estimate the prevalence as well as modifiable and non-modifiable risk factors for cognitive impairment.

In screening for dementia, the 3MS is the ideal and most commonly used instrument in clinical settings. However, the CCHS—HA 2009 cognition module measured four main domains of cognitive tasks. They include immediate and delayed recall which relate to memory function and the animal-naming and Mental Alternation Test which also relate to executive function [30]. The outcome variable, cognitive impairment in the CCHS—HA 2009 cognition module is a derived variable based on the above-mentioned domains of cognitive tasks. It sums up the number of component tasks where the respondent scored in the lowest cognitive functioning category. Hence, higher scores were equivalent to lower functioning [30]. The outcome variable has five categories ranging from (0–4), with a minimum value of 0 and a maximum value of 4. In all the four domains used to derive the cognitive impairment variable, a task was coded as "not applicable" or "not attempted" if the person was not ready to hear the recording, did not hear the recording clearly or did not give permission to start the recording. If there were problems with the computer application or the transcription of responses, the task was coded as "not stated" or "not started". All these were combined to form a category in the outcome variable called "not stated" and coded as 9. In our recoding process, category 0 which stood alone was coded as ("no"=0) to represent respondents without cognitive impairment, categories (1–4) were collapsed

and recoded as ("yes"=1) to represent presence of cognitive impairment and category 9 stood alone as "not stated" and was treated as missing values.

The 3MS as a well-established standard cognitive impairment screening test has been validated with a cut-off score of ≤ 77 [33]. The CCHS—HA cognition module has been validated by Findlay et al [30] in an earlier study. The CCHS—HA cognition module covers similar cognitive domains as does the 3MS. However, no one has ever compared these two screening tests to see how they are comparable. Given the absence of other data, we thought it worthwhile to use these two different datasets to measure cognitive impairment since they cover similar cognitive domains.

Also, in this study, there were variations in the sampling frames of the two data sources. Whereas, the CSHA-1 sample was conducted strictly among seniors (65+), the CCHS—HA sample was conducted among middle aged (45+) participants although our analysis was limited to only those 65+ years. Therefore, differences in sampling frames could have affected prevalence estimates of cognitive impairment. Table 5-1 shows a list of similar items included in assessing cognitive impairment using 3MS and cognition task domains in both CSHA-1 and CCHS—HA respectively.

Table 5- 1 Comparison of items used to assess cognitive impairment in the CHSA and CCHS-HA samples

CSHA (3MS)	CCHS-HA (Domains)
When and where born	
Three words	
Counting and world backwards	
First recall	Immediate recall-word recall 1
Today's date	
Spatial orientation	
Naming	
Four-legged animals	Animal naming
Similarities	
Repetition	Mental Alternation Test
Read and obey/ "close your eyes"	

Writing	
Copying two pentagons	
Three stage command	
Second recall	Delayed recall- word recall 2

5.3.3.2 Predictors/covariates

We are interested in the prevalence of cognitive impairment by comparing two same age cohorts at two different time points. However, we also assessed the association between predictor variables and cognitive impairment over time by sex. Guided by previous literature, a number of modifiable and non-modifiable risk factors or covariates were assessed in both cohort samples.

The following predictor variables were included in this analysis;

Sex ("male"=1 *vs* "female"=2),
Age (65–74, 75–84, 85+ years)
Area of residence ("rural"=1 *vs* "urban"=2),
Educational level ("Less than secondary", "Secondary graduation", "Some post-secondary graduation", "Post-secondary graduation")
Province ("Atlantic", "Quebec", "Ontario", "Prairies", "British Columbia")
Marital status ("Married/common law", "Widowed/divorced/separated", "Single/never married")
Cultural or racial background ("Caucasian/white"=1 and "all other race/non-white"=0),
Self-rated health ("excellent/very good/good"=0 and "fair/poor"=1)
High blood pressure ("yes"=1 and "no"=0)
Heart disease ("yes"=1 and "no"=0)
Arthritis ("yes"=1 and "no"=0)
Parkinson disease ("yes"=1 and "no"=0)
Diabetes ("yes"=1 and "no"=0)
Stroke ("yes"=1 and "no"=0).

Covariates such as hearing problems and vision problems were recoded slightly different due to the way data were collected. In the CSHA-1 sample, hearing problems and vision problems were coded yes and no. Therefore, the two variables were also recoded as hearing problems ("yes"=1 and "no"=0) and vision problems ("yes"=1 and "no"=0). However, in the CCHS–HA sample the two variables have categories ranging from 1–6 and 99 for not stated, don't know or refusal. Therefore, the variables were recoded as hearing problems ("category 1/no"=0, "categories 2–6 /yes" =1). All other categories that were do not know, refusal and not stated together formed the recoded category as ("not stated category"=99) and were treated as missing values. Also, the same process was done for vision problems. Vision problems variable was recoded as ("category 1/no"=0, "categories 2–6/yes" =1). All other categories that were labeled as do not know, refusal and not stated were grouped as ("not stated category"=99) and treated as missing values. In all the included covariates, participants who indicated not stated, do not know, refusal, not applicable were regarded as missing values and were excluded from subsequent analyses.

5.3.4 Statistical analysis

The analysis of this study was in two phases. The first phase examined the time prevalence of cognitive impairment between the two cohorts using age–sex standardization comparison methods. We standardized the prevalence estimates of cognitive impairment in the two cohorts using the Canadian 2001 population census. These estimates were used to generate proportions and 95% confidence intervals (CI) in both samples. Standardized prevalence estimates were also conducted by sex and age categories. The age categorized for analysis were 65–74 years, 75–84 years and 85+ years.

The second phase of the analyses used logistic regression models to assess the association between modifiable and non-modifiable risk factors for cognitive impairment by sex differences. We performed multiple imputations to cater for the many missing values recoded in our study and to prevent selection bias and loss of information. We generated imputations using the chained equations procedure in STATA. In order to accurately carter for missing values, we conducted multiple imputations consisting of the outcome variable and all the predictors or covariates. After the imputation process, we retrieved all the missing values in both samples for the model building.

Logistic regression models were employed at the univariate analyses stage between each predictor and outcome (cognitive impairment) in the two cohorts. Unadjusted odds ratios (UOR), with 95% confidence intervals (CI) as well as p-values were reported. Covariates or predictors with univariate $p<0.20$ were maintained for further use in the multivariate analysis [34]. Known risk factors of cognitive impairment were included in the multivariate building stage regardless of significance level.

In the multivariate model building, a logistic regression model was also used to examine the association between predictor variables and the outcome (cognitive impairment) and a manual backward elimination process was used to remove insignificant variables one at a time. All other variables recording a significance level of $p<0.05$ were retained in subsequent analyses. Significant potential confounders were also tested. Insignificant variables at the univariate analysis stage were tested for confounding and they were not confounders and were left out of the final model. Four logistics regression models were built; 1) univariate association between predictor variables and outcome in both groups 2) multivariate analysis between predictor variables and outcome in the two samples 3) association between predictor variables and outcome in males 4) association between predictor variables and outcome in females. We also checked the overall significance of all the logistic regression models in both samples by using a likelihood ratio test. Stata 14 [35] was used to complete all the statistical analyses.

5.4 Results

5.4.1 Characteristics of the study population

This study analysis was limited to the final unweighted subsamples of 8504 and 7764 of seniors aged 65 years and older for the survey years 1991/92 and 2008/09 respectively. In both samples, a majority of the respondents were females (59.7%) and (60.4%) respectively. Most of the study population fell within the age groups 65–74 years (44.2%) and (51.8%). Whereas in the 1991 sample many had secondary graduation education (42.6%), the majority of the 2009 sample respondents had postsecondary graduation (43.1%). Many participants in both samples were still married or in common law relationships (51.3%) and (49.7%) respectively. Majority of the respondents lived in urban areas in both samples (85.9% *vs* 77.9%). Table 5-2 below shows the demographic characteristics of respondents for both study samples.

Table 5- 2 Sociodemographic description of CSHA (1991) and CCHS-HA (2009) samples.

	CSHA	**CCHS-HA**
N	8504 (100%)	7764 (100%)
Province		
Atlantic	1709 (20.1%)	2009 (25.9%)
Quebec	1718 (20.2%)	1460 (18.8%)
Ontario	1709 (20.1%)	1509 (19.4%)
Prairies	1631 (19.2%)	1852 (23.9%)
British Columbia	1737 (20.4%)	934 (12.0%)
Sex		
Male	3430 (40.3%)	3078 (39.6%)
Female	5074 (59.7%)	4686 (60.4%)
Age categories (years)		
65–74	3759 (44.2%)	4019 (51.8%)
75–84	3535 (41.6%)	2525 (32.5%)
85+	1210 (14.2%)	1220 (15.7%)
Marital Status		
Married/common-law	4363 (51.3%)	3858(49.7%)
Widowed/divorced/separated	3562 (41.9%)	3502(45.1%)
Single/never married	579 (6.8%)	404 (5.2%)
Area of residence		
Rural	1196 (14.1%)	1713 (22.1%)
Urban	7308 (85.9%)	6051 (77.9%)
Education		
Less than secondary	2444 (28.7%)	2871 (37.0%)
Secondary graduation	3619 (42.6%)	1127 (14.5%)
Other post-secondary	1292 (15.2%)	420 (5.4%)
Postsecondary graduation	1149 (13.5%)	3346 (43.1%)

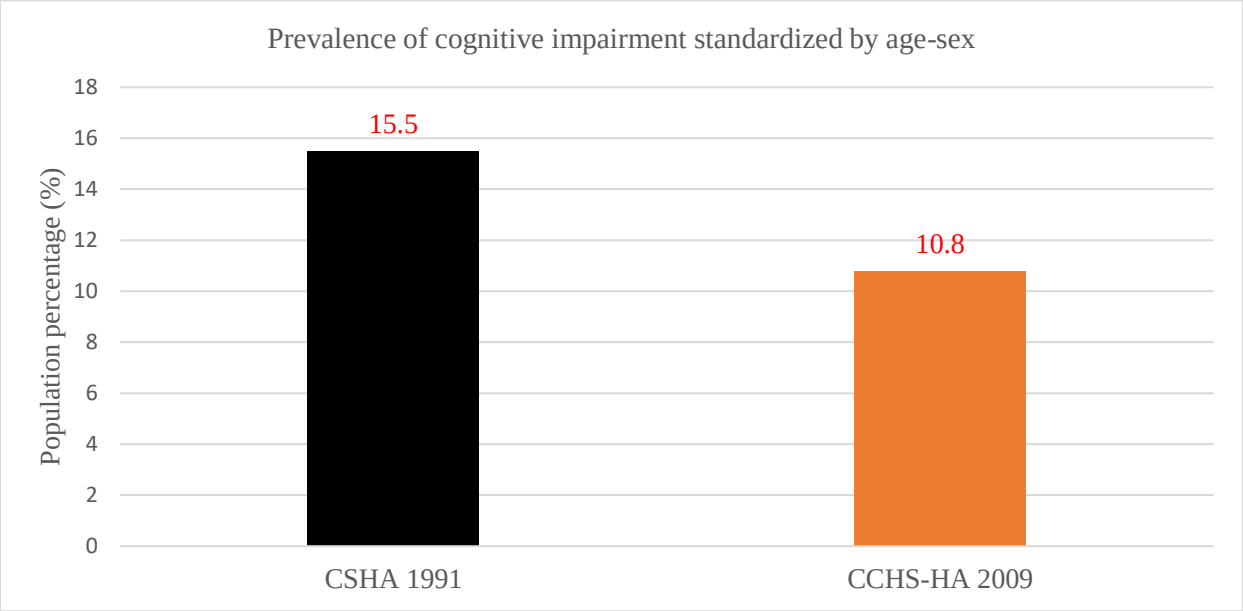
5.4.2 Age–sex standardized prevalence of cognitive impairment between 1991 to 2009

In the first phase of our analysis, respondents with complete data on cognitive function were used to estimate the age-sex-standardized population of those with cognitive impairment and proportions with 95% confidence intervals in the two cohorts were generated. A total of (N=8,504) and (N=7,764) participants for the CSHA-1 and CCHS–HA samples respectively were used for the analysis.

In the 1991 Canadian study of Health and Aging (CSHA), the non-standardized prevalence of cognitive impairment was 17.39% of Canadians (65+ years). The 2009 Canadian Community Health Survey–Healthy Aging (CCHS–HA) estimated a non-standardized prevalence of cognitive impairment at 10.62% of Canadians (65+ years). However, when the two

samples were age-sex-standardized, CSHA recorded an overall prevalence of cognitive impairment of 15.5% whilst that of the CCHS–HA study reported an overall cognitive impairment prevalence of 10.8%. Comparison of standardized prevalence across time showed a decrease in the prevalence of cognitive from 15.5% in the CSHA study to 10.8% in the CCHS–HA study, adjusted for age and sex (Figure 5-2). It shows an overall decrease of 4.7% during the 18 years period.

Figure 5- 2 Prevalence of cognitive impairment comparisons, 1991 and 2009



Whereas men had a higher prevalence of cognitive impairment in CSHA-1 study, women had a higher prevalence of cognitive impairment in CCHS–HA (with a prevalence of 16.0% in 1991 for men *vs* 11.6% for women in 2009). In general, between 1991 and 2009 men had a significant reduction in the prevalence of cognitive impairment compared to women (6.4% men *vs* 3.5% women).

Also, in this study, we reported a significant decrease in the prevalence of cognitive impairment between men and women in especially old–old (75–84 years) and oldest–old (85+ years) age groups. The decrease was higher in men compared to women. Cognitive impairment prevalence in the young–old (65–74 years) decreased marginally from 10.7% (95%CI= 9.2–12.1) in 1991 to 9.2% (95%CI= 7.8–10.5) for men in 2009.Women recorded a slight decrease from

12.6% (95%CI=11.2–14) in 1991 to 7.9% (95%CI= 6.7–9.1) in 2009. This translates into a percentage decrease of (4.7% for women *vs* 1.5% for men).

In addition, the proportion of older people with cognitive impairment decreased considerably for the old–old (75–84 years) and oldest–old (85+ years) age groups. Cognitive impairment prevalence reduced significantly from 46.0% in 1991 to 6.3% in 2009 for men and from 37.5% in 1991 to 7.5% in 2009 for women (85+ years). A percentage decrease of (39.7% men *vs* 30% women) among the oldest–old age groups (85+ years) as shown in Table 5-3.

Table 5- 3 Age–Sex standardized prevalence of cognitive impairment for men and women (65+ years) in 1991 and 2009, and differences in 1991 and 2009.

	CSHA 1991 %(95%CI)	**CCHS–HA 2009** %(95%CI)	**Difference**
Men			
65–74 years	10.7% (9.2–12.1)	9.2% (7.8–10.5)	–1.5%
75–84 years	21.9% (19.7–24.1)	8.4% (6.6–10.3)	–13.5%
85+ years	46.0% (40.9–51.2)	6.3% (3.8–8.7)	–39.7%
Women			
65–74 years	12.6% (11.2–14)	7.9% (6.7–9.1)	–4.7%
75–84 years	17.3% (15.7–18.9)	11.8% (10.2–13.3)	–5.5%
85+ years	37.5% (34.2–40.8)	7.5% (5.7–9.3)	–30%
By sex, standardized to 2001 Canadian population census			
Men	16.0% (14.9–17.2)	9.6% (8.6–10.7)	–6.4%
Women	15.1% (14.2–16.1)	11.6% (10.7–12.6)	–3.5%
Overall prevalence	15.5% (14.8–16.3)	10.8% (10.1–11.5)	–4.7%

5.4.3 Characteristics associated with cognitive impairment between 1991 and 2009 (univariate analysis)

In the second phase of our analysis of risk factor profile, complete cases, as well as missing values retrieved from the multiple imputation procedure, were used in the univariate as well as multivariate analyses. The univariate analysis results are presented in Table 5-4. Female sex was a protective factor for cognitive impairment in both cohorts even though not significant for CSHA-1 sample. Relative to the young-old age group (65–74 years) the unadjusted odds of reporting cognitive impairment increases with age. In both cohorts, respondents in the oldest-old age group (85+ years) were more likely to report cognitive impairment (OR=7.83, $p<0.001$, CSHA *vs* OR=2.40, $p<0.001$, CCHS–HA).

Educational attainment was a significant protective factor for cognitive impairment. In comparison to the less than secondary graduation category, those with postsecondary graduation were at a low odds to report cognitive impairment [0.11 (p<0.001, CHSA) and 0.76 (p<0.001, CCHS–HA)] respectively. Also, other protective factors of cognitive impairment in both cohorts include being white who also lived in an urban area.

