MULTIMORBIDITY AND HEALTH OUTCOMES: EVIDENCE OF LONGITUDINAL STUDIES

by

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ABSTRACT

Multimorbidity, the coexistence of multiple chronic diseases within one individual, is becoming increasingly prevalent, particularly among older adults. Multimorbidity has posed substantial challenges to healthcare systems worldwide. However, there is limited evidence on the impact of multimorbidity on health outcomes; especially longitudinal research is lacking. The objective of this thesis was to investigate the association between multimorbidity and health outcomes over time by conducting three studies.

Study one, a large population-based prospective cohort study of 14,573 patients examined the impact of multimorbidity on health-related quality of life (HRQoL) following total hip arthroplasty and total knee arthroplasty. A linear mixed-effects model was used to test the effects of multimorbidity and the number of chronic conditions on improvements in HRQoL. Findings show that multimorbidity adversely affected improvements in HRQoL. A higher number of chronic conditions was associated with increasing reductions in HRQoL improvements.

Study two, a systematic review, assessed the longitudinal association between multimorbidity and depressive symptoms among older adults. PUBMED, EMBASE and PSYCINFO were systematically searched to identify longitudinal studies among adults aged 50 or above, published in English up to December 2020. A total of 20 studies including 57,349 participants were identified. Findings show that most studies detected a positive association between multimorbidity and more depressive symptoms over time.

Study three, another large population-based prospective cohort study, analyzed three-year follow-up data of 16,919 community-dwelling older adults aged 65 and older in the Canadian

Longitudinal Study of Aging (CLSA). Multivariate logistic regression models with analytic weights were built to examine the association between multimorbidity and depressive symptoms over time, and investigate the role of social support in this relationship. Results show that participants with multimorbidity had 1.3 times the odds of having depressive symptoms three years later, compared to those without multimorbidity. Social support served as a protective factor, buffering the negative impact of multimorbidity on depressive symptoms.

In conclusion, multimorbidity adversely affects HRQoL and mental health; social support may buffer the negative impact of multimorbidity on depression among older adults. These findings provide new and important evidence that can inform clinical practice, policy, and future research regarding the management of multimorbidity.

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DEDICATION

In memory of my beloved grandmother

For my parents, my inspiration

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PREFACE

Publication Information and Author Contributions

Chapter 3 in the dissertation has been published in a peer-reviewed journal. The paper presented in Chapter 3 has been slightly modified from the published version to make the language more consistent with the other chapters in this dissertation.

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Author contributions:

I led the study and was responsible for the conception, design, development and management of the study, conducting the analysis and interpretation of the data, writing the first draft and revising the manuscript. My co-authors, Dr. L.M. Lix and Dr. E.R. Bohm provided guidance on study conception and design, analysis and interpretation of data and critical revision of the manuscript. Mr. O. Ayilara contributed to the analysis and interpretation of data. Dr. R. Sawatzky contributed to the interpretation of data and critical revision of the manuscript.

CHAPTER 1: INTRODUCTION

1.1 Background

1.1.1 The burden of chronic diseases

Chronic diseases have become a significant burden to individuals and our health care system. Three in five Canadians aged 20 and above have a chronic disease and four in five are at risk to be diagnosed with a chronic disease (Public Health Agency of Canada, 2013). The prevalence of chronic diseases is increasing by 14% per year in Canada (Elmslie, 2011). Recent studies have shown that 46% of adult Canadians have one of the following five common chronic diseases: 6 million have hypertension, 3 million have osteoarthritis, 2 million have diabetes, 1.2 million have major depression, and 0.75 million have chronic obstructive pulmonary disease (COPD) (Elmslie, 2011). Four major chronic diseases, including cardiovascular diseases (heart disease and stroke), cancer, chronic respiratory diseases (asthma and COPD) and diabetes are the cause of 65% of all deaths in Canada each year, as well as the leading causes of death globally (Roberts et al., 2015). In addition, depression and anxiety disorders are the first and sixth leading causes of years of life lost due to disability globally, respectively (WHO, 2017a). Treatment of chronic diseases consumes 67% of all direct health care costs, which amounts to $190 billion annually; $68 billion of which is attributed to treatment, with the remainder to lost productivity (Wolff et al., 2002).

It is well-established that many risk factors contribute to the development of a chronic condition (WHO, 2010). Identified risk factors for chronic diseases can be categorized into three groups. One group involves non-modifiable biomedical risk factors such as age and heredity. A second group includes modifiable health behavioral risk factors, such as smoking, unhealthy

diets, physical inactivity and harmful use of alcohol, which can lead to intermediate pre-disease changes like high blood pressure, raised glucose levels, abnormal blood lipids, and obesity (WHO, 2010). Rising obesity rate is another driver for the epidemic of chronic diseases (Sturm, 2002). Obesity rates are increasing among Canadians, especially in children, youth and indigenous peoples. For example, one in four children is obese or overweight; one in six adults over 20 years old is obese (Elmslie, 2011). Lastly, social, cultural, economic and environmental factors can place individuals at risk of multimorbidity (WHO, 2005). For example, lower socioeconomic status is an underlying structural cause of common chronic diseases, reflecting people's physical and social environments which determine opportunities and health behavior. (WHO, 2010).

1.1.2 Multimorbidity: aging, demographic and epidemiologic transitions

Multimorbidity refers to the coexistence of multiple chronic diseases within an individual where no single disease holds priority over the others (Fortin et al., 2012, 2010). Although the term is sometimes used interchangeably with the term comorbidity (Feinstein, 1970), the two are different in the sense that comorbidity refers to additional conditions that exist alongside the dominant disease that is the focus of attention (the index disease). More than one third of individuals with physical multimorbidity are also affected by mental health disorders (Gaulin et al., 2019). The prevalence of multimorbidity ranges from 13% to 72% in the general population (Fortin et al., 2012) and from 55% to 98% among older people (Marengoni et al., 2011) depending on the data source, measures, and cutoff points of number of conditions used. Multimorbidity has become one of the greatest health-related challenges facing health care systems and governments worldwide (Pearson-Stutttard et al., 2019).

The increase in the prevalence of chronic diseases and multimorbidity is mainly a consequence of the demographic and epidemiologic transitions which have happened in developed countries and is still underway in less-developed countries worldwide (Omran, 2005). Demographic transition refers to the changes in population structure from high birth and death rates to lower birth and death rates (Lee, 2003). The aging of the population represents a significant demographic change affecting modern society. As more people live longer, chronic diseases, most commonly conditions developed during middle and old age, have emerged as major causes of disability and functional dependency. This demographic shift presents new challenges to governments, health care systems, and societies around the world (WHO, 2018). Globally, average life expectancy has substantially increased over past decades. In 2017, it was 71.5 which was 7 years longer than in 1990 (United Nations, 2017). In developed countries, the average life expectancy was around 80 years, in contrast to around 50 in the early 20th century. The trend of longer life expectancy is projected to continue (Oeppen and Vaupel, 2002). As a result, the global population is aging rapidly. Between 2015 and 2050, the proportion of the world's population aged over 60 years will nearly double, from 12% (900 million) to 22% (2 billion) (WHO, 2018). According to national population data (Statistics Canada, 2020), 20% of the Canadian population was 65 years and older in 2020. By 2026, Canada is expected to join Japan and other "super-aged" countries, as the proportion of people aged 65 and older will exceed 21% of the total population.

Another major driver of the increasing prevalence of chronic disease and multimorbidity is the epidemiological transition which refers to the change of diseases from infectious or communicable diseases to non-communicable or chronic diseases (Omran, 2005). In combination, the demographic and epidemiologic transitions increase the number of older

people, as well as the number of chronic diseases and multimorbidity over time. In addition to fundamental elements to improve standard of living such as proper waste disposal, clean water, sanitation, and temperature-controlled living, advances in medical technology and improved working environments all contributed to large reductions in communicable diseases (Stambler et al., 2018). Significant progress has also been made in reducing deaths from chronic diseases in the last quarter of the 20th century, which has been largely attributed to advances in medical care and health promotion activities (Stambler et al., 2018).

1.1.3 Multimorbidity: complex needs of care and challenges to health services

People living with multimorbidity have higher rates of disability, decreased quality of life, frailty, psychological distress, and increased risk of death (Barnett et al., 2012; Fortin et al., 2006, 2004; Gijsen et al., 2001; Marengoni et al., 2011; Mello et al., 2014; Nunes et al., 2016; Read et al., 2017; Ryan et al., 2015; Violan et al., 2014; Vogeli et al., 2007), They are also found to more frequently receive inpatient and ambulatory care (Salisbury et al., 2011; Wolff et al., 2002). Complex care needs among patients with multimorbidity are both costly and challenging to manage. In modern medicine, effective management of multimorbidity has become one of the greatest challenges facing patients, families, health care providers and society (Barnett et al., 2012; Fortin et al., 2014; Sakib et al., 2019; St. John et al., 2021). The growing presence of multimorbidity in the population places substantial pressure on many health care systems to transform from a fragmented medical model of illness with a single disease orientation, to more integrated models of care for multimorbidity with a holistic approach of assessing an individual's health and planning treatment effectively (Sinnott et al., 2013). These trends call for high quality evidence in order to better understand the associations between multimorbidity and health

outcomes and relevant factors that may mitigate the negative impacts of multimorbidity, in order to reduce the burden on both patients and the health care system (Pearson-Stutttard et al., 2019).

Despite the increasing prevalence of multimorbidity and its major challenges, studies on care of individuals with multimorbidity are limited (Smith et al., 2012). Limited longitudinal research has been published on health outcomes of multimorbidity; large prospective studies are needed to provide evidence for program planning, interventions and management of multimorbidity (France et al., 2012; Xu et al., 2017). A thorough understanding of health outcomes, such as quality of life and mental health associated with multimorbidity would be necessary to develop healthcare services and treatment guidelines to meet the care needs of Canadians with multimorbidity.

1.2 The present thesis

1.2.1 Study objectives

To contribute towards the knowledge base in the area of management of multimorbidity, as well as to address notable gaps in the existing multimorbidity literature, the present thesis aims to provide evidence for future development of effective intervention strategies by employing population-based data and longitudinal study designs.

Specifically, my dissertation research has the following three objectives:

- **Objective 1**: to estimate change in quality of life among patients with multimorbidity who underwent total hip and knee replacements (THA, TKA) using the Winnipeg Regional Health Authority Joint Replacement registry clinical data.

- **Objective 2:** to conduct a systematic review of the existing scientific evidence concerning longitudinal studies on the relationship between multimorbidity and depression among older adults.
- **Objective 3:** to determine the longitudinal association between multimorbidity and depression among older Canadian adults who live in the community, and whether the association is buffered by social support.

The above objectives were achieved by conducting three studies: 1) a study focusing on the relationship between the presence of multimorbidity and quality of life in a clinical sample, 2) a systematic literature review focusing on the evidence regarding the association between multimorbidity and depression, and 3) a study focusing on the association between multimorbidity and depressive symptoms and the role of social support in this relationship in a community setting sample of older adults aged 65 or older who participated in the Canadian Longitudinal Study on Aging (CLSA).

1.2.2 Overview of the dissertation

This dissertation is composed of six chapters. Chapter 2 presents a review of current literature documenting important epidemiological aspects of multimorbidity, which include definition, measurement, operationalization, prevalence, disease clusters and patterns, risk factors, and health outcomes of multimorbidity.

Chapter 3 is the first manuscript focusing on objective one of the dissertation research. It involved a large population-based prospective cohort study examining the effects of multimorbidity on health-related quality of life (HRQoL) in a clinical setting. Using data from the Winnipeg Regional Health Authority joint replacement registry of14,573 patients, HRQoL

was measured prior to and one year following surgery using the Oxford Hip Score (OHS) and Oxford Knee Score (OKS), and the 12-Item Short-Form Health Survey Physical and Mental Component Summary scores (PCS and MCS, respectively). Multimorbidity was defined as the concurrence of two or more self-reported chronic conditions. A linear mixed-effects model was used to test the effects of multimorbidity and the number of chronic conditions on improvements in HRQoL, which reflects various aspects of health status, and has been associated with both health and social outcomes (Ware JE, Kosinski M, 1994).

Chapter 4 is the second manuscript focusing on objective two of the dissertation research, a systematic review of current literature on the longitudinal association between multimorbidity and depression among older adults aged 50 and above. Depression is a prevalent and disabling condition in older adults that negatively influences quality of life and increases the risk of mortality. Previous reviews based on cross-sectional studies have found that multimorbidity was associated with depression. This study aims to assess whether multimorbidity increases the risk of depression among older adults over time. PUBMED, EMBASE and PSYCINFO were systematically searched to identify articles published in English up to December 2020. Due to considerable variability in measures, samples and methodologies used across studies, a meta-analysis could not be conducted; a narrative review was conducted instead.

Chapter 5 is the third manuscript focusing on objective three of the dissertation research. It involved a large nation-wide population-based prospective cohort study following 16,919 community-dwelling CLSA participants from both the comprehensive and tracking cohorts over three years in Canada. Multimorbidity was defined as having three or more chronic conditions. The 10-item Center for Epidemiologic Studies Depression scale (CESD-10) was used to measure depressive symptoms at both the baseline and the three-year follow-up. The 19-item Medical

Outcomes Study (MOS) Social Support Survey was employed to assess perceived social support. Functional status was assessed using modified questions from the Older Americans' Resources and Services (OARS) Multidimensional Functional Assessment Questionnaire including Activities of Daily Living (ADLs) and the Instrumental Activities of Daily Living (IADLs) for CLSA participants. A series of multivariate logistic regression models with analytic weights were built to examine the association between multimorbidity and depressive symptoms among older adults aged 65 to 85 at baseline; and investigate if social support plays a protective role in this relationship buffering the negative impact of multimorbidity.

Chapter 6 is an overall discussion of all three studies carried out in this dissertation research. This chapter presents key findings, implications and contributions of this dissertation research regarding multimorbidity and quality of life and depressive symptoms. Strengths and limitations of the research are also discussed. Finally, directions for future research and program planning are proposed with the aim to meet the care needs of people living with multimorbidity.

CHAPTER 2: LITERATURE REVIEW OF MULTIMORBIDITY

2.1 Definition and operationalization

Multimorbidity refers to the coexistence of multiple chronic diseases within an individual where no single disease holds priority over the others (Fortin et al., 2012, 2010). Multimorbidity is often interchangeably used with the term "comorbidity" (Feinstein, 1970), which refers to a medical condition that exists along with the dominant condition (the index disease). The term, multimorbidity is distinct from comorbidity, however, because there is no primary or index condition. With its focus on the co-occurrence of diseases in the same person, and the person being affected by multiple conditions simultaneously, multimorbidity is more reflective of the disease burden of the patient than comorbidity (Batstra et al., 2002). Although multimorbidity has become one of the main challenges facing both healthcare providers and governments globally (Goodwin et al., 2014; Mangin et al., 2012), the complex nature of multimorbidity has resulted in inconsistencies in its conceptualization and definition. The great heterogeneity in the definition of multimorbidity makes it challenging to compare findings across studies examining the burden of multimorbidity (Willadsen et al., 2016). It has been recommended that when evaluating multimorbidity research, researchers should consider which types of conditions and the number of chronic conditions that were used to define multimorbidity in the study (Fortin et al., 2012).

Two major operational approaches have been utilized to measure multimorbidity in the scientific literature of current epidemiological and clinical studies. Currently the most common approach to measure multimorbidity involves a simple counting of coexistent conditions (Almirall and Fortin, 2013; Stewart et al., 2013). It is common for researchers to create their

own list of chronic conditions ranging from 4–147 different conditions based on the objectives and data source used in the studies (Willadsen et al., 2016). However, it has been suggested that using at least 12 or more commonly accepted chronic conditions to define multimorbidity could drastically reduce the discrepancy in estimates of prevalence of multimorbidity (Fortin et al., 2012). A cut-off point of two or more conditions is commonly used to define multimorbidity, although there are also relevant studies in which multimorbidity was defined as three or more chronic conditions simultaneously in one individual (Almirall and Fortin, 2013; Roberts et al., 2015).

A second commonly used approach to measuring multimorbidity are cumulative indices, such as the Charlson Comorbidity Index (Charlson et al., 1987), the Index of Co-Existent Diseases (ICED) (Greenfield et al., 1993), the Cumulative Illness Rating Scale (CIRS) (Linn et al., 1968), and the Kaplan Index (De Groot et al., 2003). These cumulative indices incorporating both number and severity of the co-occurring conditions are constructed measures to assess morbidity burden by differentially weighting a range of conditions based on mortality, severity, and resource utilization (De Groot et al., 2003). In addition to these traditional methods used to define multimorbidity, medication classes counts (10+ regular medication classes) was also recommended by the UK National Institute for Health and Care Excellence in the clinical setting, when using general practice electronic medical records to identify those with higher risk of multimorbidity (Farmer et al., 2016).

2.2 Prevalence

Partially owing to advancement of technology in medicine and improvements in health care, many people survive and live with multiple chronic conditions, which makes

multimorbidity a prevalent phenomenon, especially among older population in high income countries (Barnett, 2012). For example, in a community setting, a systematic review demonstrated that 55% to 98% of older adults aged 60 years and older were affected by multimorbidity based on studies conducted in the Netherlands, USA, Canada, Australia, Sweden, and Spain (Marengoni et al., 2011). A recently published large national wide population-based study in Canada showed that multimorbidity was common, and the average number of chronic conditions was 3.1 among those aged 45-85 community-dwelling participants in the Canadian Longitudinal Study on Aging (CLSA) (St John et al., 2021). Data from the US showed that one in four adults had multimorbidity in the general population (Ward et al., 2014). A systematic review and meta-analysis including 70 studies in a community setting from 49 countries estimated an overall prevalence of multimorbidity of 33.1%, with a considerable difference between high income countries and low-income countries of 37.9% and 29.7%, respectively (Nguyen et al., 2019).

In clinical settings, data from primary care practices in Scotland revealed an overall multimorbidity prevalence of 23.2%, rising to 67.0% in those aged 65 years or older (Barnett et al., 2012). In Quebec, Canada, it was reported more than 95% of primary care patients aged above 65 years had multimorbidity (Fortin et al., 2005a). A systematic review of 39 studies demonstrated that multimorbidity prevalence ranged from 12.9% in primary care patients aged 18 years and older to 95.1% in those aged above 65 years living in Italy, UK, Australia, Spain, Canada, Ireland, Germany, US, Sweden, Netherlands, Greece, Switzerland, and Spain (Violan et al., 2014).

Multimorbidity increases substantially with age and is very common in older adults aged 65 and above; yet it is often found to be prevalent in other age groups (Barnett et al., 2012; Sakib

et al., 2019). For example, a recent large population-based study using the CLSA data reported a multimorbidity prevalence of 39.6% with a mean number of chronic conditions of 2.41 (99% CI 2.37–2.46) among 45-64 years old Canadians living in the community (Sakib et al., 2019). Another study using the Canadian Chronic Disease Surveillance System data reported a multimorbidity prevalence of 26.5% among 40 years and older Canadians (Feely et al., 2017). In the general Canadian population, a study estimated a multimorbidity prevalence of 42.6% among adults aged 18 years and older, using electronic medical record data from the Canadian Primary Care Sentinel Surveillance Network (Nicholson, 2016). In Ontario, one study using population-based administrative data reported that the prevalence of multimorbidity was 24.3% in 2009, which was a 40% increase from the prevalence of 17.4% in 2003 among residents in the province (Koné Pefoyo et al., 2015). In Alberta, a study reported a multimorbidity prevalence of 36% among individuals aged 18 years and above in the Health Quality Council of Alberta 2012 Patient Experience Survey (Agborsangaya et al., 2013).

2.3 Clusters and patterns of multimorbidity

Previous research has uncovered various disease pairs and clusters in multimorbidity. For example, a systematic review of 23 observational studies assessed the most frequent twenty disease pairs from 165 combinations of disease pairs among older adults (Sinnige et al., 2013). Depression was the disease that was found to be the most frequently clustered and paired with eight different conditions, followed by hypertension and diabetes (Sinnige et al., 2013). The highest rates were among the pairs that included hypertension, coronary artery disease, and diabetes mellitus (Sinnige et al., 2013). Another review of 14 studies identified 97 patterns containing two or more diseases and 63 clusters of three or more diseases among general populations, with three groups of most frequent patterns: 1) a combination of cardiovascular and

metabolic diseases; 2) clusters involved at least one mental health problem; and 3) clusters with at least one musculoskeletal disorder (Prados-Torres et al., 2014). A recent British population-based retrospective cross-sectional study of 826,936 primary care patients showed five consistent clusters of multimorbidity: 1) anxiety and depression; 2) heart failure, atrial fibrillation, chronic kidney disease, chronic heart disease, stroke/transient ischaemic attack, peripheral arterial disease, dementia and osteoporosis; 3) osteoarthritis, cancer, chronic pain, hypertension and diabetes; 4) chronic liver disease and viral hepatitis; and 5) substance dependency, alcohol dependency and HIV (Bisquera et al., 2021).

2.4 Risk factors

Identifying risk factors of multimorbidity is important in planning for prevention and management of multimorbidity. Increasing scientific research globally provides evidence that many factors have contributed to the development of multimorbidity, such as age, sex, life styles and socio-economic status. For example, a comprehensive systematic review of studies published between 1990 to 2010 showed that older age, female sex, and low socioeconomic status were associated with multimorbidity among older adults (Marengoni et al., 2011).

