Mortality among the Canadian population with multimorbidity: a retrospective cohort study

by

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Abstract

The association between multimorbidity and mortality was well established based on the previous studies. However, there is limited evidence of excess mortality in people with multimorbidity among the Canadian population, and a study with a larger sample size is recommended. Furthermore, it has been recommended to examine multimorbidity mortality among individuals under the age of 65, as some research demonstrated that it has become a serious issue for the middle-aged population as well. Therefore, this thesis examined the association between multimorbidity and mortality based on the linked database of CCHS (Canadian Community Health Survey)-CVSD (Canadian Vital Statistics Death Database) which included a study sample representative of the general population of Canada. The results of the study suggest that people with multimorbidity had a significant lower cumulative survival probability in comparison to those without multimorbidity during the 14-year follow up period, after adjusting for all confounding effects. The effects of multimorbidity on mortality increased from the oldest (65 years old and above) to the youngest age group (35 to 49 years old). Additionally, when the interactions between different chronic diseases were considered, it was found that subjects with COPD and without diabetes had a significantly higher risk of death in comparison to those without COPD and diabetes. This risk was further increased in subjects with both COPD and diabetes. In summary, our study results contributed to the body of knowledge showing multimorbidity was associated with excess mortality and it also provided evidence describing the joint effects of comorbidity on mortality in the middle-aged and senior Canadian population. Further studies focusing on investigating

multimorbidity and mortality in the middle-aged Canadian population, as well as exploring other potential comorbidities associated with excess mortality, are necessary to the management of multimorbidity. More public health programs should be initiated to prevent chronic diseases and multimorbidity, which in turn, would save lives, improve quality of life, and save healthcare dollars.

Preface

This thesis is an original work by Xiang Xiao. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Health Research Ethics Board (Project: "The prevalence and determinants of multimorbidity and the effect of multimorbidity on mortality in the Canadian population"; No: Pro00100947, 05/10/2020).

Versions of Chapters 3 are being prepared for publication in peer-reviewed journals. X. Xiang was responsible for study design, data analysis, manuscript writing, and manuscript revision for the studies included in this thesis. A. Senthilselvan provided guidance to the study design, data analysis, manuscript writing, preparation for submission, and manuscript revision. J. Beach contributed to the manuscript revision.

Dedication

The work presented here is dedicated to my family members for the overwhelming support they provided during my graduate study journey.

I would like to acknowledge the overwhelming support of my father. Without him, I would not be in the position where I am today.

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List of Abbreviations

BMI	Body mass index
BP	Blood Pressure
CT	Computerized tomography
COPD	Chronic Obstructive Pulmonary Disease
CI	Confidence interval
CCHS	Canadian Community Health Survey
CVSD	Canadian Vital Statistics Death Database
DALYs	Disability-adjusted life year
EUROSCOP	European Respiratory Society Study on Chronic Obstructive Pulmonary Disease
FEV_1	Forced expiratory volume in 1 second
ER	Emergency room
HR	Hazard ratio
HBP	High Blood Pressure
ICSs	Inhaled corticosteroids
ISOLDE	Inhaled Steroids in Obstructive Lung Disease
IL-6	Interleukin-6
GBD	Global Burden of Diseases, Injuries, and Risk Factors Study
LHS	Lung Health Study
MSHA	Manitoba Study of Health and Ageing
MeSH	Medical Subject Headings
NICE	National Institute for Health and Care Excellence

OR	Odds ratio
OLIN	Airway obstruction in North Sweden
P	P-value
RDC	Research Data Center
RA	Rheumatoid Arthritis
SES	Socio-economic status
TORCH	Towards a Revolution in COPD Health
UK	United Kingdom of Great Britain and Northern Island
US	United States of America
WHO	World Health Organization

Chapter 1
Introduction

1.1. Background of the problem

Multimorbidity, defined as one person having two or more chronic diseases concurrently, has been a rising public health issue in recent years in developed and developing countries.[1,2] Many studies have shown that multimorbidity is associated with increased hospitalization, the need for health care resources, and health care costs.[3,4] Furthermore, multimorbidity was found to be associated with excess mortality,[5] and several factors have been shown to modify the effect of multimorbidity on mortality.[6] For example, a study based on the UK biobank found that being physically active lowered the risk of all-cause mortality in people with multimorbidity compared to being inactive.[7] Additionally, older adults with multimorbidity were found to have an elevated risk of death.[8] However, there has been a debate about whether the middle-aged population, rather than the elderly, is more likely to die after developing multimorbidity.[9]

Evidence showed that there was an additive effect associated with specific comorbidity combinations in patients with multimorbidity, which was related with a higher risk of all-cause death than the presence of only one condition.[10] For instance, patients with COPD and diabetes had a 50% increased risk of death in comparison to COPD patients without diabetes.[11] While the underlying biological mechanism is still unknown, several hypotheses have been proposed in studies on commodities.[12] As a result, comorbidity has been increasingly examined and regarded as one of the determinants of multimorbidity.

1.2 Study objectives

The primary study objective of this thesis is to examine the overall and age-group specific effect of multimorbidity on mortality in the middle-aged and older Canadian populations. The secondary objective of this thesis is to examine the overall and age-group specific effect of specific chronic disease combinations on morality in the middle-aged and older Canadian populations.

1.3 Thesis submitted for partial fulfillment of MSc

The thesis follows the format of a paper-based thesis. The thesis begins with a review of the literature on multimorbidity, the association of multimorbidity with mortality, and the risk factors for multimorbidity as well as comorbidity (Chapter 2). The study results are presented in Chapter 3, which addressed the two objectives outlined in Section 1.2. The final chapter (Chapter 4) includes a summary of the findings in the study, limitations, and the study conclusions.

Chapter 2 includes a literature review of multimorbidity in general with a focus on the association between multimorbidity and mortality. The review begins with the definition and burden of multimorbidity, the epidemiology of multimorbidity, disease combinations in multimorbidity, and the biological mechanism of multimorbidity. This is followed by a review of the effect of multimorbidity on mortality, potential confounders for the association between multimorbidity and mortality, associations between the nine chronic diseases that were used to define multimorbidity and mortality, and associations between combinations of specific chronic diseases and mortality. Finally, the review is concluded with a summary and the rationale for the proposed objectives in the thesis.

Chapter 3 provides the results of the study, which was based on data obtained from

linking CCHS Annual Components (2.1, 3.1, 2007-2014) with the Canadian Vital Statistics Death Database (CVSD) 2003-2017. In the first part of Chapter 3, results from the study examining the association between multimorbidity and mortality in middle-aged and older Canadians (objective 1) are provided. In the second part of Chapter 3, results from the study examining the effect of the nine chronic diseases, which were used to define multimorbidity, on mortality (objective 2) are provided. The specific interactions between different chronic diseases were also reported in the second part of Chapter 3.

Chapter 4 provides a summary and discussion of the findings from the study. Finally, the thesis concluded with a description of the limitations and strength of the study, and future recommendations for research.

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Chapter 2

Literature Review

2.1 Methods

Chapter 2 includes the literature review of epidemiology of multimorbidity and the effect of multimorbidity on mortality. The first part of the review consists of definitions, burden, and epidemiology of multimorbidity, common disease patterns and combinations and biological mechanisms, and management of multimorbidity. The literature review was conducted using PubMed, literature databases. Only articles, abstracts and reports written in English were considered for the literature review.

2.2 Definition of multimorbidity

The concept of multimorbidity was first brought up by German researchers.[1] However, there was continued confusion between comorbidity and multimorbidity, and the two terms were often used interchangeably in researches articles.[1] The creation of a MeSH in January 2018 which distinguished comorbidity from multimorbidity provided a clear guidance to the researchers.[2] Despite two terms focused on one person having several chronic diseases concurrently, the emphasis of comorbidity is on the presence of one or more other chronic diseases, in addition to the index chronic disease whereas there is no index chronic disease in multimorbidity and none of the chronic diseases is given priority over the others.[1]

Although a distinction between comorbidity and multimorbidity has been made, there is still a lack of consensus on the definition of multimorbidity.[3] The definition of multimorbidity has varied across studies including outcomes of interest, number of chronic diseases considered and disease severity.[4] The heterogeneity in the definition of

multimorbidity between studies has made the comparison and interpretation of the reported prevalence difficult. A recent systematic review found that the diverse perspectives (e.g., epidemiology, primary care, or clinical practice) contributed to the inconsistency of the multimorbidity definition.[5] From an epidemiological perspective, multimorbidity was described as "*The co-occurrence of two or more chronic medical conditions in one person*" according to the World Health Organization's 2015 global report on ageing and health.[6] In contrast, Willesden and colleagues defined multimorbidity from a clinical perspective. In order to classify and define multimorbidity, they suggested that multiple factors such as the effect of disease and its severity should be incorporated into the definition.[4] Lastly, in the context of primary care, Le Reste and colleagues defined multimorbidity as "*any combination of chronic disease with at least one other disease (acute or chronic) or biophysical factor (associated or not) or somatic risk*".[7]

Even though there is great heterogeneity in definitions, the co-occurrence of two or more chronic medical conditions in one person was defined as multimorbidity by the World Health Organization. The WHO definition of multimorbidity has been broadly accepted and used widely. A recent systematic review by Johnson and colleagues suggested that definitions of multimorbidity should be carefully chosen according to the research outcomes and the target population. They also emphasized that the cut off of the number of diseases should be stated explicitly and consistent with other studies.[8]

2.3 Burden of multimorbidity

Multimorbidity has been a rising public health concern over the past twenty years in the developed and developing countries.[9, 10] The growing number of people with multimorbidity has posed a significant social, health and economic burden on several

levels.[3,11,12] As the prevalence of multimorbidity increases substantially with age, it has posed a great health burden on older adults and resulted in lower quality of life, and a greater risk of mortality or disability in older adults.[13-15] Apart from the impact of multimorbidity on older adults, researchers have also shown that it has an adverse influence on the working population including lower work productivity, and increased absenteeism.[16,17] Furthermore, the growing prevalence of multimorbidity has led to increasing healthcare costs for people with multimorbidity.[18] A retrospective cohort study of older adults aged 66 years and above with diabetes in Ontario, Canada reported that there was a significant increase in average cost per patient from $1,275 (adjusted for 2010 dollars) for those without comorbid conditions to $7,318 (adjusted for 2010 dollars) for those with three or more chronic diseases.[19]

In addition to the burden of multimorbidity at the individual level, it has increased the pressure on health care systems.[20] There is a growing need for healthcare utilization for people with more than one chronic disease, including greater outpatient visits and hospitalizations.[21,19] In a study conducted on older adults aged 65 years and above in Switzerland, there was an increase of approximately four fold in consultations per year compared to those without multimorbidity.[22] A cross-sectional survey on adults aged 18 years and above in Alberta, Canada reported that people with multimorbidity had twice the odds of hospitalization compared to those without multimorbidity.[23] Moreover, the results also showed that people with five or more chronic conditions had three times the odds of hospitalization compared to those free of multimorbidity.

2.4 Epidemiology of Multimorbidity

The prevalence of multimorbidity has increased over recent years in developed

countries.[24,25] Recent studies have also reported that the prevalence of multimorbidity is increasing in low- and middle-income countries and is getting closer to that reported in developed countries.[9,26,27] These changes indicate that multimorbidity is becoming a public health issue globally.[27] Due to variations in study designs, study populations and definitions of multimorbidity, the reported prevalence of multimorbidity has varied widely between countries. Multimorbidity is more likely to be prevalent in older adults.[25,28] The prevalence of multimorbidity varied from 14.0% among those 12 years and older to 81.3% among those 60 years and older.[29,30] Furthermore, several studies have examined the prevalence of multimobidities in different countries and found an S-shaped pattern in prevalence as people get older. The prevalence of multimorbidity remained low, and nearly constant before 40 years of age followed by a sharp increase from 40 years old to 70 years old and levelling off around the ages of 70.[31-33]

Sex is an important factor associated with multimorbidity. The results of multiple studies investigating sex differences showed that multimorbidity was more prevalent in females than in males.[34,35,32] However, in contrast, some studies have reported that there was no significant difference in the prevalence of multimorbidity between males and females.[36,37,31] While the reasons for sex disparities in the prevalence of multimorbidity are unknown, one of the hypotheses, known as the “male-female health-survival paradox”, suggests that the greater prevalence of multimorbidity in females is due to the longer survival of females compared to males.[38] A recent study of the Scottish population reported that the greater prevalence in women was the result of the greater frequency of physical and mental disease problems in females compared to males.[39]

In Canada, an increase in the prevalence of multimorbidity has been observed over

recent years, similar to what has been reported in other developed countries.[40,41] The prevalence of multimorbidity was 14.0% in subjects aged 12 years and older in a study using the data from CCHS 2013/2014.[29] Another Canadian study examining sociodemographic factors associated with multimorbidity reported that the prevalence of multimorbidity was greater in those of female sex, and in subjects with lower income and education.[42]

2.5 Common disease patterns and combinations in multimorbidity

The WHO definition of multimorbidity as having at least two chronic diseases is commonly used by researchers. However, some chronic diseases trend to cluster together rather than occurring independently.[43] Several articles have examined multimorbidity patterns, or combinations of chronic diseases in multimorbidity, [44-46] while standard criteria to determine multimorbidity patterns have not yet been established. Based on Schellevis and colleagues' statements, multimorbidity could be classified according to the relationship between individual chronic disease conditions, including concurrent, cluster, casual, and complicated comorbidity.[47]

A recent systematic review has shown that there are three main multimorbidity patterns: (i) cardiovascular and metabolic disorders; (ii) mental health related problems; and (iii) musculoskeletal disorders.[5] The category "cardiovascular and metabolic disorders" was found to be one of the prevalent multimorbidity patterns in females and males aged 65 year and older in another study.[48] Furthermore, Sinnige and colleagues found similar results suggesting that depression was the most common condition found in clustered combination among 165 combinations of comorbidity based on European and North American populations.[49] People with mental health problems are likely to have other conditions which could exacerbate or precipitate chronic illness.[50] For example, a diagnoses of chronic

obstructive pulmonary disease (COPD) has been associated with a greater likelihood of having mental health disorders.[51,52] However, due to the complexity of the relationship between chronic disease and various types of co-occurrence of chronic conditions, multimorbidity patterns are not well defined. There is no agreement among researchers on the third most common multimorbidity pattern. Some researchers concluded that the third most common multimorbidity pattern is musculoskeletal disorders.[53,54] However, others argued that neuropsychiatric disorders are the third most common multimorbidity pattern.[48]

Although general patterns of multimorbidity have been examined and reported by a number of researchers, the effect of specific combinations of chronic diseases cannot be ignored. A study of patients in the United States has shown that certain combinations of chronic diseases had a higher risk of decline in physical function than other combinations.[55] For example, people with chronic respiratory disease, congestive heart failure, and diabetes had higher odds of experiencing decline in health compared to other chronic disease combinations.[56] It has been suggested that the interaction between the patterns should be investigated in future research.[48]