We found seven modifiable risk factors of cognitive impairment at the univariate analysis for both cohorts. Participants who rated their health as poor were 2.11times (p<0.001) and 1.48 times (p<0.001) more likely to report cognitive impairment in the CSHA and CCHS–HA cohorts respectively compared to those with good self-rated health. In addition, those with heart disease were 1.02 times (p=0.772) and 1.17 times (p<0.001) likely to report cognitive impairment in the CSHA and CCHS–HA cohorts respectively compared to those compared to those without heart problems. Also, Parkinson disease was a significant risk factor for cognitive impairment (OR=2.45, p<0.001, CSHA *vs* OR=1.59, p=0.020, CCHS–HA). We found an insignificant positive relationship between diabetes and cognitive impairment in both cohorts.

Furthermore, stroke was positively associated with cognitive impairment at both time points. Respondents suffering from a stroke in the CSHA cohort had 2.04 (p<0.001) higher odds of reporting cognitive impairment compared to 1.52 (p<0.001) odds in the CCHS–HA cohort. Those living with hearing problems were 2.63 times (p<0.001) more likely to report cognitive impairment in the CSHA cohort compared to 1.91 times (p<0.001) in the CCHS–HA cohort.

Surprisingly, marital status was a significant risk factor for cognitive impairment at both time points. Those who were single or never married were likely to report cognitive impairment in both cohorts (OR=1.61, p<0.001, CSHA *vs* OR=1.13, p=0.124, CCHS–HA). This study showed some contrasting differences. Whereas arthritis was a protective factor for cognitive impairment in the CSHA cohort, it became a risk factor in the CCHS–HA cohort (OR=0.95, p=0.376, CSHA *vs* OR=1.11, p=0.002, CCHS–HA). Similar results were reported for vision problems and high blood pressure. Vision health problems was a risk factor for cognitive impairment in the CSHA cohort but became a protective factor in the CCHS–HA cohort (OR=2.37, p<0.001, CSHA *vs* OR=0.89, p<0.001, CCHS–HA). In a similar vein, high blood pressure was a significant protective factor for cognitive impairment in the CSHA cohort but

became an insignificant risk factor in the CCHS–HA cohort (OR=0.84, *p*=0.004, CSHA *vs* OR=1.02, *p*=0.656, CCHS–HA).

In summary, our univariate analysis revealed sex, educational level, an area of residence and race as the four shared protective factors for cognitive impairment for both cohorts. Also, both modifiable and non-modifiable risk factors for cognitive impairment such as age, self-rated health, Parkinson, diabetes, hearing problems, stroke, and marital status were noted in both study samples. Three factors such as arthritis, vision problems, and high blood pressure reported contrasting results in both cohorts (see Table 5-4).

Table 5- 4 Univariate analysis of risk factors for cognitive impairment between CSHA 1991 and CCHS-HA 2009.

	CSHA 1991		**CCHS-HA 2009**	
Characteristics	**OR, 95% CI**	**p-Value**	**OR, 95% CI**	**p-Value**
Sex				
Male	Reference			
Female	0.93 (0.83–1.04)	0.201	0.92 (0.86–0.99)	0.026
Age categories, years				
65 - 74	Reference		Reference	
75 - 84	2.66 (2.32–3.06)	<0.001	1.44 (1.33–1.56)	<0.001
85 and above	7.83 (6.70–9.17)	<0.001	2.40 (2.19–2.63)	<0.001
Marital status				
Married/common law	Reference		Reference	
Widowed/div./separated	1.70 (1.51–1.90)	<0.001	1.24 (1.16–1.33)	<0.001
Single/never married	1.61 (1.31–1.98)	<0.001	1.13 (0.97–1.33)	0.124
Ethnic background				
Non-white	Reference		Reference	
White	0.43 (0.29–0.63)	<0.001	0.67 (0.56–0.81)	<0.001
Educational level				
Less than secondary	Reference		Reference	
Secondary graduation	0.26 (0.23–0.30)	<0.001	0.69 (0.62–0.77)	<0.001
Some post-secondary	0.19 (0.15–0.23)	<0.001	0.61 (0.51–0.72)	<0.001
Postsecondary graduation	0.11 (0.08–0.14)	<0.001	0.76 (0.71–0.82)	<0.001
Area of residence				
Rural	Reference		Reference	
Urban	0.70 (0.61–0.80)	<0.001	0.87 (0.81–0.95)	<0.001
Self-rated Health				
Good health	Reference		Reference	
Poor health	2.11 (1.87–2.40)	<0.001	1.48 (1.37–1.61)	<0.001
High blood pressure				

No	Reference		Reference	
Yes	0.84 (0.75–0.95)	0.004	1.02 (0.95–1.09)	0.656
Heart disease				
No	Reference		Reference	
Yes	1.02 (0.90–1.14)	0.772	1.17 (1.08–1.26)	<0.001
Stroke				
No	Reference		Reference	
Yes	2.04 (1.65–2.52)	<0.001	1.52 (1.29–1.80)	<0.001
Arthritis				
No	Reference		Reference	
Yes	0.95 (0.85–1.06)	0.376	1.11 (1.04–1.19)	0.002
Parkinson				
No	Reference		Reference	
Yes	2.45 (1.67–3. 57)	<0.001	1.59 (1.08–2. 34)	0.020
Diabetes				
No	Reference		Reference	
Yes	1.00 (0.84–1.20)	0.976	1.09 (0.99–1.19)	0.065
Hearing problems				
No	Reference		Reference	
Yes	2.63 (2.32–2. 98)	<0.001	1.91 (1.74–2. 09)	<0.001
Vision problems				
No	Reference		Reference	
Yes	2.37 (2.07–2. 73)	<0.001	0.89 (0.82–0.98)	<0.001

5.4.4 Characteristics associated with cognitive impairment between 1991 and 2009 (multivariate analysis)

Our multivariate analyses used univariate variables with *(p <0 .20)* in the logistics regression model building process. Table 5-5 represents the final multivariate logistics regression model for cognitive impairment among Canadians (65+ years) with adjusted covariates and/or predictor variables. This study generated odds ratios to estimate the association between modifiable and non-modifiable risk factors of cognitive impairment between two cohorts. We interpreted results in this model focusing on shared risk factors, protective factors as well as contrasting findings between the two times separated points.

We found five common risk factors for cognitive impairment between the two cohorts. These include age, self-rated health, stroke, Parkinson's disease, and hearing problems. We found that odds of developing cognitive impairment increases with increasing age. Compared to

the young–old age groups (65–74 years) respondents in the oldest–old age groups (85+ years) were more likely to report cognitive impairment (OR=6.63, $p<0.001$, CSHA *vs* OR=2.19, $p<0.001$, CCHS–HA). In a similar vein, seniors who rated their health as poor in the CSHA cohort were 1.69 times ($p<0.001$) more likely to report cognitive impairment compared to 1.33 times ($p<0.001$) in the CCHS–HA cohort. Respondents suffering from stroke or effects of stroke were more likely to report cognitive impairment (OR=2.09, $p<0.001$, CSHA *vs* OR=1.29, $p<0.001$, CCHS–HA) than those without stroke. In addition, the odds of reporting cognitive impairment were more likely in respondents with Parkinson's disease compared to those without the disease (OR=1.99, $p=0.002$, CSHA *vs* OR=1.34, $p=0.152$, CCHS–HA). Also, people with hearing problems had 58% higher odds ($p<0.001$) of reporting cognitive impairment in the CSHA cohort compared to a 54% higher odds ($p<0.001$) in the CCHS–HA cohort.

We also found six shared protective factors of cognitive impairment. Females in 1991 were 13 %($p=0.049$) less likely to report cognitive impairment compared to 10 %($p<0.001$) of females in 2009. Secondly, "white" respondents were less likely to report impairment compared to their non–white counterparts (OR=0.34, $p<0.001$, CSHA *vs* OR=0.54, $p<0.001$, CCHS– HA). Participants who lived in the urban area were less likely to report cognitive impairment compared to their colleague's rural dwellers (OR=0.82, $p=0.014$, CSHA *vs* OR=0.90, $p=0.011$, CCHS– HA). Educational attainment was a protective factor for cognitive impairment in both cohorts. Compared to the less than secondary graduation, those who attained postsecondary education were less likely to report cognitive impairment (OR=0.10, $p<0.001$, CSHA *vs* OR=0.88, $p<0.001$, CCHS– HA). We found a negative relationship between high blood pressure and cognitive impairment. Hypertensive respondents in the CSHA cohort had a 0.82 ($p=0.003$) lower odds of reporting cognitive impairment compared to a 0.93 ($p=0.056$) lower odds in the CCHS– HA cohort. Similarly, respondents with heart disease were also less likely to report cognitive impairment (OR=0.80, $p=0.002$, CSHA *vs* OR=0.94, $p=0.157$, CCHS– HA).

Additionally, we found contrasting risk factors for cognitive impairment in this study. These include marital status, arthritis, diabetes, and vision problems. Compared to married respondents, those who were single or never married were 1.55 times ($p<0.001$) more likely to report cognitive impairment in the CSHA cohort but this was not a risk factor in the CCHS– HA cohort. Also, diabetic respondents in the CCHS– HA cohort were 1.04 times ($p=0.407$) likely to

report cognitive impairment but not a risk factor in the CSHA cohort. In addition, respondents with vision health problems were more likely to report cognitive impairment (OR= 1.35, $p<0.001$) in the CSHA cohort but not in the CCHS– HA cohort (see table 5.5). This study, however, found one protective contrasting factor in our analysis. Arthritis was a protective factor for cognitive impairment in 1991(OR= 0.74, $p<0.001$) but was not a protective factor in 2009.

Overall, this study found five modifiable and non-modifiable risk factors of age, self-rated health, stroke, Parkinson and hearing problems to be associated with cognitive impairment. We also found six common protective factors for cognitive impairment to include sex, cultural or racial background, an area of residence, high blood pressure, heart disease, and education. Four factors of marital status, diabetes, arthritis, and vision health problems produced divergent results.

Table 5- 5 Multivariate analysis of risk factors for cognitive impairment between CSHA 1991 and CCHS-HA 2009.

	CSHA 1991		**CCHS-HA 2009**	
Characteristics	**OR, 95% CI**	**p-Value**	**OR, 95% CI**	**p-Value**
Sex				
Male	Reference		Reference	
Female	0.87 (0.75–0.99)	0.049	0.90 (0.83–0.97)	0.004
Age categories, years				
65–74	Reference		Reference	
75–84	2.37 (2.04–2.75)	<0.001	1.39 (1.28–1.51)	<0.001
85 and above	6.63 (5.53–7.96)	<0.001	2.19 (1.99–2.41)	<0.001
Marital status				
Married/common law	Reference		Reference	
Widowed/div./separated	1.15 (0.99–1.33)	0.065	N/A	N/A
Single/never married	1.55 (1.22–1.97)	<0.001	N/A	N/A
Ethnic background				
Non-white	Reference		Reference	
White	0.34 (0.22–0.53)	<0.001	0.54 (0.45–0.65)	<0.001
Educational level				
Less than secondary	Reference		Reference	
Secondary graduation	0.28 (0.24–0.32)	<0.001	0.77 (0.69–0.86)	<0.001
Some post-secondary	0.17 (0.14–0.21)	<0.001	0.65 (0.55–0.78)	<0.001
Postsecondary graduation	0.10 (0.08–0.14)	<0.001	0.88 (0.81–0.95)	0.001
Area of residence				
Rural	Reference		Reference	

Urban	0.82 (0.70–0.96)	0.014	0.90 (0.83–0.98)	0.011
Self-rated Health				
Good health	Reference		Reference	
Poor health	1.69 (1.46–1.97)	<0.001	1.33 (1.22–1.45)	<0.001
High blood pressure				
No	Reference		Reference	
Yes	0.82 (0.71–0.93)	0.003	0.93 (0.87–1.00)	0.056
Heart disease				
No	Reference		Reference	
Yes	0.80 (0.70–0.92)	0.002	0.94 (0.86–1.02)	0.157
Stroke				
No	Reference		Reference	
Yes	2.09 (1.63–2.68)	<0.001	1.29 (1.09–1.53)	<0.001
Arthritis				
No	Reference		Reference	
Yes	0.74 (0.65–0.84)	<0.001	N/A	N/A
Parkinson				
No	Reference		Reference	
Yes	1.99 (1.29–3.06)	0.002	1.34 (0.90–2.0)	0.152
Diabetes				
No	Reference		Reference	
Yes	N/A	N/A	1.04 (0.96–1.15)	0.407
Hearing problems				
No	Reference		Reference	
Yes	1.58 (1.36–1. 84)	<0.001	1.54 (1.40–1. 69)	<0.001
Vision problems				
No	Reference		Reference	
Yes	1.35 (1.14–1. 60)	<0.001	N/A	N/A

5.4.5 Characteristics associated with cognitive impairment in the 1991 sample by sex

Two logistic regression models by sex were built using the CSHA study sample. Six modifiable and non-modifiable risk factors were common between males and females. Table 5-6 presents these common risk factors for both sexes. Factors including age, marital status, self-rated health, stroke, hearing problems, and visions problems were risk factors for cognitive impairment in both sexes. Compared to the young–old age groups (65–74years) males in the oldest–old age group (85+ years) were 6.51 times (p<0.001) more likely to report cognitive impairment compared to 6.95 times (p<0.001) for females in the same age group. Relative to married respondents, single or never married males were 2.10 times (p<0.001) more likely to

report cognitive impaired compared to 1.37 times (p=0.042) for females. Both males and females with poor self-rated health were more likely to report cognitive impairment compared to those with good self-rated health (OR=1.64, p<0.001, male *vs* OR=1.67, p<0.001, female). In addition, participants suffering from stroke were more likely to report cognitive impairment in both sexes. Compared to stroke-free participants, males were twice as likely (OR = 2.19, p<0.001) to report cognitive impairment than females (OR = 1.89, p<0.001). Also, males with hearing problems were 1.71 times (p<0.001) more likely to report depression compared to 1.51 times (p<0.001) for females. Vision problems were also significantly associated with cognitive impairment in both sexes (OR=1.33, p=0.045, male *vs* OR=1.40, p=0.002, female).

We found three common protective factors of cognitive impairment between males and females. Cultural or racial background, educational level, and arthritis were protective factors for cognitive impairment. Compared to "non-white", white males had a 59% (p=0.008) lower odds of reporting cognitive impairment as against a 71% (p<0.001) lower odds in white females. Respondents with the highest educational level (postsecondary graduation) in both sexes were less likely to report cognitive impairment (OR=0.09, p<0.001, male *vs* OR=0.11, p<0.001, female) compared to the reference group (less than secondary graduation). Arthritis was also a significant protective factor for males and females in the 1991 cohorts (OR=0.77, p<0.001, male *vs* OR=0.73, p<0.001, female).

Our study found high blood pressure and heart disease as the two unique protective factors for females only. Females with high blood pressure had a 20% (p=0.010) lower odds of reporting cognitive impairment but not for males. In a similar vein, females with heart disease had a 23% (p=0.004) lower odds of reporting cognitive impairment but not for males. We did not find any protective factor for the male sex. On the contrary, we found Parkinson disease as the only unique risk factor for males but not for females. Males with Parkinson disease were 2.91 times (p<0.001) more likely to report cognitive impairment compared to females.

Our study found age, marital status, self-rated health, stroke, hearing problems and vision problems as common risk factors between males and females in the CSHA cohort. We also found cultural or racial background, education, and arthritis as shared protective factors for cognitive impairment for both males and females. Protective factors of high blood pressure and heart disease were uniquely negatively associated with cognitive for females only. Also,

Parkinson disease was uniquely positively associated with cognitive impairment for males only. There was no unique risk factor for cognitive impairment for females (see Table 5-6).

Table 5- 6 Multivariate analysis of risk factors for cognitive impairment for CSHA 1991 cohort by sex.