For non-modifiable risk factors, previous research revealed that multimorbidity is linked to age and sex. Regarding age, there was an S-shaped curve for the association between age and prevalence of multimorbidity: the prevalence of multimorbidity was found to be low (20% or lower) before about age 40 years, then increased dramatically, and finally peaked at 75% around the age of 70 years (Fortin et al. 2012). Furthermore, a systematic review of 39 studies including a total of 70,057,611 primary care patients in 12 countries found that older age increased the odds of having multimorbidity (odds ratio [OR], 1.26 to 227.46) (Violan et al., 2014). In Canada,

a recent large national population-based cohort study including 21,241 community-living individuals from the Canadian Longitudinal Study of Ageing (CLSA) study demonstrated that multimorbidity was strongly associated with older age: the mean number of conditions was 2.1 in those aged 45 to 54; 2.9 in those 55 to 64; 3.8 in those aged 65 to 74, and 4.8 in those aged 75 and older (St. John et al., 2021). Similarly, a 10-year follow-up study including 4,564 participants aged 50 years and older in the English Longitudinal Study of Aging suggests that older individuals were more likely to develop multimorbidity (Mounce et al., 2018).

Research demonstrates that sex is another risk factor associated with multimorbidity, and that multimorbidity is more commonly found in women than in men (Alimohammadian et al., 2017; Marengoni et al., 2011; St John et al., 2021; Violan et al., 2014). For example, a study using CLSA data of 21,241 community-dwelling participants, aged 45–85 years in Canada indicated that female sex was associated with higher odds of multimorbidity [odds ratio:1.83 (95% CI 1.72 to 1.95)] (St John et al., 2021). Similarly, a large cross-sectional cohort study including 49,946 participants, aged 40–75 years living in Western Asia found that the prevalence of multimorbidity was significantly higher in women (25%) than in men (13.4%) in all age-groups (Alimohammadian et al., 2017). Furthermore, another large population-based study of 1,272,685 adults in Scotland demonstrated that women had higher rates of overall multimorbidity than men at all ages overall, although multimorbidity of physical conditions was only consistently found more common in men (Agur et al., 2016).

In addition to non-modifiable risk factors, modifiable factors such as unhealthy life styles and obesity are also associated with multimorbidity. According to the WHO, the most common modifiable risk factors linked to the development of the majority of chronic diseases are four unhealthy lifestyles: smoking, unhealthy diets, physical inactivity and harmful use of alcohol,

which can lead to intermediate pre-disease changes like high blood pressure, raised glucose levels, abnormal blood lipids, and obesity (WHO, 2010). Furthermore, a recent large prospective cohort study of 291,778 participants aged 43 to 58 years at baseline from seven European countries with a follow-up of 11 years demonstrated that healthy lifestyles were strongly inversely associated with multimorbidity among individuals with cardiovascular disease, diabetes, and cancer (Freisling et al., 2020). Another population-based Finnish longitudinal study including 32,972 participants aged 50 years and older found that smoking, physical inactivity, high BMI and low fruit and vegetable consumption were risk factors for incident multimorbidity (Mounce et al., 2018).

Evidence suggests that the rising obesity rate is another driver for the epidemic of chronic diseases, and being obese is also a modifiable risk factor for multimorbidity (Mounce et al., 2018; Sturm, 2002). A study of pooled data of 120,813 adults (mean age 51.4 years) from 16 prospective cohort studies conducted in the USA and Europe found that being overweight increased the risk of developing cardiometabolic multimorbidity two times after adjustment for sociodemographic and lifestyle factors (Kivimäki et al., 2017). A 20-year prospective cohort study from Australia of 13,714 participants aged 45–50 years reported that obesity, hypertension, physical inactivity, smoking, or having other chronic conditions were related to a higher risk of multimorbidity among middle-aged women (Xu et al., 2018). In addition, data from the 10-year follow-up data of 4,564 older adults aged 50 years and above in the English Longitudinal Study of Aging suggested that the risk to develop multimorbidity was higher for obese participants, and those with the lowest levels of physical activity, or feeling lack of control over life events (Mounce et al., 2018).

Previous research demonstrates that multimorbidity is also strongly linked to structural risk factors such as adverse socioeconomic circumstances; the prevalence of multimorbidity is higher among ethnic minorities and those with a lower level of education and income (Marengoni et al., 2011; Mounce et al., 2018; Rocca et al., 2015; St Sauver et al., 2015; Van den Akker et al., 1998). For example, a Scottish study revealed that multimorbidity may occur 10–15 years earlier among young and middle-aged individuals living in the most deprived neighborhood compared to those living in the most affluent areas (Barnett et al., 2012). Data from the Survey of Health, Aging and Retirement in Europe (SHARE) showed that older adults with a low level of education and wealth had higher rates of multimorbidity and mortality than their counterparts with high socioeconomic status (Kok et al., 2008). A cross-sectional study of chronic disease data from 28 countries in the World Health Survey (2003) showed that higher education was significantly associated with a decreased risk of multimorbidity in low and middle-income countries (Afshar et al., 2015).

In Canada, a recent large national population-based cohort study including 21,241 community-living individuals aged 45 to 85 years found that participants with lower income and less education were more likely to have a higher number of chronic conditions (St. John et al., 2021). Similarly, a population-based study in Ontario found a higher prevalence of multimorbidity among lower income groups, which may be attributed to lower income itself, older age, being not married, physical inactive, heavy smoking and obesity (Mondor et al., 2018).

2.5 Health outcomes

Research has documented adverse health outcomes of multimorbiditiy, such as higher rates of disability, decreased quality of life, frailty, psychological distress, increased risk of death and more frequent health service use (Barnett et al., 2012; Fortin et al., 2006, 2004; Gijsen et al., 2001; Marengoni et al., 2011; Mello et al., 2014; Nunes et al., 2016; Read et al., 2017; Ryan et al., 2015; Violan et al., 2014; Vogeli et al., 2007). This section will focus on impacts of multimorbidity on mortality, physical functioning, mental health, and health-related quality of life.

2.5.1 Mortality

Multimorbidity is found to be linked to an increased risk of mortality. A systematic review and meta-analysis of 26 studies showed that multimorbidity was positively associated with mortality [HR: 1.44 (95%CI: 1.34; 1.55)] among older adults aged 60 above (Nunes et al., 2016). The risk of death increased with the number of chronic conditions [HR: 1.20 (95%CI: 1.10; 1.30)]. Individuals with 2 or more conditions were 1.73 times more likely, [1.73 (95%CI: 1.41; 2.13)] and with 3 or more conditions 2.72 times [2.72 (95%CI: 1.81; 4.08)] more likely to die compared with those with no multimorbidity (Nunes et al., 2016).

Research also revealed that the risk of mortality depends on different combinations of chronic conditions among those living with multimorbidity. A large population-based prospective cohort study of registry data including 3,986,209 adults (18+) in Denmark found that various disease clusters of multimorbidity increased the risk of mortality; and the number of the disease clusters was positively associated with the risk (Willadsen et al., 2018). The neurological–cancer combination increased the odds of mortality more than six times (OR, 6.35),

the cardiovascular–lung cluster increased the odds more than 5 times (OR, 5.75), and the most prevalent disease cluster, musculoskeletal–cardiovascular doubled the odds of mortality (OR, 2.03) (Willadsen et al., 2018). Similarly, another recent large population-base study of National Health Interview Survey (NHIS) and the National Death Index (NDI) data reported that multimorbidity was associated with mortality in older adults (50+) in the USA. The complex cardiometabolic cluster had the highest mortality risk with a Hazard Ratio (HR) of 5.30, 99.5% CI [4.52, 6.22] (Zheng et al., 2021). Furthermore, evidence shows that the effect of multimorbidity was mediated by functional conditions. Data from 1751 community-dwelling adults aged 65 and older from the Manitoba Study of Health and Aging (MSHA) demonstrated that multimorbidity predicted mortality (hazard ratio 1.04, 95% CI 1.00 to 1.08) after adjusting for age, sex, education, marital status, living arrangement, and Center for Epidemiologic Studies Depression Scale (CES-D) and the Mini-Mental State Examination (MMSE) scores. However, after adjusting for functional status, the effect of multimorbidity was no longer significant (St. John et al., 2014).

2.5.2 Physical functioning

Multimorbidity has been found to be associated with increases in functional limitations. For example, a systematic review of 37 studies demonstrated that multimorbidity was consistently associated with functional decline (Ryan et al., 2015). Furthermore, it showed that increasing numbers of chronic condition counts and disease severity predicted worsening functional decline (Ryan et al., 2015). Similarly, a cross-sectional analysis of data in the National Health and Nutrition Examination Survey (NHANES) from 2005 through 2012 demonstrated a dose-response relationship between the number of chronic conditions and functional limitations. The positive association between multimorbidity and functional limitations were stronger among

women than among men, and stronger among adults aged 75 or older than those aged 65 to 74 (Jindai et al., 2016).

Similarly, a large population-based analysis of the MHSA data demonstrated that multimorbidity predicted disability among community-dwelling adults aged 65 and older in Manitoba. In the cross-sectional analysis, each additional chronic illness increased the odds of disability by 1.35 times [adjusted OR 1.35, 95% CI (1.29 to 1.42)] after adjusting for age, sex, education, the MMSE and CES-D scores. In the longitudinal analysis, each additional chronic illness increased the likelihood of disability by 1.15 times at five-year follow-up [adjusted OR 1.15, 95% CI (1.09 to 1.24)] after adjusting for the same covariates plus functional status at baseline (St. John et al., 2019).

2.5.3 Mental health

In addition to increasing long-term mortality and functional impairment, multimorbidity has detrimental effects on mental health. A recent large prospective study analyzed 24-year follow-up data of 252,002 US community-dwelling participants aged 25-75 years in three nationally-sampled prospective cohorts, the Nurses' Health Study (NHS), NHS II, and Health Professionals Follow-up Study (HPFS) (Wei and Mukamal, 2019). It showed that multimorbidity was strongly associated with increased risk of suicides. This risk was two- to three-fold higher in adults with the highest vs lowest quartile of multimorbidity: NHS hazard ratio (HR) = 3.01 (95% confidence interval [CI] = 1.48-6.11); NHS II HR = 3.04 (95% CI = 1.82-5.09); HPFS HR = 1.74 (95% CI = 1.08-2.81) (Wei and Mukamal, 2019). In addition, a cross-sectional study of 4,184 older adults aged 65 above in the US showed that multimorbidity increased the occurrence of anxiety by 2.3 folds among participants (Gould et al., 2016). Many clusters of multimorbidity

containing cancer, arthritis, high blood pressure, heart conditions lung disease and diabetes were found to be significantly associated with anxiety (Gould et al., 2016).

Depression is a prevalent mental condition across the globe, affecting about 7% of the world's older population (WHO, 2017b). Understanding the association between multimorbidity and depression, especially in older adults is important, given the negative health outcomes associated with the former in this population, which include higher rates of mortality (Blazer, 2003; Cuijpers et al., 2014), impaired executive function (WHO, 2020), increased disability (Fiske et al., 2009) and poor quality of life (Brett et al., 2012).

A large number of studies show a positive relationship between specific chronic physical conditions and depression (Anderson et al., 2001; Matcham et al., 2013; Rudisch and Nemeroff, 2003). One study, for example, showed that heart disease may cause depression due to dysfunction in the sympathetic, neuroendocrine, autonomic, immune, and inflammatory systems (Krishnan et al., 1996). The prevalence rates of depression were found to be up to three times higher in patients with type 1 diabetes and twice as high in people with type 2 diabetes compared with the general population worldwide (Roy and Lloyd, 2012). Depression is also frequently observed among patients with stroke (Pan et al., 2011), cancer (Fann et al., 2009) and hypertension (Bogner and De Vries, 2008; Bosworth et al., 2003). However, there is less research on the association between multimorbidity and depression, despite the finding that depression is the single most common comorbid conditions in older adults (Sinnige et al., 2013). A recent meta-analysis of 40 studies found that people living with multimorbidity were three times more likely to have depressive disorder than those with no individual physical chronic condition, and two times more likely than those without multimorbidity (Read et al., 2017).

However, all of the studies included in the review were cross-sectional analyses which did not allow assessment of whether morbidity preceded depressive symptoms or vice versa.

2.5.4 Health-related quality of life

Health-related quality of life (HRQoL) is a multidimensional concept covering significant functional, psychological, and social aspects of a person's health (Centers for Disease Control and Prevention, 2000; Gandek et al., 2004; McHorney, 1999).Although it is often interchangeably used with quality of life (QoL), HRQoL focuses on factors affecting the health status of an individual. In contrast, QoL involves all factors that may impact life (Torrance, 1987). HRQoL has become an increasingly important instrument of patient-reported outcomes (PROMs), which are widely used to facilitate patient-focused care and medical decision making (Remick et al., 2020). Nonetheless, the association between multimorbidity and HRQoL is not well-studied and longitudinal evidence is scarce (Kanesarajah et al., 2018; Makovski et al., 2019; Marengoni et al., 2011). For example, a systematic review including research published from 1990 through November, 2010 identified six articles on multimorbidity and HRQoL in older adults. The authors found that the majority of the studies reported that multimorbidity was associated with poor quality of life; however, only one study included in the review was with a longitudinal study design (Marengoni et al., 2011). Similarly, another systematic review of research that included studies up until March 2017 retrieved only eight articles. The studies were all cross-sectional and showed that multimorbidity was associated with poorer HRQoL in mid-aged adults (Kanesarajah et al., 2018). In the review, two studies found that adults with multimorbidity at early mid-life reported poorer HrQoL compared to those with multimorbidity at late mid-life, while another study found the opposite. Prevalent clusters of multimorbidity were also identified, and researchers further looked at the relationship between disease clusters

and quality of life. The results showed that individuals in the mental health cluster had poorer HRQoL compared to those in the cardiovascular disease CVD cluster of multimorbidity. Also, women reported lower HRQoL than men among participants living with multimorbidity (Kanesarajah et al., 2018).

Recently, a systematic review and meta-analysis of cross-sectional studies quantified the hazardous effects of multimorbidity on HRQoL(Makovski et al., 2019). The synthesized results showed that each additional chronic condition was associated with a reduction of the mean scores of HRQoL that ranged from -1.55% for the mental component summary score (MCS) of the pooled SF-36, SF-12 and SF-8 scales, to −4.37% for the physical health domain of the WHOQoL-BREF (Makovski et al., 2019). Furthermore, a large prospective study of NHS and NHS II cohorts of 252,002 adults examined the effects of multimorbidity on HRQoL(Wei and Mukamal, 2019). The results demonstrated that multimorbidity predicted worse mental HRQoL. Higher quartiles of multimorbidity were associated with worse MCS scores of SF-36 in a dose-response manner (Wei and Mukamal, 2019).

2.6 Discussion

This review of current literature of multimorbidity shows that multimorbidity, the co-existence of multiple chronic conditions within one individual, is common, especially among older adults. The lack of an established, standard conceptualization and definition of multimorbidity has resulted in heterogeneity in estimates of prevalence of multimorbidity, and had made it challenging to compare findings across studies. The most prevalent pairs of diseases of multimorbidity are those including hypertension, coronary artery disease, and diabetes mellitus. Depression is the disease most frequently emerging in multimorbidity clusters,

followed by hypertension and diabetes. Older age, female sex, unhealthy styles, and low socioeconomic circumstances are all risk factors for multimorbidity. Multimorbidity is associated with a greater likelihood of mortality, functional limitations, mental health disorders, especially anxiety and depression, and poor quality of life.

Despite multimorbidity having attracted increasing attention from the research community worldwide, it is under-researched (Fortin et al., 2005b; The Academy of Medical Sciences, 2015). The existing evidence on multimorbidity is limited, especially longitudinal research; most of the findings on multimorbidity have been based on studies with a cross-sectional design. Prospective epidemiological research on incidence, clusters and patterns of conditions, risk factors, and impacts of multimorbidity over time and the underlying pathogenic mechanisms is warranted to better understand multimorbidity, which helps to inform clinical practice, create evidence-based strategies and policies to prevent or delay the burden of multimorbidity, and improve management and care of people with multimorbidity.

PREFACE TO CHAPTER 3

In Chapter 2, the literature review of multimorbidity, it was demonstrated that poor quality of life was one of the major consequences of multimorbidity (Marengoni et al., 2011). Health-related quality of life (HRQoL) is a multidimensional concept covering significant functional, psychological, and social aspects of an individual's health (Centers for Disease Control and Prevention, 2000; Gandek et al., 2004; McHorney, 1999). HRQoL has become an increasingly important instrument of patient-reported outcomes (PROMs), which are widely used to facilitate patient-focused care and medical decision making (Remick et al., 2020).

To address objective 1 in this dissertation research, chapter 3 presents the first study in this dissertation research. Employing a population-based prospective study design, this study focused on the longitudinal association of multimorbidity and HRQoL among patients following total hip arthroplasty (THA) and total knee arthroplasty (TKA) for osteoarthritis in the Winnipeg regional joint replacement registry. This registry collects data from many hospitals and surgeons, and captures virtually all hip and knee operations performed within the region and approximately 75% of those undertaken in Manitoba (Singh et al., 2016). Osteoarthritis is a chronic condition that may lead to joint failure and disability, adversely affecting HRQoL (Public Health Agency of Canada, 2010; Yang et al., 2017). The aging of the population is driving the increasing prevalence of osteoarthritis and this trend is projected to continue (Birtwhistle et al., 2015; Woolf, 2015). Approximately 3.9 million (13.6%) Canadians aged 20 years and older had osteoarthritis and the incidence was 8.7 per 1,000 persons (219,000 new cases) during 2016–2017 in Canada (Public Health Agency of Canada, 2020). Total hip (THA) and total knee arthroplasty (TKA) usually result in improved HRQoL for patients with osteoarthritis, as assessed by PROMs (Ethgen et al., 2004).

Using data from 14,573 patients who underwent TKA and THA, I examined the effect of multimorbidity on changes of in condition-specific and general HRQoL in patients one year after surgeries. HRQoL was measured prior and one year following surgery using the condition-specific measures including Oxford Hip Score (OHS) and Oxford Knee Score (OKS), and the general measure of 12-Item Short-Form Health Survey (SF-12) Physical and Mental Component Summary scores (PCS and MCS, respectively). Multimorbidity was defined as the concurrence of two or more self-reported chronic conditions from a list of 14 conditions. A linear mixed-effects model was used to test the effects of multimorbidity and the number of chronic conditions on improvements in HRQoL.

CHAPTER 3: THE EFFECT OF MULTIMORBIDITY ON CHANGES IN HEALTH-RELATED QUALITY OF LIFE

Abstract

Aims

The aim of this study was to assess the effect of multimorbidity on improvements in health-related quality of life (HRQoL) following total hip arthroplasty (THA) and total knee arthroplasty (TKA).

Patients and Methods

Using data from a regional joint registry for 14,573 patients, HRQoL was measured prior and one year following surgery using the Oxford Hip Score (OHS) and Oxford Knee Score (OKS), and the 12-Item Short-Form Health Survey Physical and Mental Component Summary scores (PCS and MCS, respectively). Multimorbidity was defined as the concurrence of two or more self-reported chronic conditions. A linear mixed-effects model was used to test the effects of multimorbidity and the number of chronic conditions on improvements in HRQoL.

Results

Almost two-thirds of patients had multimorbidity, which adversely affected improvements in HRQoL. For THA, mean improvements in HRQoL scores were reduced by 2.21 points in OHS, 1.62 in PCS, and 4.14 in MCS; for TKA, the mean improvements were reduced by 1.71 points in OKS, 1.92 in PCS, and 3.55 in MCS (all $p < 0.0001$). An increase in the number of chronic conditions was associated with increasing reductions in HRQoL improvements.

Conclusion

Multimorbidity adversely affects improvements in HRQoL following THA and TKA. Our findings are relevant to healthcare providers focused on the management of patients with chronic conditions and for administrators reporting and monitoring the outcomes of THA and TKA.

Key words: Multimorbidity, Clinical registry, Joint replacement, Quality of life

3.1 Introduction

Multimorbidity is commonly defined as the simultaneous occurrence of two or more chronic conditions. More than 95% of primary care patients aged >65 years have multimorbidity (Fortin et al., 2005a), which is associated with a variety of adverse outcomes, including increased hospitalization, suboptimal care, complications, and increased healthcare costs (Brettschneider et al., 2013; Vogeli et al., 2007; Wolff et al., 2002). The prevalence of multimorbidity is increasing due to longer life expectancy and the growing number of people who live with chronic conditions (Divo et al., 2014).

Health-related quality of life (HRQoL) is a broad, multidimensional concept covering significant domains of daily functioning and subjective experience, such as physical functioning, role and social functioning, somatic sensation, perceived health, and subjective well-being (Centers for Disease Control and Prevention, 2000; Gandek et al., 2004; McHorney, 1999). It is important to address HRQoL as it has been associated with health and social outcomes (Ware, Kosinski, 1994) which may contribute to the worsening of the course of the diseases. Arthritis is a common chronic condition that can adversely affect HRQoL (Elders, 2000). Total hip (THA) and total knee arthroplasty (TKA) usually result in improved HRQoL as assessed by patient reported outcome measures (PROMs) (Ethgen et al., 2004). As the number of arthroplasties that are undertaken continues to rise (Kurtz et al., 2007), interest in the use of PROMs as part of national registries that are used to monitor the appropriateness of care, improvements in the quality of care, and the performance of a health system has also increased (Department of Health, 2008; Rolfson et al., 2016; Swedish Knee Arthoplasty Register Annual Report *2016*, 2016).