2.6 Biological mechanism of multimorbidity

The biological mechanism of multimorbidity has been hypothesized as the result of sustained low level chronic inflammation and various hormone imbalances, which are the mediators for developing chronic disease.[57] It has been discovered that chronic inflammation is frequently present as an underlying factor in the development of specific comorbidities.[58] The hypothesis of inflammation as a risk factor for multimorbidity was examined in a recent cohort study from Italy.[59] A higher level of Interleukin (IL-6), an inflammatory marker, at the baseline and an increasing level of IL-6 as the result of ageing were associated with the

development of multimorbidity in older adults, providing evidence for the biological changes related to ageing as a contributing factor for the development of multimorbidity.[59] Similar results were found in another longitudinal study conducted by the same investigators, providing further evidence to support the hypothesis that inflammation associated with ageing increases the risk of multimorbidity.[10] Other studies also showed that ageing of the immune system, caused by natural processes, is associated with the development of multiple chronic diseases.[60,61] In summary, the mechanism for development of multimorbidity is not fully understood and future research is needed.[57]

2.7 Management of multimorbidity

Managing multimorbidity has always been a difficult topic for both physicians and patients because standard clinical guidelines are primarily developed for single diseases.[62] Patient-orientated and self-management approaches have been frequently mentioned as the strategy to cope with multimorbidity.[63] A summary of clinical guidance for multimorbidity from the National Institute for Health and Care Excellence (NICE) emphasized the importance of an individualized treatment strategy to maximize benefits while reducing damage.[64] Several studies have indicated that a patient-centered approach is effective in the management of multimorbidity.[65-67] A randomized control trial using a self-management program as the intervention in patients with multimorbidity showed a significant improvement in frequency of visits, self-efficacy, and quality of life.[68] However, pragmatic cluster-randomized trials conducted in England and Scotland showed that a patient-centered strategy improved the patient's perceptions of the quality of care rather than increasing the survival of patients.[63] Despite the fact that the findings on the relationship between patient-centered healthcare approaches were inconclusive, a Cochrane review conducted in 2016

suggested that future investigation is needed, and the intervention should be structured in terms of allowing comprehensive tests to be carried out that add to the available evidence.[69]

2.8 Multimorbidity and mortality

Previous studies have demonstrated a positive association between multimorbidity and mortality.[30,70-72] It has been suggested that the association between multimorbidity and mortality is analogous to physiologic mechanisms that an individual with a single disease has an increased risk of death.[30] In addition, the presence of multimorbidity may be more likely to have an impact on physiological systems as a result of the interaction between multimobidities and disease treatments.[73,74] A systematic review on the relationship between multimorbidity and mortality found 20 out of 26 studies showed a significant positive relationship.[30] Moreover, a study of Austrian women aged 73 to 78 years have demonstrated an increasing linear relationship between both weighted and unweighted multimorbidity indices, and mortality.[75] A longitudinal study of 16,091 adults from the United States reported that the mortality rate increased by 23% per additional increase in the number of chronic diseases after adjusting for all the covariates (HR=1.23; 95% CI:1.19, 1.28).[76] A study of older adults aged 65 and above in Hong Kong also reported that individuals with multimorbidity had higher mortality rates than those without multimorbidity.[77] Other studies did not find a negative impact of multimorbidity on mortality,[78-80] and it has been suggested that factors such as disease severity, disability, and comorbidity, rather than multimorbidity, better predict mortality.[81]

Increased mortality has been found with certain combinations of chronic diseases. A prospective cohort study of the Danish adult population reported that a more than six-fold increase in mortality was observed in individuals diagnosed with a neurological–cancer as

part of a comorbidity (OR=6.35; 95% CI: 5.71, 7.06) compared to the subjects without any combinations of the 10 selected disease groups.[82] In addition, a prospective cohort study of Australian adults aged 65 years and above showed that cardiovascular disease combined with gastrointestinal disease had resulted in a reduction of 50% in the survival times in comparison to those without chronic diseases. [83]

2.9 Factors related with the association between multimorbidity and mortality

2.9.1 Socioeconomic status

Several studies have examined how socioeconomic status modifies the association between multimorbidity and mortality.[34,84-86] For example, a study based on the Danish National Health Survey 2010 with 239,547 individuals aged 25 to 89 years found that people with multimorbidity who had a higher education level had lower 1-year cumulative mortality than those who had a lower education level.[87] However, similar results were not observed in a study based on British civil servants aged 35 to 55 years which reported that education levels did not affect mortality among those with multimorbidity. Their findings, however, are likely to be limited to individuals living in high-income regions and with relatively stable employment.[88]

Another socioeconomic factor related to the association between multimorbidity and mortality is deprivation. It has been shown that individuals who lived in the poorest area with deprivation decile of 10 in Scotland suffered from multimorbidity years earlier compared to those who lived in the most affluent area.[34] Moreover, multimorbidity was also associated with more severe health conditions for the population who lived in poor areas.[89] For example, a recent follow-up study of older adults in primary care in Quebec reported a substantial increase in all-cause mortality rates was only found among people with a

physical and mental health comorbidity in the least deprived areas, and not among the people who were living in moderately or most deprived areas.[90] A cohort study of approximately a million individuals in England reported similar results and concluded that the discrepancy in life expectancy between people with different socioeconomic status was attributed to both delayed onset of multimorbidity and better survival after being diagnosed with multimorbidity.[91] In addition, income is also a confounder in the association between multimorbidity and mortality. For example, a longitudinal follow-up study of adults in Ontario from 1994 to 2013 reported that greater mortality was found in areas with the lowest income.[92] The study also reported that the impact of economic disparities on the association between multimorbidity and mortality varied depending on the type of chronic disease, with the impact being greatest among those having chronic respiratory disorders.[92]

2.9.2 Health behaviors

Healthy lifestyle is one of the known confounders in the relationship between multimorbidity and mortality. Adherence to a healthy lifestyle has been reported to result in a significant reduction of all-cause mortality in people with multimorbidity.[93] For example, a study based on the UK biobank with people aged 8 to 73 years reported that the highest risk of death was found to be in the people who were inactive compared to those who were active, after adjusting for confounders.[94] In the presence of multimorbidity, individuals with moderate physical activity had a 51% lower risk of deaths (HR= 0.49; 95% CI:0.29–0.80) than those with low physical activity. Individuals with the highest level of physical activity had a 71% lower risk of death than those with the lowest level of physical activity (HR= 0.29; 95% CI: 0.13, 0.61).[94] Similar results were found in a study of older adults in Spain examining leisure time physical activity.[95]After controlling for age, sex, education, smoking

status, alcohol consumption, body mass index, and waist circumference, the study found that physically active older adults had a 35% lower risk of death than those who were not physically active (95% CI:0.50-0.84).[95]

The effect of alcohol consumption on the association between multimorbidity and mortality has also been examined in previous studies. For example, a longitudinal study based on the UK biobank with a sample of 500,769 participants aged 37 to 73 years demonstrated that drinking alcohol 1 to 3 times/month and 1 to 4 times/week was associated with a reduction of 19% (95% CI: 0.76-0.86) and 22% (95% CI: 0.74-0.81) risk of all-cause mortality, respectively, in comparison to never drinking or on special occasions only.[96] Abstaining or quitting from drinking among people with health problems has been suggested as a possible reason for the protective effect of alcohol on mortality.[97] The modification effect of smoking on the association between multimorbidity and mortality has been examined in a study based on three prospective cohorts of community-dwelling adults in the United States. In this study, tobacco use was shown to have a negative effect on the relationship between multimorbidity and mortality.[98] Similar results were reported in another follow-up study of 6,287 South Asian adults aged greater than 20 years.[99] The results showed that smokers had a higher risk of deaths associated with multimorbidity in comparisons to those who never smoked after adjusting for potential confounders (HR=1.27; 95% CI: 0.93,1.73).[99] A U-shaped relationship was observed between body mass index and all-cause mortality after adjusting for multimorbidity and other potential confounders in a longitudinal study based on the UK biobank.[96] In this study underweight participants had a 1.04 times greater risk of death and, obese and overweight participants had a 1.12 times greater risk of death in comparison to those who were normal weight after controlling

multimorbidity and potential confounders in the Cox's regression of all-cause mortality.[96] A possible explanation for the association between underweight and mortality is that those who are underweight may have poorer health, which may result in an increased risk of death.[100]

2.9.3 Individual factors

Age is one of the most well-known factors which has an effect on the association between multimorbidity and mortality.[99,101,102] A Canadian retrospective study examining whether multimorbidity has an impact on all-cause mortality reported that a higher risk of death was observed in people with multimorbidity after adjusting for potential confounders (RR=14.7; 95% CI: 14.48,14.91).[103] Moreover, this study also reported that the effect of multimorbidity on mortality decreased from older adults to children.[103] Similar results were observed in a study using data from the UK biobank.[96] However, another study of older adults in Manitoba did not find a significant association between multimorbidity and mortality after adjusting for functional status.[104] One possible explanation which has been suggested is that disability, instead of multimorbidity, has a greater impact on mortality in the elderly population.[105,106]

Sex has been shown to modify the association between multimorbidity and mortality.[103] In a longitudinal study of older adults in Latin America conducted from 2000 to 2015, females with hypertension or musculoskeletal disorders/diabetes mellitus/mental disorders had a higher risk of death compared to males, after adjusting for potential confounders (HR=6.15 95% CI :2.32, 16.32 vs. HR= 2.94; 95% CI: 2.02, 4.29).[107] It has been suggested that disease combinations and their related fatality rates may explain sex disparities in survival following the onset of multimorbidity.[107] However, the role of sex in the association between multimorbidity and mortality has remained controversial. A

longitudinal study based on the national survey of older adults in Spain has reported that among people with multimorbidity females had greater survival probability compared to males ($p<0.001$).[108] In contrast, results of another cohort study based on senior patients with multimorbidity in a dedicated residential unit for complex needs did not find a significant difference in the 1-year mortality between males and females.[109] In addition to sex differences in the association between multimorbidity and mortality, a study based on the 2010 Danish National Health Survey of subjects aged 25 years and older reported that stress levels showed a dose-response association with mortality among people with multimorbidity.[110] Similar results were reported in another follow-up study of a matched cohort in Denmark conducted between 1997 to 2014.[111] In this study, people with one or more physical diseases had an increase in excess mortality related to bereavement which is associated with stress.[111]

There has been a debate on whether marital status modifies the association between mortality and multimorbidity. A study has shown that participants who were widowed or divorced had a greater risk of all-cause mortality in comparison to those who were married after adjusting for multimorbidity and other confounders.[112] However, a study based on elderly adults in the community aged 65 and older in Manitoba found no association between marital status and mortality associated with multimorbidity.[22]

2.10 Association between specific chronic diseases and mortality

2.10.1 Asthma and mortality

Asthma is a common, chronic respiratory condition that can present with episodic wheezing, coughing, and difficulty breathing due to increased airway responsiveness and inflammation.[113] According to the Public Health Agency of Canada, it affects more than 3.8

million Canadians.[114] Children are more likely to be affected by asthma than adults and it is the primary cause of hospitalization in children.[115] Asthma was found to be associated with a higher risk of death among people with asthma than that in healthy subjects. For example, a study based on Copenhagen City Heart Study showed that subjects with asthma had poor survival probability compared to subjects without asthma, particularly in women with asthma having a 1.7 increased risk of deaths than women without asthma (95% CI: 1.3, 2.2).[116] Similar results were also found in another study.[117] However, there has been a debate about whether asthma itself or other respiratory diseases and smoking were the underlying causes of the reduction in survival in people with asthma. In a longitudinal study of the United States population, it was reported that subjects with asthma who were not exposed to other factors, including smoking, were not found to have worse survival in comparison to age matched controls.[118] Previous studies have also reported that subjects with asthma who had comorbidities including COPD had an increased risk of death.[119,120] Whereas, recent studies have reported that death from asthma itself is preventable with better diagnosis, improved management, and treatment during asthma exacerbations.[121]Asthma mortality rates declined substantially at the beginning of the 1990s when regular use of inhaled corticosteroids (ICS) was introduced for the control of asthma episodes.[122] The recent report of the Canadian Chronic Disease Surveillance System reported that asthma mortality declined from 11.2 per 1,000 in 2000-2001 to 8.4 per 1,000 in 2011-2012.[114] Although the asthma mortality rate continues to decrease, a study of asthma deaths in England has shown that socioeconomic status can modify the association between asthma and death.[123] In addition, the study also indicated that excessive use of inhaled β2-agonists resulted in an increase in asthma mortality.

2.10.2 Arthritis and mortality

One of the most prevalent forms of autoimmune joint disease is rheumatoid arthritis, which accounts for a significant percentage of worldwide disability.[124] The presence of persistent inflammation and increasing joint damage are key characteristics of patients with rheumatoid arthritis.[125] Studies have reported that subjects with rheumatoid arthritis had a roughly 50% increased risk of early death and a reduction of a maximum 10 years in average lifespan in comparison to the general population.[126] The higher mortality of rheumatoid arthritis has been reported only among older males.[127] Inflammatory markers, such as C-reactive protein, that indicate disease activity are also thought to be a significant predictor of rheumatoid arthritis mortality.[128] Studies have also shown that comorbidity in patients with arthritis, especially cardiovascular disease, has a significant impact on the survival of patients with rheumatoid arthritis.[129,130] In an American study based on a cohort of patients with rheumatoid arthritis, it was reported that individuals with rheumatoid arthritis were more likely to die from heart-related diseases than community controls of the same age and sex.[131] It has been hypothesized that an unexplained risk of cardiovascular disease deaths among subjects with rheumatoid arthritis was possibly related to systemic inflammation.[132]

Despite the evidence that rheumatoid arthritis was associated with greater risk of all-cause mortality (HR=1.56, 95% CI: 1.44, 1.69) than the general population, mortality rates associated with rheumatoid arthritis appear to be decreasing over time.[133] In a recent report from the Canadian Chronic Disease Surveillance System, there was a decline in the age-standardized mortality rates of rheumatoid arthritis over the past decades among both males and females with rheumatoid arthritis.[134] A systematic review also reported that there was a decline in mortality associated with rheumatoid arthritis in recent years, but the mortality among those with rheumatoid arthritis is still greater than that in the general population.[135]

2.10.3 Diabetes and mortality

Diabetes mellitus, commonly known as diabetes, is a common chronic metabolic disease caused by insufficient production or improper use of insulin.[136] There are two major types of diabetes mellitus. Patients with type 1 diabetes typically produce insufficient insulin to control their blood sugar.[137] Patients with type 2 diabetes cannot properly use the insulin they produce may also have an insulin deficiency.[138] It is recognized that diabetes is associated with excess mortality.[139] Various risk factors such as sex and race have been found to modify the association between mortality and diabetes.[140] For example, a study based on the vital statistics database of the Canadian population showed that mortality rates increased with age, despite whether diabetes was an underlying or contributing cause of death.[141]

However, there is an argument that the complications associated with diabetes rather than diabetes itself contribute to the worse survival among diabetic patients.[142] A systematic review has shown that the presence of diabetic foot ulceration in diabetes patients was a significant determinant of mortality with approximately a two-times increased risk of death than those diabetes patients without foot ulceration.[143] Despite the excess mortality associated with diabetes, studies have shown that diabetes mortality rates have decreased over the past decades.[144] Based on a report of Statistics Canada, there was an average 2.1% reduction per year in the all-cause mortality rates among diabetic patients from 2000 to 2016, which was likely due to better treatment and care.[145] However, diabetic patients still have a higher risk of death than those without diabetes. Recognizing the multifactorial nature of diabetes mortality enables us to intervene more effectively in the death of diabetic patients.