CSHA 1991 Sample				
	Males		Females	
Characteristics	**OR, 95% CI**	**p-Value**	**OR, 95% CI**	**p-Value**
Age categories, years				
65 - 74	Reference		Reference	
75 - 84	2.48 (2.00–3.08)	<0.001	2.32 (1.89–2.86)	<0.001
85 and above	6.51 (4.87–8.70)	<0.001	6.95 (5.46–8.85)	<0.001
Marital status				
Married/common law	Reference		Reference	
Widowed/div./separated	1.10 (0.88–1.38)	0.418	1.14 (0.94–1.39)	0.193
Single/never married	2.10 (1.38–3.19)	<0.001	1.37 (1.01–1.87)	0.042
Ethnic background				
Non-white	Reference		Reference	
White	0.41 (0.21–0.79)	0.008	0.29 (0.16–0.53)	<0.001
Educational level				
Less than secondary	Reference		Reference	
Secondary graduation	0.33 (0.27–0.41)	<0.001	0.24 (0.20–0.29)	<0.001
Some post-secondary	0.22 (0.15–0.31)	<0.001	0.15 (0.11–0.19)	<0.001
Postsecondary graduation	0.09 (0.06–0.14)	<0.001	0.11 (0.08–0.16)	<0.001
Self-rated Health				
Good health	Reference		Reference	
Poor health	1.64 (1.31–2.06)	<0.001	1.67 (1.37–2.03)	<0.001
High blood pressure				
No	N/A	N/A	Reference	
Yes	N/A	N/A	0.80 (0.67–0.95)	0.010
Heart disease				
No	N/A	N/A	Reference	
Yes	N/A	N/A	0.77 (0.64–0.92)	0.004
Stroke				
No	Reference		Reference	
Yes	2.19 (1.54–3.11)	<0.001	1.89 (1.34–2.67)	<0.001
Arthritis				
No	Reference		Reference	
Yes	0.77 (0.64–0.93)	<0.001	0.73 (0.61–0.86)	<0.001
Parkinson				
No	Reference		Reference	
Yes	2.91 (1.58–5.37)	0.001	N/A	N/A

Hearing problems				
No	Reference		Reference	
Yes	1.71 (1.37–2. 12)	<0.001	1.51 (1.22–1. 86)	<0.001
Vision problems				
No	Reference		Reference	
Yes	1.33 (1.01–1. 75)	0.045	1.40 (1.13–1. 72)	0.002

5.4.6 Characteristics associated with cognitive impairment in the 2009 sample by sex

The same methods that were used to analyze the CSHA sample were used for the CCHS–HA sample. Table 5-7 shows both modifiable and non-modifiable risk factors associated with cognitive stratified by gender. We found four common risk factors for cognitive impairment among males and females in our analyses of the CCHS–HA sample.

Shared risk factors such as age, self-rated health, stroke and hearing problems were positively associated with cognitive impairment in both males and females. In comparison to the young-old age group (65–74 years) male seniors in the oldest–old age group (85+ years) were 1.99 times (p<0.001) more likely to report cognitive impairment compared to 2.27 times (p<0.001) for female seniors in the same age group. Male respondents with poor self-rated health had a 28% (p=0.501) higher odds of reporting cognitive impairment compared a 36% (p<0.001) higher odds in females. Also, stroke was a significant risk factor for cognitive impairment in males but not females (OR=1.52, p<0.001, male *vs* OR=1.10, p=0.406, female). In addition, hearing problems were significantly associated with cognitive impairment in both males and females (OR=1.50, p<0.001, male *vs* OR=1.58, p<0.001, female).

We also found three shared protective factors for cognitive impairment between males and females. These include heart disease, education, and cultural or racial background. Male seniors with heart disease were had 0.99 (p<0.896) odds of reporting cognitive impairment compared to 0.91(p=0.101) odds in female seniors. Relative to other races, white males had a 43% (p<0.001) lower odds of reporting cognitive impaired compared to a 49 %(p<0.001) lower odds among females.

This study found marital status and Parkinson disease as unique risk factors for cognitive impairment among males only. Compared to those who were married or in common law, male-only respondents who were single or never married were likely to report cognitive impairment

(OR=1.15, *p*=0.282). Also, male respondents with Parkinson disease were 1.84 times more likely (*p*=0.044) to report cognitive compared to those without the disease.

Furthermore, we found diabetes and arthritis as unique risk factors for cognitive impairment among females only. Compared to non-diabetic respondents, females with diabetes were 1.10 times (*p*=0.153) likely to report cognitive impairment. Similarly, arthritis was also positively associated with cognitive impairment for females but not for males (OR=1.04, *p*=0.414).

On the contrary, we found high blood pressure as a risk factor for males but a protective factor for females. While males with high blood pressure were 1.04 (*p*=0.501) times likely to report cognitive impairment, females with high blood pressure had a 14% (*p*=0.002) lower odds of reporting cognitive impairment.

In summary, we found age, self-rated health, stroke and hearing problems as shared risk factors for cognitive impairment in the CCHS–HA cohort for both sexes. We also found heart disease, education and cultural or racial background as shared protective factors. Marital status and Parkinson's disease were found to be unique risk factors for males only in this study. Similarly, diabetes and arthritis were found to be uniquely associated with cognitive impairment for females only. One contrasting finding was the association between high blood pressure and cognitive impairment. While it was a risk factor for males, it was a protective factor for females.

Table 5- 7 Multivariate analysis of risk factors for cognitive impairment for CCHS-HA 2009 cohort by sex.

CCHS-HA 2009				
	Males		Females	
Characteristics	**OR, 95% CI**	**p-Value**	**OR, 95% CI**	**p-Value**
Age categories, years				
65 - 74	Reference		Reference	
75 - 84	1.26 (1.11–1.43)	<0.001	1.48 (1.33–1.65)	<0.001
85 and above	1.99 (1.69–2.34)	<0.001	2.27 (2.01–2.57)	<0.001
Marital status				
Married/common law	Reference		Reference	
Widowed/div./separated	1.23 (1.08–1.40)	0.002	N/A	N/A
Single/never married	1.15 (0.89–1.48)	0.282	N/A	N/A
Ethnic background				
Non-white	Reference		Reference	

White	0.57 (0.43–0.74)	<0.001	0.51 (0.39–0.67)	<0.001
Educational level				
Less than secondary	Reference		Reference	
Secondary graduation	0.78 (0.27–0.41)	0.010	0.77 (0.67–0.88)	<0.001
Some post-secondary	0.75 (0.15–0.31)	0.035	0.58 (0.46–0.73)	<0.001
Postsecondary graduation	0.91 (0.06–0.14)	0.128	0.86 (0.77–0.95)	0.005
Self-rated Health				
Good health	Reference		Reference	
Poor health	1.28 (1.12–1.47)	<0.001	1.36 (1.21–1.53)	<0.001
High blood pressure				
No	Reference		Reference	
Yes	1.04 (0.93–1.16)	0.501	0.86 (0.78–0.95)	0.002
Heart disease				
No	Reference		Reference	
Yes	0.99 (0.87–1.12)	0.896	0.91 (0.81–1.02)	0.101
Stroke				
No	Reference		Reference	
Yes	1.52 (1.18–1.96)	0.001	1.10 (0.87–1.40)	0.406
Arthritis				
No	Reference		Reference	
Yes	N/A	N/A	1.04 (0.95–1.14)	0.414
Parkinson				
No	Reference		Reference	
Yes	1.84 (1.02–3.33)	0.044	N/A	N/A
Diabetes				
No	Reference		Reference	
Yes	N/A	N/A	1.10 (0.97–1.25)	0.153
Hearing problems				
No	Reference		Reference	
Yes	1.50 (1.30–1. 73)	<0.001	1.58 (1.38–1. 80)	<0.001
Vision problems				
No	Reference		Reference	
Yes	0.85 (0.74–0. 97)	0.015	N/A	N/A

To summarize, the significant findings arising from our analyses revealed some changes in the risk factors for cognitive impairment over time and that the etiologies of such impairment vary by sex (see Table 5-8). Respondents in the CSHA 1991 sample reported more significant risk factors for cognitive impairment compared to their counterparts in the CCHS–HA 2009 sample. Males reported more significant risk factors for cognitive impairment in both study samples than females.

Table 5- 8 Summary table of significant risk factors for cognitive impairment in general and by sex

Overall analysis			**Stratified by Sex**			**Stratified by Sex**	
CSHA 1991	**CCHS-HA 2009**		**CSHA 1991**			**CCHS-HA 2009**	
			Males	**Females**		**Males**	**Females**
Age	Age		Age	Age		Age	Age
Marital status			Marital status			Marital status	
SRH (poor)	SRH (poor)		SRH (poor)	SRH (poor)		SRH (poor)	SRH (poor)
Stroke	Stroke		Stroke	Stroke		Stroke	
Parkinson disease			Parkinson disease			Parkinson disease	
Hearing problems	Hearing problems		Hearing problems	Hearing problems		Hearing problems	Hearing problems
Vision problems			Vision problems	Vision problems			

Note: SRH (poor) means poor Self-Rated Health

5.5 Discussion

The first objective of this study estimated the prevalence of cognitive impairment between two-time separated points among Canadian seniors using population-based cohorts. These results tend to suggest that cognitive impairment in Canada may have declined over an 18-year period (between 1991 and 2009) despite the aging population. Our finding supports two recent European studies where both prevalence and incidence of dementia were reported to have decreased despite population aging [12, 47]. Our study finding, however, contradicts recent Canadian studies that found increasing prevalence of dementia [48, 49]. We found that men had a higher prevalence of cognitive impairment in CSHA study whilst women reported a higher prevalence of cognitive impairment in CCHS–HA study. Our findings are in keeping with recent studies in Spain and Japan where men and women differently reported a higher prevalence of cognitive impairment [39, 45]. Our finding is however at odds with what Mathews et al [47] found in their comparative study of dementia prevalence. They found that women were consistently more likely to report higher dementia prevalence compared to men.

In addition, our study found that even though there was a general decrease in cognitive impairment, the effect of the reduction was more prominent in men than in women. Also, we reported age- and sex-specific differences in the prevalence of cognitive impairment. Both men and women in all age groups reported a decrease in cognitive impairment though the effect of the decrease was more significant in men than women. Our finding contradicts an earlier finding where little or no differences exist in the prevalence of cognitive impairment between men and women [37]. On the other hand, seniors in the old-old (75–84 years) age groups and oldest-old (85+ years) age groups reported significant decreases in cognitive impairment prevalence.

In our multivariate analyses, we assessed the association between predictor variables and cognitive impairment between the two-time separated points. We also assessed sex differences in modifiable and non-modifiable risk factors for cognitive impairment and whether modifiable risk factors change over time. We found that cognitive impairment was associated with a number of modifiable and non-modifiable risk factors. Firstly, we found five common risk factors for both study samples. Seniors who were much older, poorly rated their health, suffered a stroke, had Parkinson disease and hearing problems were more likely to report cognitive impairment. The above finding is consistent with what has been earlier reported in the literature [38–41].

Secondly, we found six common protective factors of cognitive impairment in both cohorts in our study. These include female sex, cultural or racial background, an area of residence (rural *vs* urban), high blood pressure, heart disease, and higher educational level. Meng and D'Arcy [44] in an earlier systematic review, for instance, found that low education increases the risk of dementia and the vice versa. This has been corroborated by other studies [12, 37, 39, 40]. We found that "whites" were less likely to report cognitive impairment compared to other races. This confirms a similar study in the United States where blacks were more likely to report cognitive decline compared to whites [37]. A systematic review conducted in Australia using 14 longitudinal population-based studies of cognitive aging in 12 countries and 5 continents also found that Asians had a faster decline in cognition compared to whites which confirm our current finding [42]. Our finding that urban residents were less likely to report cognitive impairment confirms what has been previously reported [46]. Female sex was protective for cognitive impairment. This confirms an earlier study where women were found to have performed better than males in both verbal and memory tests [42]. A possible explanation is that since both men and women are afforded equal educational opportunities in Canada unlike in other developing countries, education could have modified this relationship. Also, our protective factors of high blood pressure and heart disease could be as a result of the effective treatment and management of these chronic diseases in Canada over the years.

Furthermore, we found some contrasting findings in this study. Four factors of marital status, diabetes, arthritis, and vision health problems produced divergent results in our comparative study. There were risk factors or protective factors that were unique to either of the cohorts. For instance, we found that marital status (single or never married) was significantly associated with cognitive impairment in the CSHA cohort but was not a risk factor in the CCHS–HA cohort. This finding confirms earlier reported studies [41, 43]. Lipnicki et al [43] for example reported that married compared to single status was a protective factor for the decline in executive function and reduces cognitive impairment risk. Also, respondents with diabetes in the CCHS–HA cohort were more likely to report cognitive impairment but not in the CSHA cohort. This finding is in keeping with what has been reported [39, 41, 45]. This current finding could be explained by the recent increase in the incidence and prevalence of Type 2 diabetes in Canada, one of the fastest growing diseases in the country. In the CSHA cohort arthritis was a protective

factor for cognitive impairment. This contradicts an earlier study where those with arthritis had 24% higher odds of developing cognitive impairment [38].

Sex makes a difference in our risk to most health conditions including cognitive impairment. Therefore, we stratified our analysis by sex in order to assess whether modifiable and non-modifiable risk factors of cognitive impairment change over time between the two cohorts.

In the CSHA cohort, our study found age, marital status, self-rated health, stroke, hearing problems and vision problems as common risk factors for both sexes as earlier reported [38–41]. We also found race, education, and arthritis as shared protective factors for cognitive impairment for both males and females. This is in keeping with what several other studies found [12, 37, 39, 40, 42, 44]. Protective factors of high blood pressure and heart disease were uniquely negatively associated with cognitive impairment for females only. Also, Parkinson disease was uniquely positively associated with cognitive impairment for males only. Our finding even though significant is different from what Lipnicki et al [43] reported. They reported unique risk factors for cognitive impairment for men only to include men with more physical activity and those who smoke. There was no unique risk factor for cognitive impairment for only females in this cohort.

Surprisingly, diabetes which is generally thought to be a risk factor for cognitive impairment was not associated with the outcome in the CSHA cohort. This is at odds with previous results [39, 41, 45]. This sample could not, however, report any association between diabetes and cognitive impairment in both males and females stratified analysis. Similarly, the CSHA could not report any risk factors of cognitive impairment that were either specific to males or females.

In the CCHS–HA, we found age, self-rated health, stroke and hearing problems as shared risk factors for cognitive impairment cohort for both sexes. This is in line with what has been reported in the literature [38, 39, 41]. We also found heart disease, education, and race as shared protective factors. Other studies have previously reported similar findings [12, 37, 39, 40, 42, 44].

In our study, there were risk factors that were specific to males only. Marital status and Parkinson disease were found to be unique risk factors for males only in this study. Our finding

coincides with what Yen et al [41] reported where being single was associated with higher odds of developing cognitive impairment.

Conversely, females that were diabetic had 10% higher odds of developing cognitive impairment. In the same vein, females with arthritis were likely to report cognitive impairment. Risk factors such as diabetes and arthritis were found to be uniquely associated with cognitive impairment for females only. The finding on diabetes as a risk factor for cognitive impairment for female only is at odds with what Lipnicki et al [43] reported. They reported that men rather than women were at a reduced risk of cognitive impairment or dementia if they had diabetes. Additionally, the same study reported a significant association between cognitive impairment and arthritis in males but not females which contradict our finding [43]. The association between cognitive impairment and high blood pressure produced contrasting results. While it was a risk factor for males, it was equally a protective factor for females.

Our current findings give suggestive evidence that sex differences exist in the association between predictor variables and outcome over time. In the CSHA sample, the effect of common risk factors for cognitive impairment in both sexes is more prominent in males than females. In CSHA cohort sample even though both males and females reported shared risk factors for cognitive impairment, males had higher odds of cognitive impairment different from females on most of the shared risk factors investigated, including marital status, stroke and hearing problems. Similarly, the effect of the predictor variables on the outcome (cognitive impairment) in CCHS–HA sample is more prominent in females compared to males. Females in this cohort had higher odds of reporting cognitive impairment than males in most of the common risk factors measured.

We also found that modifiable risk factors or predictors of cognitive impairment changed over time by sex. Whereas there were no unique risk factors for cognitive impairment in the CSHA cohort for females only, over time, earlier protective factors such as diabetes and arthritis became risk factors for female only. Also, our study found that unique risk factors of cognitive impairment for males only increased from one to two. Parkinson disease was the only unique risk factor for males only in the CSHA cohort, but marital status became an additional risk factor for males only in the CCHS–HA cohort.

5.5.1 Strengths and limitations of the study

The major strength of this study is the use of nationally representative and large population-based study samples to estimate cognitive impairment prevalence among Canadian seniors (65+ years) over an almost two-decade period. To the author's knowledge, this study is the first of its kind to use population-based study samples to examine the prevalence of cognitive impairment on a national scale. Most studies conducted in the country in the past were either province-specific or point prevalence estimates. Our study provided that comparative aspect which is lacking in the literature.

Another strength of our study is its ability to establish the age-cohort effect relationship between cognitive impairment and predictor variables as well as its prevalence over time. Our study has explicitly established that. Later generations were less likely to report cognitive impairment compared to earlier generations. This was evident in the significant reduction in the prevalence of cognitive impairment in later generations.