Changes in PROMs following surgery are sensitive to various baseline patient characteristics. The International Society of Arthroplasty Registers (ISAR) (Rolfson et al., 2016) recommend using case-mix adjustment models for reporting and comparing PROMs. While multimorbidity is common in patients undergoing THA or TKA (Inacio et al., 2015; Peter et al., 2015) little has been published about its effect on improvements in either condition-specific or general HRQoL following surgery. For example, in an extensive systematic review of patient characteristics affecting the outcome of THA or TKA, Santaguida et al. (Santaguida et al., 2008) did not describe the effects of comorbid conditions. Previous studies that have examined multimorbidity have only considered postoperative scores (Peter et al., 2015), only included improvements in condition-specific and not general HRQoL measures (Hawker et al., 2013), or used measures that did not directly assess function (Greene et al., 2015).

3.1.1 Objective

The aim of this study was to explore the effect of multimorbidity on changes in HRQoL in patients undergoing THA or TKA. We hypothesized that multimorbidity would have an adverse effect on postoperative improvements in both general and condition-specific measures of HRQoL.

3.2 Methods

We undertook a secondary analysis of data collected at the joint replacement registry in the Winnipeg Health region, which is the largest in Manitoba, Canada. The study was approved by the University of Manitoba Health Research Ethics Board. Manitoba has a universal single payer healthcare system, serving an ethnically diverse population of 1.2 million. Approximately 3000 primary and revision joint replacements are performed per year among 19 surgeons in the

two tertiary and four community hospitals within the Winnipeg Health region (Singh et al., 2016). The registry captures virtually all operations involving the hip and knee performed within the region and approximately 75% of those undertaken in Manitoba. The registry includes the demographics of the patients, the associated medical conditions, surgical technique, implant details, and complications, in addition to both general and condition-specific HRQoL measures. Other than demographics and surgical details, the information is self-reported and collected using preoperative questionnaires completed in the clinic one month prior to surgery and mailed questionnaires completed one year postoperatively (Singh et al., 2016). The initial cohort included all patients who underwent primary THA or TKA for osteoarthritis between 1 April 2009 and 31 March 2015 (n=18,097). Patients from one hospital (n=1,040) were excluded in 2011, because preoperative questionnaires were not distributed that year. Complete pre- and postoperative HRQoL data were available for 8,517 patients who were included in the complete case analysis. A total of 14,573 patients had either pre- or postoperative HRQoL data and this cohort was used for an imputed case analysis (Fig. 3.1). In addition to medical conditions and self-reported measures of HRQoL, we included data on age, gender, and body mass index (BMI) in order to control for their potential confounding effects (Chen et al., 2016; Ethgen et al., 2004; Santaguida et al., 2008).

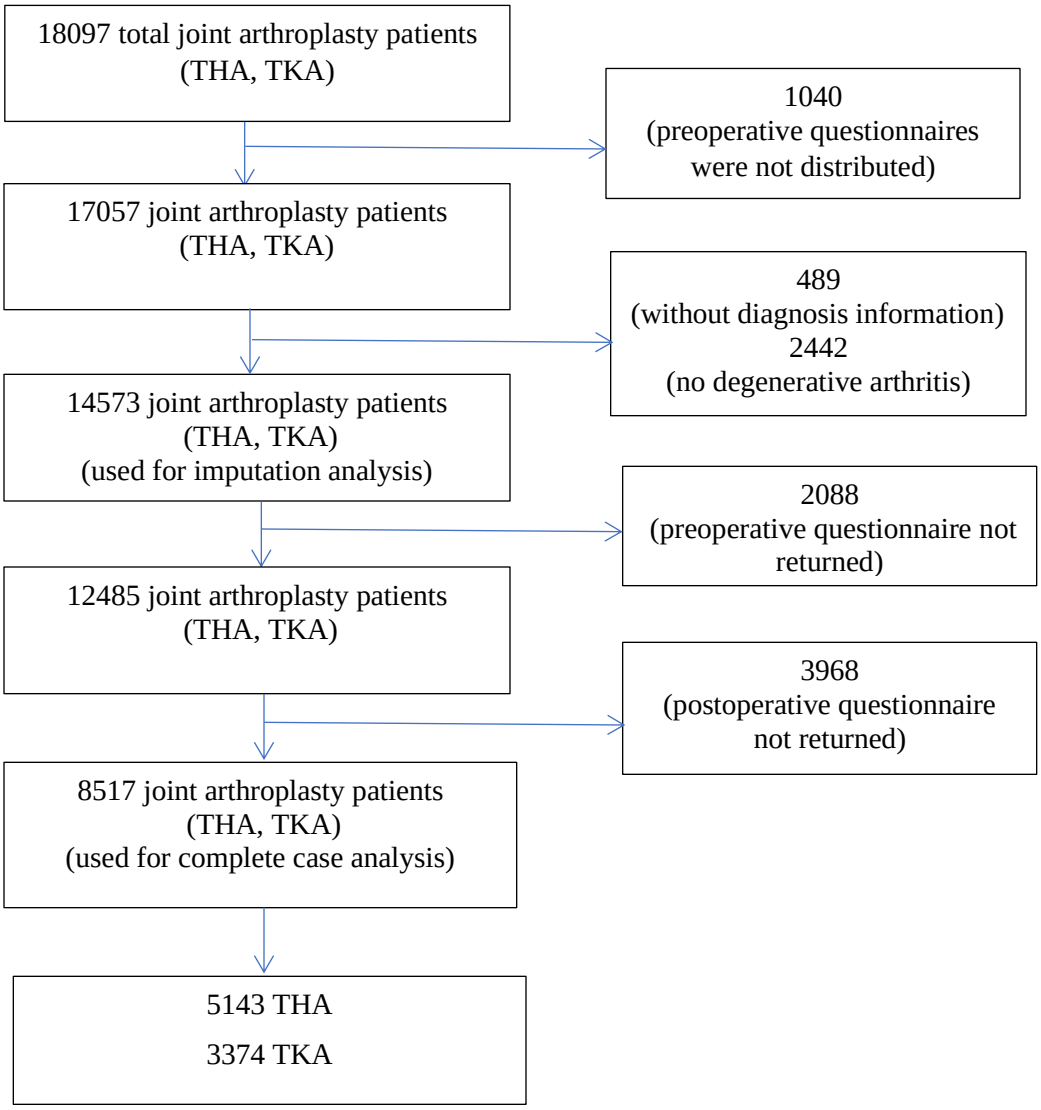

Figure 3.1 Study flowchart

Medical conditions were captured using the self-reported American Academy of Orthopaedic Surgeon's Baseline Medical Questionnaire (The American Academy of Orthopaedic Surgeons, 1998) which records 14 chronic health conditions (yes/no) including heart disease, high blood pressure, lung disease, diabetes, stomach ulcer, kidney disease, liver disease, anaemia or other blood disease, cancer, depression, osteoarthritis or degenerative arthritis other than hip or knee, back pain, rheumatoid arthritis, and "other". Multimorbidity was defined as two or more concurrent conditions from this list. Condition-specific scores were assessed using the 12-Item Oxford Hip Score (OHS) (Dawson, Fitzpatrick, Carr, 1996) and Oxford Knee Score (OKS) (Dawson et al., 1998). These contain 12 questions assessing pain and function of the hip or knee in relation to activities of daily living. Each question uses a five-point ordinal response and total scores range from 12 to 60, with lower scores corresponding to better health. These scores are well validated (Murray et al., 2007) and have been used in many clinical studies and joint replacement registries. General HRQoL was assessed using the 12-Item Short-Form Health Survey questionnaire (SF-12) version 2 (Ware et al., 1996; 2005), a validated instrument widely used to assess physical and mental health. Physical Component Summary (PCS) and Mental Component Summary (MCS) scores are produced which can range from 0 (worst) to 100 (best). Scores are normalized so that values above or below 50 are better or worse, respectively, than their corresponding values in the general population of the United States.

3.2.1 Statistical analysis

Descriptive statistics including means and standard deviations, frequencies, and percentages were used to describe the characteristics of the patients. Patients who did and did not complete the questionnaire pre- and postoperatively were described by their demographic characteristics. Comparisons were conducted using independent sample t-tests for continuous

measures and chi-squared tests of independence for categorical variables. A linear mixed-effects model (Fitzmaurice et al., 2011) was used to estimate the effect of multimorbidity on changes between the pre- and postoperative HRQoL measures. Each model initially included both a random intercept and a random slope for time (i.e., pre- vs postoperative) and the multimorbidity (present vs absent) fixed effect. However, a model with only a random slope proved to be a better fit to the data as judged by the Akaike Information Criterion (Laird, NM, Ware, 1982). Each model also included the two-way interaction between multimorbidity and time. All models were adjusted for the main effects of age (<45, 45 to 54, 55 to 64, 65 to 74, 75 to 84, >85 years), gender (male, female), and BMI (<18.5, 18.5 to 24.9, 25.0 to 29.9, >30.0kg/m2). We also assessed the association between the number of chronic conditions (zero, one, two, three, four or more, based on the original 14 conditions) and change in HRQoL using a similar model and the same confounding covariates as defined above.

Standardized residuals were used to assess the presence of influential observations in the models. Multicollinearity was assessed using variance inflation factors in which large values are indicative of potential collinearity amongst covariates. Given that outcomes may differ between patients who undergo THA or TKA (Jones et al., 2000), all analyses were stratified by the type of arthroplasty. Complete case analysis was conducted for patients with no missing pre- and postoperative observations. Multiple imputation models were constructed to address non-response and these are reported as the main analysis. The mechanism of missing data was assumed to be arbitrary because there was no consistent pattern of differences in demographic characteristics for patients who completed each questionnaire (responders) and those who did not (non-responders) pre- and postoperatively. Markov chain Monte Carlo multiple imputation, which assumes a multivariate normal distribution for the missing observations, was adopted

(Schafer, 1997; 2002). The assumption of normality was assessed visually using quantile-quantile plots. Ten imputed data sets were generated. This number is sufficient to achieve 95% efficiency for high proportions of missing observations.(Schafer, 1998). All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina). Statistical significance was assessed using a nominal α=0.05.

3.3 Results

Table 3.1 shows the preoperative demographic characteristics, BMI, and comorbidity of the cohort with complete data. The mean age of the patients was 67.9 years (17 to 102), 58.2% were female and 65.6% were overweight or obese.

Table 3.1 Preoperative characteristics of the study cohort stratified by multimorbidity status, complete case analysis

	THA		TKA		Overall
	With multimorbidity n (%)	Without multimorbidity n (%)	With multimorbidity n (%)	Without multimorbidity n (%)	
Total	1903 (56.4)	1471 (43.6)	3234 (62.9)	1909 (37.1)	8517
Age, years†	69.2 ± 9.9	66.3 ± 11.5	68.2 ± 9.4	67.4 ± 10.0	67.9± 10.1
Male	757 (39.8)	780 (53.0)	1114 (34.5)	907 (47.5)	3558 (41.8)
Female	1146 (60.2)	691 (47.0)	2120 (65.6)	1002 (52.5)	4959 (58.2)
Normal weight	628 (33.0)	629(42.8)	942 (29.1)	737(38.6)	2936 (34.5)
Overweight	590 (31.0)	461 (31.3)	662 (20.5)	489 (25.6)	2202 (25.9)
Obese	685 (36.0)	381 (25.9)	1630 (50.4)	683 (35.8)	3379 (39.7)
Chronic Conditions					
Hypertension	1219 (64.1)	297(20.2)	2238 (69.2)	475 (24.9)	4229 (49.7)
Other Osteoarthritis	1146 (60.2)	151 (10.3)	1946 (60.2)	200 (10.5)	3443 (40.4)
Back Pain	1105(58.1)	132 (9.0)	1676(51.8)	115 (6.0)	3028 (35.6)
Diabetes	329 (17.3)	31 (2.1)	823 (25.5)	52 (2.7)	1235(14.5)

Heart Disease	338 (17.8)	19(1.3)	532 (16.5)	32 (1.9)	921 (10.8)
Depression	266 (14.0)	25 (1.7)	524 (16.2)	29 (1.5)	844 (9.9)
Rheumatoid Arthritis	244 (12.8)	26 (1.8)	461 (14.3)	39 (2.)	770 (9.0)
Stomach Ulcer	150 (7.9)	7(0.5)	298 (9.2)	7(0.4)	462 (5.4)
Cancer	151 (7.9)	17(1.1)	232 (7.2)	21 (1.1)	421 (4.9)
Anemia	118 (6.2)	*	196 (6.1)	10(0.5)	329 (3.9)
Lung Disease	142 (7.5)	*	238 (7.4)	*	391 (4.6)
Kidney Disease	57 (3)	*	97 (3.0)	*	159 (1.9)
Liver Disease	24 (1.3)	*	57 (1.8)	*	82 (1)
Other Condition	522 (27.4)	90 (6.1)	913 (28.2)	114 (6)	1639 (19.2)
Number of Chronic Conditions					
0	-	662 (45.0)	-	807 (42.5)	1469(17.3)
1	-	809 (55.0)	-	1102 (57.7)	1911 (22.4)
2	806 (42.4)	-	1273 (39.4)	-	2079 (24.4)
3	592 (31.1)	-	976 (30.2)	-	1568 (18.4)
4+	505 (26.5)	-	985(30.5)	-	1490 (17.5)

Abbreviations: THA, total hip arthroplasty; TKA, total knee arthroplasty

[†]Numbers reported are mean ± standard deviation; * indicates cell sizes suppressed due to low frequencies (e.g., ≤ 6)

The most common chronic condition was hypertension (49.7%), followed by other osteoarthritis (40.4%) and back pain (35.6%). Overall, almost two thirds (60.3%) of the cohort met our definition of multimorbidity, having more than two chronic conditions. A total of 56.4% and 62.9% of patients in the THA and TKA groups, respectively, had multimorbidity. Most multimorbid patients in both groups had either two or three conditions. Compared with patients without multimorbidity, those with multimorbidity in both groups were more likely to be female and older; they also were more likely to be obese ($p<0.001$). The demographic characteristics of the responders and non-responders, pre- and postoperatively, are shown in Table 3.2.

Table 3.2 Comparison of demographic characteristics of questionnaire respondents and non-respondents

		Preoperative			**Postoperative**		
	THA	Respondents	Non-Respondents	p-value	Respondents	Non-Respondents	p-value
N	5533	4859	674		3729	1804	
Age, years	67.2 (11.3)	66.8 (11.3)	70.2 (11.5)	<0.0001	68.2 (10.8)	65.4 (12.1)	<0.0001
Female (%)	2989 (54.0)	2606 (53.6)	383 (56.8)	<0.0001	2049 (55.0)	940 (52.1)	0.05
	TKA						
N	9040	7626	1414		6012	3028	
Age, years	67.0 (9.8)	66.9 (9.8)	67.1 (9.7)	0.67	67.9 (9.6)	65.1 (9.8)	<0.0001
Female (%)	5476 (60.6)	4619 (60.6)	857 (60.6)	0.98	3634 (60.5)	1842 (60.8)	0.72

Abbreviations: THA total hip arthroplasty, TKA total knee arthroplasty, SD standard deviation. All numbers reported are mean (SD) unless otherwise noted.

Preoperatively, THA non-responders tended to be older and female. These differences were not seen in the TKA group. Postoperatively, THA non-responders tended to be younger men while TKA non-responders tended to be younger overall.

3.3.1 HRQoL and multimorbidity

Multimorbid patients who underwent THA and TKA had worse pre- and postoperative MCS scores, PCS scores, OHS, and OKS compared with those without multimorbidity. Regardless of the morbidity status, statistically significant improvements in HRQoL scores were observed ($p<0.001$). However, multimorbid patients undergoing THA and TKA had larger improvements in the MCS score, smaller improvements in the PCS score and similar improvements in OHS and OKS compared with those without multimorbidity (Table 3.3). The linear mixed-effects models (Table 3.4) confirmed that multimorbidity had a statistically significant adverse effect on changes in HRQoL for those undergoing THA or TKA. For the THA group, improvements decreased the mean MCS scores by 4.14 points, the mean PCS scores by 1.62 points, and the mean OHS by 2.21 points. Similar estimates were seen in the TKA group (all $p<0.001$).

Table 3.3 Mean (SD) HRQoL scores for the study cohort stratified by multimorbidity status, multiple imputation analysis

	THA			TKA		
Measure	**With multimorbidity**	**Without multimorbiditiy**	**p-value**	**With multimorbidity**	**Without multimorbiditiy**	**p-value**
Preoperative MCS	47.77 (12.37)	52.01 (11.92)	<.0001	49.71 (12.34)	53.42 (11.38)	<.0001
Postoperative MCS	52.24 (10.01)	54.33 (8.89)	<.0001	51.18 (10.62)	53.65 (9.80)	<.0001
Mean Improvement	4.47 (11.62)	2.31 (11.37)	<.0001	1.46 (10.71)	0.22 (10.34)	<.0001
Preoperative PCS	27.48 (7.71)	29.87 (8.65)	<.0001	29.17 (7.86)	31.50 (8.27)	<.0001
Postoperative PCS	42.05 (11.02)	46.82 (10.40)	<.0001	39.45 (10.48)	43.91 (10.16)	<.0001
Mean Improvement	14.57 (11.26)	16.95 (11.18)	<.0001	10.28 (10.65)	12.40 (10.87)	<.0001
Preoperative Oxford	46.02 (7.30)	43.34 (8.30)	<.0001	43.13 (7.53)	41.02 (7.91)	<.0001
Postoperative Oxford	20.50 (9.03)	18.51 (8.70)	<.0001	25.02 (10.11)	22.79 (9.79)	<.0001
Mean Improvement	25.53 (10.46)	24.83 (10.66)	<.0001	18.11 (10.55)	18.23 (10.62)	<.0001

Abbreviations: THA total hip arthroplasty, TKA total knee arthroplasty, MCS SF-12 Mental Component Summary, PCS SF-12 Physical Component Summary, OHS Oxford hip score, OKS Oxford knee score, SD standard deviation. PCS and MCS values can range from 0 to 100, with higher scores indicating better health-related quality of life (HRQOL). OHS and OKS scores can range from 12 to 60, with higher scores indicating poorer HRQOL.

Table 3.4 Linear mixed-effects model results for the effect of multimorbidity on improvement in HRQoL score for THA and TKA cohorts, multiple imputation analysis

	MCS		PCS		OHS/OKS	
	Δ (SE)	**p-value**	**Δ (SE)**	**p-value**	**Δ (SE)**	**p-value**
Multimorbidity						
(Reference: no multimorbidity)						
THA	-4.14 (0.35)	<.0001	-1.62 (0.27)	<.0001	-2.21 (0.24)	<.0001
TKA	-3.55 (0.30)	<.0001	-1.92 (0.23)	<.0001	-1.71 (0.20)	<.0001
Number of Chronic Conditions						
(Reference: 0 conditions)						
THA: 1	-0.44 (0.42)	0.29	-0.74 (0.36)	0.0412	-0.90 (0.28)	0.0011
THA: 2	-2.05 (0.44)	<.0001	-2.17 (0.38)	<.0001	-1.88 (0.28)	<.0001
THA: 3	-3.60 (0.43)	<.0001	-3.40 (0.38)	<.0001	-2.66 (0.32)	<.0001
THA: 4+	-5.95 (0.48)	<.0001	-4.88 (0.41)	<.0001	-3.72 (0.31)	<.0001
TKA: 1	0.21 (0.36)	0.5660	-0.60 (0.30)	0.0457	-0.02 (0.25)	0.9225

TKA: 2	-1.26 (0.34)	0.0002	-2.37 (0.28)	<.0001	-1.20 (0.25	<.0001
TKA: 3	-2.63 (0.35)	<.0001	-3.23 (0.28)	<.0001	-1.78 (0.26)	<.0001
TKA: 4+	-6.00 (0.36)	<.0001	-4.87 (0.29)	<.0001	-3.32 (0.27)	<.0001

Abbreviations: Δ = estimated change, SE standard error, THA total hip arthroplasty, TKA total knee arthroplasty, MCS SF-12 Mental Component Summary, PCS SF-12 Physical Component Summary, OHS Oxford Hip Score, OKS Oxford Knee Score.

The mixed-effects models that included the number of chronic conditions showed that estimates of the magnitude of reduction in the improvements in the HRQoL scores increased in absolute value as the number of conditions increased (Table 3.5). This was the case for all measures with the exception of MCS in the TKA group. For example, patients undergoing THA with more than four chronic conditions had 5.95 points less improvement in the mean MCS, 4.88 points less improvement in the mean PCS, and 3.72 points less improvement in the mean OHS compared with those without a chronic condition. Similarly, patients undergoing TKA with more than four chronic conditions had 6.00 points less improvement in mean MCS, 4.87 points less improvement in mean PCS, and 3.32 points less improvement in mean OKS scores compared with those without a chronic condition. Similar effects of multimorbidity on the adjusted mean change in HRQoL scores were found for the complete case analysis (Table 3.5). However, the standard errors of the estimates were substantially larger for the complete case analysis than for the imputed analysis.