2.10.4 High blood pressure and mortality

High blood pressure (HBP or hypertension) is a disease where one's blood flow characterised by increases in mean systolic and/or diastolic blood pressure such that it constantly imposes a higher pressure against the wall of blood vessels.[146] According to the American Heart Association, people with HBP or hypertension are characterised by having a systolic pressure of 140 mmHg or higher, or a diastolic pressure of 90 mmHg or higher over time.[147] HBP is well-known as a "silent killer" because and many people present no symptoms or signs that are usually hard to notice. Only a few people experience symptoms such as headaches or shortness of breath.[148] According to the World Health Organization (WHO), an estimated 1.13 billion people worldwide suffer from hypertension, with the condition being more prevalent in middle- or lower-income countries.[149] Hypertension is associated with a risk of cardiovascular disease.[150] Studies have shown that people with hypertension are more likely to die of cardiovascular disease. [151,152] One study reported the risk of cardiovascular deaths was two times higher for every 20 mm Hg increase in systolic blood pressure (BP) to > 115 mm Hg.[153]

Unlike for some other chronic diseases, the mortality of hypertension can be modified by targeting risk factors. There are several factors associated with the mortality of HBP, such as lifestyle factors.[154] For example, a study has shown that physically active people with HBP have a lower risk of mortality than physically inactive ones.[155] Healthy diet pattern was also suggested as being associated with lowering blood pressure.[156] Moreover, a prospective cohort study based on preterm infants has shown that having a genetic background of elevated adult blood pressure was associated with lower mortality among preterm infants.[157] Despite the negative impact of hypertension on mortality, the

impact of hypertension on age standardized mortality has decreased over recent years in Canada, based on data from the Canadian Chronic Disease Surveillance System due to outstanding hypertension awareness, treatment, and control among developed countries.[158] However, the relative risk of death continues to increase, and people with hypertension had about a 60% higher risk of death than those without hypertension[151]

2.10.5 COPD and mortality

The chronic disease that induces airflow obstruction and breathing-related issues is referred to as chronic obstructive pulmonary disease (COPD).[159] People with COPD usually experience symptoms such as frequent coughing or wheezing, shortness of breath, and difficulty taking a deep breath,[159] but may be asymptomatic in people younger than 55 years old.[160] Like other chronic diseases, the slow progression of COPD often occurs over many years. The presence of additional exacerbations, an extension in airflow, and a shortened life span are associated with increasing disease severity.[160] According to Statistics Canada, COPD was the fourth leading cause of death in 2019 [161] and is estimated to be the third most common cause of mortality globally.[162] It is worth mentioning that the impact of COPD on mortality depends on the severity of the disease.[163] For example, a global multi-center study based on the Towards a Revolution in COPD Health (TORCH) trial has shown that respiratory disease contributed to 40% of death in patients with severe COPD, followed by 35% of those with cardiovascular disease.[164] Another study based on the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP) and Inhaled Steroids in Obstructive Lung Disease (ISOLDE) showed similar results, that benign (i.e. non-cancer) respiratory disease became the major cause of deaths as COPD severity increased. Moreover, patients with cancer and cardiovascular disease contributed largely to

the deaths of patients with mild COPD.[163]

There are other risk factors associated with COPD mortality as well. For example, lower survival probability was associated with a reduction of airflow.[165] A national cohort study of Americans has found that for every 50% reduction in forced expiratory volume in one second (FEV_1), there was a 92% increased risk of death for those with COPD, regardless of smoking status and sex.[165] Furthermore, smoking has been shown to be associated with COPD mortality based on the Lung Health Study (LHS) in the United States. The study results have shown a significant decline in all-cause mortality rates among people with mild to moderate COPD and assigned to a smoking cessation program compared to those people who received usual care.[166] COPD mortality has also been reported to be higher in the elderly population and in males.[167]

The mortality of COPD was reported to be decreased from 1996 to 2012 for men only based on a study of Ontario population.[168] However, there has been discussion that the COPD mortality rate is likely to be underestimated due to underdiagnosis and misidentification of the cause of death in the presence of comorbidity.[169] For example, instead of listing COPD as the primary cause of death, there was a greater likelihood that it was treated as the contributory cause of death or even completely ignored on the death certificate.[170] Moreover, since COPD patients are also more likely to die from cardiovascular disease or lung cancer, COPD is likely to be underestimated as the cause of death. Therefore, applying all-cause mortality rates is suggested for further study, and it is important to standardize reporting of the underlying causes of death in COPD.[169]

2.10.6 Heart disease and mortality

Heart disease consists of various types of disorders that either impair the structure or

function of the heart.[171] In ischemic heart disease, plaque accumulates on the inside walls of coronary arteries, finally hardening or rupturing, causing a heart attack or death.[172] In addition, heart failure is a common type of heart disease and is characterized by an insufficient blood supply to the body.[173] Heart disease is widely acknowledged as a major cause of death on a global scale [174] and the second most common cause of death in Canada.[175] According to a 2015 report, the number of people who died due to heart disease was increased to 9.1 million globally from 2005 to 2015.[174]

There are several risk factors associated with heart disease mortality. For example, a report on heart disease in Canada showed that people with heart failure had an increased risk of death compared to those without it among the middle-aged population. Lower mortality rate ratios were found to be in people aged 85 years old and above.[172] Females with heart disease had a greater likelihood of dying than their male counterparts due to differences in physiology and pathophysiology of the heart.[176] Studies on sex difference in survival after a myocardial infarction showed that younger women had a greater death rate than men.[177,178] Other risk factors, such as cigarette smoking and hypertension, were associated with heart disease death as well.[179] Fortunately, due to changes in lifestyle factors and improvement in treatment, the mortality rate of heart disease has significantly decreased in Canada and has become the second most common cause of death since 2007. The continuous monitoring of known risk factors is essential for preventing deaths from heart disease.[180]

2.10.7 Cancer and mortality

Cancer is a major cause of mortality, and contributes to reducing lifespan around the world.[181] It is often a fatal disease characterised by the human body's cells' uncontrollable proliferation and spread throughout the body.[182] As a consequence, either cancerous or not

cancerous (benign) tumors are formed. The majority of cancerous tumours are malignant and life-threatening. A cancer can move to adjacent tissue as well as propagate throughout the body. Unlike cancerous tumors, benign tumors do not typically spread throughout the body; therefore they are less likely to result in death.[182] Research has shown that cancer is responsible for 30% of all deaths in Canada, with 83,300 people expected to die from cancer in 2020.[183] A study based on the UK biobank has shown that among older patients with one long-term condition was more likely to die from cancer than those patients without any long-term conditions after adjusting for confounders (HR=1.50, 95% CI: 1.41-1.60).[96]

Due to the complexity and variety types of cancer, a number of determinants are associated with cancer mortality. For example, the risk of death varies depending on the type of cancer.[184] According to the most recent study on global cancer, 18.0% of people diagnosed with lung cancer died in 2020, which ranked among the leading cause of cancer deaths. More than 9.4% of cancer deaths were people with colorectal cancer, followed by 8.3% due to liver cancer.[185] Additionally, females and males have a different survival rates when diagnosed with cancer. A global study found that males with lung cancer had around twice the risk of death as females.[185] Lower education levels are associated with a higher risk of cancer mortality.[186] The study reported that men with less than secondary education had a 68% higher risk of death than those with a college degree.[186] The argument that the disparities in cancer mortality may be due to differences in smoking patterns or dietary habits was hypothesized.[187]

Additionally, based on a report from research on the Canadian population, people aged 85 years old and above were found to have a higher frequency of cancer deaths than those younger than 85 years old.[188] Cancer may not be the most important cause of death in

older age groups. A study on an American population has shown that people aged 80 years old and above had a two-fold greater the risk of mortality due to heart disease in comparison to cancer.[189] Despite the excess mortality from cancer, there was a decline in cancer mortality over time based on the most recent report on Canada cancer statistics.[190] It showed that mortality rates of leading types of cancers decreased in 2020 for both sexes.[190] Measures such as screening to reduce cancer mortality rates will be required in order to maintain the current low cancer death rate.[191]

2.10.8 Stroke and mortality

Stroke is a disease that occurs when a blood vessel supplying the brain is blocked (ischemic stroke) or ruptured (hemorrhagic stroke), leading often to an immediate loss of brain function. Weakness, numbness, headaches, and coordination and balance problems are some of the possible symptoms of a stroke.[192] Stroke is a major cause of disability globally.[192] People who have had a stroke may continue to suffer from the symptoms, permanently and their quality of life is likely to worsen.[193] The report of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) in 2017 reported that stroke resulted in the loss of 132.1 million DALYs worldwide.[194]

There are several determinants of stroke mortality. According to a study based on the Canadian Chronic Disease Surveillance System, the overall mortality rate for men with strokes was greater than for women at all ages.[195] Stroke mortality also increased with age, and the majority of stroke-related deaths occurred in the elderly population aged 65 years and above.[194] Lower socioeconomic status is one of the determinants of stroke mortality.[196] A study following a group of stroke survivors in the United States has shown that people in lower socioeconomic groups, such as those with a lower level of education and lower

income, had higher long-term stroke mortality rates than those in higher socioeconomic groups.[194] Another study on hospitalized stroke patients in Canada has shown that patients in rural hospitals had higher 30-day in-hospital mortality than those in urban hospitals, and the availability of CT scanners may explain the discrepancy.[192] Moreover, hypertension is well-known to be a primary cause of stroke mortality.[194]

Fortunately, stroke mortality has declined in many countries around the world.[197] For example, a recent study on the Brazilian population has shown that stroke mortality was reduced by 50% (IRR=0.50; 95% CI 0.31–0.94).[198] There is evidence that Canada and the United States experienced a decline in stroke mortality as well.[199] There are several hypothesized reasons for the reduction in stroke mortality, such as more healthy lifestyles, physical activity, and smoking patterns.[200] For example, a study of the English population found that reducing case fatality through improved stroke treatment was significantly related to lower stroke mortality.[201] Thus, it is believed that stroke deaths could be drastically reduced by modifying risk factors and improving access to health care for people who have had a stroke.

2.10.9 Mood disorders and mortality

Mood disorders refer to the group of mental diseases that directly impair one's mood, energy, and motivation. Major depressive disorder and bipolar disorder are the most well-known examples within the category of mood disorder.[202] The age of onset of mood disorder varies between different types of mental diseases. For example, like other chronic diseases, depressive disorders generally first appear at the median age of 32 years, while bipolar disorders typically develop around 20 years.[203,204]

Furthermore, there is an association between the presence of a mood disorder and

poorer quality of life [205,206] and increased mortality.[207] A systematic review on mood disorders and mortality has shown that people with depression had an overall 1.81(95% CI: 1.58,2.07) relative risk of death in compassion to those without depression,[207] whereas other studies did not find a significant impact of a mood disorder on mortality. For example, a study of a cohort with a 20-year follow-up showed no significant differences in mortality between those having 1 or 2 mood disorders and those having none of the conditions, after adjusting for other confounding variables.[208] Another follow-up study of four epidemiologic catchment areas in the United States reported similar findings.[209] There was also evidence of a protective impact on mortality in older patients with severe depression, although the effect was not statistically significant.[210]

Several risk factors are associated with mood disorder and mortality. Suicide has been shown to primarily contribute to the increased death rate of those with mental disorders.[211] Additionally, people with mood disorders who were hospitalised had a much higher suicide rate than those who were in the community or outpatients.[212] Comorbidity such as respiratory disease has also been shown to result in elevated mortality in people with a mood disorder.[213] It has been hypothesised that somatic illness contributed far more to the excess mortality rates than mental disorders did; therefore, it is likely to act as a confounding or mediating factor.[214] Comorbid alcohol and drug use were also suggested to be associated with a higher risk of death in people with a mood disorder.[215] Depression has been associated with an increased death rate that is unequally distributed between women and men. Men patients with mood disorders were more likely to die than women patients with mood disorders. [216] Although there are several hypothesized associations between mood disorder and mortality, the current knowledge of mood disorder and mortality is still limited;

and the underlying mechanism still remains unknown. Further research is needed to guide the prevention and management of mood disorders.