We also examined sex differences in both the prevalence of and risk factors for cognitive impairment. This allows for sex-specific interventions to be tailored towards specific groups where it is most needed. Also, the CHSA and CCHS–HA study cohorts were among the few population-based studies in Canada to have specifically measured cognition and to shed light on cognitive impairment or dementia in Canadian adults.

Despite these strengths, there are a number of limitations in our study that must be highlighted. Firstly, in our CSHA sample, the issue of imperfect sensitivity arises. Our analyses used the community sample to estimate both prevalence and predictors of cognitive impairment. However, the study recorded a high sensitivity value of 98.6% at baseline (CSHA-1) in the 3MS screening process, we cannot be sure that cognitively normal participants were not added to mild cognitive impairment cases.

Secondly, the 2009 CCHS—HA cognition module did not accept proxy responses (other people responding on behalf of the respondents). This probably explains why the cognitive master file recorded a much lower response rate of 62.4% compared to the 74.4% response rate recorded in 2009 CCHS—HA main file. Therefore, there is a possible underestimation of the prevalence of lower cognitive functioning in the CCHS—HA sample.

Thirdly, non-clinical measures of cognitive functioning such as computer-assisted interviews and questionnaires were used in the CCHS—HA Cognition Module unlike the 3MS used in the CSHA sample. This is problematic because a clinical assessment is necessary to measure the sensitivity and specificity of a screening test in the cognitive decline or dementia identification process.

In addition, our study could not include other important risk factors of cognitive impairment such as traumatic brain injury, obesity, smoking status, depression, sleep disturbances, hyperlipidemia and known protective factors such as physical activity, income, Mediterranean diet, cognitive training, moderate alcohol consumption, and social engagement [31]. This is because some of these factors were not part of the CSHA sample which is the baseline data to be used for our comparison. Therefore, for easy comparison, we used variables that were available in both study samples.

Finally, differences in sampling frames between the two data sources (CSHA-1 sample and CCHS—HA sample) as well as differences in the measurement of cognitive impairment could have affected prevalence estimates of the disease.

5.6 Conclusion

Our study provides evidence of a reduction in the prevalence of cognitive impairment in the context of an aging population in Canada in population-based cross-sectional studies. It reinforces the suggestion that although increased prevalence of cognitive impairment could have been influenced by many factors such as stroke management, increased vascular incidents and diabetes prevalence, the decrease prevalence recorded in our study may be as a result of improvement in the prevention and treatment of vascular morbidity as well as higher educational attainment, that seem to have had a greater effect in the Canadian context [12, 47]. The reduction we found in our study is in keeping with earlier literature that identified major risk reduction factors in high-income countries such as better prevention and treatment strategies for vascular diseases and improvements in education as the reason for the decline in cognitive impairment or dementia despite population aging [12, 47].

This study also highlights the importance of cohort effect in public health prevention and treatment strategies. Our results provide suggestive evidence regarding how different

experiences shared by successive generations predisposes them to different patterns of disease risk in these generations. It also establishes changes in modifiable risk factors of cognitive impairment over time and in different generations.

Also, our study showed that age and sex differences exist in the risk factors for cognitive impairment and that these factors change over time. Therefore, it will be beneficial for public health interventions to be channeled towards particular age and sex groups.

We recommend a future longitudinal population-based study that looks at associations found in this study. Such studies should concentrate on specific risk factors for cognitive impairment to help establish temporality. In our study, Parkinson disease stood out as the most consistent risk factor for cognitive impairment for males only and deserves specific policy intervention. There is also the need for future studies to focus on the effectiveness of existing interventions to establish the extent to which they are meeting the demands of these vulnerable populations. With the aging population in Canada, public health policy interventions that are age and sex bias are urgently needed to help tackle age-related conditions particularly dementia and cognitive impairment.

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CHAPTER 6 – PREVALENCE OF CHRONIC DISEASES AND MULTIMORBIDITY IN CANADA: CONTRASTING TRENDS

A version of this chapter has been submitted to BMC Public Health Journal for publication review.

6.1 Abstract

Background: The prevalence of chronic diseases and multimorbidity (two or more diseases) are on a steady rise in most western societies owing to an increasing aging population and life expectancy. In the Canadian context, there is a lack of studies on trends in chronic diseases prevalence that differentiate between population aging effects and other factors. The study aims to (1) estimate prevalence and trends in chronic diseases and multimorbidity in Canada from 1978 to 2014; (2) assess the contribution of both population aging and other associated factors in chronic diseases and multimorbidity prevalence and trends in Canada.

Methods: A cross-sectional trend analysis, using three data sources: 1) Canada Health Survey of a nationally representative sample in 1978, and 2) Canadian National Population Health Survey, cross-sectional version 1994/1995–1998/1999 and Canadian Community Health Survey between 2000/2001–2013/2014. Age-sex standardization was assessed in order to estimate chronic diseases and multimorbidity trends and prevalence rates over time. As cross-sectional surveys, with slightly different diagnostic criteria used over the years, the level of evidence generated is generally descriptive.

Results: A decrease from 31.0% to 26.7% in the prevalence of chronic diseases was found between 1978 to 2014, a significant decrease of 4.3 percentage points. Standardization to the population in 2014 showed the same decrease of 4.3 percentage points. The decrease in prevalence was significant for both women, and men (4.9 *vs* 3.7). An increase from 19.4% to 32.1% between 1978 to 2014 in the prevalence of multimorbidity was recorded, a significant increase of 12.7 percentage points for both men and women. Standardization to the population in 2014 reduced the increase to 12.4 percentage points. The increase in prevalence was significant for both men and women, and in the age groups over 75+ years. However, men had a higher percentage point increase (13.1 *vs* 11.9) than women. About 2.4% of respondents were likely to report multimorbidity due to aging. More women than men (4.4% *vs*1.6%) reported multimorbidity due to population aging.

Conclusions: The prevalence of chronic diseases decreased over time while multimorbidity increased between the period 1978–2014. We conclude that population aging partly accounts for the rise in multimorbidity we found in this study. Which means that increased survival after

multimorbidity diagnosis owing to effective treatment of chronic diseases, early diagnosing of chronic diseases, and health-seeking behaviors are responsible for the larger part of the rise.

Keywords: Chronic diseases, multimorbidity, prevalence, and aging population

6.2 Introduction

Most Western countries have witnessed a substantial rise in the prevalence of diseases owing to the continuous increase in both the number of older persons and life expectancy of those with chronic conditions [1]. This increase is part of the demographic transition which has seen chronic diseases surpassing infectious diseases as the cause of death and disability. Multimorbidity, which refers to the presence of two or more chronic diseases in one individual is increasing with rapidity in recent times [2]. To estimate the magnitude of this phenomenon, a number of studies have been conducted worldwide. In the US for instance a rise in multimorbidity was observed over a ten-year period using data from health surveys and health care insurance organizations [3–5]. Similar studies in Canada have looked at both the prevalence of chronic diseases and multimorbidity and their economic burden on the country [6, 7]. Wang et al [45] in a recent Chinese study found low income status, female sex, the area of residence (rural) and increasing age (older adults) as significant risk factors for multimorbidity. Taylor et al [8] in a recent study in Australia found that population aging only partly accounts for the rise in multimorbidity. It is expected that chronic diseases and multimorbidity will continue to rise and even in the future as long as the world's population ages [9]. The expected continuous rise in multimorbidity is likely to impact negatively on resource allocation and health care systems globally and that is a source of concern for policymakers [10].

The Canadian health care system as with most health care systems is built around the treatment of single diseases [11]. This makes it difficult for primary care professionals to care for patients with multimorbidity. Persons with multimorbidity do not get maximum care due to the how most health care systems are structured [12, 13]. They are also more likely to frequent and stay longer in hospitals as well as incur higher health care costs and increased use of polypharmacy that may result in adverse drug effects [14].

In light of the challenges posed by chronic diseases and multimorbidity, several countries are planning to reform their health care systems and equip them with the needed equipment and expertise in order to better manage the growing proportion of older people with chronic conditions [15]. Besides the aging population, other contributing factors including improved disease detection and advancement in medical treatments are considered major determinants of these phenomena [16].

In the Canadian context, there is a lack of studies on trends in the prevalence of chronic diseases that distinguished between effects of population aging and these other contributing factors. There is a general perception that chronic diseases and multimorbidity are mostly found in the middle-aged and older populations. As a result, most future projections on the number of people with one or more chronic diseases usually focus on the aging population to the neglect of other important determinants. The inability of previous studies to distinguish between the effect of aging population as against other factors on the prevalence of chronic diseases and multimorbidity has the tendency to deny younger populations and other segments of the population appropriate health care. Such a distinction is needed to guide future projections and policy interventions.

The existence of annual cross-sectional health surveys on the prevalence of chronic diseases and their risk factors in Canada provides a golden opportunity to assess how these disease trends change over time. Estimates of chronic diseases and multimorbidity trends were derived from three sets of national health surveys over a 36-year period. These include the Canada Health Survey (CHS), National Population Health Surveys (NPHS) and Canadian Community Health Surveys (CCHS). A window of opportunity to measure general disease trends in a population is offered by the availability of these nationally representative data sources [19].

The two objectives of this study are:

1) To describe the trends in the prevalence of chronic diseases and multimorbidity in Canadians by sex, age groups, educational levels and geographic areas (province and region of residence) between 1978 to 2014.
2) To assess the contribution of both population aging and other associated factors in chronic diseases and multimorbidity prevalence and trends in Canada.

6.3 Methods

6.3.1 Data Sources

Statistics Canada conducts annual health surveys in which randomly chosen residents residing throughout the country are invited to answer questions regarding their health. We used data from 3 different but similar sets of Canadian health surveys for this project. For easy comparison across all the fiscal years and for the sake of avoiding overcrowding in our graphs, the ten provinces of Canada were regrouped into five regional blocks as: (Newfoundland and Labrador (NL), New Brunswick (NB), Nova Scotia (NS), Prince Edward Islands (PEI) =Atlantic), Manitoba (MB), Saskatchewan (SK), Alberta (AB) as Prairies. Quebec (QC), Ontario (ON) and British Columbia (BC) each stood alone.

Our first source of data was the Canada Health Survey which intended to gather information regarding the general health at the population level for purposes of planning and evaluating health policies and programs [17]. The focus of the survey was on three broad areas of risk factors, health status, and consequences. Risk factors were measured based on lifestyle, bio-medical and environmental. The survey commenced in July 1978 and ran until March 1979 using face to face questionnaire and other instrumented measures such as blood sample measurement, blood pressure, cardiorespiratory fitness, height, weight, and skinfold [17]. The results of the physical measures were recorded in physical measures questionnaire. Statistics Canada collected the interview component data while the physical measures component data were collected by nurses employed by the Victorian Order of Nurses [17]. The questionnaire captured content areas of lifestyle, reported health, health care utilization, emotional health, household characteristics, and demographic characteristics [17]. Questionnaire data were captured directly onto computer-readable files using 100% verifications. Weights were also conducted to estimate the provincial population by age and sex [17]. All non-response and inconsistent data were coded as unknown. A total of 31668 participants responded to the survey [17]. This survey was terminated after one year due to government-wide budget cuts. However, major components of this survey metamorphosed into the National Population Health Survey (NPHS) which started in 1994, our second set of health survey data.

The National Population Health Survey (NPHS) was both a cross-sectional as well as a panel study. The NPHS was carried out by Statistics Canada [44]. In the 1994 NPHS data

collection process, face-to-face interviews were used to collect data from 17276 household respondents nationally [44]. Between 1994 and 1998, the NPHS survey collected cross-sectional data on a representative sample of the Canadian population every two years [The initial 1994 survey sample served not only as a cross-sectional survey but also served as a basis for a cohort panel interviewed at two-year intervals [44]. That cohort project ended in 2010/2011 after its ninth cycle of data collection or 16 years of follow-up].

The Canadian Community Health Survey (CCHS) replaced the NPHS which is the third source of our data. The CCHS also used similar sampling procedures just as the CHS and NPHS data sources. Data collection in the CCHS surveys were initially conducted every 2 years as follows; 2001 (CCHS 1.1), 2003 (CCHS 2.1), 2005 (CCHS 3.1), and 2007 (CCHS 4.1) [45]. Between the reference year of 2001 to 2007 large sample sizes of about 130 000 respondents were interviewed. In 2007, the CCHS however made major changes to the design and changed the sample to about 65000 each year [45]. From 2007 onwards, data are collected using questionnaire and released on an ongoing yearly basis instead of the two years intervals previously conducted. About one-half of the sample was interviewed in person and one-half by telephone using computer-assisted telephone interviewing [45]. In addition, the CCHS survey cycles also included an off-year survey on topics of special significance e.g. mental health, nutrition and among others [45].

Statistics Canada adjusted the yearly samples surveyed taking into account the population structure of the Canadian population. In all the surveys, Statistics Canada supplies a survey weighting factors based on sex, age, marital status, provincial difference, rural/urban differences, and educational levels so researchers can generate population estimates [17, 44, 45]. Also, in all these surveys between 1978 to 2014, the questions on chronic diseases were largely similar and respondents aged 12 years and over were part of this analysis [17, 44, 45]. The current study did not require ethics approval as this is a secondary analysis of anonymized survey data that contains no personal identifiers.

6.3.2 Definition of selected chronic diseases

We selected twelve chronic conditions as part of this analysis:

(1) Asthma

(2) Respiratory problems (chronic bronchitis, emphysema and chronic obstructive pulmonary disease (COPD)
(3) Mental illness (depressive symptoms)
(4) High blood pressure
(5) Diabetes
(6) Stroke
(7) Intestinal or stomach ulcers
(8) Cancer
(9) Heart disease
(10) Migraine headaches
(11) Back problems
(12) Arthritis

The selection of these chronic conditions was based on the following two criteria 1) availability of data on these conditions in the surveys used, and 2), all the selected chronic conditions have been included in previous research about the measurement of chronic diseases and multimorbidity [19]. Chronic diseases and multimorbidity prevalence estimates were produced for 1978, 1994, 1996, 1998, 2001, 2003, 2005, 2007, 2009, 2010, 2011, 2012, 2013 and 2014. The year 2008 was omitted from the analysis because that national survey only surveyed respondents 45+years of age.

We evaluated two definitions of chronic disease prevalence and prevalence of multimorbidity. We first defined the prevalence of chronic diseases as the self-reported occurrence of any of the twelve chronic diseases in any of the survey years. Secondly those who reported two or more chronic diseases (2+) in the same person were regarded as having multimorbidity. The above definitions have also been used in previous research [19].

Chronic diseases and multimorbidity prevalence were analyzed by age, sex, province of residence and educational level. Respondents were categorized according to their highest level of education such as basic (less than secondary), medium (secondary education, some post-secondary and post-secondary education) and high (university degree and post-graduate education). Based on the province of residence, we categorized respondents into five regional blocks namely, Atlantic, Prairies, Quebec, Ontario, and British Columbia. We also categorized respondents into five age groups of (12–24, 25–54, 55–64, 65–74, 75+ years) taking into account sex differences.

6.3.3 Statistical analyses

The analyses of this study were mainly estimating frequencies and proportions by sex, age group, province, and educational level. Two different methods were used in that regard. Firstly, Statistics Canada survey specific sampling weights were used to estimate population frequencies. The second method of our analysis of frequency data was the use of direct standardization. As population-weighted estimates may change over time, as a result of changes in the demographic structure of the population standardization was performed based on the population size, age and sex distributions in 2014 [18]. We categorized the participants into groups of three namely ;(those who did not report any chronic disease= (0), reported at least one chronic disease= (1) and reported 2+ chronic diseases= (2)). All other values such as "not stated", "don't know", "not applicable" and "refusal" were treated as missing values and deleted from subsequent analyses. Population proportions were generated to reflect the age-sex groupings within the eligible population of the country in each year. The standardized estimates were calculated to enhance the comparison of frequencies over time. Stratified analyses were performed according to sex, age groups, educational level and the province of residence.

Prevalence estimates were conducted with and without standardization using the year 2014 as a reference. Since Canada's population has been aging since 1960, in order to estimate the effect of aging on the prevalence of chronic diseases and multimorbidity, we compared the non-standardized trend and the standardized trend. The difference of such comparison is an indication of the effect of aging on the two conditions. We therefore divided the difference between non-standardized and the standardized trend by the non-standardized trend which gave us the effect of population aging on chronic diseases and multimorbidity prevalence.

Our study results are presented in both tabular and graphic forms. Proportions and percentages were used to estimate age, provincial, education and sex differences in chronic diseases and multimorbidity prevalence over time. All analyses of these National Health surveys data were conducted using SPSS version 24 and STATA software.