Table 3.5 Comparison of the estimated effect of multimorbidity on HRQoL change for complete case and multiple imputation analyses

	MCS		PCS		OHS/OKS	
	Δ (SE)	**p-value**	**Δ (SE)**	**p-value**	**Δ (SE)**	**p-value**
Complete Case						
THA	-4.68 (0.47)	<.0001	-2.05 (0.36)	<.0001	-2.36 (0.34)	<.0001
TKA	-4.03 (0.40)	<.0001	-2.17 (0.31)	<.0001	-1.82 (0.29)	<.0001
Multiple Imputation						
THA	-4.14 (0.35)	<.0001	-1.62 (0.27)	<.0001	-2.21 (0.24)	<.0001
TKA	-3.55 (0.30)	<.0001	-1.92 (0.23)	<.0001	-1.71 (0.20)	<.0001

Abbreviations: Δ = estimated change, SE standard error, THA total hip arthroplasty, TKA total knee arthroplasty, MCS SF-12 Mental Component Summary, PCS SF-12 Physical Component Summary, OHS Oxford Hip Score, OKS Oxford Knee Score.

3.4 Discussion

Using data from 14,573 patients who underwent elective THA or TKA for osteoarthritis, we examined the effect of multimorbidity on improvement in HRQoL following surgery. As in previous studies (Peter et al., 2015), we found that multimorbidity was common, with almost two-thirds of patients reporting two or more comorbid conditions. We also confirmed the effectiveness of THA and TKA at improving HRQoL and similar to others (Ethgen et al., 2004). we saw large improvements in OHS, OKS, and SF-12 PCS scores. We found that multimorbidity had clinically significant implications for improvements in HRQoL. Generally, patients with multimorbidity had poorer pre- and postoperative HRQoL scores, and smaller improvements compared with patients without multimorbidity. These differences tended to be more apparent in general HRQoL (MCS, PCS) compared with condition-specific measures such as the OHS and OKS. Specifically, differences in pre- and postoperative scores and improvements in both MCS and PCS were either similar to or exceeded the minimum clinically important differences (MCID) for the PCS of 3.3 points and MCS of 3.8 points (Diaz-Arribas et al., 2017). The only exception was the MCS for patients undergoing TKA, in whom neither group (group with multimorbidity or group without multimorbidity) had a clinically significant improvement following surgery.

The relationship between multimorbidity and condition-specific HRQoL as measured using the OHS and OKS was less pronounced. Differences in pre- and postoperative scores between patients with multimorbidity and those without multimorbidity were approximately 70% of the MCID of 5 points for the OHS and 4 points for the OKS (Beard et al., 2015); however, differences between the groups in improvements in these scores were not clinically significant. These unadjusted observations were generally confirmed with the mixed-effects model analysis controlling for age, gender, and BMI. However, the estimated effect of multimorbidity on

improvement in MCS scores, OHS, and OKS was larger, and the effect on PCS scores smaller, than the unadjusted analysis. The larger estimated differences in the improvement in Oxford scores (2.21 for the THA group and 1.71 for the TKA group) is approximately one half of the MCID. The deleterious effect of multimorbidity is further supported by our finding of a dose-response relationship: an increasing number of chronic conditions was associated with reduced gains in all measures of HRQoL for both the THA and TKA groups. Sir John Charnley noted the negative effect of comorbidities on the outcome of THA in 1979. Patients with a worse Charnley comorbidity score tended to have less improvement following surgery (Charnley, 1979). This has been confirmed by others (Garellick et al., 1998) and also found to be true for patients undergoing TKA (Dunbar et al., 2004). However, these authors did not examine the effect of multiple comorbid conditions, but simply their presence or absence. Peter et al (2015) examined the relationship between postoperative general and condition-specific HRQoL measures. As in the current study they found that an increasing number of chronic conditions was associated with worse postoperative HRQoL. However, they did not examine the effect of multimorbidity on improvements in HRQoL. Hawker et al (Hawker et al., 2013) assessed the impact of the number of chronic conditions on functional improvement following THA and TKA. They defined a good outcome as one with an improvement in Western Ontario and McMaster Universities osteoarthritis index (WOMAC) scores greater than half of the standard deviation of the mean difference between pre- and postoperative scores. Similar to the current study, they found that an increasing number of medical conditions was associated with a smaller likelihood of obtaining a good result. However, they did not examine its effect on general HRQoL, nor did they report on its relationship to pre- and postoperative scores. Greene et al. (2015) found no relationship between preoperative morbidity and postoperative PROMs in a large sample of patients from the Swedish Hip Arthroplasty Registry. However, the morbidity data were obtained from

administrative data which were likely to under-report the presence of medical conditions, and the PROMs data consisted of the Euro-Qol questionnaire (EQ-5D) and a visual analogue scale (VAS) and therefore lacked validated measures of physical function, mental health, and joint-specific scores as contained in the current study. This may have resulted in their failure to detect an effect of multimorbidity on HRQoL scores.

Our study adds to existing literature by showing that multimorbidity has an adverse effect on pre- and postoperative HRQoL scores, and is associated with less improvement for patients undergoing THA or TKA. These findings are more pronounced for general HRQoL measures than for condition-specific measures. This is not surprising, given that the OHS and OKS were designed to be relatively free of influence from factors other than the operation being examined (Dawson et al., 1996; 1998).

Our findings have relevance in several areas. First, they are important to care providers when counselling patients with multimorbidity about the outcome of THA or TKA. Second, they confirm the importance of, and potential need to control for, chronic conditions when analyzing measures of HRQoL for public reporting, quality assurance, or healthcare improvement initiatives. Third, they further support the concept that Oxford scores alone cannot be used to determine appropriateness for surgery (Judge et al., 2011) as they are affected by the presence of multimorbidity. A key strength of this study is that the data are from a regional registry including many centres and surgeons, which improves the generalizability of the findings. Additionally, multiple imputation models were used in order to maximize the use of all available data, thus strengthening the precision of the analysis. Furthermore, well-validated and accepted measures of HRQoL were used, thus providing the opportunity to compare our results with those from

future studies. Another advantage was that an inclusive list of 14 medical conditions was used to define multimorbidity.

However, we recognize some limitations. Some potentially important conditions, such as peripheral vascular disease and psychosis, were not included in the preoperative questionnaire (Peter et al., 2015). Furthermore, multimorbidity was assessed by counting the number of conditions rather than their severity. Lastly, although clinical registry data provide excellent sources for clinicians to evaluate outcomes of treatments and improve quality of care for patients, they are often incomplete as registries are not designed for research purposes (Bell and Fairclough, 2014; O'Reilly et al., 2010). In our study, multiple imputation was conducted to maximize utilization of the available data to reduce bias and increase precision. However, missing data were assumed to be missing at random, an assumption that could not be formally tested. Also, non-responders had slightly different demographic characteristics than responders, and this may limit the generalizability of our findings. In the future, besides employing advanced statistical approaches at the analysis stage to deal with missing data, clinical registries also need to focus more on improving data capture. Given our findings, further research is warranted. Multimorbidity was defined according to the patients' self-reporting of chronic conditions. Information about multimorbidity captured from sources of clinical data might provide a different picture of health, would be less sensitive to measurement bias and might enable the assessment of the severity of chronic conditions. The effects of other potential confounding variables recognized as having an effect on HRQoL, such as health behaviors, social support, and medications could be explored. A clear understanding of the relationship between multimorbidity and HRQoL will enable both researchers and healthcare professionals to deliver more comprehensive care to patients with multimorbidity who are considering THA or TKA.

3.5 Conclusion

In conclusion, the presence of multimorbidity reduced gains in both general and condition-specific HRQoL after adjustment for age, gender, and BMI in patients who underwent THA or TKA. There was a dose-response effect for the number of conditions, which was particularly evident when there were two or more chronic conditions. These results are important for healthcare providers focused on the management of patients with chronic conditions, and for reporting and monitoring the outcome of THA and TKA. Further research is needed to investigate the severity of each condition and other potential confounding variables that might also affect HRQoL in patients undergoing arthroplasty.

PREFACE TO CHAPTER 4

Chapter 3 showed that multimorbidity is associated with lower HRQoL, indicating poor physical and mental health in people living with multimorbidity. Depression is one of the most common mental disorders, significantly affecting about 7% of the world's older population with a major impact on global public health (WHO, 2017b). It is important to understand the risk of depressive symptoms associated with multimorbidity among older adults given that depression is a prevalent and disabling mental health condition that negatively influences quality of life and increases the risk of mortality in this population (Blazer et al., 1991; Brett et al., 2012; Cuijpers et al., 2014; Fiske et al., 2009). Furthermore, the clinical assessment of patients with both depressive symptoms and chronic medical conditions is complicated. Major depression in these patients frequently goes undetected and untreated (Katon, 1984; Wang et al., 2007). However, there has been limited research on the association between multimorbidity and depression, despite the finding that depression is the single most common comorbid conditions in older adults (Sinnige et al., 2013). Most of the existing evidence is based on cross-sectional studies (Read et al., 2017).

To address objective 2 in this dissertation research, chapter 4 presents the second study of the dissertation research, which was a systematic review of the existing scientific evidence concerning longitudinal studies on the relationship between multimorbidity and depression among older adults. To the best of our knowledge, there has been no systematic review or meta-analysis conducted on this subject. In this study, we aimed to determine whether multimorbidity was positively associated with increased depressive symptoms or onset of depression among older adults over time. PUBMED, EMBASE and PSYCINFO were systematically searched to identify research articles published in English up to December 2020.

CHAPTER 4: MULTIMORBIDITY AND DEPRESSION IN OLDER ADULTS: A SYSTEMATIC REVIEW OF LONGITUDINAL STUDIES

Abstract

Background: Multimorbidity and depression both affect health adversely in older adults. Previous reviews based on cross-sectional studies have found that multimorbidity is associated with depression. This study aims to assess whether multimorbidity increases the risk of depression among older adults over time.

Methods: PUBMED, EMBASE and PSYCINFO were systematically searched to identify articles published in English up to December 2020. We included longitudinal studies which reported the association between multimorbidity and depressive symptoms among adults aged 50 years or older. Studies focused only on specific chronic conditions were excluded.

Results: A total of 20 studies including 57,349 participants in community and clinical settings were included. Seventeen studies provided information on change of depressive symptoms, three on both change of depressive symptoms and incidence of depression, and three on the incidence of depression only. Most studies demonstrated a positive association between multimorbidity and more depressive symptoms and incident depressive symptoms later on, although four studies suggest that this relationship appears to depend on age, functional status, or time to death.

Conclusions: Multimorbidity is recognized widely as having negative impacts on health outcomes. This systematic review suggests that multimorbidity predicts future depressive

symptoms in older adults. This highlights the need to carefully monitor symptoms of depression in patients with multimorbidity.

Key words: multimorbidity, depression, longitudinal studies, older adults

4.1 Introduction

Multimorbidity, defined as the presence of multiple chronic conditions, is especially common among older adults, affecting more than half of the older population in many industrialized countries, such as the United States, Australia, the Netherlands, and Canada (Marengoni et al., 2011). The prevalence of multimorbidity is increasing due to longer life expectancy and perhaps the growing number of people who live with chronic conditions (Barnett et al., 2012; Divo et al., 2014). Multimorbidity is associated with poor outcomes including disability, decrease in quality of life, psychological distress, high health care costs and increased risk of death (Barnett et al., 2012; Fortin et al., 2006; Marengoni et al., 2011; Violan et al., 2014; Vogeli et al., 2007). The association between multimorbidity and mental health is less well understood, however.

Depression is one of the most common mental health disorders affecting about 7% of the world's older population with a major impact on global public health (WHO, 2017b). Notably, depressive symptoms are associated with an increased mortality (Blazer, 2003; Cuijpers et al., 2014), impaired executive function (WHO, 2020), increased disability (Fiske et al., 2009), and a lower quality of life (Brett et al., 2012) among older adults. It is, therefore, important to understand the risk of depressive symptoms associated with multimorbidity among older adults. The clinical assessment of patients with both depressive symptoms and chronic medical conditions is complicated, and major depression frequently goes undetected and untreated among them (Katon, 1984; Wang et al., 2007).

A large number of studies show a positive relationship between specific chronic physical conditions and depression (Anderson et al., 2001; Matcham et al., 2013; Rudisch and Nemeroff, 2003). One study, for example, showed that heart disease may cause depression due to

dysfunction in the sympathetic, neuroendocrine, autonomic, immune, and inflammatory systems (Krishnan et al., 1996). The prevalence rates of depression were found to be up to three-times higher in patients with type 1 diabetes and twice as high in people with type 2 diabetes compared with the general population worldwide (Roy and Lloyd, 2012). Depression is also frequently observed among patients with stroke (Pan et al., 2011), cancer (Fann et al., 2009) and hypertension (Bogner and De Vries, 2008; Bosworth et al., 2003).

However, there is less research on the association between multimorbidity and depression, despite the finding that depression is the single most common comorbid condition in older adults (Sinnige et al., 2013). A recent meta-analysis of 40 studies found that people living with multimorbidity were three times more likely to have depressive disorder than those with no individual physical chronic condition, and two times more likely than those without multimorbidity (Read et al., 2017). However, all of the studies included in the review were cross-sectional analyses which did not allow assessment of whether morbidity preceded depressive symptoms or vice versa. Furthermore, this review did not focus specifically on the association between multimorbidity and depression in older adults.

To the best of our knowledge, there has been no systematic review or meta-analysis conducted to address the longitudinal association between multimorbidity and depression. Therefore, this present systematic review sought to explore literature on the association between multimorbidity and depression among older adults in cohort studies with a longitudinal design. We aimed to determine whether multimorbidity was positively associated with increased depressive symptoms or onset of depression over time.

4.2 Methods

4.2.1 Search strategy

Electronic databases including PubMed, EMBASE and PsycINFO databases were searched for articles published up to December 8 2020 when the search was conducted. The search strategies were developed in consultation with a university librarian specialized in health science research, taking into account a broad range of terms and phrases used in definitions of multimorbidity and depression in health sciences. The terms used in the search included multimorbidity, comorbidity, chronic illness, chronic disease, physical condition, physical disease, medical condition, depression, and depressive symptoms and depressive disorders (Appendix A). Reference lists of potentially eligible articles were searched by hand to identify additional studies missed by our search strategy.

4.2.2 Study selection

Retrieved articles were considered eligible for the review if they met all of the following inclusion criteria: (1) The sample population included older adults aged 50 and above. We used this cut-off point since the definition of older age varied between countries. Also, initially, we constrained the sample age at 65 or above, a cut-off commonly used in developed countries, but there were very few articles retrieved; (2) The studies were longitudinal cohort studies; (3) The studies had to include measures of both multimorbidity and depression/depressive symptoms; (4) The studies examined the association between multimorbidity (exposure) and depression/depressive symptoms (outcome), even if this was not the primary focus of the study. Studies focused only on the association between specific chronic conditions (but not multimorbidity) and depression/depressive symptoms were excluded. Regarding multiple studies on the same dataset, only the most recent study with the most detailed information was included. Title and abstract of all articles identified through electronic research and hand-search were first reviewed independently by two reviewers (LZ and VM) to exclude irrelevant articles. Full texts of all potentially relevant studies were then also screened independently by two reviewers (LZ

and VM) using a checklist developed based on inclusion and exclusion criteria. Lastly, two reviewers (LZ and VM) met to discuss questionable cases, resolved discrepancies and made a decision on the final list of articles to be included for the review.

4.2.3 Data extraction and quality assessment

The following information was extracted from each article: first author's name, year of publication, country of origin of the studies, follow-up period, sample size, age, sex, study setting, measures of multimorbidity, measures of depression or depressive symptoms and key findings regarding the relationship between multimorbidity and depression. Study quality was assessed using the Newcastle–Ottawa Scale for cohort studies (Wells et al., 2012), which assesses the selection of participants, methods to control for confounding and assessment of the outcome.

4.3 Results

4.3.1 Studies included

Figure 4.1 presents a flowchart summarizing the process of identification of citations included in the study. Our search strategy yielded 1190 citations from electronic databases. A hand search from reference lists identified five additional potentially relevant citations. After removing 163 duplicates, 1032 citations were excluded after the first screening of titles and/or abstracts for inclusion and exclusion criteria, leaving 144 citations for further full text screening. After further assessment of these citations, 124 were excluded (see Appendix B) for reasons listed in Figure 4.1, leaving 20 for final inclusion in the review. Generally, all the studies were of moderate to high quality based on the Newcastle-Ottawa quality assessment scale (Appendix C).

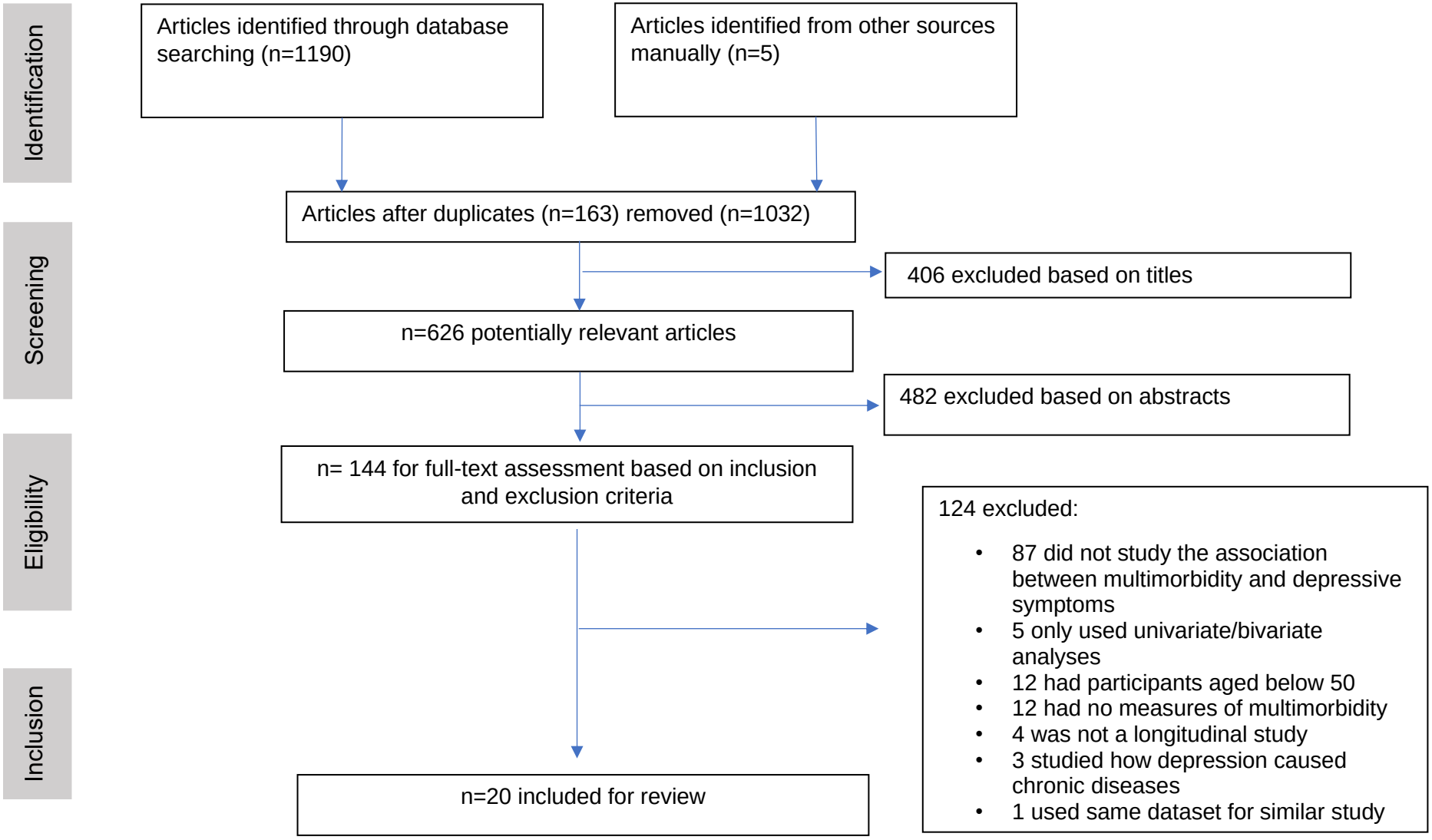

Figure 4.1 Study flowchart of articles included in the review

Table 4.1 presents the characteristics of the prospective cohort studies reviewed. Of these, three (Curyto et al., 1999; Dent et al., 1999; Roberts et al., 1997) were published between 1990 and 1999; five (Chou, 2008; Oslin et al., 2002; Sachs-Ericsson et al., 2007; Stommel et al., 2004; Vink et al., 2009) between 2000 and 2009; and twelve (Assari and Lankarani, 2017; Eliyan et al., 2020; Fauth et al., 2012; Feng et al., 2013; Hsu, 2015; Marroig et al., 2019; Rast et al., 2014; Sutin et al., 2013; Tsai, 2013; Turuba et al., 2019; Wilson-Genderson et al., 2017; Wu et al., 2012) between 2010 and 2020. The included studies had total follow-up periods ranging from 3 months to 30 years. Ten studies were conducted in the United States (Assari and Lankarani, 2017; Curyto et al., 1999; Eliyan et al., 2020; Oslin et al., 2002; Rast et al., 2014; Roberts et al., 1997; Sachs-Ericsson et al., 2007; Stommel et al., 2004; Sutin et al., 2013; Wilson-Genderson et al., 2017); two in Taiwan (Hsu, 2015; H. Tsai, 2013); one each in Australia (Dent et al., 1999), Canada (Wu et al., 2012), England (Chou, 2008), the Netherlands (Vink et al., 2009), Singapore (Feng et al., 2013), and Sweden (Fauth et al., 2012). One (Marroig et al., 2019) included data from ten European countries (Austria, Belgium, Denmark, France, Germany, Italy, Netherlands, Spain, Sweden and Switzerland); and one (Turuba et al., 2019) was conducted in four countries (Canada, Albania, Brazil and Columbia). All but two studies (Oslin et al., 2002; Stommel et al., 2004) were conducted in community dwelling populations with three studies (Fauth et al., 2012; Hsu, 2015; Wu et al., 2012) including both community and institutional populations.