2.11 Association between comorbidity and mortality

2.11.1 COPD and diabetes

Comorbidities are prevalent among patients with COPD.[217-219] The overall health status of COPD patients with comorbidities is usually lower, along with increased utilisation of medical services and higher mortality than COPD patients without comorbidities.[217,220] Several comorbidities have been reported among COPD patients.[221] Diabetes is a common comorbidity in COPD patients.[104] The prevalence of diabetes in COPD patients was 10.3% in a rehibition center population[222] and 14.5% in stage 3 or 4 COPD patients.[223] In addition, COPD patients with diabetes have an increased risk of death.[224] In a population-based cohort study of subjects with airway obstruction in North Sweden (OLIN), there was a 50 % increase in the risk of death (HR=1.50; 95% CI: 1.07, 2.10) than COPD subjects without diabetes after adjusting for potential confounders.[225] A cross-sectional study of patients hospitalized for COPD exacerbation found that patients with diabetes had nearly double the risk of death (OR=1.93; 95% CI: 0.43, 8.64) than patients without diabetes.[226] Another cohort study using the Taiwan Longitudinal Health Insurance Database reported a similar association.[227] They reported that COPD patients with pre-existing diabetes had a 24.4% greater risk of death (HR=1.24; 95% CI: 1.010, 1.532) in comparison to COPD patients without pre-existing diabetes during the 10-year follow-up period.[227]

There are various hypothesized mechanisms for diabetes to occur as a comorbidity of COPD. A cohort study in Sweden has shown that poor lung function is associated with a higher likelihood of developing diabetes.[228] However, they only included subjects with

impaired lung function rather than subjects with diagnosed with COPD.[229] While the most prevalent symptoms of COPD are predominantly in the lungs, it is often referred to as a complicated, multicomponent illness that has long-term systemic inflammation as one of its components.[230] Some studies have shown that the increased levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8 in COPD patients[231] are also relevant as risk factors for type 2 diabetes.[232] Moreover, this could be a possible mechanism contributing to the excess mortality in COPD patients with diabetes. In their study, the proliferation of respiratory infections has been shown to rise when blood glucose levels increase. In turn, this caused patients to be vulnerable to bacterial lung infection and resulted in a significant increase in mortality.[233]

2.11.2 Asthma and mental health problems

Mental health problems such as anxiety and depression have been reported in asthma patients.[234,235] A community-based study of 2,168 participants in the Dallas Health Study has shown that asthma patients were more likely to have a prior diagnosed mental health disorder after controlling for potential confounders (OR=1.810; 95% CI 1.280, 2.559).[236] In addition, an analysis of data from 54 countries from a World Health Survey by the WHO reported that diagnosed depression was significantly associated with the diagnosis of asthma after controlling for age and sex, which confirms that the morbidity of asthma and mental health problems is a global public health issue.[237] The prevalence of asthma, and mental health problems among asthma patients has varied across various studies. A cross-sectional study of 20,272 American adults aged 20-79 years from the 2007-2012 National Health and Nutrition Examination Survey reported that 8.9% of asthma subjects had major depression and 44.1% felt anxious for more than five days in the past 30 days. Another population household

interview of Australian adults aged 18 years old and above reported that there were 16.2% of subjects diagnosed with a mental health condition in the last 12 months among 834 subjects with asthma.[238]

In addition, asthma patients with mental health disorders were more likely to have frequent healthcare utilization, such as asthma-related emergency department visits,[239,240] and higher risk of mortality.[241,242] The biological mechanism underlying the link between asthma and mental health problems is not fully understood. A systematic review of the possible hypothesis about the association of asthma and major depression suggested that dysregulation of the hypothalamic pituitary adrenal axis is likely to result in a higher risk of developing both asthma and major depression as well as other pathologic factors such as obesity and oxidative stress.[243] A genetic study of Finnish twins reported that common genetic factors and shared familial vulnerability could contribute to the association between atopic illness such as asthma and depressive symptoms.[244] However, the specific genes still remain unknown.

2.12 Summary of literature review

The literature review in this chapter provided a general overview of multimorbidity based on existing research papers and systematic reviews. It is worth noting that the literature review did not apply a systematic framework; one can only refer to the review as a general overview of relevant literature since there is a relatively large sample of research papers and reviews included in the reviews. The first part of the literature review mainly focused on the epidemiology and factors associated with multimorbidity and mortality. This review found literature is relatively consistent in terms of risk factors. However, the effect of a few factors on the association between multimorbidity and multimorbidity mortality varied

between studies. It has been suggested that possible confounding variables such as characteristics of the study population need to be considered when comparing any new data with the existing literature. The second part of the literature review focused on the relationship between mortality and multimorbidity and chronic disease combinations, which corresponds to the primary objective of the study. The findings of the literature review provided strong evidence to support the association between mortality and multimorbidity across the different studies. There were many possible hypotheses suggested by research and reviews. However, the biological mechanisms underlying this association have not been fully understood yet.

2.13 Rationale of the study

The primary objective of this thesis is to examine whether or not the presence of multimorbidity in middle-aged and older Canadians is associated with a greater risk of mortality. To the best of the author's knowledge, no study of mortality and multimorbidity has been conducted to date based on the general Canadian population using a national database. Therefore, the findings of this study will contribute to the body of knowledge about the effect of mortality on multimorbidity in the Canadian population using the linked databases of CCHS and CVSD.

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Chapter 3

Mortality among the Canadian population with multimorbidity: a retrospective cohort study

3.1 Introduction

The increasing age and prevalence of multimorbidity in Canada and worldwide has attracted public health attention during recent years.[1] Studies have demonstrated that multimorbidity is more prevalent in older adults.[2,3] It has also been reported that multimorbidity is associated with a greater risk of disability, frailty and reduction in quality of life with consequent costs to society as a whole.[4,5] Additionally, multimorbidity is positively related to the mortality rate when comparing subjects with and without multimorbidity.[6] A longitudinal study, the National Health and Nutrition Examination Survey (NHANES) from the USA reported that participants had a 23% increased risk of death for each additional morbidity after adjusting for potential confounders (HR=1.23; 95% CI: 1.19, 1.28; $p<0.001$).[7] A Canadian longitudinal study conducted in Ontario reported that people with multimorbidity had a higher risk of death than those without which was independent of their age.[8] However, increased risk of death associated with multimorbidity was not observed in some studies.[9,10] Multimorbidity in the elderly population appears to be multifactorial and is associated with sociodemographic characteristics,[11] health behavior[7] and frailty.[12] In a population-based cohort study from Denmark, subjects with lower levels of education had a greater risk of mortality in comparison to those with higher levels of education.[13] Studies have also reported that the risk of mortality associated with multimorbidity decreased with ageing.[14]

Although most of the published studies have considered all comorbidities to have

similar risk associated for mortality, it is likely that certain comorbidities have a greater risk of mortality than others. For example, it has been reported that COPD patients with diabetes have a higher risk of mortality in comparison to COPD patients without diabetes.[15] Subjects with asthma and mental health problems were reported to have an increased risk of death in comparison to those who had only asthma.[16] Thus, considering the most prevalent or harmful combination of comorbidities rather than treating them individually may allow health professionals to intervene and prevent death. However, studies on multimorbidity and its effect on mortality are limited, especially in the Canadian population. Additionally, only a limited number of studies have examined the joint effect of chronic diseases on mortality.

The primary objective of this study was to examine the relationship between multimorbidity and all-cause mortality in the middle-aged Canadian population. The secondary objective was to examine the independent and interaction effects of chronic diseases on mortality. A population-based inception cohort study was conducted by linking Canadian Community Health Survey (CCHS) data with Canadian Vital Statistics Death (CVSD) data.

3.2 Methods

Data Source

The Canadian Community Health Survey (CCHS) is a cross-sectional survey including the population aged 12 years and above administrated by Statistics Canada.[17] The information collected in CCHS included demographic characteristics, health status, health care utilization, and health determinates. The CCHS target population includes people living in ten provinces and three territories, excluding those living on reserves and aboriginal settlements, those full-time in the Canadian forces, the institutionalized population, 12-17

years old children living in foster care, and persons living in the health regions of Région du Nunavik and Région des Terres-Cries-la-Baie-James in Quebec. A multi-stage sampling allocation strategy was used to provide a representative sampling distribution to the health regions and the provinces. The first CCHS was conducted in 2000/2001 (Cycle 1.1) and was followed by Cycle 2.1 in 2003/2004, and Cycle 3.1 in 2005/2006 with a total sample size of approximately 13,000. Starting in 2007, the sample size was increased to approximately 65,000 in each cycle and conducted annually instead of every two years. The data from the ten CCHS cycles (2003/2004, 2005/2006, 2007-2014) are considered in this study. As the age-standardized mortality rates of the participants in CCHS conducted in 2000/2001 was lower than the other CCHS years, the data from this survey were excluded from this study because of the potential to introduce healthy respondent bias.[18]

The Canadian Vital Statistics Death Database (CVSD) included information of all deaths registered in Canada annually and monthly from 1921 onwards.[19] Reports of deaths were submitted to Statistics Canada through the province and territorial vital statistics registries. The information related to each death included age, sex, marital status, place of residence, birthplace of the deceased, date of death, cause of death as classified by International Classification of Diseases (ICD) (using the version in effect at the time of death), province or territory of occurrence of death, place of accident (for most non-transport accidental deaths) and results of autopsy if one was held. If the autopsy was held, the results of the autopsy were taken into account in establishing the cause of death.[19]

Data linkage

The linkage of CCHS to CVSD was given approval by the Chief Statistician of Canada.[20] The subjects from CCHS (2003/3004, 2005/2006, 2007-2014) who

granted permission to share and link their survey answers were included in the linkage process. The cohort files were created by a probabilistic linkage of CCHS subjects to Derived Record Depository (DRD) in the Social Data Linkage Environment (SDLE) to enhance data quality. In the interest of creating more accurate results, probabilistic record linkage employed several non-unique identifiers, such as name, sex, date of birth, and postal code, to determine the likelihood of records referring to the same individual.[18] An adjustment was made to account for records that were not captured in the DRD and those who did not provide permission for their survey answers to be shared and linked.[21] The same linkage methodology was used with CVSD (January 1, 2000 to December 31, 2017) to create analytical files. For the CCHS and CVSD data examined in the linkage, the merging keys produced from the SDLE were utilized to link cohort and analytical files.

Study sample

CCHS cohort files were linked to the CVSD to identify those who died from January 1, 2000 to December 31, 2017. A linking key (Stc_id) in the cohort files and analytical files was used for the linkage. In total, 629,835 (80.82%) CCHS subjects were successfully linked to death records held with CVSD from January 2003 to December 2017. Twenty individuals were removed due to logical inconsistency (i.e., death date prior to interview date), and 194,925 CCHS-CVSD subjects aged less than 35 years old were also excluded from the study, which resulted in 434,885 subjects for the final analyses with a maximum follow-up of 14 years. The details of exclusion and inclusion during the follow up are shown in the flow chart (Figure 3.1). Participants were excluded if the recorded death date was before the CCHS interview date in the CVSD database. In total 64,725 respondents died between the year of CCHS interview, and

the end of follow-up (December 31, 2017) and 370,160 respondents were censored.

Outcomes

The outcomes for this study were death during the period of follow-up or remaining alive at the end of follow-up (December 31, 2017), and the time (survival time) to death or end of follow-up (censored). The survival time as the period was determined from the CCHS interview date (baseline) to the date of death or end of follow-up.

Main exposure variable

The main exposure (independent) variable was multimorbidity which was defined from the responses to the question which had an opening statement *"Now I'd like to ask about certain chronic health conditions which you may have. We are interested in "long-term conditions" which are expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional. Do you have <conditions>?"* Wordings of the questions remained similar in all the CCHS cycles considered in this study. Instead of including all the chronic illnesses, this study focused on nine chronic diseases that have a high prevalence and a significant effect on health care utilization. The nine chronic diseases were asthma, arthritis, cancer, hypertension, diabetes, heart disease, stroke, mood disorder, and COPD. These chronic diseases were also considered in several previous studies on multimorbidity.[22,23,24] Multimorbidity was defined by the respondent's self-report of having two or more chronic diseases.[25] The respondents who did not report any of the nine selected chronic diseases were defined as those "without multimorbidity". Thus, the reference group was those without any morbidity, but it is not the entire group without multimorbidity. A dichotomous variable was defined to indicate multimorbidity with "1" indicating presence of multimorbidity and "0" indicating absence of morbidity. The respondents who reported a single chronic disease were

excluded in this study.

Independent variables

Socio-demographic characteristics and health behaviors considered in this study were identified based on existing literature focusing on multimorbidity and mortality and were obtained from each cycle of CCHS. These factors were considered as potential confounders for the association between multimorbidity and mortality in this study. All the baseline factors were categorized as follows in the analysis: age (35-49, 50-64, 65 years and above), sex (female and male), cultural background (white, non-white), body weight (underweight, normal weight, overweight, obese), marital status (single, widowed/divorced/separated, common-law/married), provinces of residence (Births Columbia, Prairies, Ontario, Quebec, Atlantic, Territories), household income (less than $39,999, $40,000 to $59,000, $60,000 to $79,999, $80,000 or more), highest household education (less than secondary school graduation education, secondary school graduation no post-secondary, some post-secondary education, and post-secondary and above), smoking status (non-smoker, smoker at time of CCHS interview), alcohol (no, moderate, heavy), physical activity (inactive, moderate, active), stress (not and not very stressful, somewhat, extreme) and year of entry into the cohort.

Statistical analysis

For each CCHS cycle, the follow up was described using the frequency and proportion of deaths, mean and total follow-up time. Smoothed Kaplan-Meier curves were used to describe the overall survival distribution of subjects with and without multimorbidity. The association of multimorbidity and the nine individual chronic diseases with mortality was described by the unadjusted hazard ratios with 95% confidence intervals using Cox's proportional hazards models. The unadjusted hazard ratio of multimorbidity

was also obtained for each CCHS cycle to examine the consistency of association of multimorbidity with mortality between CCHS cycles. Cox's proportional hazard regression was used to determine the adjusted hazard ratio of multimorbidity after controlling for the significant baseline factors. Smoothed Kaplan-Meier curves were also used to describe survival distribution of subjects with and without multimorbidity in the three age groups (35 to 49, 50 to 64 and 65 years and above). The distribution of incidence of death for the categories of the baseline factors were obtained and an unadjusted hazard ratio was used to describe the strength of the association between the baseline factors and mortality for the whole sample and three age groups. Hazard ratios for multimorbidity were obtained for the three age groups after adjusting for the significant baseline factors. The assumptions of the proportional hazards model were validated visually by plots of log[log(survival time)] vs. log(time). Although the proportional hazard assumption was violated in people aged 65 years and above, since the sample size in this study is very large, results would be robust to any violation of the model assumptions. Plausible interactions between multimorbidity and baseline factors were also examined.

The independent association between the nine chronic diseases and mortality was determined by replacing multimorbidity with nine binary variables representing each of the nine chronic diseases in the Cox proportional hazards models. Adjusted hazard ratios for the nine chronic diseases were also estimated, along with plausible interactions between chronic diseases. To account for survey design, non-response and refusal to link, design weights provided by Statistics Canada were used in all the analyses. Bootstrap weights (with 500 iterations) were applied to estimate variances and 95% confidence intervals as suggested by Statistics Canada to adjust for the complex survey design.[25] Stata/MP 16 (StataCorp LP,

College Station, TX) and SAS 9.4 (SAS Institute Inc., Gary, North Carolina, USA) were used for statistical analyses.

3.3 Results

Table 3.1 shows information by CCHS cohort on the number of deaths. Number of deaths and total follow-up time decreased from CCHS 2003/2004 to CCHS 2014 which was expected since subjects interviewed in earlier survey years were older and had a higher risk of death during the follow-up compared to those interviewed in the latter surveys.

Figure 3.2 shows Kaplan-Meier survival curves for multimorbidity of the whole study population with and without multimorbidity. There was a notable difference in the survival distribution between the two groups in the smoothed Kaplan-Meier curves. At the end of follow up, roughly 87% of people without multimorbidity remained alive, while nearly half of those with multimorbidity died during follow-up. These differences in the survival distribution are also evident from unadjusted hazard ratios of multimorbidity with the overall risk of death being significantly greater for subjects with multimorbidity in comparison to those without multimorbidity (HR=6.15; 95 % CI: 5.91, 6.41; $p<0.001$) (Table 3.2). When each of the nine chronic diseases that were used to define multimorbidity were considered one at a time simultaneously, and unadjusted for other chronic diseases and potential confounders, each chronic disease was associated with increased risk of death, with the lowest and highest risk being in subjects with mood disorder and stroke respectively. The increased risk of death associated with multimorbidity was also observed for each CCHS cycle and hazard ratios were comparable between the CCHS cycles except for a slightly increased hazard ratio for the last CCHS cycle (Table 3.3).