6.4 Results

6.4.1 Trends in Chronic disease prevalence

Results from Table 6-1 show the individual crude prevalence of the twelve selected chronic diseases between 1978 and 2014. A stable prevalence of asthma and stroke was recorded between 2007 and 2014. In addition, at mid-point in 2007, the prevalence of back problems, breathing problems, intestinal or stomach ulcers, migraine headaches and depressive symptoms plateaued and were on the decline by 2014. On the other hand, at mid-point in 2007 prevalence of arthritis, cancer, diabetes, heart disease, and high blood pressure was on the increase and continued until 2014. However, the increase in some chronic diseases should be interpreted with caution because our prevalence estimate is unable to deduce as to what extent are these conditions under control. Our results show that whiles the number of chronic diseases may be increasing, the actual number of people with chronic diseases is decreasing possibly because the number of people with multiple chronic diseases is on the rise.

Table 6-1 Crude prevalence of the twelve selected chronic diseases at beginning (1978), mid-point (2007) and end (2014)

Variables	**1978**	**2007**	**2014**
Arthritis	11.4	20.8	25.1
Asthma	2.4	8.5	8.5
Back problems	7.6	22.7	21.0
Breathing problems	2.5	6.9	5.7
Cancer	2.1	2.5	2.7
Diabetes/endocrine	2.7	7.2	9.3
Heart disease	3.4	6.7	7.4
High blood pressure	16.0	21.1	24.7
Intestinal or stomach ulcers	2.2	3.4	2.6
Migraine headaches	3.8	10.4	9.4
Depressive symptoms	7.7	7.6	6.8
Stroke	1.2	1.6	1.6

Chronic disease prevalence was 31.0% in 1978 and 26.7% in 2014. This represents a 4.3 percent decrease between1978–2014 (Table 6-2, Figure 6-1). Standardization to the population in 2014 showed the same decrease of 4.3 percent. The decrease in prevalence was significant for both women and men (Figure 6-1). Chronic diseases prevalence rose sharply in both men and

women between 1994 and 1998 but has since decreased and is on the decline (see Figure 6-1). This could possibly be explained by differences in sampling and changes in interview methods or as a result of a data artifact.

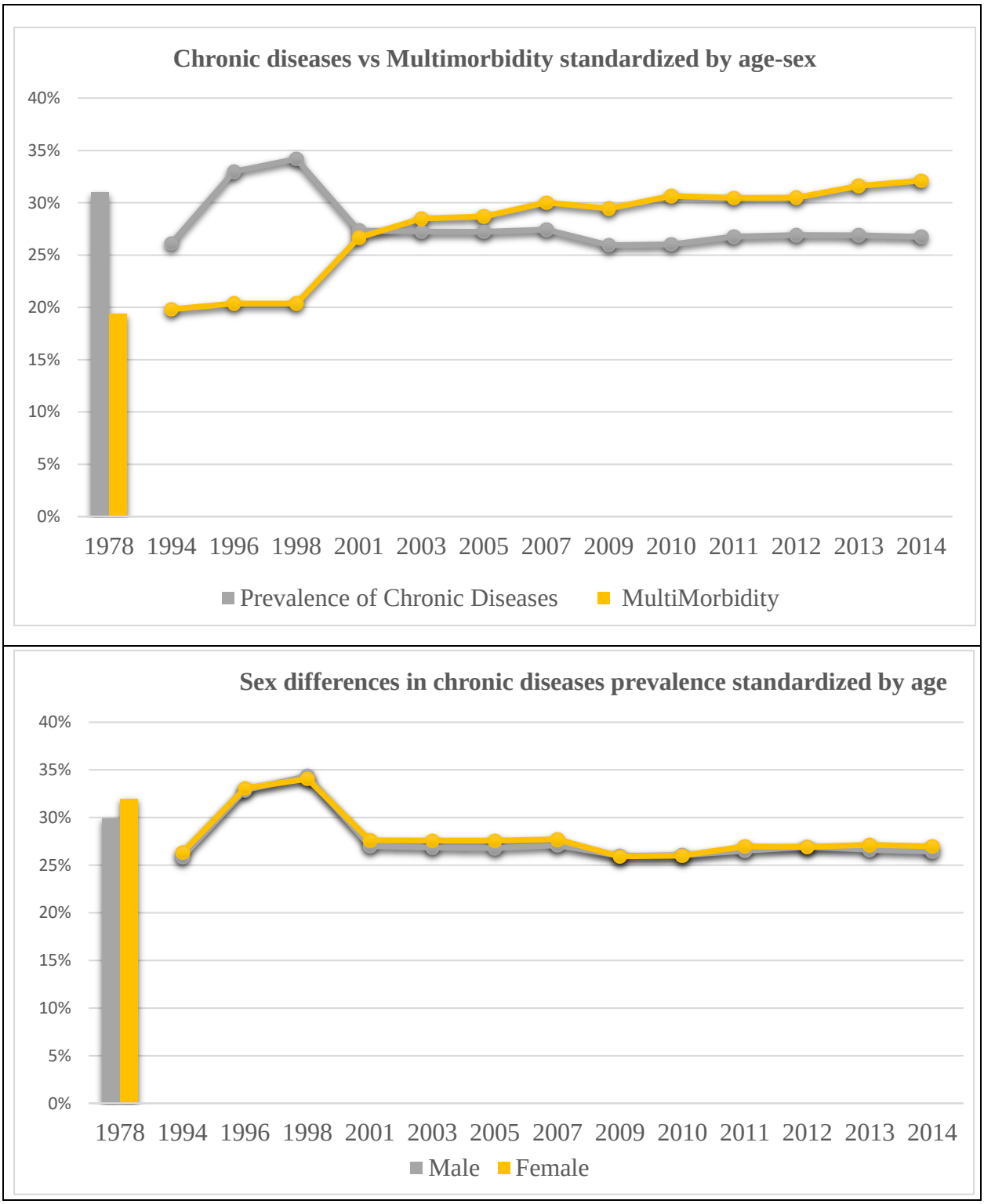
Table 6-2: Trends in the prevalence of self-reported chronic diseases in Canada, 1978–2014

	Crude percentage of persons with any chronic disease and crude percentage change in trends 1978-2014															
	1978		1994	1996	1998	2001	2003	2005	2007	2009	2010	2011	2012	2013	2014	**Crude change (% pts[2])**
Men and women																
12–24 yrs	24.8		20.1	48.9	52	23.3	23.2	23	23.6	21.4	22.1	21.8	21.7	21.6	21.2	-3.6
25–54 yrs	40.8		23.2	25	24.7	27.2	27.1	27.2	27.3	25.1	25.8	25.9	26.2	26.2	25.7	-15.1
55–64 yrs	34		30.3	30.1	30.2	29.8	30.1	30.2	30	29.4	29.1	30.2	30.6	29.9	29.8	-4.2
65–74 yrs	29.5		30.4	31.2	30.6	29.3	29	29.4	29.1	28.2	27.5	29.4	29.5	29	28.9	-0.6
75+ yrs	27.3		33.5	28.8	30.7	27.7	26.6	26	26	25.1	24.9	25.5	25.5	26.6	26.6	-0.7
Total	31		26.1	33	34.2	27.3	27.2	27.2	27.4	25.9	26	26.8	26.9	26.9	26.7	-4.3
Total std[1]	31		25.9	32	34.2	27.3	27.2	27.2	27.5	26	26.1	26.8	26.9	26.8	26.7	-4.3
Men																
12–24 yrs	23.3		18	47.3	50.6	21.4	21.6	21.4	21.7	19.9	20.9	20	20.1	19.7	19.7	-3.6
25–54 yrs	39.1		22	24.3	23.5	26.2	25.9	26.4	26.3	24.2	24.8	25.2	26	24.9	24.4	-14.7
55–64 yrs	34.3		32.1	30.6	31.8	30.5	30.6	30.3	30	30	29.9	30.3	30.9	30.6	30	-4.3
65–74 yrs	31		34.6	32.3	31.8	30.2	29.4	29.3	30.1	29.6	28.6	29.6	29.7	29.3	29.1	-1.9
75+ years	27.5		33.7	30.3	31.7	29.3	28.1	27.2	27.1	26.7	26.2	27.2	27.3	27.7	28.1	0.6
Total	30		25.8	32.9	34.3	27	26.9	26.8	27.1	26	26	26.5	26.9	26.6	26.4	-3.6

Total std[1]	30		25.5	31.9	34.4	27	26.8	26.8	27.1	25.9	26.1	26.5	26.8	26.5	26.3	-3.7
Women																
12–24 yrs	26.3		22.1	50.5	53.5	25.1	24.8	24.6	25.4	22.8	23.3	23.7	23.2	23.6	22.7	-3.6
25–54 yrs	42.5		24.2	25.7	25.7	28.1	28.2	26.4	28.3	25.8	26.6	26.5	26.3	27.2	26.8	-15.7
55–64 yrs	33.7		28.7	29.6	28.7	29.1	29.7	30.2	30	28.9	28.4	30.1	30.4	29.2	29.7	-4.0
65–74 yrs	28.1		27.2	30.3	29.6	28.5	28.7	29.5	28.3	27.1	26.6	29.3	29.3	28.8	29.1	1.0
75+ yrs	27.5		33.3	27.9	30.2	26.8	25.6	25.2	25.3	24	24	24.4	24.3	25.8	25.6	-1.9
Total	32		26.3	33.1	34.1	27.6	27.6	27.6	27.7	25.9	26	27	26.9	27.1	27	-5.0
Total Std[1]	31.9		26.3	32.2	34.1	27.6	27.6	27.6	27.8	26	26.1	27	27	27.2	27	-4.9

[1] Total prevalence for men and women, men, and women, standardized according to the age distribution in 2014
[2]Percentage points

Figure 6- 1 The prevalence of at least one chronic disease compared to multimorbidity in Canada, by sex over the period 1978–2014.



6.4.2 Trends in multimorbidity prevalence

Multimorbidity prevalence was 19.4% in 1978 and 32.1% in 2014. This represents a 12.7 percent increase for both sexes (Figure 6-2, Table 6-3). Standardization to the population in 2014 reduced the increase to 12.4 percent. The increase in prevalence was significant for both men and women (Figure 6-2, Table 6-3), and in the age groups over 75 years (Table 6-3). However, men had a higher percentage point increase (13.1 vs 11.9) than women (Table 6-3).

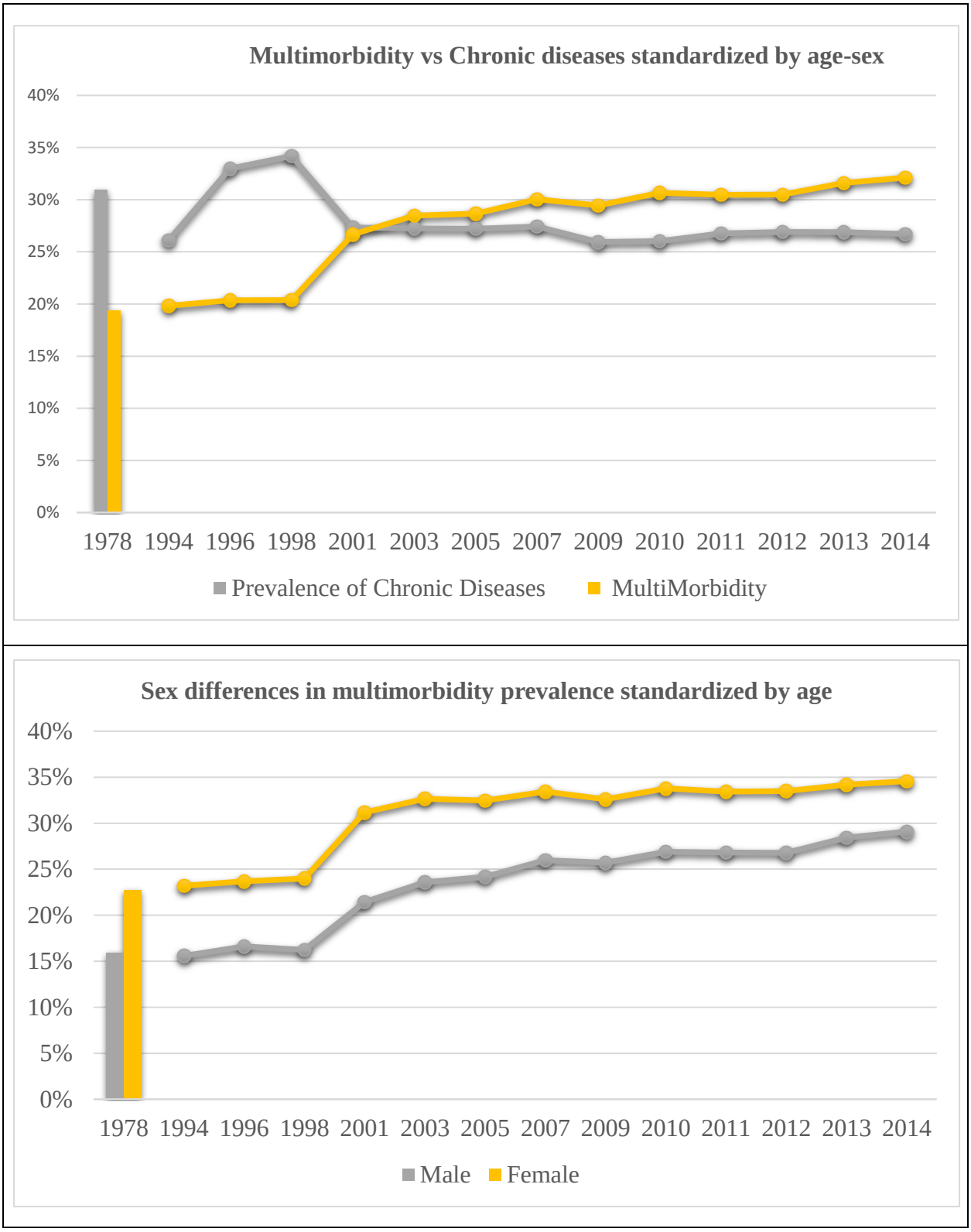
Table 6-3: Trends in the prevalence of self-reported multimorbidity in Canada, 1978–2014

	Crude percentage of persons with two or more diseases(multimorbidity) and crude percentage change in trends 1978-2014															
	1978		1994	1996	1998	2001	2003	2005	2007	2009	2010	2011	2012	2013	2014	**Crude change (% pts[2])**
Men and women																
12–24 yrs	4.4		8	8.5	8.1	9.4	8.3	8.2	8	5.7	6.5	5.9	6.3	5.9	5.9	1.5
25–54 yrs	20.1		11.4	8.5	11.8	17.8	15.5	15.8	15.6	13.1	14	12.9	12.5	13.3	13.3	-6.8
55–64 yrs	34.4		22.9	24.5	23.2	30.1	31.7	32.1	31.7	30.9	32.6	31.2	30.6	31.8	32.3	-2.1
65–74 yrs	47.2		35.8	38.9	41	44.2	47.4	46.6	46.8	46.8	47.4	46.5	45.8	45.6	45.7	-1.5
75+ yrs	52.7		44.1	51.1	50.9	54.2	58.1	58.7	59.3	60.5	60.9	60	59.3	58.4	58.2	5.5
Total	19.4		19.8	20.4	20.4	26.7	28.5	28.7	30	29.5	30.7	30.5	30.5	31.6	32.1	12.7
Total std[1]	19.2		19.4	20.5	19.9	26.4	28.1	28.3	29.7	29.1	30.2	30	29.9	31.1	31.6	12.4
Men																
12–24 yrs	3.4		5	8.1	7.3	6.1	5.5	5.7	5.5	4	4.5	4.1	4.5	4.5	4.3	0.9
25–54 yrs	15.7		8.6	8.7	8.8	13.4	12.5	12.6	12.5	10.6	11.7	10.5	9.8	10.7	10.8	-4.9
55–64 yrs	30.1		17.8	19.7	17.6	25	26.8	28.3	28.2	28.2	29.8	28.7	27.8	29.5	30.8	0.7
65–74 yrs	42.2		32.5	35	34.7	40.6	44	43.1	44.4	44	44.9	44.4	43.7	44.7	45.1	2.9
75+ yrs	47.5		40.3	46.4	48.4	49.5	53.5	54.7	56	57.1	57.9	56.2	55.5	55.4	55.2	7.7

Total	16		15.6	16.6	16.2	21.4	23.6	24.2	26	25.7	26.9	26.8	26.8	28.4	29.1	13.1
Total std[1]	15.7		15	16.6	15.8	21.1	23.2	23.8	25.6	25.4	26.5	26.4	26.3	28	28.6	12.9
Women																
12–24 yrs	5.5		10.8	8.9	8.8	12.5	11	10.6	10.5	7.4	8.5	7.7	8	7.4	7.6	2.1
25–54 yrs	24.4		13.7	14.1	14.3	21.7	18.3	18.7	18.2	15.2	15.9	15	14.8	15.3	15.4	-9.0
55–64 yrs	38.5		27.2	29	28.5	34.9	35.8	35.3	34.6	33.2	35	33.2	32.9	33.7	33.6	-4.9
65–74 yrs	51.8		38.3	42.2	45.9	47.3	50.2	49.6	48.8	49	49.5	48.3	47.4	46.4	46.2	-5.6
75+ yrs	56.6		46.2	54	52.4	57	60.8	61.2	61.4	62.7	62.8	62.5	62	60.5	60.2	3.6
Total	22.7		23.2	23.7	24	31.2	32.6	32.5	33.4	32.6	33.8	33.4	33.5	34.2	34.6	11.9
Total std[1]	22.6		22.8	23.9	23.5	30.9	32.3	32.1	33.1	32.1	33.3	33	32.8	33.6	34	11.4

[1] Total prevalence for men and women, men, and women, standardized according to the age distribution in 2014
[2]Percentage points

Figure 6- 2 The prevalence of multimorbidity compared to chronic diseases prevalence in Canada, by sex over the period 1978–2014.