Seven studies included specific populations, such as black and white Americans (Assari and Lankarani, 2017, Sachs-Ericsson et al., 2007), indigenous groups (Curyto et al., 1999), older adults with disabilities (Fauth et al., 2012), individuals with chronic kidney disease (Feng et al., 2013), psychiatric hospital inpatients (Oslin et al., 2002), and patients with breast, colon, lung or prostate cancer (Stommel et al., 2004). The sample sizes ranged from 204 to 46,087 for a total of 57,349 participants. Eight studies (Assari and Lankarani, 2017; Chou, 2008; Sachs-Ericsson et

al., 2007, Dent et al., 1999; Fauth et al., 2012; Stommel et al., 2004; Turuba et al., 2019; Wu et al., 2012) focused on older adults aged 65 and above and the rest on individuals aged 50 and above. The percentage of females ranged from 45.6% to 72%, although the proportion was unclear in four studies (Chou, 2008; Marroig et al., 2019; Roberts et al., 1997; Tsai, 2013) (Table 4.1).

4.3.2 Measures of multimorbidity and depressive symptoms

In the studies included in the review, chronic diseases used to define multimorbidity were mostly self-reported from lists of 5 to 25 conditions (Table 4.1). Multimorbidity in all but three studies was measured by a count of the number of chronic conditions. In the three studies, multimorbidity was measured with the Comorbidity Index (CMI) (Curyto et al., 1999), and the Charlson Comorbidity Index (CCI) (Eliyan et al., 2020; Sutin et al., 2013), respectively, which account for both the number of conditions and severity of the conditions. Depressive symptoms were measured by self-reported symptoms using the Centre for Epidemiologic Studies Depression (CES-D) scale in fifteen studies; the NSHAP Depressive Symptoms Measure (NDSM) in one study (Eliyan et al., 2020), the Geriatric Depression Scale in two studies (Feng et al., 2013; Oslin et al., 2002); the EURO-D symptom scale in one study (Marroig et al., 2019); and the 12 items adapted from Primary Care Evaluation of Mental Disorders (PRIME-MD) mood disorders section in one study (Roberts et al., 1997) (Table 4.1).

Table 4. 1 Characteristics of included studies at baseline

First author, Publication year	**Country**	**Sample**	**Sample size**	**Age (in years) at baseline**	**Women (%)**	**Follow-up period**
Assari, 2017	US	Community	1493	65+	61.8	3 years (2 waves)
Chou, 2008	England	Community	3858	65+	Not reported	2 years (2 waves)
Curyto, 1999	US	Community (Great Lakes Native Americans)	204	55+	63.3	1.5-2 years (2 waves)
Dent, 1999	Australia	Community	299	75+	51.5	3 years (2 waves)
Eliyan, 2020	US	Community	1793	57+	51.8	10 years (2 waves)
Fauth, 2012	Sweden	Community and institutional (older adults with some disability)	779 (pooled samples from 4 studies)	70+	64.3	12 years (3-6 waves)

Feng, 2013	Singapore	Community (older adults with chronic kidney disease)	362	55+	45.6	4 years (2 waves)
Hsu, 2015	Taiwan	Community (99%), institutional (1%)	2,584	60+	48.7	14 years (3+ waves)
Marroig, 2019	Austria, Belgium, Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland	Community	21,253	50+	unclear	8-9 years (4 waves)
Oslin, 2002	US	Clinical (Inpatients in a psychiatric hospital)	671	60+	72.0	3 months (2 waves)
Rast, 2014	US	Community	2,526	50+	51	12 years (7 waves)

Roberts, 1997	US	Community	2,219	50+	unclear	1 year (2 waves)
Sachs-Ericsson, 2007	US	Community	2406	65+	63.0	3 years (2 waves)
Stommel, 2004	US	Clinical (Patients with breast, colon, lung or prostate cancer)	860	65+	46.4	1 year (4 waves)
Sutin, 2013	US	Community	1,482 (for morbidity analyses)	60+ (for morbidity analysis)	47.0	30 years (up to 21 waves; mean= 4.7 waves)
Tsai, 2013	Taiwan	Community	4,440	53+	unclear	8 years (3 waves)
Turuba, 2019	Canada, Albania, Brazil, Columbia	Community	1,360	65-74	48.3	2 years (2 waves)
Vink, 2009	the Netherlands	Community	1712	55–85	49.2	9 years (4 waves)

Wilson-Genderson, 2017	US	Community	3,396	50-74	61.2	8 -10 years (4 waves)
Wu, 2012	Canada	Community and institutional	3,652	65+	63.7	10 years (3 waves)

4.3.3 Association of multimorbidity with depression

All reviewed longitudinal studies but three provided information on change of depressive symptoms, with three (Chou, 2008, Curyto et al., 1999; Roberts et al., 1997) also reporting on the incidence of depressive symptoms. Three studies (Eliyan et al., 2020, Turuba et al., 2019; Vink et al., 2009) focused on multimorbidity and the incidence of depression only (Table 4.2). Most studies included generally showed that multimorbidity predicts more depressive symptoms. This was the case regardless of the multimorbidity and depressive symptoms measures used, the country in which the study was conducted, population investigated, and type of analyses conducted (Table 4.2).

Table 4. 2 Summary of findings on longitudinal association between multimorbidity and depressive symptoms among older adults

First author, publication year	Multimorbidity (MM) measure				Depression measure (used in MM analysis)	Results
	Measure	Type of measure	# of conditions	Included conditions		
Assari, 2017	Number of chronic conditions	Self-report	12	hypertension, heart problem, diabetes, cancer, kidney disease, arthritis or rheumatism, intestinal disorders, liver disease, urinary tract disorders, eye diseases, respiratory disease, and any other major health problem.	8-item Center for Epidemiological Studies-Depression Scale (CES-D-8)	MM was associated with increased depressive symptoms in both black and white participants.

Chou, 2008	Number of chronic conditions	Self-report	8	cardiovascular diseases, lung diseases, bone diseases, cognitive diseases, diabetes, stroke or cerebral vascular disease, Parkinson's disease, and cancer	CES-D-8	MM was associated with depression onset (OR 1.18, CI 1.06–1.32), but not with persistence of depressive symptoms among those depressed at baseline.
Curyto, 1999	Comorbidity Index (CMI)	Self-report	21	Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease,	20-item Center for Epidemiological Studies-Depression Scale (CES-D-20)	Participants who were not depressed at baseline and follow-up (the 'never depressed') had a lower MM score at baseline, compared to those who remained depressed, became depressed, and those who had remitted depression from baseline to

				mild liver disease, diabetes mellitus, hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, tumor, leukemia, lymphoma, moderate or severe liver disease, metastatic solid tumor, AIDS		follow-up, after controlling for age, education and functional abilities.
Dent, 1999	Number of chronic conditions	Assessed by physician	12	Cardiovascular, cerebrovascular, peripheral vascular, respiratory, musculoskeletal, vision, deafness, obesity, gait	CES-D-20	MM did not predict depressive symptoms at follow-up after controlling for CES-D and disability at the first wave.

				ataxia, gait slowing, Parkinsonism, cognitive impairment		
Eliyan, 2020	Charlson Comorbidity Index (CCI)	Not reported	Not reported	Not reported	NSHAP Depressive Symptoms Measure (NDSM)	Having MM at baseline predicted onset of depressive symptoms among participants with normal olfactory function (OR = 1.51, 95% CI = 1.08-2.11).
Fauth, 2012	Number of chronic conditions	Self-report	11	Arthritis, hip fracture, osteoporosis, stroke, heart attack, chest pain/angina, diabetes, asthma, coughing with yellow	CES-D-10	MM was associated with increased depressive symptoms, after controlling for age group, gender, years of education, marital status (widowed or not), and institutionalization.

				phlegm, malignant tumor, Parkinson's disease.		
Feng, 2013	Number of chronic conditions	Self-report, confirmed by checking the use of specific medications	11	Cataracts, glaucoma, eye diseases, asthma, chronic obstructive pulmonary disease, arthritis, hip fracture, cancer, and other problems (e.g., thyroid disorders, gastrointestinal and liver, gynecologic, neurologic, etc.).	15-item Geriatric Depression Scale (GDS-15)	MM was associated with an increased risk of depression at follow-up after controlling for age, gender, marital status, housing type, functional status, diabetes, hypertension, cardiovascular disease, other illnesses, cognitive impairments, smoking, physical activity, eGFR, albumin, and hemoglobin.
Hsu, 2015	Number of chronic conditions	Self-report	9	Diabetes mellitus, heart disease, stroke, cancer, lung diseases,	CES-D-10	A MM-risk trajectory derived from analyzing chronic conditions over time was associated with

				rheumatism/arthritis, liver or gallbladder disease, gastrointestinal disorders, and renal disease.		increased depressive symptoms, relative to a low risk trajectory group after controlling for age, sex, years of education, and marital status, smoking, drinking alcohol, physical activity, and the health examination.
Marroig, 2019	Number of chronic conditions	Self-report	12	Heart attack, high blood pressure or hypertension, high cholesterol, a stroke or cerebral vascular disease, diabetes or high blood sugar, chronic lung disease, cancer or malignant tumour, stomach or duodenal	EURO-D symptom scale	MM was associated with increased depressive symptoms across age groups in all countries studied.

				ulcer, peptic ulcer, Parkinson's disease, cataracts, hip fracture or femoral fracture.		
Oslin, 2002	Number of chronic conditions	Reported by collateral contacts	20	Alzheimer's disease, anemia, arthritis, circulation problem, cancer, diabetes mellitus, emphysema, glaucoma, high blood pressure, heart trouble, kidney problem, Parkinson's disease, skin disorder, stomach disorder, speech disorder, thyroid disease, ulcer,	Geriatric Depression Scale—Collateral version (GDS-C)	MM was associated with increased depressive symptoms and reduced odds of a 50% improvement in depressive symptoms after controlling for age, sex, race and marital status. These effects were no longer statistically significant when disability was controlled for in analyses.

				urinary disorder, and other.		
Rast, 2014	Number of chronic conditions	Self-report	5	Hypertension, diabetes, cardiovascular diseases (CVD), stroke and cancer	CES-D-8	The relationship between MM and depressive symptoms depended on time to death; e.g., 2+ chronic conditions was associated with increased depressive symptoms up to 6 years before death, but was no longer significant from then on.
Roberts, 1997	Number of chronic conditions	Self-report	12	Heart trouble, high blood pressure, asthma, chronic bronchitis, arthritis, emphysema, diabetes, stroke, cancer, cataracts,	12 items adapted from Primary Care Evaluation of Mental Disorders (PRIME-MD)	MM was associated with increased depressive symptoms of major depression in the full sample and among those not depressed at baseline after controlling for age, gender,

				osteoporosis, and circulatory problems	mood disorders section	marital status, education, financial problems, problems with normal daily activities, cognitive difficulties, life events, neighborhood problems, social isolation, and social support.
Sachs-Ericsson, 2007	Number of chronic conditions	Self-report	5	heart problems, hypertension, diabetes, stroke, and cancer.	CES-D-20	MM was not predictive of change in depressive symptoms.
Stommel, 2004	Number of chronic conditions	Self-report	11	Arthritis, hypertension, heart disease, emphysema, chronic lung disease, stroke, diabetes, fractured hip, bladder control, loss of eyesight, and hearing loss	CES-D-20	MM was associated with increased depressive symptoms after controlling for gender, race, marital status, education, caregiver status, previous emotional problem and diagnosis information. No significant

						association was found for 1 or 2 chronic conditions.
Sutin, 2013	Charlson Comorbidity Index (CCI)	Medical history taken by nurse practitioner	19	Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, Cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes mellitus, hemiplegia, moderate or severe renal disease, diabetes with end-organ	CES-D-20	Participants with MM reported more depressive symptoms than those without MM after controlling for sex, educational level, and ethnicity. MM contributed to a greater increase in depressed affect in older age.

				damage, any tumor, leukemia, lymphoma, moderate or severe liver disease, metastatic solid tumor, and AIDS		
Tsai, 2013	Number of chronic conditions	Self-report	14	Hypertension, diabetes, heart diseases, stroke, cancer, lung diseases, arthritis/rheumatism, gastric ulcer/gastric diseases, liver/gallbladder diseases, hip fracture, cataract, kidney diseases, gout and bone spurs	CES-D-10	MM was positively associated with depressive symptoms at 4-year follow-up for younger (53-64) and older (>=65) participants after controlling for sex, age and education level. At 8-year follow-up, the association was significant only for the younger age group.

Turuba, 2019	Number of chronic conditions	Self-report	8	Hypertension, diabetes, cancer, lung diseases, heart diseases, stroke, arthritis, and osteoporosis.	CES-D-20	MM was not associated with incident depressive symptoms in any of the study regions after controlling for age, gender, marital status, education, smoking, drinking alcohol, physical activities, health care use, social support and psychological violence from partners.
Vink, 2009	Number of chronic conditions	Self-report	5	Diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease, arthritis, and cancer.	CES-D-20	MM was associated with increased likelihood of onset of depressive symptoms (OR 1.32, 95% CI= 1.16–1.51)

Wilson-Genderson, 2017	Number of chronic conditions	Self-report	5	Arthritis, diabetes, heart disease, hypertension, and pulmonary disease.	CES-D-10	Participants who developed MM had higher levels of depressive symptoms over time, relative to individuals who did not transition to MM after controlling for age, sex, being African American, and income.
Wu, 2012	Number of chronic conditions	Diagnosed by physician	25	Not reported	CES-D-20	MM was associated with increased depressive symptoms after controlling for sex, marital status, urban/rural residence, visible minority status, and education.

4.3.3.1 Multimorbidity and change of depressive symptoms

Fourteen out of eighteen studies carried out in a community setting found that multimorbidity was positively related to depressive symptoms over time. For example, the largest study (Marroig et al., 2019) involved 21,253 adults aged 50 above who participated in the Survey of Health, Ageing and Retirement in Europe (SHARE) in ten European countries (Austria, Belgium, Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland). The results showed a significant positive association between multimorbidity across time and the average number of depressive symptoms at ages 60, 65 and 70 in all countries studied. One study from the US (Sutin et al., 2013) with a follow-up duration of 30 years investigated the trajectory of depressive symptoms and associated factors that may contribute to increases in depressive symptoms across adulthood. The results showed that older participants of 65+ with greater multimorbidity burden had more depressive symptoms than those with less multimorbidity over time.

Three studies looked at the association between multimorbidity and depressive symptoms over time among both community and institutional living older adults. For example, a study from Taiwan (Hsu, 2015) analyzed data from a nation-representative panel survey conducted from 1993 to 2007. They grouped chronic diseases as cardiovascular disease (CVD), chronic non-specific lung disease (CNSLD), arthritis, cancer, gastrointestinal disease (GI), and kidney disease. These conditions were further grouped as low risk, GI & CNSLD risk, CVD risk only, and multiple risks group. The results showed that the multiple-risk group trajectory was positively related to more depressive symptoms at follow-up. One study from Canada (Wu et al., 2012) revealed that increasing numbers of chronic condition counts was related to increased

depressive symptoms and higher risk of major depression over time in older adults aged 65 above living in community and institutional settings.

In contrast, five studies on community dwelling populations detected either none or a weak association. Specifically, one study in the UK (Chou, 2008) investigated the role of hearing and vision loss among older adults aged 65+ in the English Longitudinal Study of Ageing. They reported that multimorbidity was not associated with persistence of depressive symptoms among those depressed at baseline. One study in Australia (Dent et al., 1999) examined the effect of multimorbidity, neurodegenerative syndromes and functional disability on depression over time among community-living older adults aged 75 above. The results showed that the total number of diseases did not predict the CES-D scores at follow-up three years later after controlling for CES-D and disability at baseline. Multimorbidity, therefore, seemed to affect depression through disability; i.e., chronic diseases leading to disability, which in turn could increase depressive symptoms. Another study from the US (Sachs-Ericsson et al., 2007) examining the relationship between body mass index (BMI) and subsequent depressive symptoms found that multimorbidity at baseline did not predict increased depressive symptoms three years later among both black and white Americans. One study in Taiwan (Tsai, 2013) focused on the association between nutritional risk, functional dependence and multimorbidity with depressive symptoms in people aged 53 years and over. The results showed that multimorbidity was positively associated with increased depressive symptoms at 4-year follow-up in both younger (aged 53-64) and older (aged 65+) groups. The odds ratios (OR) were 1.18 (95% CI 1.04 to 1.34) and 1.21 (CI 1.12 to 1.31), respectively. However, at 8-year follow-up, the association was significant only in the younger age group (OR 1.28, 95% CI 1.13 to 1.44). Lastly, one study in the US (Rast et al., 2014) explored how and when multimorbidity affected

depressive symptoms in late life, particularly near the end of life. They found that the relationship between multimorbidity and depressive symptoms depended on time to death; e.g., 2+ chronic conditions was associated with increased depressive symptoms up to 6 years before death, but this relationship was no longer significant from then on. Individuals appeared to experience stable or decreasing depressive symptoms towards the end of life relative to those without multimorbidity.

Seven studies examined the association between multimorbidity and depression in specific populations. For example, one study (Fauth et al., 2012) analyzed longitudinal data pooled across 4 Swedish studies and reported that multimorbidity was positively related to increased depressive symptoms among very old adults (mean age = 86) with disability. One study from Singapore (Feng et al., 2013) showed increased odds of experiencing more depressive symptoms four years later in those with multimorbidity at baseline (OR 1.36, 95% CI 1.02 to 1.82) among patients with chronic kidney disease. One study from the US (Oslin et al., 2002) showed that the total number of chronic conditions negatively affected the improvement of depressive symptoms after treatment among patients in a psychiatric hospital (OR 0.86, 95% CI 0.79 to 0.94). The effect of these conditions on depression was mediated by disability. Another American study (Stommel et al., 2004) was a 3-month longitudinal investigation on the course of depressive symptoms in geriatric patients with breast, colon, lung, or prostate cancer. The results showed that patients with multimorbidity (3 or more chronic conditions) had average total depression scores that were 2.35 points higher ($p < .01$) than those without multimorbidity.

4.3.3.2 Multimorbidity and onset of depression

Five studies examined the association between multimorbidity and onset of depression. Noticeably, one study using multi-regional data (Turuba et al., 2019) found no statistically significant association between multimorbidity at baseline and onset of depressive symptoms two years later among older adults aged from 65 to 74 living in the community. The rest of the studies detected positive association longitudinally. For example, a study in the UK (Chou, 2008) focusing on the role of hearing and vision loss among older adults aged 65+ reported that multimorbidity was associated with the incidence of depressive symptoms. One study in the US (Curyto et al., 1999) investigated depression longitudinally in 204 Great Lakes Native Americans aged 55 and above. The results showed that participants who did not report depressive symptoms at baseline and follow-up (the "never depressed") had a lower multimorbidity score at baseline, compared to those who remained depressed, became depressed, and those who had remitted depression from baseline to follow-up. Another study in the US (Eliyan et al., 2020) examined the relationship between olfactory function and development of depression. The results showed that multimorbidity at baseline predicted onset of depressive symptoms among participants with normal olfactory function (OR = 1.51, 95% CI = 1.08-2.11). Finally, one more study from the US (Roberts et al., 1997) studied the effect of aging on rates of depressive symptoms among community residents aged 50 above, prospectively. The results demonstrated that multimorbidity was associated with increased major depressive symptoms one year after among those who did not report depressive symptoms at baseline (OR 2.97, 95% CI 1.86 to 4.75) and in the full sample including both those with and without depressive symptoms at baseline (OR 4.47, 95% CI 3.06 to 6.52).

4.4 Discussion

To the best of our knowledge, this is the first systematic review to explore the impact of multimorbidity on both change of depressive symptoms and incidence of depressive symptoms over time among older adults in community, institutional and clinical settings. Prior systematic reviews have examined the impact of chronic illness on depression (Hasan et al., 2014; Huang et al., 2009; Read et al., 2017). However, most of the work has either focused on single conditions (Hasan et al., 2014; Huang et al., 2009) or included only cross-sectional studies (Read et al., 2017) which could not assess the temporal association between chronic illness and depressive symptoms in the context of aging. Our review of 20 longitudinal studies found that older adults with multimorbidity generally reported more depressive symptoms over the course of follow-up in community, institutional and clinical settings. This association points to the demand to achieve better mental health outcomes among older adults with multimorbidity.