The incidence of death and unadjusted hazard ratio for the baseline factors are shown

in Table 3.4. The incidence of death was greater for males than females with the overall risk of death being significantly greater for males than for females (HR=1.19; 95 % CI: 1.16, 1.23). Overall risk of death was greater for subjects who were white (in comparison to non-white), underweight, widowed or divorced (in comparison to those who were single), living in Atlantic provinces (in comparison to British Columbia), household income less than $39,999, less than secondary school education, smokers (in comparison to non-smokers), non-alcohol drinkers, those who reported being physically inactive, and those who reported a lower stress level (Table 3.4).

A positive association between multimorbidity and mortality was also found when stratified by age groups, and the difference in the survival distribution between subjects with and without multimorbidity decreased from the younger age group to the older age groups (Figure 3.3). As shown in Table 3.5, these differences were further evident in the unadjusted hazard ratios of multimorbidity with the hazard ratio being the highest in the youngest age group (HR= 4.77; 95% CI: 3.94, 5.77) and lowest in the oldest age group (HR=1.52; 95% CI:1.74,1.90).

When each of nine chronic disease was considered separately in the Cox's proportional hazards model, all the nine chronic diseases were significantly associated with a higher risk of death regardless of the age groups. Subjects with cancer had the highest risk of death in the two younger age groups, while subjects with stroke had the highest risk of death in the oldest age group. The lowest risk of mortality was observed in subjects having asthma and arthritis in the youngest and middle age groups, respectively. Subjects with arthritis and high blood pressure had the lowest mortality risk in the oldest age group.

Age-specific incidence of death and unadjusted hazard ratios are shown for the

baseline factors in Table 3.5. Male subjects had a higher incidence of deaths than female in all the three age groups. In all the age groups, subjects who were married or in a common-law relationship had a lower risk of death than those who were single. Moderate and heavy drinkers had a significantly lower risk of death in comparison to non-drinkers in all the age-groups except that a lower risk for heavy drinkers in the youngest age group was not statistically significant.

In multivariable analysis, the hazard ratios between multimorbidity and mortality were adjusted for significant baseline factors in the three age groups (Table 3.6). In all three age groups, multimorbidity was associated with an increased risk of mortality after adjusting for significant baseline factors. Adjusted hazard ratios for multimorbidity decreased from the youngest age group (HR= 3.77; 95% CI: 3.04, 4.67) to the oldest age group (HR= 1.71; 95% CI: 1.63, 1.80). The adjusted hazard ratios for sex, household income, education, and smoking were similar in the three age groups. Moderate and heavy drinkers had a significantly lower risk of death in comparison to non-drinkers in the three age groups except that for the heavy drinkers in the youngest age group. However, the difference was not significant. Physical activity and stress level were significantly associated with risk of death in the middle-aged and oldest age groups. Race and province of residence were significantly associated with risk of death only in the oldest age group.

Interactions between multimorbidity and the baseline factors that were significant in the Cox's proportional hazards models for the three age groups were further examined. In the multivariable proportional hazards model for 35 to 49 years, interactions of alcohol drinking and education with multimorbidity were significant (Table 3.7). In subjects with multimorbidity, there was a 48% significant reduction in the risk of death in the moderate

drinkers (HR=0.52; 95% CI: 0.36, 0.73; p<0.001) and a non-significant 38% reduction in the heavy drinkers (HR=0.72; 95% CI:0.41,1.27; p=0.26) in comparison to non-drinkers. Whereas, in subjects without multimorbidity, there was a non-significant increased risk of death in moderate drinkers and a significant increased risk of death in heavy drinkers (HR= 2.05; 95% CI: 1.37,3.07; p=0.001) in comparison to non-drinkers (Table 3.7). In subjects with multimorbidity, a significant protective effect was only observed for some post-secondary education. In the subjects without multimorbidity, a significant protective effect was observed only for post-secondary education and above.

In the multivariable proportional hazards model for 65 years and above, interactions of obesity and marital status with multimorbidity were significant. In this age group, there was a significant reduction in the risk of death for all the body weight categories in both subjects with and without multimorbidity (Table 3.8). However, the reduction in the risk of death associated with body weight categories was greater in subject with multimorbidity than in those without multimorbidity. The protective effect of the common-law and married categories and increased the risk of death for widowed, divorced and separated categories (in comparison to the single category) were observed in both subjects with multimorbidity and without multimorbidity. The effects of appeared stronger in subjects without multimorbidity than those with multimorbidity (Table 3.8).

In a further multivariable analysis, multimorbidity was replaced with binary variables indicating each of the nine chronic diseases considered simultaneously in the proportional hazards model for the three age groups. In these models, race, physical activity, stress and year of entry into the cohort were not significant for the younger age group (Table 3.9). Physical activity and year of entry into the cohort were significant in the model for the

middle age group (50 to 64 years). All the baseline factors were significant in the oldest age group. After adjusting for the significant baseline factors, all the nine chronic diseases except asthma and heart disease, were significantly associated with risk of death in the youngest age group, all the chronic diseases except asthma, arthritis, and mood disorder were significantly associated with risk of death in the middle age group and all the chronic diseases except for asthma and arthritis were significantly associated with risk of death in the oldest age group (Table 3.9). As indicated by these results, asthma was not associated with death in any of the three age groups after adjusting for the effect of other chronic diseases and significant baseline factors. Subjects with cancer had the highest risk of death among the nine chronic diseases in the younger and middle-aged groups. In the oldest age group, subjects with COPD and cancer had the highest risk of death. It is also worth noting that mood disorders had a marginally significant protective effect against death risk in the oldest age group (HR=0.92; 95% CI: 0.86, 0.99).

The significance of plausible interactions between the nine chronic diseases and baseline factors were examined in the Cox's proportional hazards models for the three age groups. Interactions between asthma and mood disorder, and COPD and diabetes were significant in the older age group (Table 3.10). In this age group, among subjects with asthma and without mood disorder, there was an increased risk of death (HR= 1.19; 95 % CI: 1.04, 1.36). Subjects with mood disorder were less likely to die among subjects with asthma (HR=0.91; 95 % CI:0.72, 1.15) with the differences not being significant. As indicated in Table 3.10, subjects with COPD and without diabetes had a greater risk of death (HR= 1.93; 95% CI:1.66, 2.24) and this risk increased among subjects with both COPD and diabetes (HR=2.59; 95% CI:2.01, 3.34).

3.4 Discussion

In this retrospective cohort study, the relationship between multimorbidity and all-cause mortality among CCHS participants aged 35 years and above was examined. In addition, age-group specific relationships between mortality and each of the nine chronic diseases that were used to define multimorbidity were determined.

A positive association between multimorbidity and risk of death after adjusting for potential confounders was found in this study. A similar result has been observed in previous studies examining the relationship between multimorbidity and mortality.[26,27] In a meta-analysis based on 26 studies, it was reported that people aged 65 years old and above with multimorbidity had a 1.73 times higher risk of all-cause mortality (HR=1.73; 95% CI: 1.41, 2.13),[28] which was very similar to the findings in this study for subjects aged 65 years and above (HR=1.71;95% CI:1.63, 1.80). In a 9-year follow-up study based on the data from the 1999 Large Health Survey of Veteran Enrollees in the United States, it was reported that an increase in the number of comorbid medical disorders was associated with a higher risk of all-cause mortality after correcting for confounding effects.[29] In a study examining the underlying biological mechanism for the relationship between multimorbidity and mortality, it was reported that the impact of multimorbidity on mortality is probably similar to the physiological mechanisms of increasing mortality risk in individuals with a single disease.[28]

In this study, the effect of multimorbidity on the risk of deaths decreased from the youngest age group to the older. Subjects in the youngest age group (35 to 49 years) had 3.77 times (95 % CI: 3.04, 4.67) greater the risk of death in comparison to the two older age groups, 50 to 64 years and 65 years and above (HR=2.64; 95 % CI: 2.36, 2.95 and HR=1.71; 95% CI:1.63,1.80, respectively). Evidence for a lower risk of mortality in people with

multimorbidity while ageing can be found in other studies.[8,30,26] For example, a study based on a UK biobank reported that all-cause mortality was greater in the middle-aged subjects than the older subjects, particularly in males.[14] A prospective cohort study of older adults in central Italy has shown that disability, rather than multimorbidity, had a greater impact on mortality in the elderly aged over 80 years and above.[31] In another study, it was reported that a survival effect could be a possible explanation, with the hypothesis being that subjects with life-threatening multimobidities die before they could age.[32]

In this study, significant interactions were observed between demographic and socioeconomic characteristics and multimorbidity when stratified by age groups. Some post-secondary education had a protective against the risk of death in comparison to less than secondary education in subjects with multimorbidity in the 35 to 49 years age group. This is in agreement with a study based on a Danish population which reported that a lower level of education was associated with a higher risk of overall mortality adjusting for the effect of multimorbidity, life factors, and quality of life.[13,33]

Among subjects aged 35 to 49 years with multimorbidity, a significant reduction in the risk of death was found among moderate drinkers (HR=0.52; 95% CI: 0.36, 0.73; p<0.001) and a non-significant reduction in the heavy drinkers (HR=0.72; 95% CI:0.41,1.27; p=0.26) in comparison to non-drinkers. Similar results were reported in a study based on the UK biobank with alcohol consumption having a protective effect against the risk of all-cause mortality across all drinking categories (1-3 times/month,1-4 times/week, and daily or almost daily) when compared to never drinkers or special occasion drinkers.[14] The finding in the present study of a protective effect of multimorbidity with mortality observed among moderate drinkers in comparison to that of the non-drinkers in the age group 35 to 49 years was

unexpected. A healthy response bias or abstainer bias [34] among non-drinkers may be a possible explanation with possibly some of the non-drinkers being advised to quit drinking because of their poor health status by their healthcare professionals.[35]

In subjects aged 65 and above, there was a significant reduction in the risk of death in all the body weight categories in comparison to underweight among both subjects with and without multimorbidity. Similar to the finding in this study, a study based on the UK biobank including subjects aged 37 to 73 years old reported that subjects who were underweight had a higher risk of death in comparison to those who were normal weight after adjusting for confounding effects (HR=1.04; 95% CI: 1.037, 1.048).[14] Subjects who are underweight generally have worse health than the general population, which could explain the disparity in mortality risk between underweight and the other categories of obesity.[36] Low weight may also be a consequence of poor health. We also found that a lower risk of death in subjects who were in the common-law and married category and an increased risk of death was found in subjects who were in the widowed, divorced and separated category in comparison to those who were single. This was present in both subjects with multimorbidity and without multimorbidity. Similar results were found in a study based on self-reported data from the 2008 and 2010 Health and Retirement Study of Americans aged 50 years old and older, which reported that people who were married had the lowest odds of mortality across all the categories (i.e., widowed, divorced, never married) after adjusting the potential confounders.[33] In contrast, a study of community-dwellers who aged 65 years old and above from the Manitoba Study of Health and Ageing did not find marital status to have an effect on the association between multimorbidity and mortality.[10]

When the separate effect of each chronic disease that was used to define

multimorbidity, was examined jointly in this study, all the chronic diseases except asthma were associated with an increased risk of death after adjusting the potential confounders. In this study, subjects aged 35 to 49 years old were found to have a higher risk of death for the majority of the nine chronic diseases than subjects who were in the older age group. This finding was in agreement with the results when we considered multimorbidity. Subjects with cancer had the highest risk of death among the nine chronic disease for each age group in this study, which was expected since cancer is a leading cause of death in Canada and worldwide.[37] The report of a mood disorder was also associated with excess mortality among the younger age group. A meta-analysis has similarly reported that excess mortality was found in depressed subjects compared to non-depressed subjects (overall RR=1.81; 95% CI: 1.58, 2.07).[38] A marginal protective effect of a mood disorder on mortality in older adults was observed in this study. Similar results were found in a study based on older adults aged 60 years old and above in five contiguous central North Carolina counties with depression measured using symptom counts having a non-significant protective effect on mortality in both unadjusted (RR=0.96; 95% CI: 0.40, 2.34) and adjusted models ($RR_{\text{adjusted model1}}$= 0.88; 95% CI: 0.35, 2.21; $RR_{\text{adjusted mode2}}$=0.62; 95% CI: 0.24,1.57).[39] Lower suicide rates in older populations may be one possible explanation, since it has been suggested that suicide is the major cause of death among people with a mood disorder.[40]

Among the nine chronic diseases considered in this study, arthritis had the relatively low but insignificant risk of death in all the age groups. It was expected since arthritis mortality was reported to decline over recent years due to better control of inflammation associated with arthritis.[41] Some studies have shown that subject with arthritis had an

increased risk of death[42] and the risk increased with ageing.[43] In this study, an increased risk of death was not observed for arthritis in the older age group. One possible explanations is that other chronic diseases such as heart-related disease, rather than arthritis, contribute largely to the death in the older age groups.[44] We also found that asthma had a lower risk of death than the other chronic diseases in all age groups but the differences were insignificant. However, other studies have reported the opposite relationship.[45] The significantly lower risk of death in patients with asthma compared to many other chronic diseases may be due to better diagnosis and control at an early stage of the disease.[46]

In this study, significant interactions between asthma and mood disorder and diabetes and COPD, with risk of death were found in subjects aged 45 to 64 years. The coexistence of mood disorder in patients with asthma has previously been reported to be associated with increased mortality.[47] For example, a cohort study of asthma patients in the United States based on data from the National Veterans Affairs and Centers for Medicare and Medicaid Services Encounter databases, found that among veterans with asthma aged 46 to 64 years old, coexisting mental disorder was associated with increased all-cause mortality in comparison to those with asthma only, after adjusting the confounding effects (adjusted OR=1.48, 95% CI: 1.03, 2.10).[48] Although there have been a few studies focusing on the association of asthma-mental illness comorbidity with mortality, one such study reported that patients with depression had a greater number of emergency room visits due to asthma-related complications.[49] However, in this study, there was a non-significant protective effect of mood disorder on all-cause mortality among subjects with asthma. The contrasting difference in the results between this study and the previous studies may be

related to several factors including the population studied, the definition of a mood disorder, and the length of the follow up. In this study, among subjects with COPD, those without diabetes was associated with an increased risk of death compared to those without diabetes and COPD after adjusting other confounding effects. This risk was elevated even more in subjects with both COPD and diabetes. The joint effect of diabetes and COPD on mortality has also been investigated in other studies. In a multicenter cohort study of 2,164 COPD patients, COPD patients with diabetes had an increased risk of death in comparison to those COPD patients without diabetes. (HR=1.7; 95% CI:1.2, 2.4).[50] In another cohort study based on the Taiwan Longitudinal Health Insurance Database, similar results were reported in that COPD patients with pre-existing diabetes had a 24.4% greater risk of death (HR=1.24; 95% CI: 1.010, 1.532) compared to COPD patients without pre-existing diabetes.[51] The underlying biological mechani.sm is still unknown and possibly multifactorial. It has been suggested that the increased the glucose concentration in the airway in diabetes may stimulate or maintain the development of airways bacteria. As a consequence, patients with diabetes are more susceptible to bacterial lung infection, which may result in more severe symptoms related to COPD and an increased risk of mortality.[52]

This study has both strengths and limitations. Firstly, the majority of the previous studies on multimorbidity and mortality were based on provincial databases, whereas this study was based on a nationwide health survey representing the entire Canadian population. The large sample size potentially reduced selection bias and sampling errors. To the best of the author's knowledge, it is the first study using a linked database of CCHS-CVSD data to examine the relationship between multimorbidity and mortality among the Canadian population. Recognizing multimorbidity associated mortality is multifactorial, this study

included a wide range of confounders in the analysis to adjust for possible confounding. Furthermore, this study examined the joint effects between chronic diseases among subjects with multimorbidity. These results may guide the healthcare professional to intervene, provide appropriate treatment and manage comorbidity. There are some limitations in the study as well. Unlike other studies where chronic diseases were weighted according to the severity of the diseases and the effects of disease-related functional impairment,[53] the effect of each chronic disease was weighted the same in this study. Additionally, the presence of chronic disease was identified by self-report of a health professional diagnosis, which could lead to potential underestimation of multimorbidity.