6.4.3 Proportion of trends attributed to aging of the population

There are no overall differences in the proportion of chronic disease prevalence attributed to aging and other contributing factors. However, some sex differences exist with regards to effects of population aging and chronic disease prevalence. For men, there was a 2.7% lower level of reporting chronic diseases prevalence due to population aging compared to a 2.04% increase among women (Table 6-4). In other words, chronic disease prevalence due to population aging was more prominent in women compared to men. Overall, it is estimated that 2.4% of the respondents were more likely to report multimorbidity due to population aging. Women had a higher proportion of reporting multimorbidity (4.2%) as a result of population aging as compared to men (1.5%).

Table 6-4 Proportion of the trend in the prevalence of chronic diseases and multimorbidity attributed to aging of population, over the period 1978-2014

	Proportion of trend attributed to aging of the population[1]
	Health surveys
Any chronic disease	
Total population (12+ years)	0
Men	-2.70%
Women	2.04%
Multimorbidity	
Total population (12+ years)	2.36%
Men	1.53%
Women	4.20%

[1]Proportions represent an indication of the effect of aging of the population on chronic diseases and multimorbidity prevalence. Proportions were derived at by dividing the total crude change-total crude change standardized /total crude change (based on the data in Tables 6-2 and 6-3)

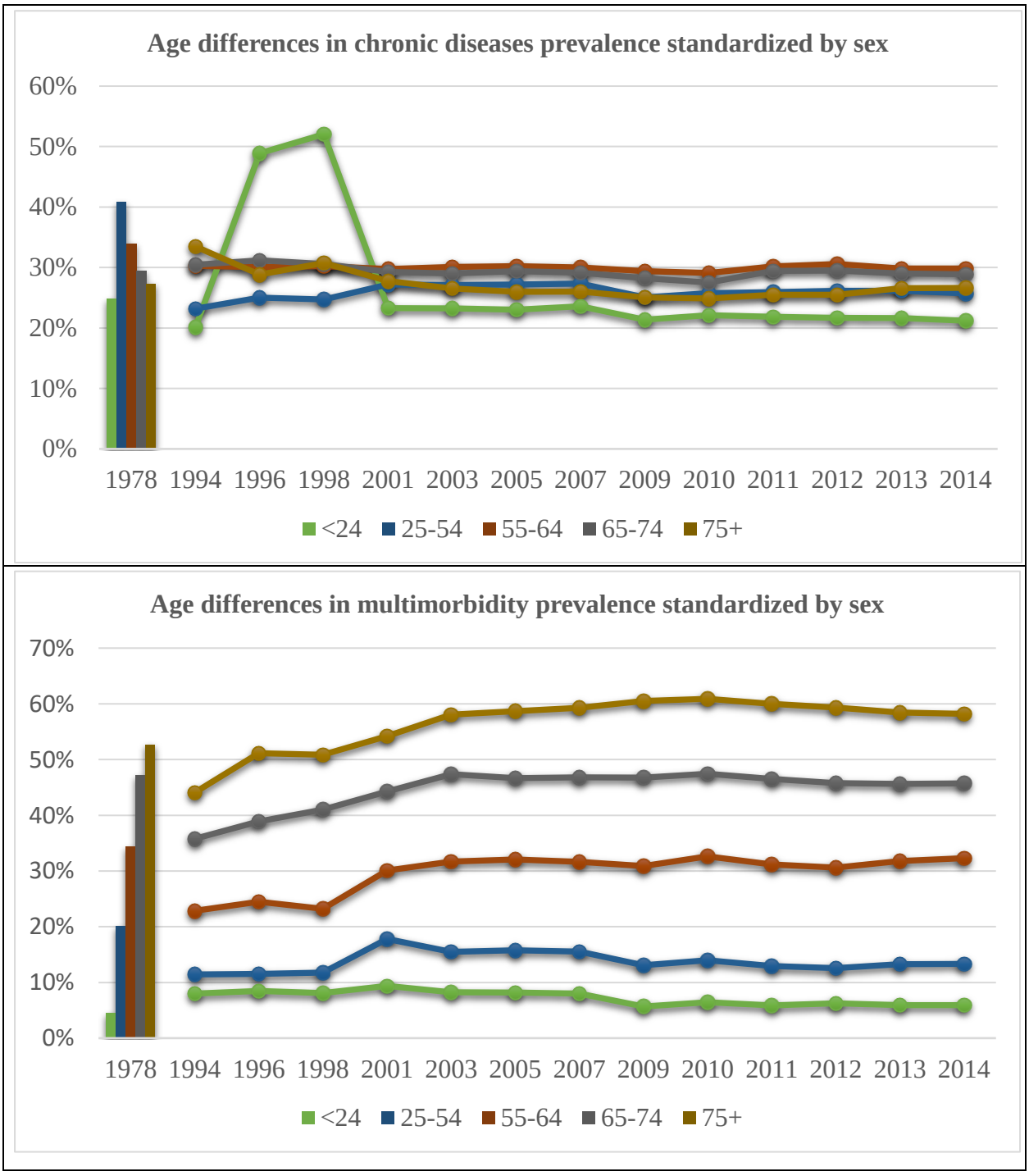
6.4.4 Age differences in the prevalence of chronic diseases and multimorbidity

The decrease in chronic diseases was more prominent among men and women in the age range “25–54 years” compared to those ≤24 years (younger cohorts), “55–64 years” (middle-aged), “65–74 years” (young-old) and “75+years” (older-old). In both men and women, chronic diseases increased sharply in the youngest age group (≤24 years) between 1994 to 1998, then reversed and went on a steady decline (Figure 6-3).The sharp rise in the prevalence of chronic diseases between 1994 to 1998 could possibly be due to a data artifact of some sort. The prevalence of chronic diseases decreased quite significantly during these 36 years, from 30% in 1978 to 26.4% in 2014 among men and from 32% to 27% among women. Though the decreasing

trend in chronic diseases in Canada was greater in women than in men, women were still more likely to report chronic disease compared to men.

Also, multimorbidity was more prevalent among the older-old group (75+years) compared to other age groups (Figure 6-3). Increasing multimorbidity was observed in men between 1978 to 2014 from as low of 16% in 1978 to a high as 29.1% in 2014, constituting a 13.1 percent increase. Women also reported a substantial increase in multimorbidity from 22.7% in 1978 to 34.6%, a figure of about 11.9 percentage increase. Overall, the increasing trends in the prevalence of multimorbidity in all age groups were more common in women than in men (Table 6-3).

Figure 6- 3 The prevalence of at least one chronic disease and multimorbidity among age groups in Canada, 1978–2014.

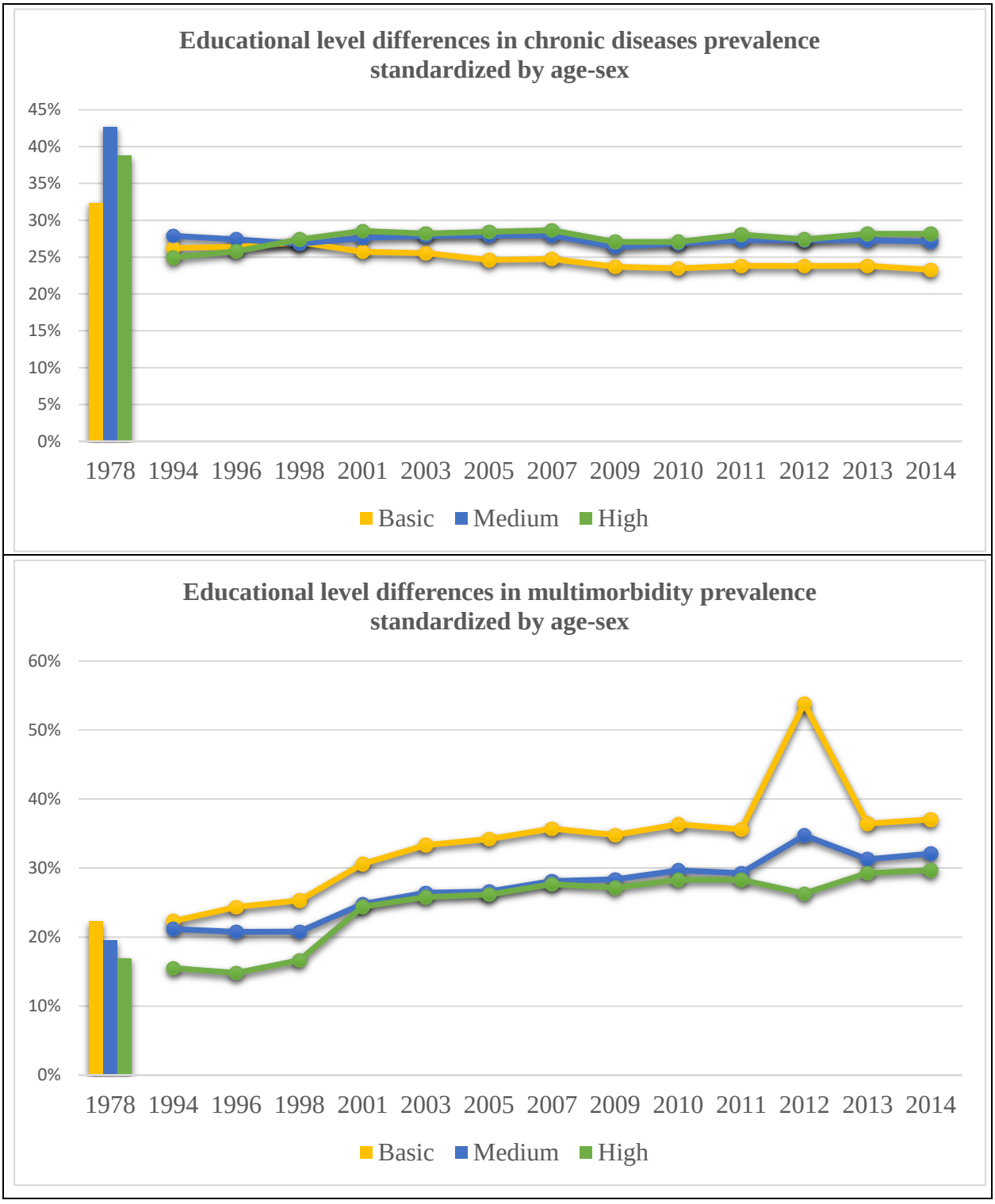


6.4.5 Educational level differences and the prevalence of chronic diseases and multimorbidity

As noted previously we categorized education into three levels, basic (less than secondary), medium (secondary education, some post-secondary and post-secondary education) and high (university degree and post-graduate education). We observed that in both men and women the decrease in chronic disease prevalence was more prominent in individuals with medium or high education compared to basic education. We also report that the differences in chronic disease prevalence among individuals in different educational groups were more pronounced in women than men. That is a proportional reduction of 9.5% in basic, 17% in medium and 14.4% in high educational levels among women, compared to 8.5% in basic, 13.9% in medium and 8.1% in high educational levels among men (data not shown). Even though the decreasing trends in chronic disease prevalence were observed in all educational groups, the gap between educational groups was less in 2014 compared to 1978 for both men and women. In 1978 the figures for chronic disease prevalence by education levels were 31.7% in basic, 39.9% in medium and 36.2% in high for men whilst for women these figures were 32.9%, 44.9%, and 42.7% respectively. Juxtaposing those figures to the 2014 figures for men of 23.2% for those with a basic education, 26% for those with a medium level of education and 28.1% for those with higher education levels, that of women's respective figures were, 23.4%, 27.9% and 28.3% (data not shown). Among all educational groups the trend in reporting at least one chronic disease has consistently declined over time (Figure 6-4).

When multimorbidity prevalence was stratified by levels of educational attainment, although multimorbidity was more pronounced among those with a basic education, we observed a consistent increase in the prevalence of multimorbidity across all the educational levels (Figure 6-4). In 1978, women with a basic education reported multimorbidity prevalence of 25.8% but this increased substantially to about 41.4% as of 2014, a 15.6 percentage point's increase as compared to an increase of 18.5% to 32% for men during the same period. Surprisingly, both men and women reported substantial increases in the prevalence of multimorbidity in 2012, 46.8% and 58.4% respectively. The substantial rise in multimorbidity recorded in 2012 among those with basic educational attainment cannot be explained although it could be a result of a data artifact. However, multimorbidity was less prominent among men and women with medium or high level of education compared to those with a basic level of education (data not shown).

Figure 6- 4 The prevalence of at least one chronic disease and multimorbidity according to level of education in Canada, 1978–2014.

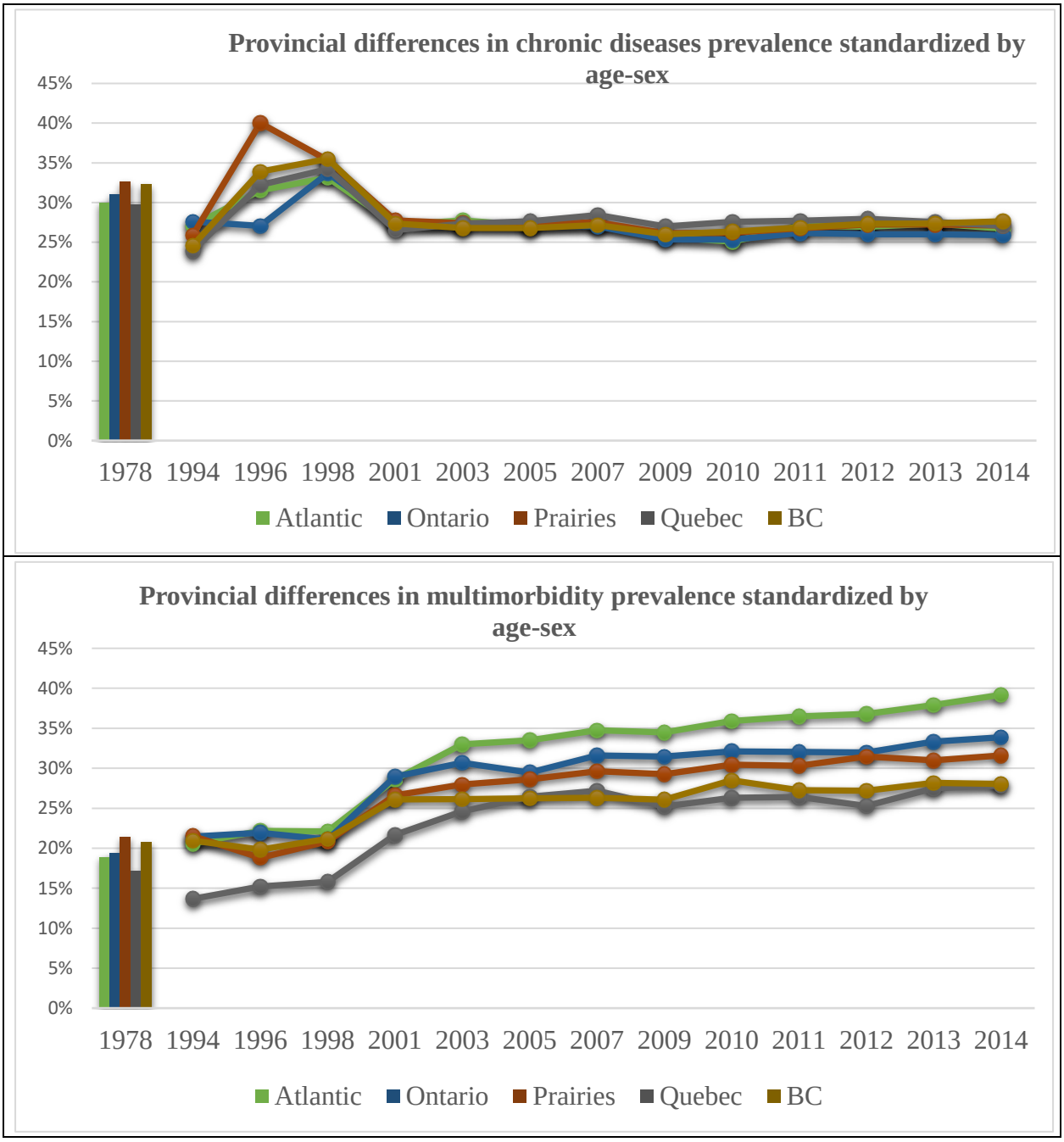


6.4.6 Provincial differences and the prevalence of chronic diseases and multimorbidity

A geographic or provincial difference in the prevalence of chronic disease at the population level also existed. Generally, the prevalence of chronic diseases across the 10 provinces has declined over time (Figure 6-5). On average, we observed a 4.2% reduction in the prevalence of chronic diseases across the country in 2014 compared to 1978. The Prairies, Ontario and British Columbia reported above average reductions in chronic disease prevalence. There was a sudden rise in chronic disease prevalence in all geographic areas between 1994 to 1998 but that decreased from 2001 and has since leveled off (Figure 6-5).