Although the majority of included studies demonstrated a positive association between multimorbidity and depressive symptoms, three studies (Dent et al., 1999; Sachs-Ericsson et al., 2007; Turuba et al., 2019) found no significant relationship. The chronic conditions included to define multimorbidity and the instrument used to measure depression in these studies did not vary considerably from those in studies that demonstrate significant findings. However, these studies had a higher attrition rate in relatively small samples of participants, suggesting that results may not be generalizable. One study (Turuba et al., 2019) had 1981 participants initially, of which 433 with depressive symptoms were excluded from the study, followed by 188 dropouts, resulting in 1360 left which was only 69% of the initial study cohort. Similarly, the other two studies (Dent et al., 1999; Sachs-Ericsson et al., 2007) had a high attrition rate of 53%

and 42%, respectively, due to death, refusal and loss of data which may account for the failure to detect an association between multimorbidity and onset of depression.

The findings of this present review also suggest that the effect of multimorbidity weakens in older age or at the end of life, as one study showed no significant association between multimorbidity and depressive symptoms in a sub-group analysis of participants aged 65+ (Tsai, 2013), and another study found no significant association at the end of life (Rast et al., 2014). Together, these results echo previous evidence about the interaction between age and depression in adults 65 years of age and older, which shows that depression is significantly lower in older age groups than any other age group (Davison et al., 2019; Patten, 2001). These findings suggest that healthy older adults with normal functioning may not be at greater risk of depressive symptoms, and that the relationship between multimorbidity and depressive symptoms may be mainly caused by physical health problems and health-related functional impairment (Djernes, 2006; Lewinsohn et al., 1991). As such, increasing functional decline or disability may serve as a mediator; i.e., chronic diseases leading to disability, which in turn could increase depressive symptoms (Dent et al., 1999; Oslin et al., 2002; Ryan et al., 2015).

The results of this review confirmed previous findings, which suggested that multimorbidity was associated with increased risk of depressive symptoms (Read et al., 2017). The negative impact of multimorbidity on depressive symptoms may relate to the idea that multimorbidity represents a life stress event (Aneshensel, 1992), requiring individuals to cope with increasing symptoms, multiple medications and complex treatment regimens, which can increase depressive symptoms or lead to the onset of depressive symptoms. The presence of multimorbidity may also result in a cascade of challenges, such as disability, loss of

independence, decreased quality of life and decline in cognition, which may lead to depression (Katon, 2003; Williamson et al., 2000).

4.4.1 Limitations

Although the current review adds to the literature by providing stronger evidence of the relationship between multimorbidity and depressive symptoms than is possible based on cross-sectional studies (Read et al., 2017), several limitations must be acknowledged. Because of the scarcity of longitudinal studies in the subject field, broad inclusion criteria were used, and consequently the heterogeneity between studies was high. The high heterogeneity between studies reviewed stemmed from various aspects, such as the multiple multimorbidity measures used, the treatment of multimorbidity in data analysis either as continuous or categorical variables and the different statistical analyses used in the studies. Hence, it was not possible to conduct a meta-analysis or sub-group analysis to quantify the risk of having worse depressive symptoms or incidence of depressive symptoms among those with multimorbidity. Also, this review only included studies published in English.

The studies included in this review also had a number of limitations. In some studies, selection bias may have been at play due to high attrition rates. Chronic conditions and depressive symptoms were mostly self-reported from questionnaires introducing the potential for inaccuracies due to either under- or over-reporting of conditions. However, prior studies have found self-report to be reliable in older adults (Bush et al., 1989; Katz et al., 1996). There was also disparity in the number of conditions included to measure multimorbidity and few studies examined the impact of different numbers of conditions, condition type and possible combinations or conditions, or condition severity. Another concern is the issue of symptom contamination in the CES-D, which was the most commonly used measure of depressive

symptoms. Clearly somatic symptoms of depression overlap with disease-related symptoms, particularly decreased energy, concentration difficulties, sleep, and appetite disturbance. Additionally, the study settings varied which adds to generalizability, but given that all studies were conducted in high income countries, the results may not apply outside these settings.

4.5 Conclusions

Multimorbidity is widely recognized as having negative impacts on health outcomes. This systematic review suggests that multimorbidity predicts future depressive symptoms in older adults, although the effect of multimorbidity might depend on age, functional status, or time to death. The findings illustrate the importance of assessing the risk of depressive symptoms when designing interventions and systems of care for people living with multimorbidity to prevent a future cascade towards poor mental health outcomes. Clinicians need to carefully consider psychological symptoms including depressive symptoms in patients with multimorbidity, especially in those with functional limitations. For example, evidence shows that social emotional support and psychotherapy can improve clinical outcomes, reduce psychosocial symptoms and lower mortality among adults with chronic conditions (Olaya et al., 2017; Robinson et al., 2017; Strom and Egede, 2012). Besides lessening multimorbidity, more research is clearly needed into the development and testing of such interventions in care models to improve older adults' quality of life.

PREFACE TO CHAPTER 5

In chapter 4, it was demonstrated that most studies included in the systematic review detected a positive association between multimorbidity and depressive symptoms among adults over time, although some studies suggest that this relationship may depend on age, functional status, or time to death. Given the scarcity of longitudinal studies in the subject field, more empirical research is needed regarding the influence of multimorbidity on depressive symptoms.

The negative impact of multimorbidity on depressive symptoms may be explained by the concepts of life stressor event caused by multimorbidity (Aneshensel, 1992); multimorbidity may contribute to higher stress in individuals coping with increasing symptoms, multiple medications and complex treatment regimens associated with multimorbidity, therefore increasing depressive symptoms. Moreover, previous research revealed that multimorbidity is associated with a cascade of challenges, such as disability, loss of independence, decreased quality of life and decline in cognition, which may ultimately lead to depression (Katon, 2003; Williamson et al., 2000). Therefore, more research is clearly warranted on factors that may help with coping with the challenges and stress of living with multimorbidity faced by older adults. Social support has been shown to play an essential role in achieving better physical health and mental health outcomes; it is an important aspect in promoting healthy aging (Uchino, 2009). Importantly, one prominent theory, the stress buffering model posits that social support benefits health by providing psychological and material resources to cope with stressful life events (Cohen and Wills, 1985; Thoits, 2011; Uchino, 2009).

To address objective 3 of this dissertation research, chapter 5 presents the third study, a population-based prospective cohort study with the aims to determine the relationship between

multimorbidity and depressive symptoms; and further explore if social support played an important role in this relationship among older adults living in a community setting. In this study, I analyzed the first wave of 3-year follow-up data of 16,919 community-dwelling in the Canadian Longitudinal Study on Aging (CLSA). CLSA is the most comprehensive national research platform on aging in Canada, collecting data covering a broad range of biological, medical, psychological, socioeconomic, and lifestyle factors that influence healthy ageing (CLSA, 2021). In this study, multimorbidity was defined as having three or more chronic conditions. The 10-item Center for Epidemiologic Studies Depression scale (CESD-10) was used to measure depressive symptoms at both the baseline and the three-year follow-up. The 19-item Medical Outcomes Study (MOS) Social Support Survey was used to assess perceived social support. Weighted multivariate logistic regression models were employed to examine the association between multimorbidity and depressive symptoms at 3-year follow-up; and further determine if social support buffers the impacts of multimorbidity on depressive symptoms.

CHAPTER 5: MULTIMORBIDITY AND DEPRESSIVE SYMPTOMS IN OLDER ADULTS AND THE ROLE OF SOCIAL SUPPORT: EVIDENCE USING CANADIAN LONGITUDINAL STUDY ON AGING DATA

Abstract

Background: The rising prevalence of multimorbidity poses challenges to health systems globally. There is limited longitudinal research on the impact of multimorbidity on mental health. The objective of this study was to investigate: 1) the longitudinal association between multimorbidity and depressive symptoms; and 2) whether social support plays a protective role in this association.

Methods: A prospective population-based cohort study was conducted to analyze 3-year follow-up data of 16,909 community dwelling participants aged 65 and above in the Canadian Longitudinal Study of Aging (CLSA). Multimorbidity was defined as having three or more chronic conditions. The 10-item Center for Epidemiologic Studies Depression scale (CESD-10) was used to measure depressive symptoms. The 19-item Medical Outcomes Study (MOS) Social Support Survey was employed to assess perceived social support. Multivariate logistic regression models were used to examine the association between multimorbidity and depressive symptoms; and investigate the role of social support in this relationship.

Results: Multimorbidity was very common among participants with a prevalence of 70.8 %. The average number of chronic conditions was 4.2. Fifteen percent of participants had depressive symptoms at baseline. Multimorbidity was associated with increased odds of depressive

symptoms at 3-year follow-up (adjusted odds ratio 1.30, 95% Confidence Interval 1.14, 1.48). There was a significant interaction effect between multimorbidity and social support on depressive symptoms three years later ($\beta = 0.19$; $p < .05$), indicating social support was a protective factor in the association between multimorbidity and depressive symptoms.

Conclusion: Multimorbidity was positively associated with depressive symptoms over time, but social support served as a buffering protective factor in this association. Strengthening social support may reduce depressive symptoms in those with multimorbidity. Future interventions and programs should invest on incorporating social support into care guidelines for individuals with multimorbidity.

Key words: multimorbidity, depressive symptoms, social support, longitudinal study, older adults

5.1 Introduction

5.1.1 Depression

Depression is one of the most common mental disorders, affecting about 7% of the world's older population with a major impact on global public health (WHO, 2017a). It was estimated that between 8-16% of community dwelling adults aged 65 and older have depressive symptoms including 1-4 % with major depression disorder (Blazer, 2003). Although depression is less prevalent in older adults than in younger individuals (Fiske et al., 2009; Hasin et al., 2005), it is well known that late life depression has adverse consequences on health, such as an increased mortality risk due to suicide (Blazer, 2003; Cuijpers et al., 2014), impaired executive function (WHO, 2020), increased disability (Fiske et al., 2009), and poor quality of life (Brett et al., 2011). Population-based evidence suggests that individuals in the general population with one or more chronic conditions have almost double the risk of major depression compared to those with no chronic conditions (Patten, 2001). The clinical assessment of patients with both depressive symptoms and chronic medical conditions is complicated, and major depression frequently goes undetected and untreated among these individuals (Katon, 1984; Wang et al., 2007). Health care costs incurred for patients with both depression and chronic physical conditions are approximately 50% greater than for those with a chronic physical condition alone (Luber et al., 2000). Sometimes, depression among older adults may get overlooked due to atypical symptoms (Fiske et al., 2009; Vieira et al., 2014), or be considered as a typical reaction due to aging (Fiske et al., 2009; Vieira et al., 2014). Moreover, antidepressants are found to be not as effective and are associated with increased complications in older adults (Almeida et al., 2010; Coupland et al., 2011).

5.1.2 Multimorbidity and depression

Multimorbidity, the presence of multiple chronic conditions, is especially common among older adults, affecting more than half of the older population (Marengoni et al., 2011). It is associated with negative consequences including higher disability, decrease in quality of life, psychological distress, high health care costs and increased risk of death (Barnett et al., 2012; Fortin et al., 2006; Marengoni et al., 2011; Violan et al., 2014; Vogeli et al., 2007). The prevalence of multimorbidity is increasing due to longer life expectancy and the growing number of people who live with chronic conditions (Divo et al., 2014). Research on the association between multimorbidity and depressive symptoms among older adults is limited; especially, longitudinal studies are scarce. A recent meta-analysis found that people living with multimorbidity were three times more likely to have depression disorder than those with no individual physical chronic condition, and two times more likely than those without multimorbidity (Read et al., 2017). However, all of the 40 studies included in the review were cross-sectional analyses in general population which did not allow assessment of whether morbidity preceded depression or vice versa.

Evidence suggests that mental health is not only influenced by biological and psychological factors, but also social elements, such as social support, which can improve depression and affect mental health outcomes among older adults (Gariépy et al., 2016; Harandi et al., 2017). The current study explores if social support can mitigate the potential negative impact of multimorbidity on depressive symptoms, using a longitudinal study design based on a stress-buffering framework of social support.

5.1.3 Social support

Social support is one of the social determinants of health in the general population (Wilkinson and Marmot, 2003). Research has demonstrated that social support plays an essential role in achieving better physical health and mental health outcomes; it is an important aspect of promoting healthy aging (Uchino, 2009). Social support represents the psychological and material resources perceived to be available or actually received from an individual's social network to cope with stress (House et al., 1985). Such support reflects the quality and functions of an individual's social relationships (Schwarzer and Leppin, 1991). Social support is commonly categorized into three types: emotional, instrumental, and informational support (Cohen et al., 2000; Cohen and Wills, 1985; House, 1981; House et al., 1985). Emotional support refers to the things that people do that make the receiver feel being loved, trusted and cared for, which can bolster their sense of value and worth. Emotional support usually takes the form of non-tangible types of assistance and may involve expression of sympathy, caring, reassurance, and trust and provision of opportunities for emotional expression and venting. Instrumental support refers to various types of tangible help including financial assistance, or the provision of material goods, and services. Informational support refers to the help that others may offer through the provision of relevant information advice, guidance, and suggestions to help the individual solve problems.

The protective effects of social support are well documented in the literature regarding its role in maintaining good health and decreasing vulnerability to physical and mental illnesses in older adults (Holt-Lunstad et al., 2010). Lack of social support can be a risk factor for developing depressive symptoms in late life (Fiske et al., 2009). In older adulthood, the exchange of support is one of the most important functional components of an individual's social network (Fiori and Jager, 2012). A systematic review including 33 studies revealed that over 90% of

studies found a significant association between social support and protection from depression in older adults aged 50 years and older (Gariépy et al., 2016). It has also been found that both adverse life events and poor perceived social support predicted long-term depressive outcome (Leskelä et al., 2006).

5.1.4 Theoretical framework

Psychological research has suggested that social support impacts mental health by influencing an individual's emotions, cognitions, and behaviors (Cohen, 1988). Social support is thought to regulate various response systems' activities to prevent extreme responses associated with dysfunction during stress. Failure in regulating these responses contributes to psychological disorders and responses from neuroendocrine, immune and cardiovascular systems. Two major theoretical models have been developed to identify how social support can influence health: stress-buffering and main effects models (Cohen and Wills, 1985; House, 1981). The direct effect model proposes that social environments can help regulate health behaviors and access to health care by providing informal resources (e.g., economic assistance, transportation) (Penninx et al., 1998). The stress buffering model (described in more detail below) suggests that social relationships can provide resources, such as social support to buffer the negative effect of stress on health (Cohen S, Underwood LG, 2000; Uchino, 2004).

5.1.4.1 The stress buffering model

The stress buffering model, focusing on the positive aspect of social relationships, asserts that social support benefits health by providing psychological and material resources to cope with stress. As such, social support may buffer the deleterious effects of life stressors, such as

illness, bereavement, crime, job loss, and social relationship crises, on an individual's health status when needed (Cohen and Wills, 1985; Thoits, 2011; Uchino, 2009).

In the stress buffering model, social support comes to play at several points to influence the appraisal and coping process in the causal reaction chain (Cohen and Wills, 1985), which may not only improve the ability to manage and reduce stress but also lower the overall perception of stress (Uchino, 2009). The belief that others will provide supportive resources during challenging time of life may enhance one's perceived ability and confidence to cope with demand, therefore leading to positive changing of the appraisal of the situation and lower level of stress (Cohen and Wills, 1985; Thoits, 1986). The belief that social support needed is at hand (perceived social support) may also dampen the emotional and physiological responses to the event or alter maladaptive behavioral responses. Intangible social support, such as emotional, information support and companionship, may lower the stress level by providing sympathy, love, a sense of belonging and solutions to the problem or distraction from the stressors. Social support may also contribute to better health by promoting healthy behavior changes such as exercise, personal hygiene, healthy diet, self-love and rest (Cohen and Wills, 1985). Research shows that social support may eliminate or weaken the negative relationship between perceived stress caused by deleterious effects of chronic conditions on health and quality of life (Dias et al., 2015). In the present study, social support was thought to serve as an insulating factor, or buffer, between the stressors, such as having multimorbidity and mental health outcomes, such as depressive symptoms, to facilitate coping with stress and protect the receivers from the negative consequence of stress.

5.1.5 The present study: objectives and hypotheses

Despite of the importance of social support, relative limited research has been conducted regarding its protective role in buffering against the negative mental health consequences that may result from multimorbidity among older adults (Ahn et al., 2017; Hsu, 2015). For example, Ahn et al., analyzed data from the 2006–2012 Health and Retirement Study in the US, and found that positive spousal support significantly weakened the deleterious effect of multimorbidity on depression among older adults aged 65 years or older (Ahn et al., 2017). Hsu analyzed data from a nation-representative panel survey in Taiwan. The results showed that multimorbidity was positively related to more depressive symptoms at follow-up; social emotional support had moderating effect on the prevention of depressive symptoms among older adults aged 60 and above (Hsu, 2015).

To contribute to the literature on multimorbidity and mental health among older adults, this study has the following two objectives: (1) To examine the association between multimorbidity and depressive symptoms over time; (2) To investigate if social support played an important protective role in this association among older Canadians aged 65 above living in a community setting. Regarding the association between multimorbidity and depressive symptoms, it was hypothesized that multimorbidity is associated with a significantly increased likelihood of having depressive symptoms over time. For the role of social support as a buffer against the negative effect of multimorbidity on depressive symptoms, a significant interaction between social support and multimorbidity was expected, such that the gap in the probability of having depressive symptoms at follow-up between participants with and without multimorbidity would become narrower as social support increases. The hypothesized interaction is graphically presented in Figure 5.1.

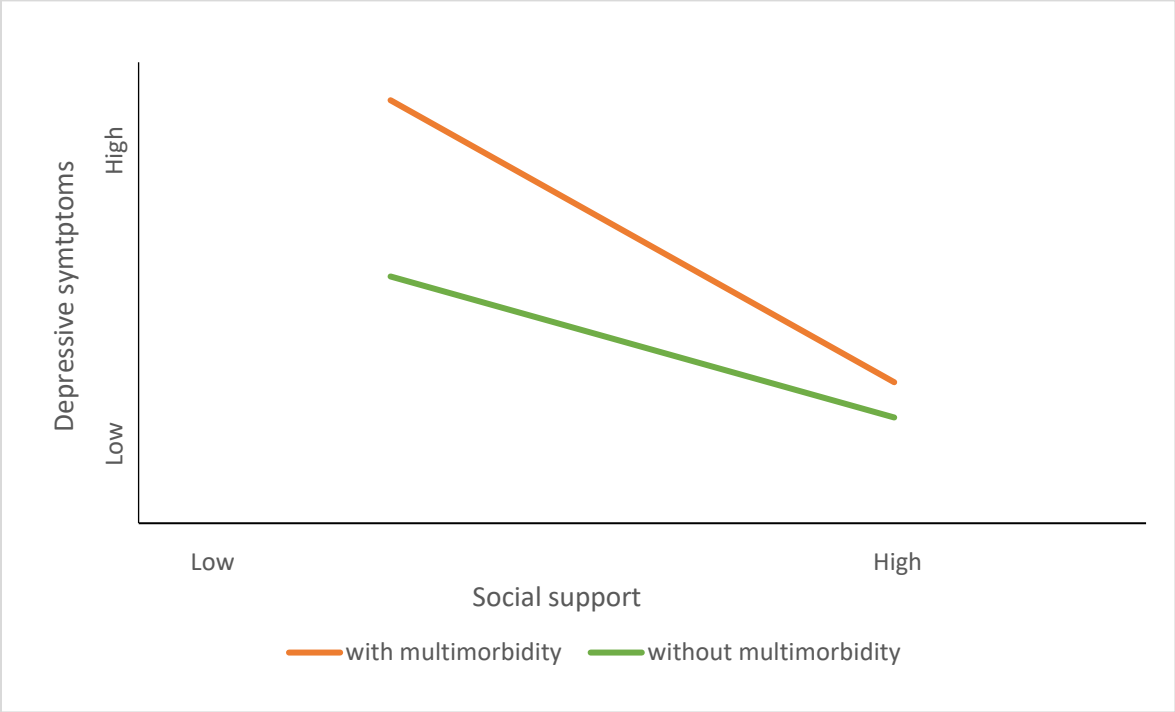

Figure 5.1 Hypothesized interaction of social support and multimorbidity on depressive symptoms at follow-up

5.2 Method

5.2.1 Study design

This population-based prospective cohort study was a secondary analysis of data collected in the Canadian Longitudinal Study on Aging (CLSA).

5.2.2 Data source

The baseline and first wave of follow-up data of the CLSA in 2018 were used for this study. CLSA is a large, Canada-wide population-based prospective cohort study launched in 2010. CLSA was designed to follow 51,338 community-dwelling Canadians, aged 45 to 85 at the

time of recruitment between September 2011 and May 2014 for 20 years or until death (Raina et al., 2009). CLSA is composed of two cohorts, a Comprehensive Cohort that completes in-home interviews and visits a CLSA data collection site (DCS) for a wide range of assessments (e.g. physical, clinical); and a Tracking Cohort that is only surveyed via computer-assisted telephone interviews. The Comprehensive Cohort is composed of 30,097 participants who were randomly (within age/sex strata) recruited within 25–50 km of the 11 DCS (Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax, and St. John's) in 7 Canadian provinces. The Tracking Cohort consists of a national, generalizable random sample of 21,241 participants who were selected within age/sex strata in each of the 10 Canadian provinces. The following groups were excluded from participation in the CLSA: people who could not communicate in one of the two official languages (English or French); those cognitively impaired at time of recruitment; full-time members of the Canadian Armed Forces; residents in a long-term care institution; and Aboriginal people living on reserves or other settlements at baseline (Raina et al., 2009).