In conclusion, multimorbidity was associated with increased all-cause mortality after adjusting for health behaviours, demographic factors, and socioeconomic status in the middle-aged to older Canadians. The association between multimorbidity and mortality was significant across all age groups with decreasing proportional risk from the younger to older age groups. Similar results were observed while examining each chronic disease that was used to define multimorbidity. All the chronic diseases except asthma were found to be associated with excess mortality regardless of the age groups after adjusting for the potential confounders. Moreover, the effect of each chronic disease except asthma on mortality decreased from the younger to older population. In this study, diabetes had an increased risk of mortality among subjects with COPD. Given that multimorbidity had a proportionately greater effect on mortality among middle-aged subjects than older subjects in this study, prevention goals should target middle-aged subjects in order to reduce excess mortality associated with multimorbidity. Additional information on the causes of death is required to delineate the mortality associated with multimorbidity from other causes and establish

causal relationships between multimorbidity and mortality.

Table 3.1 Description of follow-up from the linkage of the Canadian Community Health Surveys (2003–2014) with the Canadian Vital Statistics—Death database.

		Description of respondents who died during the follow-up				Description of respondents who were censored during the follow-up			
Year of entry	Number of people included in analysis	Number of deaths	Total survival time (days)	Mean	Proportion of deaths (%)	Number censored	Total survival time (days)	Mean	Proportion of censored (%)
2003/2004	71650	17505	49981490	2855.27	24.43	54145	287048205	5301.47	75.57
2005/2006	73085	15125	37330265	2468.12	20.70	57960	264652080	4566.12	79.30
2007	38725	6580	13771840	2092.98	16.99	32145	123540730	3843.23	83.01
2008	37495	5720	10724955	1874.99	15.26	31775	110604045	3480.85	84.74
2009	35190	4675	7974535	1705.78	13.29	30515	95018670	3113.83	86.71
2010	34935	4255	6347420	1491.76	12.18	30680	84360925	2749.70	87.82
2011	35400	3535	4584620	1296.92	9.99	31865	75935835	2383.05	90.01
2012	34995	2940	3306575	1124.69	8.40	32055	64703080	2018.50	91.60
2013	36930	2600	2341075	900.41	7.04	34330	56825425	1655.27	92.96
2014	36480	1795	1276625	711.21	4.92	34685	44855700	1293.23	95.08
Total	434885	64730	137639400	16522.13		370155	1207544695	30405.26	

Note: Figures in the table were rounded off using base-five rounding rules.

Table 3.2 The distribution of incidence of death and unadjusted hazard ratios for the nine chronic diseases and multimorbidity.

Disease group	Incidence (%)	Hazard ratio (95% CI)	p-value
Asthma			
No	0.09	1.00	
Yes	0.11	1.29 (1.23, 1.36)	<0.001
Arthritis			
No	0.07	1.00	
Yes	0.16	2.41 (2.35, 2.48)	<0.001
High Blood Pressure			
No	0.07	1.00	
Yes	0.16	2.65 (2.57, 2.73)	<0.001
Diabetes			
No	0.08	1.00	
Yes	0.20	2.97 (2.86, 3.08)	<0.001
Heart Disease			
No	0.08	1.00	
Yes	0.28	4.34 (4.19, 4.50)	<0.001
Cancer			
No	0.08	1.00	
Yes	0.31	4.68 (4.43, 4.94)	<0.001
Stroke			
No	0.09	1.00	
Yes	0.36	5.24 (4.94, 5.56)	<0.001
Mood Disorder			
No	0.09	1.00	
Yes	0.10	1.21 (1.15, 1.28)	<0.001
COPD			
No	0.09	1.00	
Yes	0.25	4.22 (4.01, 4.44)	<0.001
Multimorbidity			
No	0.04	1.00	
Yes	0.20	6.15 (5.91, 6.41)	<0.001

Table 3.3 Cumulative incidence of death and unadjusted hazard ratio of multimorbidity by CCHS cycle.

Year of entry	Incidence (%)	Unadjusted hazard ratio of multimorbidity	Lower 95% CI	Upper 95% CI
2003/2004	24.43	5.80	5.44	6.18
2005/2006	20.70	6.10	5.71	6.52
2007	16.70	5.80	5.18	6.50
2008	15.26	6.61	5.84	7.47
2009	13.29	5.91	5.16	6.77
2010	12.18	5.82	4.98	6.80
2011	9.99	6.56	5.08	8.45
2012	8.40	6.95	5.90	8.20
2013	7.04	6.48	5.33	7.88
2014	4.92	7.50	5.33	10.44

Table 3.4 Incidence of death and unadjusted hazard ratios for the baseline factors.

Baseline factors	Incidence	Hazard ratio (95% CI)	p-value
Sex			
Female	0.08	1.00	
Male	0.10	1.19 (1.16, 1.23)	<0.001
Racial Background			
Non-white	0.04	1.00	
White	0.10	2.43 (2.20, 2.69)	<0.001
Body weight			
Under weight	0.19	1.00	
Normal weight	0.09	0.42 (0.39, 0.46)	<0.001
Overweight	0.08	0.38 (0.35, 0.41)	<0.001
Obese	0.11	0.54 (0.50, 0.59)	<0.001
Marital status			
Single	0.07	1.00	
Widowed/Divorced/Separated	0.18	2.57 (2.42, 2.73)	<0.001
Common-law/Married	0.07	0.93 (0.87, 0.98)	0.009
Province of residence			
British Columbia	0.10	1.00	
Prairies	0.09	0.95 (0.91,1.00)	0.05
Quebec	0.09	0.93 (0.88, 0.97)	0.003
Ontario	0.09	0.90 (0.86, 0.95)	<0.001
Atlantic	0.11	1.11 (1.06, 1.16)	<0.001
Territories	0.07	0.77 (0.68, 0.86)	<0.001
Household income			
less than $39,999	0.16	1.00	
$40,000 to $59,999	0.09	0.51 (0.49, 0.54)	<0.001
$60,000 to $79,999	0.06	0.33 (0.31, 0.35)	<0.001
$80,000 or more	0.07	0.37 (0.36, 0.39)	<0.001
Highest household education			
Less than secondary school graduation	0.20	1.00	
Secondary school graduation, no post-secondary education	0.08	0.41 (0.39, 0.42)	<0.001
Some post-secondary education	0.09	0.42 (0.39, 0.46)	<0.001
Post-secondary and above	0.06	0.29 (0.28, 0.30)	<0.001
Smoking status			
Non-Smoker	0.09	1.00	
Smoker	0.10	1.10 (1.06, 1.14)	<0.001
Alcohol			

No	0.15	1.00	
Moderate	0.07	0.41 (0.40, 0.42)	<0.001
Heavy	0.12	0.78 (0.74, 0.81)	<0.001
Physical activity			
Inactive	0.11	1.00	
Moderate	0.06	0.59 (0.57, 0.61)	<0.001
Active	0.05	0.50 (0.47, 0.52)	<0.001
Stress			
Not and not very stressful	0.13	1.00	
Somewhat	0.07	0.53 (0.51, 0.54)	<0.001
Extreme	0.08	0.62 (0.57, 0.67)	<0.001

Table 3.5 Incidence of death and unadjusted hazard ratios for the nine chronic diseases and baseline factors by age groups.

	35 to 49 years		50 to 64 years		65 years and above	
Disease group/baseline factors	Incidence	Hazard ratio (95% CI)	Incidence	Hazard ratio (95% CI)	Incidence	Hazard ratio (95% CI)
Cancer						
No	0.02	1.00	0.05	1.00	0.26	1.00
Yes	0.16	12.77 (9.10,17.93)	0.21	4.90 (4.36, 5.51)	0.40	1.94 (1.82, 2.07)
COPD						
No	0.02	1.00	0.05	1.00	0.26	1.00
Yes	0.07	6.35 (3.91, 10.32)	0.13	3.50 (3.13, 3.92)	0.31	2.30 (2.18, 2,44)
Stroke						
No	0.02	1.00	0.05	1.00	0.26	1.00
Yes	0.09	6.09 (4.13, 8.98)	0.17	3.49 (2.92, 4.17)	0.49	2.37 (2.23, 2.53)
Diabetes						
No	0.02	1.00	0.05	1.00	0.25	1.00
Yes	0.04	3.10 (2.48, 3.86)	0.11	2.51 (2.30, 2.74)	0.33	1.50 (1.45, 1.56)
Heart Disease						
No	0.02	1.00	0.05	1.00	0.24	1.00
Yes	0.05	3.00 (2.40, 3.75)	0.13	2.77 (2.50, 3.05)	0.39	1.85 (1.79, 1.92)
Mood Disorder						
No	0.01	1.00	0.05	1.00	0.26	1.00
Yes	0.03	2.49 (2.05, 3.03)	0.08	1.78 (1.61, 1.97)	0.30	1.29 (1.21, 1.37)
High Blood Pressure						
No	0.01	1.00	0.63	1.00	0.26	1.00
Yes	0.08	2.20 (1.87, 2.60)	0.37	1.63 (1.53, 1.75)	0.08	1.12 (1.09, 1.16)
Arthritis						
No	0.01	1.00	0.05	1.00	0.25	1.00
Yes	0.03	2.08 (1.76, 2.46)	0.07	1.34 (1.25, 1.44)	0.29	1.12 (1.09, 1.17)
Asthma						

No	0.02	1.00	0.05	1.00	0.26	1.00
Yes	0.02	1.58 (1.24, 2.02)	0.08	1.47 (1.32, 1.64)	0.31	1.24 (1.18, 1.31)
Multimorbidity						
No	0.01	1.00	0.03	1.00	0.20	1.00
Yes	0.05	4.77 (3.94, 5.77)	0.10	3.16 (2.87, 3.48)	0.32	1.52 (1.74,1.90)
Sex						
Female	0.01	1.00	0.04	1.00	0.25	1.00
Male	0.02	1.56 (1.35, 1.81)	0.07	1.56 (1.45, 1.67)	0.29	1.28 (1.22,1.32)
Racial Background						
Non-white	0.01	1.00	0.03	1.00	0.17	1.00
White	0.02	1.44 (1.07, 1.94)	0.06	1.81 (1.46, 2.25)	0.28	1.66 (1.48, 1.86)
Body weight						
Under weight	0.04	1.00	0.11	1.00	0.46	1.00
Normal weight	0.02	0.42 (0.30, 0.59)	0.05	0.42 (0.34, 0.51)	0.28	0.51 (0.46, 0.56)
Overweight	0.01	0.37 (0.26, 0.53)	0.05	0.41 (0.33, 0.50)	0.23	0.40 (0.37, 0.44)
Obese	0.02	0.62 (0.44, 0.88)	0.07	0.60 (0.49, 0.74)	0.29	0.59 (0.53, 0.65)
Marital status						
Single	0.03	1.00	0.08	1.00	0.28	1.00
Widowed/Divorced/Separated	0.02	0.81 (0.65, 1.00)	0.08	0.99 (0.87, 1.13)	0.34	1.17 (1.09, 1.26)
Common-law/Married	0.01	0.40 (0.34, 0.47)	0.05	0.55 (0.49, 0.61)	0.23	0.74 (0.69, 0.80)
Province of residence						
British Columbia	0.02	1.00	0.05	1.00	0.28	1.00
Prairies	0.02	0.82 (0.64, 1.05)	0.06	1.15 (1.02, 1.31)	0.28	1.02 (0.97, 1.07)
Quebec	0.01	0.69 (0.52, 0.89)	0.06	1.12 (0.99, 1.26)	0.25	0.89 (0.84, 0.94)
Ontario	0.02	0.80 (0.64, 1.00)	0.05	1.04 (0.93, 1.17)	0.26	0.92 (0.87, 0.97)
Atlantic	0.02	0.88 (0.70, 1.13)	0.07	1.36 (1.21, 1.53)	0.29	1.08 (1.02, 1.14)
Territories	0.02	1.06 (0.72, 1.55)	0.07	1.40 (1.12, 1.75)	0.30	1.16 (0.99, 1.35)
Household income						
less than $39,999	0.03	1.00	0.09	1.00	0.30	1.00
$40,000 to $59,999	0.02	0.62 (0.59, 0.76)	0.06	0.60 (0.53, 0.69)	0.21	0.73 (0.69, 0.76)