A significant increase was observed in the prevalence of multimorbidity across the geographic areas for both men and women in 1998 (Figure 6-5). Over the last 36 years, the increase was more prominent in the Atlantic and Ontario regions of the country compared to other geographic areas (data not shown). These regions reported the highest increase of multimorbidity prevalence of, 20.3% and 14.5% respectively. This compares to the lowest increase in multimorbidity prevalence of 7.4% found in British Columbia. Except for Atlantic Canada, men in all other regions of the country were more likely to report a higher level of multimorbidity (data not shown).

Figure 6- 5 The prevalence of at least one chronic disease and multimorbidity among province of residence in Canada, 1978–2014.



6.5 Discussion

It is interesting to note that, very few studies in Canada have assessed the national trends in the prevalence of chronic diseases and multimorbidity over time [22, 23]. Other studies concentrated on the different segments of the population or just a single province or a single survey [6, 7, 26]. A few studies focusing on trends in multimorbidity prevalence also existed at the international level [19, 38, 39]. One of such studies from the Netherlands by Uijen and van de Lisdonk, [38] using electronic primary care data reported a two-fold increase in the prevalence of multimorbidity in two decades (1985 to 2005).

Few studies have assessed general population level chronic diseases trends in the past. Even the few ones conducted usually assess a total trend without distinguishing between effects of aging population and other contributing factors [4, 5]. Trend studies of such nature are difficult to compare due to large differences in the diseases included, characteristics of the datasets, standardization for sex and age, and the country or period of study [20, 21]. That notwithstanding, a number of previous studies showed similar results to our study.

We found that the prevalence of chronic diseases saw a 4.3 percentage decrease between 1978 (31%) and 2014 (26.7%). We did not find any influence of aging on the overall prevalence of chronic diseases over time even though some sex differences exist. Our finding is in agreement with a similar trend analysis of self-reported data where a reported decrease in the prevalence of chronic diseases (individuals with single conditions) over ten years was observed [39]. However, the Public Health Agency of Canada using data from various health surveys between 2000/01 and 2011/12 reported a rise in the prevalence of some specific major chronic diseases such as cancer (+1.1%), ischemic heart disease (+1%), chronic obstructive pulmonary disease (+2.5%) and diabetes (+4.2%) [24]. On the other hand, the same report indicated that due to declining rates in smoking across all age groups, major chronic diseases such as cardiovascular diseases and COPD have witnessed a decline in both incidence and mortality rates. The age-standardized incidence rate for all four major chronic conditions saw a decrease within the study period [24]. This could possibly explain the decreasing trend observed in our study.

On the other hand, our findings show a rise in multimorbidity across Canada. We found that population aging only partly accounts for the reported rise in multimorbidity in Canada

between 1978–2014. Other factors including epidemiological, medical and societal developments or circumstances as well as increased knowledge of chronic diseases and health-seeking behaviors are responsible for a substantial part of this rising trend [19]. The above findings are in keeping with recent trend analysis in the Netherlands where the prevalence of chronic diseases and multimorbidity were assessed [19]. We also found that the percentage rise in multimorbidity prevalence was higher in men than women. This suggests that multimorbidity may affect men and women differently due to differences in risk behaviors [19, 23, 38].

In general, we found that multimorbidity prevalence (for 2+ conditions) rose from 19.4% in 1978 to 32.1% in 2014 but falls below the value of 42.6% multimorbidity prevalence reported in a recent Canadian study among adults (18+ years) [22]. However, our finding is higher than the overall estimate of 26.5% (for 2+ conditions) found by Feely et al [23] in a study conducted among 40+ years Canadians using Canadian surveillance data. Some researchers are of the view that studies that use more chronic diseases and conducted in a primary care setting tend to report higher prevalence estimates than that found in general population surveys [25]. This could be true in the sense that Roberts et al [26] used just one component (2011/12) of CCHS data and reported the Canadian national prevalence of multimorbidity to be 12.9% which is significantly lower than what we reported in 2014. Some are also of the opinion that the differences in estimates could partially be explained by the difference in age groups that are studied. For instance, whereas Roberts et al [26] used respondents 20+ years, we included people of 12+ years and that might explain the differences found. However, Gross et al [27] also suggest that such differences may as well be due to self-report bias in the chronic disease measurement.

We did not observe any rise in the prevalence of chronic diseases between males and females across the different age groups. This is in keeping with a previous Swedish study where the prevalence of cardiovascular diseases did not differ by age or sex over time [28]. However, we found the effect of the decrease in chronic diseases in Canada was greater among women than in men. The decrease in chronic disease prevalence in both men and women was more apparent in the age range of 25–44 years than any other age groups.

In agreement with other studies [29, 30, 43], multimorbidity among men and women was as high as 58.2% among the old-old age group compared to all other age groups. Multimorbidity in the old-old age group (75+years) was more prominent in females compared to males (60.2%

vs 55.2%) in 2014 which is in keeping with previous studies [28, 31, 43]. Fortin et al [25] in an earlier study suggest that the type of health conditions included in each multimorbidity study may affect men and women differently. Others are of the opinion that women's willingness to seek health care and share their conditions in self-reports could explain these sex differences in multimorbidity prevalence [32]. Our observation that multimorbidity increases with age is consistent with other studies [8, 23, 38, 43].

We found a consistent decline in the prevalence of chronic disease across the various educational levels over time. Although no increasing trend in chronic disease was observed, the decrease is more pronounced in people with medium or high levels of education compared to those with a basic education. This study reported a consistent increase (except for 2012) in the prevalence of multimorbidity between 1978 and 2014 at the various educational levels in both men and women. In addition, the rise in multimorbidity was more pronounced among people with a basic educational level compared to those with medium or high levels of education. This is consistent with previous studies in which lower education levels were statistically significantly more likely to have multiple morbidities compared to those with higher education levels [8, 28, 33].

Generally, our study did not observe a significant difference in the prevalence of chronic diseases (reporting at least one chronic disease) across the 10 provinces in both sexes. However, we observed an average decline of 4.3% in the prevalence of chronic diseases across the provinces as of 2014.

However, multimorbidity rose significantly across the provinces of Canada and more importantly between both sexes. With the exception of Quebec multimorbidity was more prevalent in eastern and central Canada (Atlantic and Ontario) compared to western Canada. Our study corroborated previous studies that reported higher chronic disease prevalence in Eastern and Atlantic Canada compared to the rest of the country [23, 34, 35]. We also observed that except for Atlantic Canada, men in all other provinces reported higher rates of multimorbidity than women which is consistent with one other Canadian study [23].

It is noteworthy to state that despite long-held perceptions that chronic diseases and multimorbidity are the preserve of the elderly (75+ years) this study revealed that might be entirely true. Our results are at odds with the findings of Smith and O'Dowd [36] who described

multimorbidity as a “normal state of affairs” for seniors (65+ years). This is because, despite the fact that multimorbidity was more prominent in the old-old age group, the phenomenon was also on the rise in other age groups (those <65 years). In this vein, Mercer et al [37] are of the view that research regarding early multimorbidity prevalence, prevention and intervention should be conducted across the life course in order to cater for people who are not necessarily older adults. They also argue this will offer younger people with chronic diseases and multimorbidity the opportunity to access appropriate care services that focus on multiple chronic conditions.

The decrease in chronic diseases and the increasing trend in multimorbidity found in this study brings into play a relationship between incidence and prevalence. For instance, if new cases of a disease are developing rapidly and those people are living longer, it is expected that the prevalence of the disease will rise and vice versa. The 2017 public health agency of Canada report suggests a declining annual incidence rate for major chronic diseases, including “diabetes”, “cancer”, “chronic respiratory diseases” (CRDs) and “cardiovascular diseases” (CVDs) [24]. This decrease in incidence is not inconsistent with increasing multimorbidity if the affected individuals are surviving longer. We attempted to deduce some of the possible factors that might have contributed to the contrasting trends found in our study.

First and foremost, the influence of several lifestyles and environmental risk factors on either the decrease in chronic diseases or increase multimorbidity in Canada is well established. Tobacco smoking which is related to most major chronic conditions in Canada is on the decline while at the same time sedentary lifestyles and physical inactivity which are known risk factors for those same chronic conditions are also on the increase [24]. For instance, the 2017 report of PHAC revealed a substantial number of children, youth and adults failed to meet the Canadian Physical Activity and Sedentary Behavior Guidelines [24]. This predisposes them to obesity which eventually leads to other chronic diseases such as cancers, type 2 diabetes, hypertension and CVD [24].

Second, improved case finding owing to advances in medical technology and better disease detection might lead to an increase in the proportion of diagnosed cases [16]. The average LE at birth and health-adjusted life expectancy (HALE) in Canada has been on the increase with a slight sex difference as women are expected to live longer than men [24]. Also,

improvement in chronic diseases treatment and associated risk factors could result in longer survival for those with such conditions and the possibility to live with them for a life-time.

Third, there has been an increase in health care utilization in Canada over the past few decades, especially among seniors. The use of health care facilities in Canada has also increased among middle-aged and older adults [40]. The fact that many Canadians visit medical professionals regularly, more and earlier, early disease detection is possible.

Fourth, people are becoming more health conscious and are taking control of their own health issues. This may have led to an increase in people's knowledge of, and, willingness to seek knowledge of chronic diseases in self-report surveys [41].

We could not confidently state how the above-mentioned factors contributed to the decline of chronic diseases and the rise in multimorbidity over the 36 years period in this study. Therefore, all our explanations are hypothetical and inconclusive since evidence for the association between these factors and the decrease in chronic diseases prevalence and multimorbidity rise may be incomplete.

6.5.1 Strengths and limitations of the study

The major strength of our current study is the use of large-scale nationally representative sample surveys of the Canadian population to produce both chronic diseases and multimorbidity prevalence estimates over a 36-year period. This will help enhance preventive efforts in our quest to reduce the rise in multimorbidity prevalence. The study has also highlighted the strides Canada has made in the fight against chronic diseases and related risk factors over the years.

Another strength of this study was its ability to establish that aging alone is not a sufficient factor for the development of chronic diseases and multimorbidity, but that other determinants also contributed to the decrease in chronic diseases and rise in multimorbidity. Also, chronic diseases and multimorbidity prevalence was estimated across the 10 provinces of the country, one of the few such studies to do so.

Overall, our study findings support earlier recommendations by other researchers regarding the adoption of a multifaceted approach that includes treatment of multiple chronic diseases and the targeting of socioeconomic and behavioral risk factors that could have broader

implications and effects on a number of health outcomes including quality of life, health care costs and mortality [26, 42, 43].

A major limitation of our study is the use of crude estimates to measure chronic disease and multimorbidity prevalence. Since we relied on self-reported responses it is possible that over-reporting or under-reporting may have occurred through such a crude measure. In addition, all the surveys used here did not include respondents living in nursing homes and in Canada's northern territories. It is possible to infer that seniors living in nursing homes are more likely to report a different disease pattern.

Furthermore, our study is limited by the number and type of chronic diseases considered. This is a limitation considering the fact that Fortin et al [25] found the prevalence of chronic diseases and multimorbidity is influenced by the number of chronic diseases included in each study. This was corroborated by Rapoport et al [6] and Cazale et al [42] who considered 22 diseases and 7 diseases respectively and reported significantly different results. We considered 12 chronic diseases, based on previous research [19] and of course we were limited by the availability of data collected in the studies we used for this analysis. Finally, there was 16 years gap between 1978 and 1994 for which there is no data.

6.6 Conclusion

We observed that both population aging and other circumstances are major determinants of the prevalence of chronic diseases and multimorbidity in Canada. Our study found that the prevalence of chronic diseases declined over the 36 years period. We also found that multimorbidity increased over time and with age. Females and those with basic level education reported significant increases in multimorbidity prevalence. Although no consistent pattern existed, our study found that high rates of multimorbidity tend to be reported in eastern and Atlantic Canada compared to western Canada. Considering that the number of people with one or more chronic diseases is projected to rise in the future, both the potential and real impact of chronic disease or multimorbidity prevalence will be underestimated if population aging alone is used as the benchmark for measuring their effect on the health care system.

Future projections of chronic diseases and multimorbidity prevalence should take into consideration other driving forces besides the changing age-sex population structure. Further

studies are recommended to better understand the potential role of other societal, behavioral, economic and health care factors in the rise of multimorbidity found in this study. From a clinical treatment perspective, our study reinforces the need to adopt a framework for treating the whole patient since traditional, single-disease treatment of chronic diseases is becoming increasingly outmoded in Canada.

6.7 References

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CHAPTER 7- CONCLUSION AND POLICY AND PROGRAM IMPLICATIONS

Aging populations are a source of concern to both developed and developing countries and have burdened most health care systems and economies globally. As in the case of other developed countries, the population of Canada is also aging. As of the last Canadian census, over 15% of the country's population was over 65 years compared to 7.6% reported in 1960 [1]. Seniors (65+years) outnumbered children (0–14 years) for the first time in the country's history as reported by the last census figures [1]. It is projected that the number of people aged 65+ years will continue to increase and will account for 20.1% of the entire Canadian population by 2024 [1]. Another projection is that seniors (65+ years) will constitute 25% of the Canadian population by the year 2036 with those 85+ years as the fastest growing cohort in the country [2]. An estimated 127% growth was reported among those 85+ years within two decades (between 1993 and 2013) in this age group [2]. It is also estimated that the Canadian population will record over 62,000 centenarians (100+ years) by the year 2063 [3].

Aging population comes with its associated problems of age-related chronic diseases. Globally, chronic diseases are the main cause of death and disability. An estimated 60% of all global deaths are attributable to chronic diseases and this is expected to increase to 73% by the year 2020 [4]. In Canada, an estimated 60% of the adult population has at least one chronic disease [5]. Cancer, diabetes and cardiovascular diseases have been reported as the commonly reported chronic diseases in the country [6].

Canada is faced with two major challenges of effective health care delivery and economic burden as a result of chronic diseases due to an aging population. The country's health care system was originally designed to treat acute diseases without major aging population concerns at the time. In the advent of the aging population, however, the health care system struggles to cater for its patients who are mostly seniors with complex ongoing chronic conditions. Also, with the rise of about (75-80%) in the prevalence of chronic diseases among Canadian seniors, health care cost is also on the increase [7]. A Canadian report revealed that the aging population has a modest effect on health cost of about (0.9% per annum) and that cost increase with increasing age [8].

The main focus of public health is on prevention, especially primary and secondary prevention. In that light, knowledge about early risk factor identification and promotion of healthy lifestyles are necessary in order to combat chronic diseases and compress morbidity.