As a national research platform, CLSA data covers a broad range of biological, medical, psychological, socioeconomic, and lifestyle factors that influence disease, health and well-being, which allows multidisciplinary research on physical, mental and social perspectives of healthy aging (CLSA, 2021). The CLSA's major follow-ups are being carried out every three years after completion of the baseline data collection in 2015. All participants were also invited to complete the Maintaining Contact Questionnaire (MCQ) by telephone 18 months after the baseline interview. The first wave of follow-up (follow-up 1) data collection started in July 2015 and ended in December 2018 (CLSA, 2021). A common set of similar questionnaires to those in the baseline was created to collect data from both the Tracking and Comprehensive cohorts. The

CLSA database was designed with two sets of weights: trimmed weights and analytic weights. The trimmed weights reflect the number of participants in each sex, age group, education level and province, while the analytic weights are rescaled trimmed weights, which reflect the sample sizes within geographic strata (CLSA, 2021).

5.2.3 Study sample

In the present study, we included participants aged 65-85 at baseline in the Tracking and Comprehensive cohorts of the CLSA who provided questionnaire data at both baseline and follow-up 1. Initially, there were 21,491 eligible CLSA participants, of which 171 (0.8%) had missing data on depressive symptoms, and 503 (2.3%) on social support. From the 20,817 participants at baseline with complete data on variables of interest, 1,568 (7.5%) died, 1,176 (5.6%) withdrew from the study, 293 (1.4%) were lost to follow-up, and 712 (3.4%) had no data for depressive symptoms at follow-up. This left 16,919 (81.3%) of participants in the analysis (Figure 5.2). Chi-square analysis indicated that compared to participants included in the analysis, non-respondents were likely to be older, with lower income and higher rates of multimorbidity at baseline, although the sex distribution was similar (Table 5.1).

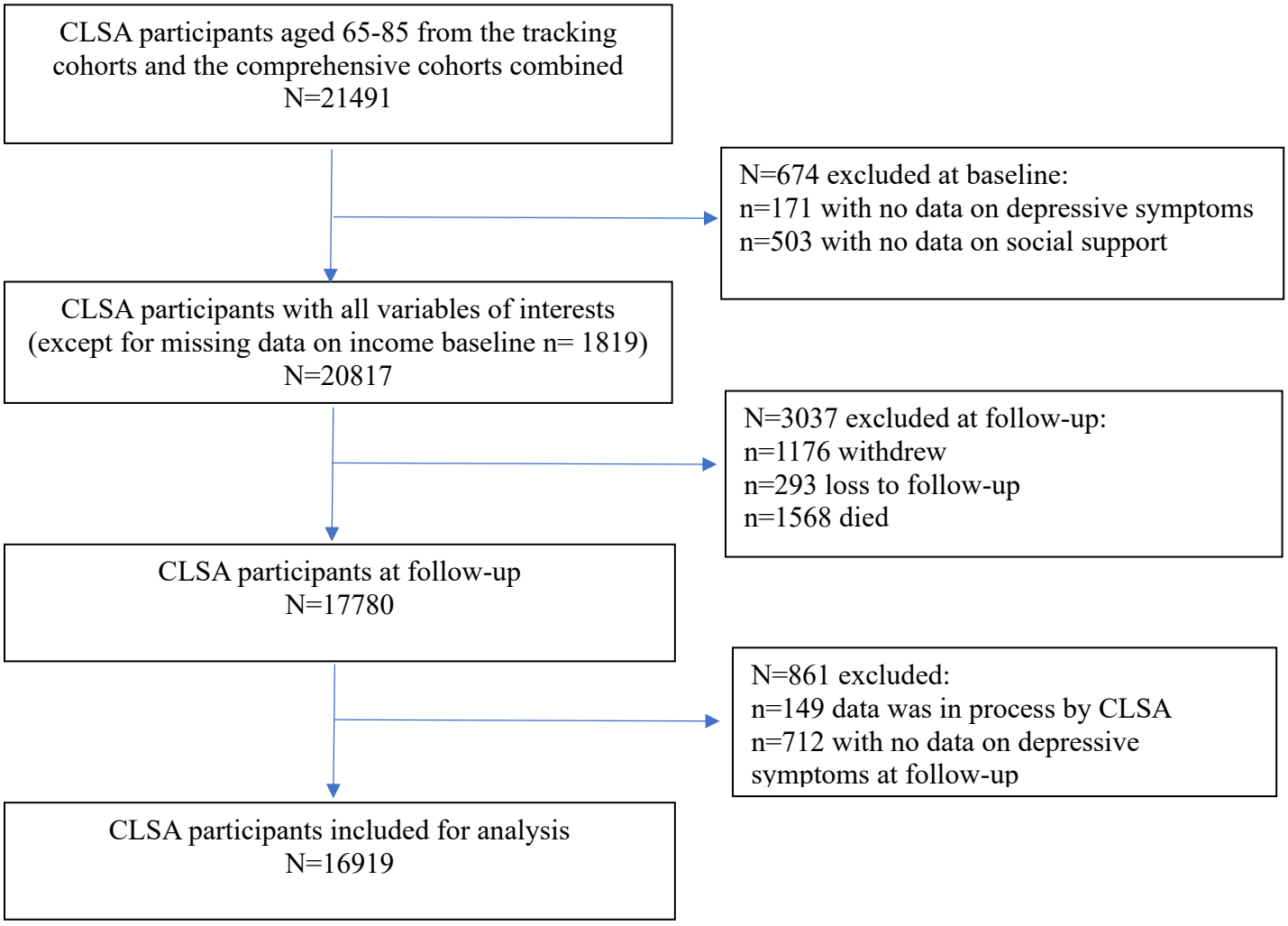

Figure 5.2 Study Flowchart

Table 5. 1 Comparison of the CLSA participants at baseline

Variable	Participants included (N=16,919) N (%)	Participants excluded (N=3,898) N (%)	P value*
Age group			p <.0001
65-74	10029 (59.3)	1736 (44.5)	
75-85	6890 (40.7)	2162 (55.5)	
Sex			P=0.3726
Male	8485 (50.2)	1924 (49.4)	
Female	8434 (49.9)	1974 (50.6)	
Income			P <.0001
< $20,000	1001(5.9)	431 (11.1)	
$20,000 to < $50,000	5545 (32.8)	1627 (41.7)	
$50,000 to < $100,000	6188 (36.6)	1050 (26.9)	
$100,000 to < $150,000	1838 (10.9)	267 (6.9)	
$150,000 or more	955 (5.6)	96 (2.5)	
No response	1001(5.9)	427 (11.0)	
Multimorbidity			p <.0001
No	4566 (27.0)	850 (21.8)	
Yes (3+ conditions)	12353 (73.0)	3048 (78.2)	

* Derived from chi-squared tests

5.2.4 Study variables

5.2.4.1 Depressive symptoms

Depressive symptoms were measured at both the baseline and the three-year follow-up, with some depressive symptoms at follow-up used as the outcome measure, and depressive symptoms at baseline controlled in the analysis. The 10-item Center for Epidemiologic Studies Depression scale (CESD-10) was used in the CLSA survey to assess depressive symptoms in participants. In the questionnaire, participants were asked 10 questions regarding feelings of depressive symptoms, loneliness, hopefulness for the future, and restless sleep where each question had four response options: "all of the time", "occasionally", "some of the time", "rarely or never". Scores of the 10 questions were summed to generate a total score ranging between 0 and 30 with higher scores indicating greater severity. In this study, the CESD scale was dichotomized into two categories: "0" with no depressive symptoms (score 0-9, reference) and "1" with some depressive symptoms (score 10 or more) in the analysis (Andresen et al., 1994). . It has been demonstrated that the CESD-10 scale predicts significant depressive symptoms with good precision, comparable to the original 20-item scale in community-dwelling older adults, when using an optimal cutoff score of 10 or greater (Andresen et al., 1994).

5.4.2 Multimorbidity

Multimorbidity was defined as having three or more chronic conditions as suggested by the American Geriatrics Society, consistent with previous research among older adults (American Geriatrics Society, 2012; Boyd et al., 2012). CLSA participants were asked about their chronic conditions that had been diagnosed by a health professional. The CLSA questionnaire includes 42 questions of ten broad categories of chronic conditions, such as

osteoarthritis (OA), arthritis, respiratory, cardiac/cardiovascular, neurological, gastrointestinal, vision, cancer, mental health, and other conditions. In this study, we excluded acute issues, infectious diseases, cognitive and mental health diagnoses, and subjective symptoms (except low back pain), consistent with previous research (St. John et al., 2021). Thirty-one physical conditions were included in the present study: OA, rheumatoid arthritis (RA), other arthritis, Chronic Obstructive Pulmonary Disease (COPD), asthma, hypertension, diabetes, heart disease, angina, myocardial infarction (MI), peripheral vascular disease (PVD), cerebrovascular disease (CVD), transient ischaemic attack (TIA), Parkinson disease, multiple sclerosis (MS), epilepsy, migraines, gastrointestinal ulcer, bowel disease (IBD) –which included Crohn's disease, ulcerative colitis and irritable bowel syndrome, allergies, bowel incontinence, urinary incontinence, cataracts, glaucoma, macular degeneration, cancer, osteoporosis, back problems, hypothyroidism, hyperthyroidism, and kidney troubles. An index variable was created to summing across all chronic conditions and then dichotomizing the resulting score into two categories: '0' as without multimorbidity (0-2 chronic conditions present; reference) and '1' as with multimorbidity (3+ conditions).

5.2.4.3 Social support

The 19-item Medical Outcomes Study (MOS) Social Support Survey was used in the CLSA survey to assess perceived social support (Sherbourne and Stewart, 1991). MOS contains four sub-scales of social support: affectionate support (3 items; involving expressions of love and affection. e.g. "someone who hugs you"); emotional/informational support (8 items; the expression of positive affect, empathetic understanding, and the encouragement of expressions of feelings, or the offering of advice, information, guidance or feedback. e.g. "someone you can count on to listen to you when you need to talk"); positive social interaction (4 items; the

availability of other persons to positively interact with. e.g. “some to get together with for relaxation”); and tangible support (4 items; the provision of material aid or behavioral assistance. e.g. “someone to help you if you were confined to bed”). The MOS has good psychometric properties with high reliability: $\alpha = 0.91$ for Affectionate Support, $\alpha = 0.92$ for Tangible Support, $\alpha = 0.94$ for Positive Social Interaction, and $\alpha = 0.96$ for Emotional/Informational Support (Sherbourne & Stewart, 1991). In the questionnaire, participants were asked how often each type of support was available to them: “all of the time” (5), “occasionally” (4), “some of the time” (3), “rarely” (2), or “never” (1). A global scale for perceived social support was created by calculating the average of the responses from all 19 MOS questions (score range = 1-5), with higher scores indicating higher level of perceived social support available. (RAND, 1993).

5.2.4.4 Functional status

Functional status was assessed using modified questions from the Older Americans’ Resources and Services (OARS) Multidimensional Functional Assessment Questionnaire including Activities of Daily Living (ADLs) and the Instrumental Activities of Daily Living (IADLs) (Fillenbaum and Smyer, 1981). The OARS scale has been previous validated (Fillenbaum and Smyer, 1981), demonstrating high correlations with physical therapist measures of self-care capacity ($r = 0.89$). The reliability is high for both ADL (Spearman rho=0.84) and IADL (Spearman rho=0.87). The ADL focused on seven basic self-maintenance activities: dressing, eating, grooming, walking, getting out of bed, bathing, and toileting. The IADL focused on seven instrumental activities to support independent living within home and community: using a telephone, walking a distance, shopping, preparing meals, housework, taking medications, and managing money. Respondents indicate if they can do each activity 1) without help, 2) with some help or 3) unable to do the activity. The functional status variable was

classified into two levels because few CLSA participants had some functional impairment. Those with no functional impairment were coded as “0” serving as the reference; and those with at least some functional impairments were codes as “1”.

5.2.4.5 Covariates

Evidence shows that levels of depressive symptoms differ by age (Patten, 2001; Sutin et al., 2013; Wu et al., 2012), sex (Kessler, 2003), marital status (Lee and DeMaris, 2007), educational level (Miech and Shanahan, 2000), income level (Blazer et al., 1991) and rural or urban area of residence (Purtle et al., 2019). I therefore included several potential confounding sociodemographic variables as covariates that were derived from the baseline CLSA survey: age, sex, marital status, education, household income, and rural versus urban area of residence.

Age was grouped into two categories: aged 65–74, 75–85 (reference). Sex included males (reference) and females. Marital status was grouped as married (married or living in common-law) and unmarried (single, never married or never lived with a partner, divorced or separated, or widowed; reference). Educational level was categorized as lower than post-secondary (elementary school, high school; reference) and at least some post-secondary (college graduate, Bachelor’s degree and post-graduate degree). Household income was assessed by asking, “What is your best estimate of the total household income received by all household members, from all sources, before taxes and deductions, in the past 12 months?” It was grouped in five levels in the CLSA data set: 1 = less than $20,000 (reference), 2 = $20,000 or more, but less than $50,000; 3 = $50,000 or more, but less than $100,000; 4 = $100,000 or more, but less than $150,000; and 5 = $150,000 or more. In addition, a “missing” category was created in order to keep those individuals (7.5%) who did not respond to this question in the analyses. The area of residence

was provided in the CLSA dataset as: Rural; Urban core; Urban fringe; Urban population centre outside a Census Metropolitan Area and Census Agglomeration; Secondary core; and Postal code link to dissemination area. This variable was recoded as 0 = rural (reference) and 1 = urban, with the latter including all non-rural categories. As recommended by CLSA when conducting weighted analyses, all ten Canadian provinces (Manitoba: reference) and DCS (1=comprehensive cohort, 0=tracking cohort, reference) were also included in the analysis as covariates (CLSA, 2017).

5.2.5 Statistical analysis

Weighted analyses were conducted to account for the complex sampling design of CLSA data and obtain unbiased estimates representing the Canadian population. The study cohort was described by means, standard deviations (SD), percentages and 95% confident intervals (CI) using the trimmed weights. A series of multivariate logistic regression models using the analytic weights were built to examine the association between multimorbidity and depressive symptoms (with no depressive symptoms/with some depressive symptoms) at follow-up. First, a basic model (Model 1) was created to estimate the association between multimorbidity at the baseline and having some depressive symptoms at follow-up. Second, model 2 added social support to determine the association between social support at baseline and depressive symptoms at follow-up. Lastly, model 3 introduced a multimorbidity-by-social support interaction term to further test whether self-reported social support mitigates the risks of depressive symptoms associated with multimorbidity over time. We included age, sex, marital status, education, household income, depressive symptoms status, functional status, and residence area, provinces and DCS, all derived from baseline data, as covariates in all three models.

As a sensitivity analysis, given that multimorbidity is associated with functional impairment (St. John et al., 2019) and social support might mitigate depressive symptoms in individuals with disability (Levy et al., 2017; Travis et al., 2004), the analyses examining the role of social support in the association between multimorbidity and depressive symptoms were repeated stratified by the level of impairment (no functional impairment and at least some functional impairment, respectively).

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Statistical significance was assessed using a nominal $\alpha = 0.05$.

5.2.6 Ethics approval

The study received research ethics board approval from the University of Manitoba, and the approval to access the data from CLSA.

5.3 Results

5.3.1 Characteristics of the study sample

Table 5.2 presents the weighted analysis of the characteristics of the study sample (N=16,919, representing 3,205,531 Canadians) at baseline. Overall, about two thirds of the participants were married (68.9 %) and most had at least postsecondary education (75.7 %). The majority had annual household income of $50,000-$100,000 (72.2 %), and lived in urban area (78.8%) with no functional limitations (86.1 %). Less than one fifth (15%) had some depressive symptoms at baseline. Most participants reported having a great amount of social support (mean 4.3). When examining the four social support subscales separately, scores on the affectionate support subscale were particularly high (mean 4.5). More than two thirds (70.8 %) of participants reported having multimorbidity (3+ conditions).

Table 5. 2 Characteristics of study sample at baseline*

Variable	**Overall**		**Without multimorbidity**		**With multimorbidity**		**p value**
	N	**%** (95% CI)	**N**	**%** (95% CI)		**%** (95% CI)	
Age							p <.0001
65-74	2,067,884.00	64.5 (63.4, 65.7)	716,125	76.6 (74.8, 78.5)	1,351,759	59.5 (58.1, 60.9)	
75-85	1,137,647.00	35.5 (34.3,36.6)	218,515	23.4 (21.5, 25.2)	919,131	40.5 (39.1, 41.9)	
Sex							p <.0001
Male	1,719,584.00	53.6 (52.4,54.9)	397,294	42.5 (40.1, 44.9)	1,322,290	58.2 (56.8, 59.7)	
Female	1,485,947.00	46.4 (45.1,47.6)	537,346	57.5 (55.1, 59.9)	948,600	41.8 (40.3, 43.2)	
Education							P=0.0902
Less than postsecondary	777,487.00	24.3 (23.2, 25.3)	212,775	22.8 (20.7, 24.8)	564,711	24.9 (23.6, 26.1)	
Postsecondary	2,428,044.00	75.7(74.7, 76.8)	721,865	77.2 (75.2, 79.3)	1,706,179	75.1 (73.9, 76.4)	
Marital status							p <.0001
Unmarried	998,384.00	31.1 (30.0,32.2)	224,976	24.1 (22.2, 26.0)	773,408	34.1 (32.7, 35.4)	

Variable	Overall		Without multimorbidity		With multimorbidity		p value
	N	% (95% CI)	N	% (95% CI)		% (95% CI)	
Married	2,207,147.00	68.9 (67.8, 70.0)	709,665	75.9 (74.0, 77.8)	1,497,482	65.9 (64.6, 67.3)	
Income:							p <.0001
< $20,000	177,905	5.5 (5.0, 6.1)	39,086	4.2 (3.3,5.1)	38,819	6.1 (5.5,6.7)	
$20,000 to < $50,000	1,104,983	34.5 (33.3, 35.6)	283,926	30.4 (28.2,32.6)	821,057	36.2 (34.8, 37.5)	
$50,000 to < $100,000	1,207,822	37.7 (36.4, 38.9)	397,313	42.5 (40.1,44.9)	810,509	35.7 (34.3,37.1)	
$100,000 to < $150,000	314,259	9.8 (9.1, 10.6)	95,350	10.2 (8.8,11.6)	218,909	9.6 (8.8, 10.5)	
$150,000 or more	158,985	5.0 (4.4, 5.5)	56,104	6.0 (4.9, 7.1)	102,881	4.5 (3.9, 5.1)	
No response	241,577	7.5 (6.9,8.2)	62,862	6.7 (5.6,7.9)	178,715	7.9 (7.1, 8.6)	
Residence area							P<0.05
rural	677,977	21.2 (20.0, 22.3)	215,466	23.1 (20.9,25.2)	462,511	20.4 (19.1, 21.7)	
urban	2,527,554	78.8 (77.7, 80.0)	719,175	76.9 (74.8,79.1)	1,808,379	79.6 (78.3, 80.9)	
Functional status							p <.0001

Variable	Overall		Without multimorbidity		With multimorbidity		p value
	N	% (95% CI)	N	% (95% CI)		% (95% CI)	
With no functional impairment	2,761,400	86.1 (85.3, 87.0)	890,002	95.2 (94.2, 96.2)	1,871,398	82.4 (81.3, 83.5)	
Mild, moderate, severe, total impairment	444,131	13.9 (13.0, 14.7)	44,638	4.8 (3.8, 5.8)	399,492	17.6 (16.5, 18.7)	
Depressive symptoms							p <.0001
With no depressive symptoms	2,723,782	85.0 (84.1, 85.9)	846,621	90.6 (89.1, 92.0)	1,877,160	82.7 (81.5, 83.8)	
With depressive symptoms (cesd score >=10)	481,749	15.0 (14.1, 15.9)	88,019	9.4 (8.0,10.9)	393,730	17.3 (16.2, 18.5)	
Multimorbidity							-
No	934,641	29.2 (28.0, 30.3)					
Yes (3+ conditions)	2,270,890	70.8 (69.7, 72.0)					
		Mean (SD)					

Variable	Overall		Without multimorbidity		With multimorbidity		p value
	N	% (95% CI)	N	% (95% CI)		% (95% CI)	
Number of physical chronic conditions	3,205,531	4.2 (0.03)	934,641	1.4 (0.02)	2,270,890	5.3 (0.03)	p <.0001
Social support (Overall)	3,205,531	4.3 (0.01)	934,641	4.4 (0.02)	2,270,890	4.3 (0.01)	p <.0001
Emotional support	3,205,531	4.3 (0.00)	934,641	4.3 (0.02)	2,270,890	4.2 (0.01)	p <.0001
Tangible support	3,205,531	4.3 (0.01)	934,641	4.4 (0.02)	2,270,890	4.3 (0.01)	p <.0001
Affectionate support	3,205,531	4.5 (0.01)	934,641	4.6 (0.02)	2,270,890	4.5 (0.01)	p <.0001
Positive social interaction support	3,205,531	4.4 (0.01)	934,641	4.5 (0.02)	2,270,890	4.4 (0.01)	p <.0001

*All numbers and percentages were weighted.