$60,000 to $79,999	0.02	0.45 (0.38, 0.62)	0.04	0.45 (0.40, 0.51)	0.18	0.65 (0.61, 0.70)
$80,000 or more	0.01	0.37 (0.31, 0.43)	0.04	0.41 (0.37, 0.44)	0.29	0.82 (0.79, 0.85)
Highest household education						
Less than secondary school graduation	0.04	1.00	0.09	1.00	0.34	1.00
Secondary school graduation, no post-secondary education	0.02	0.60 (0.48, 0.75)	0.05	0.54 (0.49, 0.59)	0.25	0.78 (0.74, 0.81)
Some post-secondary education	0.02	0.55 (0.42, 0.70)	0.07	0.70 (0.59, 0.83)	0.28	0.81 (0.74, 0.89)
Post-secondary and above	0.01	0.38 (0.33, 0.45)	0.05	0.53 (0.49, 0.57)	0.21	0.66 (0.63, 0.68)
Smoking status						
Non-Smoker	0.01	1.00	0.04	1.00	0.26	1.00
Smoker	0.02	3.72 (2.38, 3.12)	0.10	2.55 (2.27, 2.74)	0.37	1.56 (1.50, 1.63)
Alcohol						
No	0.02	1.00	0.08	1.00	0.34	1.00
Moderate	0.01	0.68 (0.57,0.82)	0.05	0.57 (0.52, 0.63)	0.23	0.63 (0.61, 0.65)
Heavy	0.03	1.28 (0.99, 1.66)	0.06	0.71 (0.62, 0.81)	0.26	0.70 (0.67, 0.74)
Physical activity						
Inactive	0.02	1.00	0.07	1.00	0.31	1.00
Moderate	0.01	0.74 (0.62, 0.88)	0.04	0.64 (0.59, 0.70)	0.19	0.58 (0.56, 0.61)
Active	0.01	0.73 (0.61, 0.87)	0.04	0.59 (0.54, 0.65)	0.16	0.50 (0.48, 0.53)
Stress						
Not and not very stressful	0.02	1.00	0.06	1.00	0.27	1.00
Somewhat	0.01	0.88 (0.76, 1.03)	0.05	0.92 (0.85, 0.99)	0.26	1.01 (0.97, 1.04)
Extreme	0.03	1.61(1.18, 2.22)	0.07	1.31 (1.14, 1.51)	0.34	1.29 (1.22, 1.58)
Year of entry						
2003/2004	0.04	1.00	0.13	1.00	0.54	1.00
2005/2006	0.03	0.90 (0.76, 1.06)	0.01	0.95 (0.88, 1.04)	0.46	0.98 (0.94, 1.03)
2007	0.03	1.34 (1.10, 1.67)	0.01	0.88 (0.79, 0.99)	0.36	0.94 (0.88, 0.99)
2008	0.01	0.76 (0.60, 0.96)	0.05	0.95 (0.84, 1.07)	0.32	0.92 (0.87, 0.98)
2009	0.01	0.76 (0.58, 1.27)	0.05	0.78 (0.67, 0.91)	0.28	0.91 (0.85, 0.96)
2010	0.01	0.90 (0.64, 1.26)	0.04	0.83 (0.72, 0.95)	0.25	0.93 (0.87. 0.99)

2011	0.01	0.89 (0.62, 1.37)	0.04	0.97 (0.77, 1.21)	0.21	0.94 (0.87, 1.03)
2012	0.01	0.92 (0.63, 1.87)	0.03	0.84 (0.69, 1.04)	0.17	0.90 (0.83, 0.97)
2013	0.01	1.09 (0.61, 2.79)	0.02	0.81 (0.67, 0.95)	0.13	0.90 (0.82, 0.98)
2014	0.01	1.31 (0.61, 1.14)	0.02	0.89 (0.69, 1.15)	0.09	0.81 (0.74, 0.89)

Table 3.6 Adjusted hazard ratios of multimorbidity and baseline factors without interactions by age groups.

	35 to 49 years	50 to 64 years	65 years and above
Disease group/baseline factors	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Multimorbidity			
No	1.00	1.00	1.00
Yes	3.77 (3.04, 4.67)	2.64 (2.36, 2.95)	1.71 (1.63, 1.80)
Sex			
Female	1.00	1.00	1.00
Male	1.83 (1.50, 2.23)	1.81 (1.65, 1.99)	1.77 (1.68, 1.85)
Racial Background			
Non-white			1.00
White	-	-	1.97 (1.71, 2.26)
Body weight			
Under weight	1.00	1.00	1.00
Normal weight	0.42 (0.27, 0.65)	0.53 (0.41, 0.70)	0.51 (0.45, 0.58)
Overweight	0.33 (0.21, 0.52)	0.50 (0.38, 0.67)	0.36 (0.31, 0.40)
Obese	0.47 (0.30, 0.74)	0.57 (0.43, 0.75)	0.35 (0.31, 0.40)
Marital status			
Single	1.00	1.00	1.00
Widowed/Divorced/Separated	0.81 (0.63, 1.04)	1.07 (0.91, 1.26)	1.21 (1.11, 1.32)
Common-law/Married	0.66 (0.53, 0.82)	0.70 (0.61, 0.80)	0.75 (0.69, 0.82)
Province of residence			
British Columbia			1.00
Prairies			0.90 (0.84, 0.96)
Quebec	-	-	0.76 (0.70, 0.82)
Ontario			0.81 (0.76, 0.87)
Atlantic			0.80 (0.75, 0.87)
Territories			0.83 (0.64, 1.08)
Household income			

less than $39,999	1.00	1.00	1.00
$40,000 to $59,999	0.78 (0.60, 1.02)	0.84 (0.70, 1.00)	0.84 (0.79, 0.90)
$60,000 to $79,999	0.78 (0.56, 1.07)	0.74 (0.63, 0.86)	0.83 (0.75, 0.91)
$80,000 or more	0.61 (0.48, 0.79)	0.66 (0.59, 0.74)	0.94 (0.89, 0.98)
Highest household education			
Less than secondary school graduation	1.00	1.00	1.00
Secondary school graduation, no post-secondary education	0.91 (0.68, 1.21)	0.72 (0.64, 0.80)	0.89 (0.84, 0.94)
Some post-secondary education	0.68 (0.50, 0.92)	0.82 (0.69, 0.97)	0.86 (0.78, 0.95)
Post-secondary and above	0.67 (0.55, 0.82)	0.81 (0.73. 0.89)	0.77 (0.73, 0.80)
Smoking status			
Non-Smoker	1.00	1.00	1.00
Smoker	1.79 (1.50, 2.14)	1.99 (1.81, 2.18)	1.30 (1.23, 1.38)
Alcohol			
No	1.00	1.00	1.00
Moderate	0.82 (0.66, 1.03)	0.72 (0.63, 0.82)	0.72 (0.69, 0.76)
Heavy	1.28 (0.92, 1.78)	0.85 (0.73, 1.00)	0.82 (0.76, 0.88)
Physical activity			
Inactive		1.00	1.00
Moderately	-	0.79 (0.71, 0.88)	0.62 (0.59, 0.65)
Active		0.73 (0.64, 0.82)	0.53 (0.49, 0.56)
Stress			
Not and not very stressful		1.00	1.00
Somewhat	-	0.82 (0.75, 0.91)	0.93 (0.90, 0.97)
Extreme		0.88 (0.74, 1.05)	0.96 (0.81, 1.14)

*Only significant variables were adjusted in the proportional hazards models.

Table 3.7 Adjusted hazard ratios for significant interactions from the multivariable proportional hazards model for 35 to 49 years.

Baseline factors	Hazard ratio (95% CI)	p-value
Alcohol (With multimorbidity)		
No	1.00	
Moderate	0.52 (0.36, 0.73)	<0.001
Heavy	0.72 (0.41, 1.27)	0.26
Alcohol (Without multimorbidity)		
No	1.00	
Moderate	1.27 (0.96, 1.67)	0.11
Heavy	2.05 (1.37, 3.07)	0.001
Education (With multimorbidity)		
Less than secondary school graduation	1.00	
Secondary school graduation, no post-secondary education	0.96 (0.59, 1.58)	0.88
Some post-secondary education	0.41 (0.25, 0.65)	<0.001
Post-secondary and above	0.83 (0.59, 1.17)	0.29
Education (Without multimorbidity)		
Less than secondary school graduation	1.00	
Secondary school graduation, no post-secondary education	0.85 (0.60, 1.19)	0.34
Some post-secondary education	0.83 (0.56, 1.23)	0.35
Post-secondary and above	0.58 (0.45, 0.76)	<0.001

Table 3.8 Adjusted hazard ratios for significant interactions from the multivariable proportional hazards model for 65 years and above.

Baseline factors	Hazard ratio (95% CI)	p-value
Body weight (With multimorbidity)		
Under weight	1.00	
Normal weight	0.50 (0.43, 0.60)	<0.001
Overweight	0.35 (0.30, 0.41)	<0.001
Obese	0.33 (0.28, 0.39)	<0.001
Body weight (Without multimorbidity)		
Under weight	1.00	
Normal weight	0.54 (0.44, 0.66)	<0.001
Overweight	0.36 (0.29, 0.44)	<0.001
Obese	0.49 (0.38, 0.61)	<0.001
Marital status (With multimorbidity)		
Single	1.00	
Widowed/Divorced/Separated	1.19 (1.07, 1.32)	0.001
Common-law/Married	0.78 (0.71, 0.87)	<0.001
Marital status (Without multimorbidity)		
Single	1.00	
Widowed/Divorced/Separated	1.28 (1.10, 1.50)	0.002
Common-law/Married	0.68 (0.58, 0.79)	<0.001

Table 3.9 Adjusted hazard ratios of nine chronic diseases without interactions by age groups.

	35 to 49 years	50 to 64 years	65 years and above
Disease group/baseline factors	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Cancer			
No	1.00	1.00	1.00
Yes	10.72 (7.61, 15.09)	4.23 (3.73, 4.79)	1.75 (1.63, 1.87)
COPD			
No	1.00	1.00	1.00
Yes	2.61 (1.55, 4.40)	1.75 (1.53, 2.01)	1.75 (1.64, 1.88)
Diabetes			
No	1.00	1.00	1.00
Yes	1.94 (1.54, 2.44)	1.76 (1.59, 1.96)	1.39 (1.33, 1.45)
Stroke			
No	1.00	1.00	1.00
Yes	1.65 (1.04, 2.62)	1.61 (1.32, 1.97)	1.49 (1.39, 1.60)
High Blood Pressure			
No	1.00	1.00	1.00
Yes	1.48 (1.23, 1.78)	1.26 (1.15,1.37)	1.06 (1.02, 1.10)
Heart Disease			
No	1.00	1.00	1.00
Yes	1.32 (0.99, 1.77)	1.65 (1.47, 1.85)	1.53 (1.47, 1.59)
Mood Disorder			
No	1.00	1.00	1.00
Yes	1.38 (1.10, 1.73)	1.09 (0.97, 1.22)	0.92 (0.86, 0.99)
Arthritis			
No	1.00	1.00	1.00
Yes	1.27 (1.05, 1.52)	1.04 (0.97, 1.22)	1.02 (0.99, 1.06)
Asthma			
No	1.00	1.00	1.00
Yes	1.10 (0.84, 1.43)	1.09 (0.96, 1.23)	1.02 (0.96, 1.08)
Highest household education			
Less than secondary school graduation	1.00	1.00	1.00

Secondary school graduation, no post-secondary education	0.85 (0.68, 1.06)	0.74 (0.67, 0.81)	0.90 (0.86, 0.95)
Some post-secondary education	0.65 (0.50, 0.85)	0.93 (0.78, 1.12)	0.90 (0.81, 1.00)
Post-secondary and above	0.65 (0.54, 0.77)	0.80 (0.74. 0.88)	0.78 (0.75, 0.81)
Smoking status			
Non-Smoker	1.00	1.00	1.00
Smoker	1.99 (1.71, 2.32)	2.05 (1.88, 2.23)	1.30 (1.24, 1.37)
Alcohol			
No	1.00	1.00	1.00
Moderate	0.84 (0.70, 1.00)	0.76 (0.68, 0.84)	0.73 (0.71, 0.76)
Heavy	1.41 (1.08, 1.83)	0.88 (0.77, 1.01)	0.81 (0.77, 0.86)
Physical activity			
Inactive		1.00	1.00
Moderately	-	0.81 (0.74, 0.88)	0.63 (0.60, 0.66)
Active		0.76 (0.69, 0.83)	0.54 (0.51, 0.57)
Stress			
Not and not very stressful			1.00
Somewhat	-	-	0.90 (0.87, 0.93)
Extreme			0.95 (0.80, 1.12)
The year of entry			
2003/2004		1.00	1.00
2005/2006		1.03 (0.95, 1.12)	1.03 (0.98, 1.08)
2007	-	0.91 (0.81, 1.03)	1.00 (0.94, 1.06)
2008		0.97 (0.85, 1.11)	0.97 (0.91, 1.03)
2009		0.80 (0.68, 0.93)	0.94 (0.88, 1.01)
2010		0.82 (0.71, 0.95)	0.95 (0.88, 1.02)
2011		0.93 (0.73, 1.19)	0.96 (0.87, 1.05)
2012		0.80 (0.64, 1.00)	0.92 (0.85, 1.01)
2013		0.79 (0.66, 0.95)	0.96 (0.87, 1.06)
2014		0.78 (0.58, 1.04)	0.88 (0.78, 0.98)

*Only significant variables were included in the model. The cell highlighted in grey indicates it were insignificant.

Table 3.10 Adjusted hazard ratios for significant interactions between comorbidities from the multivariable proportional hazards model for 50 to 64 years.

Disease groups		Hazard ratio (95% CI)	p-value
Asthma	Mood disorder		
No	No	1.00	
Yes	No	1.19 (1.04, 1.36)	0.01
No	Yes	1.17 (1.04, 1.33)	0.01
Yes	Yes	0.91 (0.72, 1.15)	0.44
Diabetes	COPD		
No	No	1.00	
Yes	No	1.83 (1.64, 2.04)	<0.001
No	Yes	1.93 (1.66, 2.24)	<0.001
Yes	Yes	2.59 (2.01, 3.34)	<0.001

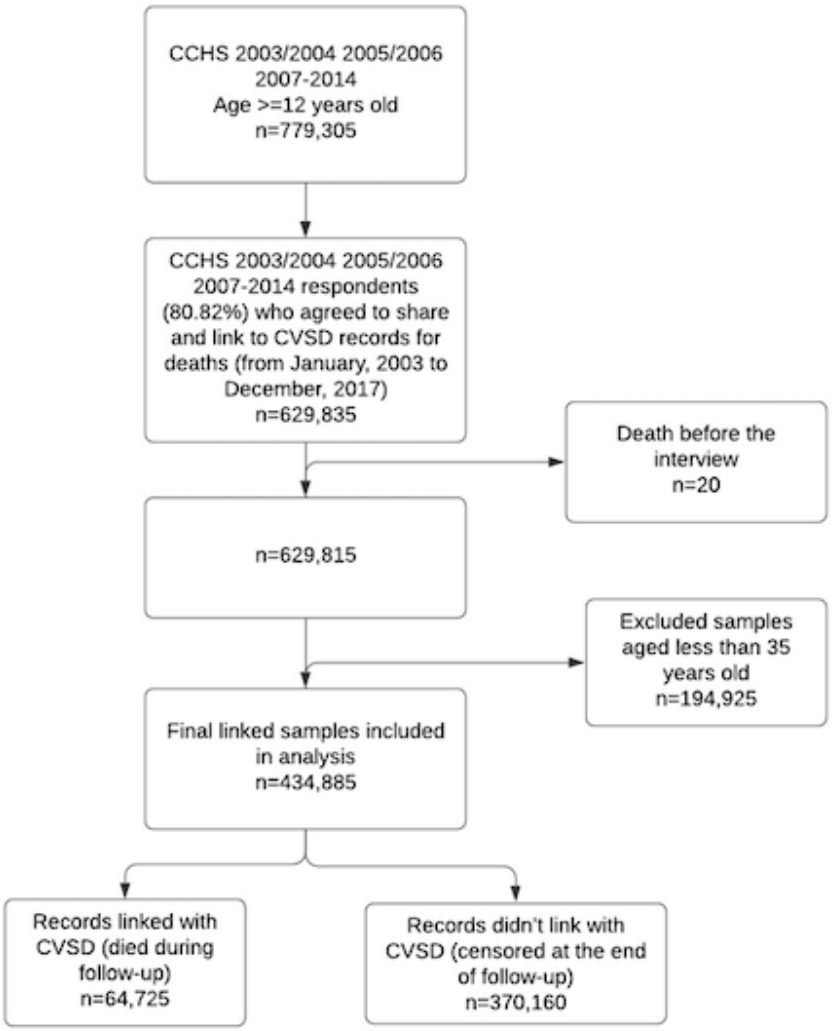

Figure 3.1 Description of inclusion and exclusion during follow-up and linkage.