Why study middle-aged and older adults and the greying tsunami? Globally, the number of people aged 60 years and over has witnessed a substantial increase. It is projected that between 2015 and 2030 those aged 60+ years will constitute 56 percent of the world's population with an increase of about 901 million in 2015 to 1.4 billion in 2030 and is expected to double to about 2.1 billion by 2050 [9]. The fastest growing age group of seniors is those aged 80+ years. Their number is estimated to increase from 125 million to about 434 million by the year 2050 [9]. Canada's population is also fast aging and as stated early, seniors outnumbered children for the first time in the country's history.

Although advances in medical, social, and economic sectors have led to an increase in life expectancy and subsequently an aging global population, it also comes with its own challenges. Social intervention programs such as social insurance and pension systems are challenged and overburdened by population aging. Other areas that are hardest hit by population aging include disease prevalence, incidence and patterns, trade, migration, economic growth and among others [10].

Therefore, aging research is crucial. There is the need to use current population-based aging studies to inform policy direction. Most countries still lack specific healthy aging programs and policies. Aging research, therefore, helps nations to adjust current policies as well as help those without current healthy aging policies, programs and interventions to recognize the possible challenge ahead [10]. Secondly, to plan for senior's population, accurate, consistent and timely data on global trends in population aging and age-related chronic diseases are necessary. Population aging and chronic disease trends are critical in measuring the current and future needs of seniors and can help set policy priorities that promote their well-being [9].

The strategies for compression of morbidity as espoused by James F. Fries guided this thesis. In his article on aging, natural death and the compression of morbidity, he suggested that early risk factor identification, promotion of health, social interaction and personal autonomy are important ingredients for the postponement of many phenomena associated with aging [11].

The primary goal of this thesis is to use nationally representative population-based survey datasets to contribute to our understanding of the interplay between population aging, chronic conditions, (both physical and mental health) and multimorbidity as well as help establish the distinctive risk factors and trends of chronic conditions among middle-aged and older adults in Canada. This may contribute to public health policy planning and decision-making process. Four separate but interlinked substantive thesis chapters highlighted the implications of population aging and chronic diseases and the need for age-friendly interventions in Canada.

7.1 Major Findings of This Thesis

In Chapter 3 of this thesis, we used systematic review and meta-analysis methods to assess the relationship between diabetes and depression and the potential for a reduction in depression if diabetes was reduced by a certain margin. Earlier empirical evidence suggests an association between diabetes and depression. However, most previous studies used cross-sectional designs to assess this relationship and thus limiting evidence of causality. In this current study, we aim to: (1) systematically examine the relationship between diabetes and the risk of developing depression using systematic review and meta-analysis in longitudinal cohort studies and (2) provide estimates of how much the incidence of depression in a population would be reduced if diabetes was reduced.

Medline/PubMed, EMBASE, PsycINFO, and Cochrane Library databases were searched for English-language published literature from January 1990 to December 2017. Longitudinal studies with criteria for depression and either self-report doctors' diagnoses or diagnostic blood test measurement of diabetes were assessed. Study results were synthesized using systematic review with meta-analysis of published literature. Publication bias, heterogeneity, and quality of the individual studies were examined. Pooled odds ratios were calculated using random effects models. The preventive impact of diabetes reduction on depression incidence was estimated using population attributable fractions (PAFs).

Twenty high-quality articles met inclusion criteria and were used in the analyses. The pooled odds ratio (OR) between diabetes and incident depression was 1.33 [95% confidence interval (CI) 1.18–1.51]. For the type of study design and method of diabetes diagnoses and their relationship with depression, the ORs were: prospective studies (OR 1.34, 95% CI 1.14–1.57),

retrospective studies (OR 1.30, 95% CI 1.05–1.62), self-reported diagnosis of diabetes (OR 1.37, 95% CI 1.17–1.60), and diagnostic blood test for diabetes (OR 1.25, 95% CI 1.04–1.52). We found that diabetes prevalence potentially accounted for over 9.5 million global cases of depression in our PAFs estimates. A 10–25% reduction in diabetes could potentially prevent 930,000–2.34 million depression cases worldwide.

Our systematic review provides fairly strong evidence to support the hypothesis that diabetes is a risk factor for the subsequent development of depression. At the same time, it shows the impact of risk factor reduction, study design, and diagnostic measurement of exposure. The review provides evidence of the need to adopt multisectoral approaches, programs, and policies aimed at combating diabetes and reducing its prevalence. Well-managed diabetes could weaken the association between the two fellow travelers of depression and diabetes.

Chapter 4 of this thesis identified shared risk factors for depression and diabetes. Although both cross-sectional and longitudinal studies have consistently reported the risk factors of depression and type 2 diabetes separately, few studies have investigated the two disorders together in the same national population sample. Literature is non-existent regarding shared risk factors of depression and diabetes at a national level in Canada. This study explores the shared risk factors of both incident depression and incident type 2 diabetes separately using data from a national longitudinal population-based survey study over a *10-year follow-up*. Sex differences in these shared risk factors of depression and diabetes are also assessed.

A secondary analysis of data from the Canadian National Population Health longitudinal Survey (NPHS) was conducted in this study. A subsample (N=4845) subjects of the entire sample of the NPHS was analyzed over a 10-year period. The modified Poisson regression was used to estimate the relative risk (RR) for the association between shared or unique risk factors and incident depression and diabetes. Stratified analyses by sex were also conducted to measure its moderating role in this relationship. We tested the goodness-of-fit for the various models.

We found the cumulative incidence rates of major depressive disorder and incident diabetes at the 10-year follow-up to be 4.1% and 10.1% respectively. We found hypertension, smoking status, physical inactivity, and overweight or obesity as the four shared risk factors between major depressive disorder and diabetes. In our stratified analysis, being underweight, having family stress, having a chronic disease and heart disease were all shared risk factors of

major depressive disorder in both sexes. Shared risk factors for incident diabetes in men and women were six namely; age, race or ethnicity, high blood pressure, smoking status, physical inactivity, and body mass index. Our results show risk factors of major depressive disorder and diabetes were not generally different in both sexes, except that their respective effects on major depressive disorder and diabetes incident were more prominent in females compared to males.

We conclude that both conditions can be potentially prevented through healthier lifestyles such as eating healthy, quitting or reducing smoking, having adequate rest, being physically active and having enough social support and that should be the focus of public depression and diabetes prevention programs. These programs should take into consideration sex differences in risk factors for the two conditions. Cigarette smoking specifically stood out as the significant risk factor for both conditions and merit specific policy interventions regarding smoking cessation, especially programs geared towards individuals with depression or diabetes.

In chapter 5, we conducted an analysis of the prevalence and modifiable risk factors for cognitive impairment between two nationally representative cohorts separated by an eighteen-year period. The prevalence of cognitive impairment or dementia is of public health concern globally especially in light of aging populations. Accurate estimates of this debilitating condition are needed for future public health policy planning. However, research regarding trends in the prevalence of cognitive impairment is scarce in the Canadian context. We investigated whether the prevalence of cognitive impairment changed over an 18-year period as well as measuring sex differences in modifiable risk factors for cognitive impairment between two-time separated cohorts.

We used baseline data of the Canadian Study of Health and Aging which was conducted between 1991 and 1992 to measure the prevalence of cognitive impairment and dementia among seniors (65+ years). The Modified Mini-Mental State Examination (3MS) was used for the screening test in the identification of cognitive impairment and dementia for the CSHA data. We compared the CSHA data with the Canadian Community Health Survey– Healthy Aging (cognition module) which also measured cognitive impairment using computer-assisted questionnaire and interviews conducted between 2008 and 2009. The community sample of 9008 respondents in the CSHA sample and a sub-sample of 13,306 respondents (65+ years) in the CCHS– HA sample were analyzed. Final subsamples of (N=8504) for the CSHA sample and

(N=7764) for CCHS– HA sample were used for analysis. In the first phase of our data analysis, prevalence estimates were calculated using age–sex standardization to the 2001 population census of Canada to generate proportions and confidence intervals for this study. In the second phase of the analysis, logistic regression analyses were performed between predictor variables and the outcome. Stratified analyses by sex were also conducted between predictor variables and the outcome.

The CSHA age and sex-specific estimates of the prevalence of cognitive impairment among respondents aged 65 years or older standardized to the 2001 Canadian population census was 15.5% in 1991. However, in the CCHS– HA sample in 2009, it shows that 10.8% of the population reported cognitive impairment, a 4.7% reduction [15.5 % (CI=14.8–16.3), CSHA *vs* 10.8 % (CI=10.1–11.5), CCHS– HA]. Whereas men had a higher prevalence of cognitive impairment in CSHA study, women had a higher prevalence of cognitive impairment in CCHS–HA (with a prevalence of 16.0% in 1991 for men *vs* 11.6% for women in 2009). In the multivariate analyses, risk factors such as age, poor self-rated health, stroke, Parkinson disease and hearing problems were common to both cohorts. Also, reported protective factors were female sex, race, an area of residence, high blood pressure, heart disease, and educational level. Sex differences in modifiable risk factors were also recorded.

Consistent with two recent European studies, this study provides evidence of a potential reduction in the prevalence of cognitive impairment despite population aging in Canada. It reinforces the suggestion that although the increased prevalence of cognitive impairment could have been influenced by many factors such as stroke management, increased vascular incidents and diabetes prevalence, the decrease prevalence recorded in our study may be as a result of improvement in the prevention and treatment of vascular morbidity as well as higher educational attainment or a general reduction in chronic diseases. Our results provide evidence regarding how different experiences shared by successive generations predisposes them to different patterns of disease risk in these generations.

Finally, chapter 6 of this thesis explored trends in the prevalence of selected chronic diseases and multimorbidity in Canada as well as estimated the influence of other contributing factors on chronic disease prevalence and multimorbidity aside from population aging. The prevalence of chronic diseases and multimorbidity (two or more diseases) are on a steady rise in

most western societies owing to an increasing aging population and life expectancy. In the Canadian context, there is a lack of studies on trends in the prevalence of chronic diseases that distinguished between effects of population aging and other factors. We aim to (1) describe the trends in the prevalence of chronic diseases and multimorbidity in Canadians between 1978 to 2014; (2) assess the contribution of both population aging and other associated factors in chronic diseases and multimorbidity prevalence and trends in Canada.

Data for this analysis were from cross-sectional studies, using three Canadian data sources: 1) Canada Health Survey of a nationally representative sample in 1978, and 2) Canadian National Population Health Survey, cross-sectional surveys of 1994/1995-1998/1999 and Canadian Community Health Survey between 2000/2001-2013/2014. Age-sex standardization was assessed in order to estimate chronic diseases and multimorbidity trends and prevalence rates over time. As cross-sectional surveys, with slightly different diagnostic criteria used over the years, the level of evidence generated is essentially descriptive.

Chronic diseases prevalence decreased from 31.0% to 26.7% between 1978 to 2014. This represents a 4.3 percentage point's decrease. Standardization to the population in 2014 showed the same decrease of 4.3 percentage points. The decrease in prevalence was significant for both women, and men (4.9 *vs* 3.7). In contrast, multimorbidity prevalence increased from 19.4% to 32.1% between 1978 to 2014. This represents a 12.7 percentage point's increase for both sexes. Standardization to the population in 2014 reduced the increase to 12.4 percentage points. The increase in multimorbidity prevalence was significant for both men and women, and in the age groups over 75+ years. However, men had a higher percentage point increase (13.1 *vs* 11.9) than women. About 2.4% of the population's multimorbidity is likely due to aging. Aging population effects of multimorbidity were more pronounced in women than men (4.4% *vs*1.6%).

Our study found that the prevalence of chronic diseases decreased over time while multimorbidity increased in Canada between the period 1978–2014. We conclude that population aging partly accounts for the rise in multimorbidity we found in this study. Which means that increased survival after multimorbidity diagnosis owing to effective treatment of chronic diseases, early diagnosing of chronic diseases, and health-seeking behaviors are responsible for the larger part of the rise.

7.2 Policy Implications and Future Research

Our systematic review showed a significant association between diabetes and depression. This was also confirmed in chapter 4 where shared risk factors of the two chronic conditions were longitudinally assessed. The results of the systematic review and the longitudinal studies strengthened the importance of targeting general risk behaviors that are not specific to a particular disease but in fact are implicated in the genesis of a range of chronic diseases. Early population-level risk factor identification strategies are critical in chronic disease prevention and should be the focus of most public health prevention policies and programs. Also, in Canada where diabetes is currently one of the fastest growing chronic diseases, decreasing its prevalence and incidence should be the target of public health prevention and promotion interventions since its reduction may also lead to the prevention of other chronic diseases such as depression.

Given that research regarding prevalence and incidence of cognitive impairment or dementia are mixed in Canada, this thesis provides some evidence that a reduction in the prevalence of cognitive impairment in the context of an aging population may be occurring in Canada. It also suggests that cohort effect exists in the prevalence of cognitive impairment where latter born Canadians were healthier than earlier born ones. The thesis also highlighted that risk factors for cognitive impairment differ by sex and change over time.

We reported divergent findings on chronic diseases and multimorbidity prevalence in Canada. Whereas chronic diseases are on the decline, multimorbidity, on the other hand, is on the rise. Meaning that the number of people with chronic diseases might not necessarily have increased but rather the number of people with multiple chronic diseases is increasing. This thesis also showed that population aging alone is not responsible for the rise in multimorbidity. Medical and societal developments or circumstances such as increased knowledge of chronic diseases and health-seeking behaviors are responsible for a substantial part of this rising trend in multimorbidity.

This thesis highlighted three major perspectives on prevention strategies and implications. Firstly, from a population health and public health prevention point of view targeting general risk behaviors that are not specific to a particular disease but in fact are implicated in the genesis of a range of chronic diseases is of paramount importance. Findings in chapter three require a holistic approach to better treatment and control of diabetes and its effects

such as depression. Chapter four highlights and recommends generic treatment of chronic diseases. Findings in chapter five show that cognitive impairment might not necessarily be on the rise, but Canada needs to reinforce its current efforts at controlling some of the risk factors for dementia such as diabetes, cardiovascular diseases, heart disease, improvement in educational attainment and among others. Our research finding in chapter six recommends a comprehensive approach to health promotion and prevention since single disease prevention strategies are no longer effective. Secondly, from a clinical treatment perspective, this thesis reinforces the need to adopt a framework for treating the whole patient since traditional, single disease-centric approaches are increasingly less inappropriate. Finally, from a research perspective, future epidemiological studies should be more focused on cognitive impairment or dementia, diabetes and mental health illness and the need to employ longitudinal study designs to help unearth primary risk factors as well trends in incidence over time in Canada.

Overall, aside from the perspectives highlighted above this thesis recommends the following specific major modifiable risk factors prevention strategies for the various chronic diseases we found.

First and foremost, we wish to state that while Canada has made significant progress in the fight against tobacco smoking (both primary and secondary smoking), there is still the need to intensify public education and awareness campaigns to further reduce tobacco smoking.

Secondly, we found that physical inactivity was linked to both depression and diabetes. The 2017 public health agency Canada report also revealed a substantial percentage of Canadian children, youth and adults are not meeting the Canadian Physical Activity Guidelines. We recommend the effective implementation of physical activity programs to help people lose weight.

In addition, sedentary lifestyles leading to overweight or obesity were associated with most chronic diseases. The 2017 public health agency Canada also reported how many Canadians failed to meet the Canadian Sedentary Behaviour Guidelines resulting in a rise in obesity. We recommend the adoption of healthy living initiatives such as subsidizing vegetables and fruits to make them more affordable to Canadians, intensifying campaigns on food marketing and enactment of a legislative instrument to increase taxes on sugary drinks in order to reduce consumption.

To sum up, if multifactorial intervention strategies are adopted including regular physical exercise, healthy diet, and reduction in tobacco smoking coupled with a decrease in risk factors for vascular diseases, psychosocial stress and major depressive disorder, we may be preventing cognitive impairment or dementia at the same time.

7.3 Conclusion

The four major take-home messages from this research include the following:

1) Diabetes is a significant causal factor in the development of future depression and that the incidence of depression could be significantly reduced if diabetes prevalence is reduced by a certain margin.

2) Risk factors such as hypertension, smoking status, physical inactivity, and overweight or obesity were found to be the four shared risk factors of major depressive disorder and diabetes and that the two diseases can be prevented through the adoption of healthier lifestyles.

3) The prevalence of cognitive impairment may be on the decline despite an aging population in Canada with sex differences in the etiologies of modifiable risk factors of cognitive impairment and that these risk factors change over time.

4) Chronic diseases are on the decline whilst multimorbidity is on the rise and that population aging only partly explains the rise in multimorbidity. Other factors are critical in multimorbidity prevalence.

The concluding public health message is that early identification of risk factors of chronic diseases and promotion of healthier lifestyle either early in life or during middle and old age will help compress morbidity and prolong life even though we are mortal.

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