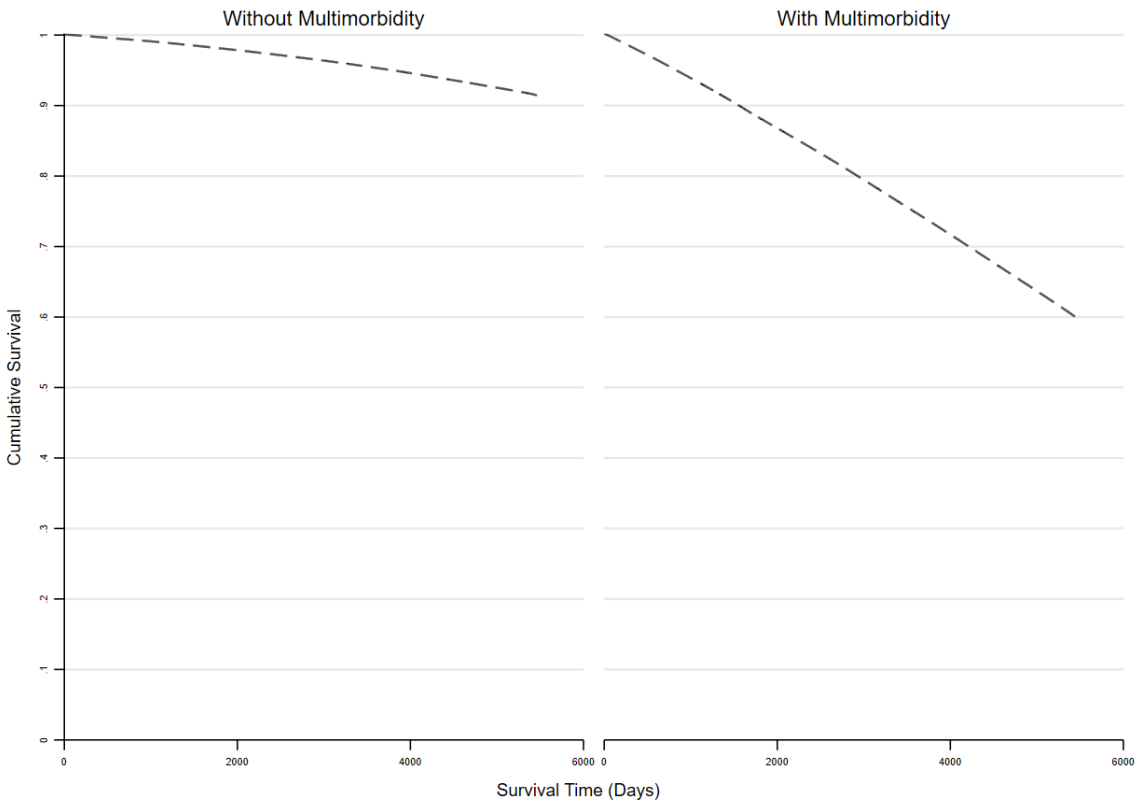

Figure 3.2 Smoothed Kaplan-Meier curves of cumulative survival probability for subjects with and without multimorbidity.

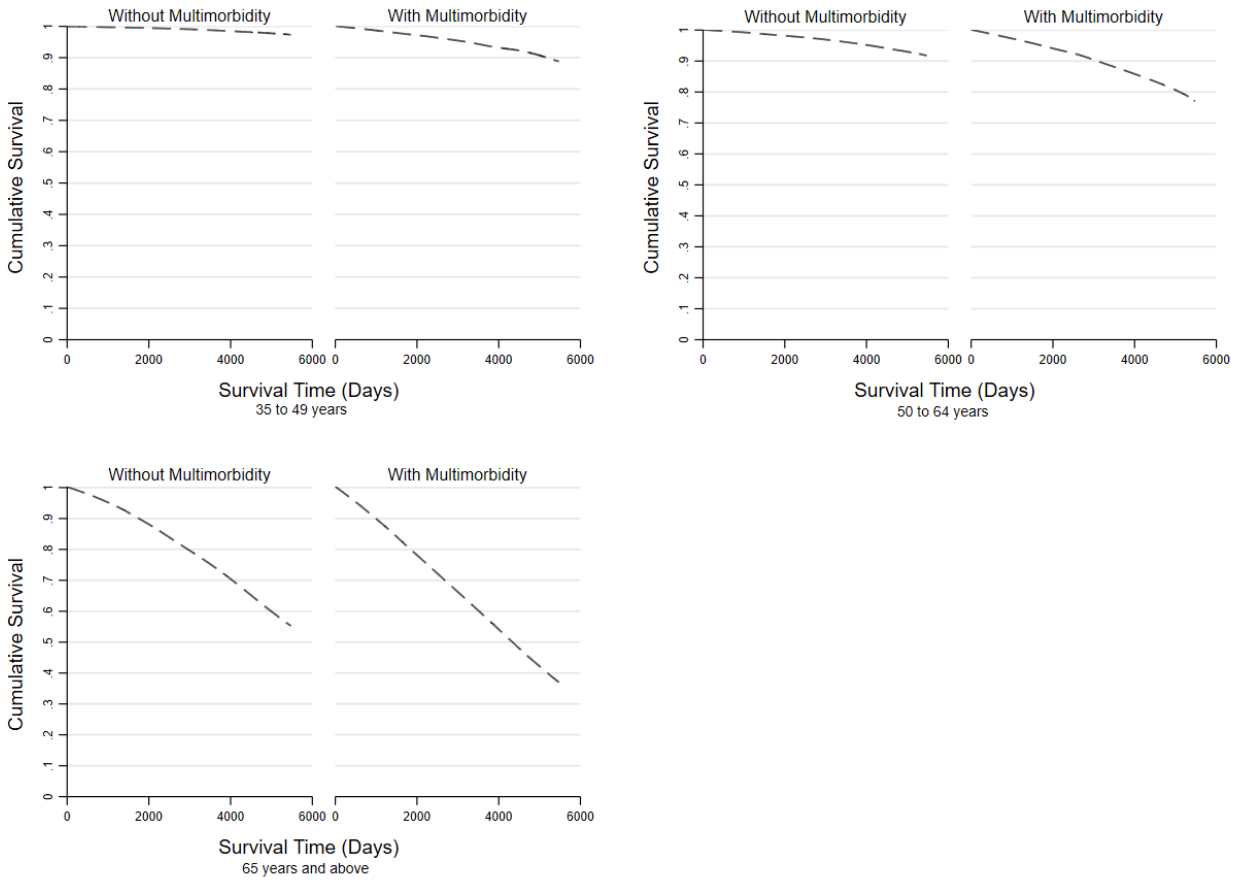

Figure 3.3 Smoothed Kaplan-Meier curves of cumulative survival probability for subjects with and without multimorbidity by age groups.

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Chapter 4

Discussion and conclusions

4.1 Summary of findings

In this thesis, the association between multimorbidity and all-cause mortality was examined in the middle-aged and senior Canadian population after adjusting for all confounding effects based on the linked database of CCHS-CVSD. Cox's proportional hazards models were used to estimate the hazard ratio of multimorbidity for the whole study sample and each age group.

Chapter 2 provided a narrative review of multimorbidity epidemiology and the effect of multimorbidity on mortality. In general, literature reviews suggested various factors as the link between multimorbidity and mortality. Specifically, a positive association was found between mortality and multimorbidity regardless of age group. Moreover, recent research on comorbidity concluded that patients with specific combinations have a higher risk of death than patients with other combinations or only one chronic disease.

In Chapter 3, CCHS-CVSD data with a maximum of 14 years follow-up was used to examine the association between multimorbidity and all-cause mortality in the middle-aged and senior Canadian population. Cox's proportional hazards models stratified by three age groups (35 to 49 years old, 50 to 64 years old, 65 years old and above) were used to estimate the hazard ratio of multimorbidity after adjusting for all confounding effects. The findings suggested that multimorbidity was positively associated with the risk of death and the proportionate effect decreased with ageing. In addition, the results of the revised Cox's models substituting multimorbidity with nine chronic diseases have shown that COPD and diabetes combined was associated with a higher risk of death (HR=2.59; 95% CI: 2.01, 3.34**)**

in comparison with those who were without diabetes and COPD after adjusting for potential confounders during the follow up. Other factors related to the association between multimorbidity and mortality were sex, racial background, body weight, marital status, province of residence, household income, education, smoking status, alcohol, physical activity and stress.

4.2 Importance of the study

Multimorbidity has become a rising concern since the number of people with more than one chronic disease has increased due to ageing.[1] Multimorbidity not only imposes a burden on the healthcare system by increasing the frequency of hospitalization and healthcare utilization,[2] but it also reduces life expectancy.[3] Many studies have focused on examining the association between multimorbidity and mortality around the world.[4-6] However, information was limited, in the Canadian population. As a consequence, the focus of this study was to use CCHS-CVSD record linkage to examine the association between multimorbidity and mortality in the middle-aged and older Canadian population. The results of Chapter 3 provided evidence showing that people with multimorbidity had higher all-cause mortality than those without it.

While previous studies have shown that multimorbidity is a common problem among the elderly that is associated with higher mortality, there is some debate about whether it also has an impact on those under the age of 65.[7] The findings of Chapter 3 demonstrated that, among those with multimorbidity, the middle-aged population had the highest risk of death when compared to the older age group. This supports prior studies and raises awareness of multimorbidity prevention in the middle-aged population. Similar results were also found in

another study based on the UK biobank.[8] The results may help develop public health policy aimed at the middle-aged population to reduce excess mortality associated with multimorbidity. It is also worth noting that this study was one of the first such longitudinal studies in Canada with a large sample size. It likely, therefore, provided more representative and relatively strong evidence of the association between multimorbidity and mortality than most of the previous studies summarized in Chapter 2, especially those based on the Canadian population.

The significant joint effect of diabetes and COPD in Chapter 3 provided evidence highlighting the harmful effect of comorbidity on mortality compared to those without comorbidity. This increased risk of death was also observed between comorbidity and single disease. Similar results was reported in the previous studies.[9-11] The underlying mechanism remains unknown, but there have been several hypotheses.[12,13] The study results confirmed the negative effect of comorbidity on mortality and highlighted the need to develop specialized treatment for patients with comorbidity.

4.3 Limitations

In this study, similar limitations may be present as in the other studies which depend on survey data. They have already largely been considered in the discussion of Chapter 3. Study outcomes of this thesis were based on self-reported assessment. Therefore, the results may be prone to recall bias. Although several determinants were considered in our analysis, residual confounding may be another limitation to consider. While the nature of CCHS was cross-sectional, there was the possibility that individuals could be represented more than once across the CCHS cycles. The respondents were not removed and would likely have been linked to the same death records. However, it is unlikely to be problematic since the

unique linking ID was provided for each linked CCHS respondent.

4.4 Conclusions

We examined the association between multimorbidity and mortality by using a linked database of CCHS-CVSD among the middle-aged and senior Canadian population. The results showed that a higher risk of death was found in people with multimorbidity than those without multimorbidity after adjusting for all confounders. Furthermore, the negative effect of multimorbidity on mortality decreased from the oldest age group to the youngest age group, which demonstrated that the proportionate risk for the middle-age group was greater than for those who were older. One possible explanation is that disability, rather than multimorbidity, contributed significantly to mortality in older adults. Comorbidity was shown to be one of the predictors of all-cause mortality, and the findings of our study confirmed previous research on the association between comorbidity and mortality.

Recognizing that multimorbidity increases the risk of death is important in prioritizing and hence allocations resources for the effective management and prevention of multimorbidity in Canada. It is also important to raise awareness that the negative effect of multimorbidity on mortality is a problem that affects not just the elderly, but also impacts the middle-aged population. Furthermore, the presence of morbidity should be treated with considerable caution and specialized treatment should be provided. Future study adopting a comprehensive multimorbidity index that weighted each chronic illness individually is needed, as each chronic disease is likely to have a different impact on mortality. More public health programs should be initiated to prevent chronic diseases and multimorbidity, which in turn, would save lives, improve quality of life, and save healthcare dollars.

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Ethics approval for the study from the University of Alberta

Notification of Approval (Renewal)

Date:	April 8, 2021
Amendment ID:	Pro00100947_REN1
Principal Investigator:	Ambikaipakan Senthilselvan
Study ID:	MS1_Pro00100947
Study Title:	The prevalence and determinants of multimorbidity and the effect of multimorbidity on mortality in the Canadian population.
Approval Expiry Date:	Thursday, April 7, 2022

Thank you for submitting this renewal application. Your application has been reviewed and approved.

This re-approval is valid for another year. If your study continues past the expiration date as noted above, you will be required to complete another renewal request. Beginning at 30 days prior to the expiration date, you will receive notices that the study is about to expire. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

All study related documents should be retained so as to be available to the Health REB upon request. They should be kept for the duration of the project and for at least 5 years following study completion.

Approval by the Research Ethics Board does not encompass authorization to recruit and/or interact with human participants at this time. Researchers still require operational approval as applicable (eg AHS, Covenant Health, ECSD etc) and where in-person interactions are proposed, institutional and operational requirements as outlined in the Resumption of Human Participant Research - June 24, 2020 must be met.

Sincerely,

Charmaine Kabatoff, REB Consultant, for

Anthony S. Joyce, PhD.
Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).