The average number of chronic conditions was 4.2. Compared to those without multimorbidity, participants with multimorbidity were more likely to be older, female, unmarried, with a lower income of $20,000 to $50,000, and living in urban area, who also reported worse health and less social support. The rate of depressive symptoms was almost doubled and the rate of functional impairment was 3.6 times higher among those with multimorbidity.

5.3.2 Prevalence of physical chronic conditions

Table 5.3 presents the weighted prevalence of physical chronic conditions reported by participants included in the study (N=16,919, representing 3,205,531 Canadians). Out of the 31 conditions, the top five prevalent conditions were hypertension (49.8 %), cataracts (47.0 %), osteoarthritis (37.0 %), allergies (35.1 %), and back problems (24.6 %). Also, notably, about one in five of older Canadians aged 65 above had cancer or diabetes.

Table 5. 3 Prevalence of physical chronic conditions at baseline

Chronic condition	**Weighted N**	**Weighted %** **(95% CI)**
Hypertension	1,596,854	49.8 (48.6, 51.1)
Cataracts	1,505,449	47.0 (45.7, 48.2)
Osteoarthritis	1,186,490	37.0 (35.8, 38.2)
Allergies	1,126,468	35.1 (33.9, 36.3)
Back problems	788,958	24.6 (23.6, 25.7)
Cancer	691,137	21.6 (20.5, 22.6)
Diabetes	619,350	19.3(18.3, 20.3)
Heart disease	503,926	15.7 (14.8, 16.6)
Osteoporosis	497,057	15.5 (14.6, 16.4)
Other arthritis	463,391	14.5 (13.5,15.4)
Hypothyroidism	464,276	14.5 (13.6, 15.3)
Urinary incontinence	379,014	11.8 (11.0, 12.6)
Migraines	376,756	11.8 (10.9, 12.6)
Asthma	329,767	10.3 (9.5,11.0)
Bowel disease	294,015	9.2 (8.5, 9.9)
Gastrointestinal ulcer	265,925	8.3 (7.6, 9.0)
Peripheral vascular disease	262,513	8.2 (7.5, 8.9)
Glaucoma	248,229	7.7 (7.1, 8.4)
Angina	236,195	7.4 (6.7, 8.0)

Chronic condition	Weighted N	Weighted % (95% CI)
Myocardial infarction	235,556	7.3 (6.7, 8.0)
Chronic obstructive pulmonary disease	219,583	6.9 (6.2, 7.5)
Macular degeneration	204,488	6.4 (5.8, 6.9)
Rheumatoid arthritis	162,820	5.1 (4.5,5.7)
Transient ischaemic attack	149,456	4.7 (4.2, 5.2)
Kidney troubles	108,022	3.4 (2.9, 3.8)
Bowel incontinence	79,924	2.5 (2.1, 2.9)
Cerebrovascular disease	69,959	2.2 (1.8, 2.5)
Hyperthyroidism	68,481	2.1 (1.8, 2.5)
Epilepsy	24,769	0.8 (0.6, 1.0)
Parkinson disease	16,415	0.5 (0.3, 0.7)
Multiple sclerosis	14,895	0.5 (0.3, 0.7)

5.3.3 Association between multimorbidity and depressive symptoms over time and the moderating effect of social support

Tables 5.4 presents results from the series of weighted logistic regression analyses. Model 1 showed that a significant positive relationship between multimorbidity and depressive symptoms (β=0.26, SE 0.06, p<0.0001), was detected at 3-year follow-up. Participants with multimorbidity had 1.3 times greater odds of having depressive symptoms at follow-up, compared to those without multimorbidity (aOR 1.30, 95% CI 1.14, 1.48). Having depressive symptoms at baseline (aOR 6.96, 95% CI 6.22, 7.78) and living with functional limitations (aOR 1.40, 95% CI 1.23, 1.61) increased the odds, while being a female (aOR 0.80, 95% CI 0.71, 0.89) and having higher income (>50,000, aOR 0.75, 95% CI 0.60, 0.93; $100,000 to < $150,000, aOR 0.64, 95% CI 0.49, 0.85; > $150,000, aOR 0.53, 95% CI 0.37, 0.75) decreased the odds of having depressive symptoms at follow-up.

Table 5. 4 Logistic model results for the association between baseline characteristics and having depressive symptoms at 3-year follow-up

	Model 1		**Model 2**		**Model 3**	
	β (SE)	**AOR (95% CI)**	**β (SE)**	**AOR (95% CI)**	**β (SE)**	**AOR (95% CI)**
Depressive symptoms at baseline						
No	reference	reference	reference	reference	reference	reference
Yes	1.94 (0.06) ***	6.96 (6.22, 7.78)	1.77 (0.06) ***	5.88 (5.23, 6.60)	1.77 (0.06) ***	5.88 (5.23, 6.60)
Sex						
Male	reference	reference	reference	reference	reference	reference
Female	-0.23 (0.06)***	0.80 (0.71, 0.89)	-0.28 (0.06) ***	0.75 (0.67, 0.84)	-0.28 (0.06)***	0.75 (0.67, 0.84)
Age group						
65-74	-0.09 (0.06)	0.91 (0.82, 1.02)	-0.08 (0.06)	0.92 (0.83, 1.03)	-0.08 (0.06)	0.92 (0.83, 1.03)

	Model 1		Model 2		Model 3	
	β (SE)	**AOR (95% CI)**	**β (SE)**	**AOR (95% CI)**	**β (SE)**	**AOR (95% CI)**
75-85	reference	reference	reference	reference	reference	reference
Marital status						
Unmarried	reference	reference	reference	reference	reference	reference
Married	0.04 (0.06)	1.04 (0.93, 1.18)	0.25 (0.06) ***	1.28 (1.13, 1.45)	0.25 (0.06) ***	1.28 (1.13, 1.45)
Household income						
<20,000	reference	reference	reference	reference	reference	reference
$20,000 to < $50,000	-0.09 (0.10)	0.92 (0.75, 1.12)	-0.03 (0.11)	0.97 (0.79, 1.19)	-0.04 (0.11)	0.97 (0.79, 1.19)
$50,000 to < $100,000	-0.29 (0.11)*	0.75 (0.60, 0.93)	-0.21 (0.12)	0.81 (0.65, 1.02)	-0.22 (0.11)	0.81 (0.65, 1.02)

	Model 1		Model 2		Model 3	
	β (SE)	**AOR (95% CI)**	**β (SE)**	**AOR (95% CI)**	**β (SE)**	**AOR (95% CI)**
$100,000 to < $150,000	-0.44 (0.14)***	0.64 (0.49, 0.85)	-0.33 (0.14)*	0.72 (0.54, 0.95)	-0.34 (0.14) *	0.72 (0.54, 0.95)
> $150,000	-0.64 (0.18)***	0.53 (0.37, 0.75)	-0.52 (0.18)**	0.59 (0.42, 0.84)	-0.52 (0.18)**	0.59 (0.42, 0.84)
No response	-0.08 (0.13)	0.92 (0.72,1.19)	-0.01 (0.13)	0.99 (0.76, 1.27)	-0.02 (0.13)	0.99 (0.76, 1.27)
Education						
Less than postsecondary	reference	reference	reference	reference	reference	reference
Postsecondary	-0.08 (0.06)	0.93 (0.82, 1.05)	-0.07 (0.07)	0.93 (0.82, 1.06)	-0.07 (0.07)	0.93 (0.82, 1.06)
Residence area						

	Model 1		Model 2		Model 3	
	β (SE)	**AOR (95% CI)**	**β (SE)**	**AOR (95% CI)**	**β (SE)**	**AOR (95% CI)**
Rural	reference	reference	reference	reference	reference	reference
Urban	0.15 (0.09)	1.16 (0.98, 1.38)	0.14 (0.09)	1.15 (0.97, 1.36)	0.14 (0.09)	1.15 (0.97, 1.36)
Functional limitations						
No	reference	reference	reference	reference	reference	reference
Yes	0.34 (0.07) ***	1.40 (1.23, 1.61)	0.32 (0.07) ***	1.38 (1.20, 1.58)	0.32 (0.07)***	1.38 (1.20, 1.58)
Multimorbidity						
No	reference		reference		reference	
Yes	0.26 (0.07) ***	1.30 (1.14, 1.48)	0.27 (0.07) ***	1.31 (1.15, 1.49)	-0.51 (0.33)	-

	Model 1		Model 2		Model 3	
	β (SE)	**AOR (95% CI)**	**β (SE)**	**AOR (95% CI)**	**β (SE)**	**AOR (95% CI)**
Social support	-	-	-0.45 (0.04) ***	0.64 (0.59, 0.68)	-0.60 (0.07) ***	-
Social support × multimorbidity	-	-	-	-	0.19 (0.08) *	-

Note: adjusted for data collection centre and residence of provinces. P< *0.05; **0.01; ***0.001.

Model 2 found that social support was negatively associated with depressive symptoms at follow-up (aOR 0.64, 95% CI 0.59, 0.68). The following were significant covariates: depressive symptoms at baseline (aOR 5.88, 95% CI 5.23, 6.60), female sex (aOR 0.75, 95% CI 0.67, 0.84), functional limitations (aOR 1.38, 95% CI 1.20, 1.58), and having higher income (>100,000 less than 150,000: aOR 0.72, 95% 0.54, 0.95; >150,000: aOR 0.59, 95% CI 0.42, 0.84). Being married (aOR 1.28, 95% CI 1.13, 1.45) became a significant risk factor for depressive symptoms at follow-up after social support was entered into the model.

Model 3 demonstrated a significant interaction of baseline multimorbidity with social support ($\beta = 0.19$; SE 0.08, $P < .05$) on depressive symptoms at follow-up (Table 5.4; Figure 5.2). Multimorbidity was no longer significant, while social support stayed inversely associated with depressive symptoms ($\beta = -0.60$, SE 0.07, $p < .0001$) at follow-up. The association remained statistically significant for all other significant covariates as indicated in model 2.

Figure 5.2 displays the interaction and shows social support increased, the gap in the probability of having depressive symptoms between participants with multimorbidity and those without it narrowed.

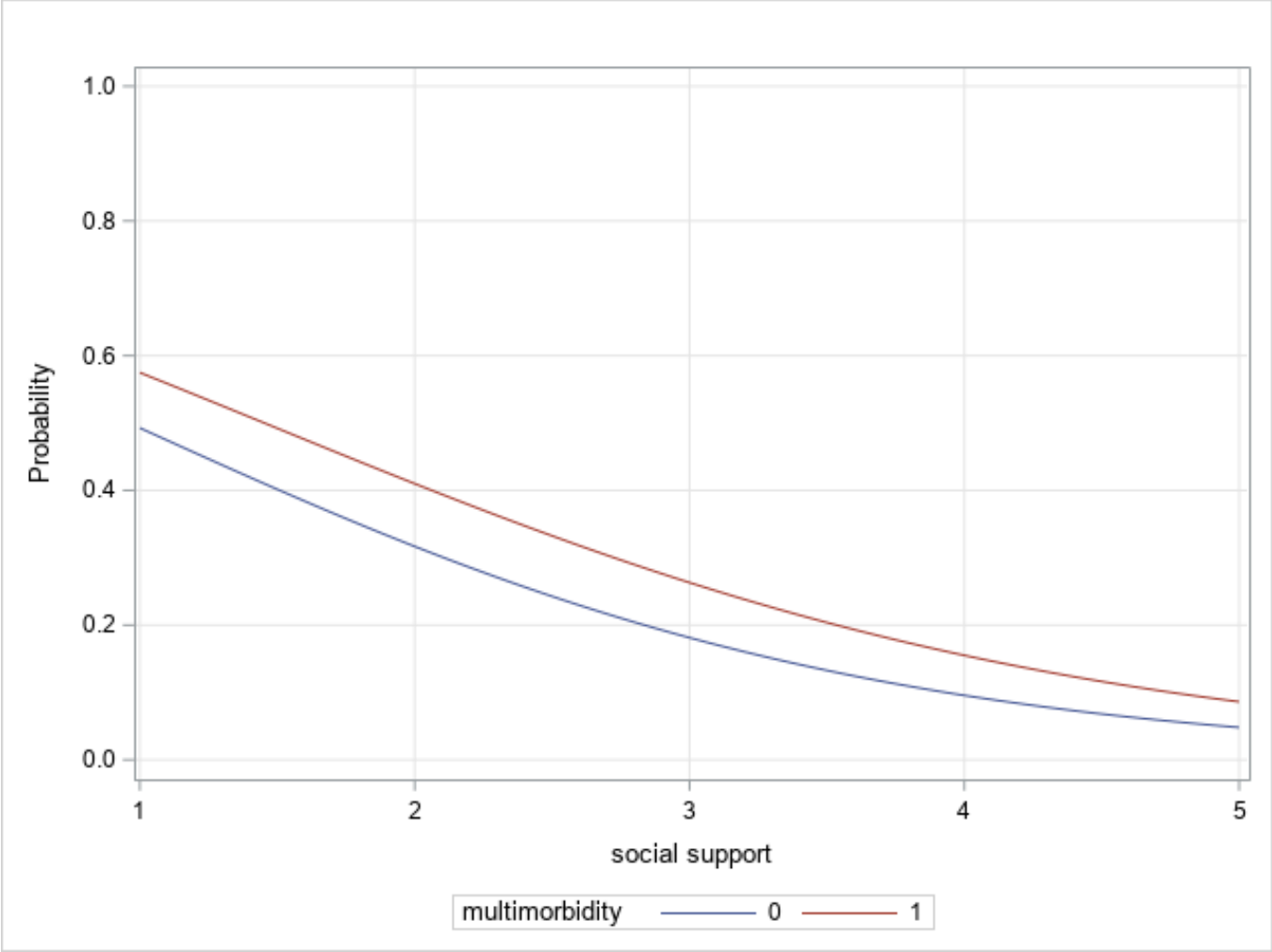

Figure 5.3 Plotting for interaction between social support and multimorbidity on depressive symptoms at 3-year follow-up among Canadians aged 65 and above

5.3.4 Functional limitations

To explore if people with functional limitations had different results, we conducted sensitivity analyses using similar logistic regression models stratified by the level of impairment (no functional impairment and at least some functional impairment; see Table 5.5).

Table 5. 5 Regression models results for the association between baseline characteristics and having depressive symptoms at 3-year follow-up, stratified by functional limitations

	Without functional limitations n= 14588			**With functional limitations n=2331**		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Multimorbidity						
No	reference		reference	reference	reference	
Yes	0.23 (0.07)**	0.24 (0.07) **	-0.33 (0.35)	0.47 (0.23)*	0.42 (0.22)	-1.89 (1.31)
Social support	-	-0.48 (0.04) ***	-0.58 (0.08) ***	-	-0.36 (0.08) ***	-0.90 (0.31)*
Social support* multimorbidity	-		0.14 (0.09)	-	-	0.56 (0.32)

Note: adjusted for age, sex, education, marital status, depressive symptoms at the baseline, household income, residence area, data collection centre and residence of provinces. * P< 0.05; ** p<0.01; *** p<0.001.

Model 1 and model 2 showed similar results in that multimorbidity was positively and social support negatively associated with having depressive symptoms at follow-up, regardless of whether participants had functional impairment or not. However, model 3 incorporating a multimorbidity by social support term found no significant interaction at follow-up in either group (without functional impairment: p= 0.10; with some functional impairment: p= 0.08). In addition, multimorbidity became non-significant once social support was entered into the model.

5.4. Discussion

The current research contributes to the growing body of literature of multimorbidity by providing evidence that social support may serve as an important protective factor against depressive symptoms among older adults with multimorbidity in a community setting. In this large population-based prospective study, I showed that multimorbidity existed in most older Canadians aged 65–85 years, and people with multimorbidity were more likely to be older men and have higher rates of depressive symptoms. Importantly, the findings demonstrated that multimorbidity was associated with 1.3 times higher odds of having depressive symptoms three years later; while perceived social support was associated with a lower risk. Moreover, the effects of multimorbidity and social support were not independent from one another, and the hypothesis of a buffering effect of social support on depressive symptoms among people with multimorbidity was supported in this study.

5.4.1 Association between multimorbidity and depressive symptoms

With this large population-based prospective cohort study, I confirmed the findings of previous cross-sectional studies on the association between multimorbidity and depressive symptoms (Read et al., 2017). Our results are also consistent with existing longitudinal studies

which have observed a positive relationship among older adults in a community setting (Assari and Lankarani, 2017; Fauth et al., 2012; Wu et al., 2012; also see chapter 4). For example, one study conducted in Canada (Wu et al., 2012) focusing on the relationship between age and depressive symptoms, revealed that increasing numbers of chronic condition counts was related to increased depressive symptoms and higher risk of major depression over time. One study in Sweden (Fauth et al., 2012) analyzed longitudinal data pooled across 4 Swedish studies and reported that multimorbidity was positively related to increased depressive symptoms among very old adults (mean age = 86) with disability. One study carried out in US included black and white Americans and found that multimorbidity was associated with increased depressive symptoms in participants over time (Assari and Lankarani, 2017).

On the other hand, some studies (Dent et al., 1999; Sachs-Ericsson et al., 2007; Turuba et al., 2019) reported conflicting results. For example, one study in Australia (Dent et al., 1999) examined the effect of multimorbidity, neurodegenerative syndromes and functional disability on depressive symptoms over time among community-living older adults aged 75 above. The results showed that the total number of diseases did not predict the CES-D scores at follow-up two years later after controlling for CES-D and disability at baseline. One study using multi-regional data (Turuba et al., 2019) found no statistically significant association between multimorbidity at baseline and onset of depressive symptoms two years later among older adults aged from 65 to 74 living in the community. One study from the US (Sachs-Ericsson et al., 2007) examining the relationship between body mass index (BMI) and subsequent depressive symptoms found that multimorbidity at baseline did not predict increased depressive symptoms three years later among both black and white Americans. Although the chronic conditions included to define multimorbidity and the instrument used to measure depressive symptoms in these studies did not

vary considerably, these studies had a higher attrition rate in relatively small samples of participants, suggesting that results may not be generalizable. In addition, some prior studies found that the association between multimorbidity and depressive symptoms weakened in older age. For example, one study showed no significant association between multimorbidity and depressive symptoms in a sub-group analysis of participants aged 65+ (Tsai, 2013), and another study found no significant association at the end of life (Rast et al., 2014). Both studies were designed differently from the current study, by using stratified analyses by age or time to death to reveal the time trends of the association. Also, these discrepancies might be attributed to longer fellow-up periods in the studies (8 years and 12 years respectively) where older participants (e.g. aged 65+ at baseline) were more likely to drop out of the studies due to deaths.

The mechanisms underlying the association between multimorbidity and depressive symptoms are not well-understood. Research suggests that multimorbidity is disproportionally high among individuals with disadvantaged social economic status, disability, pain, or cognitive impairment conditions, which may increase the risk of mental health conditions, like depressive symptoms (Bair et al., 2003; Barnett et al., 2012; Ralph et al., 2013; St. John et al., 2019; Vassilaki et al., 2015; Vogeli et al., 2007). Also, the negative impact of multimorbidity on depressive symptoms may relate to the concepts of life stressors (Aneshensel, 1992). Having multimorbidity may increase the stress stemming from challenges in daily management of multimorbidity, such as taking multiple prescribed medications, navigating healthcare systems to seek treatments for various conditions, coping with the burden of symptoms, and even loss of independence and control over one's life due to decline in cognition and physical functions, which may lead to depression (White et al., 2016; Williamson et al., 2000).

5.4.2 The buffering effects of social support

The current study found that perceived social support buffered the negative effects of multimorbidity on depressive symptoms among older adults. These findings are consistent with previous research on the potential buffering effect of social support against the harmful physical and mental health impacts of chronic conditions in older adults (Ahn et al., 2017; Bennett et al., 2006; Dias et al., 2015; Hsu, 2015; Penninx et al., 1997). For example, one population-based longitudinal study from the US reported that positive social support from spouses acted as a moderator and weakened the deleterious effect of multimorbidity on depressive symptoms (Ahn et al., 2017). Another recent American study with 8-year follow-up detected an inverse association between positive spousal support and depressive symptoms among older Hispanic Americans aged 50 above (Muruthi et al., 2020). Bennett et al. (Bennett et al., 2006) found that social support and network characteristics modify the relationship between certain measures of Alzheimer's disease pathology and the level of cognitive functions. Even at more severe levels of global disease pathology, cognitive function remained higher for participants with larger network sizes. When looking at family caregivers and spousal caregivers, several types of support may relieve physical and mental burden caused by stress of caregiving (Dias et al., 2015). Caregiving itself can be seen as a form of social support provision as well as potentially functioning as a source of distress in partners with dementia and caregiving partners (Cho et al., 2016). However, some studies reported a nonsignificant stress buffering effect of social support on psychological distress (Brandstetter et al., 2017; Doeglas et al., 2004). For example, one study aiming to investigate the patterns of functional ability, depressive feelings, and social support found that social support was not a protector against depressive feelings related to loss of functional ability among early stage rheumatoid arthritis patients (Doeglas et al., 2004).

The protective role of social support in the association of multimorbidity and depressive symptoms may be explained by the stress-buffering theory (Cohen & Wills, 1985). Active engagement in a supportive environment may lower levels of physiologic arousal reaction in the brain which protects against development of cognitive decline and depressive symptoms in addition to direct positive stimulatory effects on the brain (Mc Ewen, 1995). Furthermore, evidence suggests that social support may enhance resilience to stress via effects on the hypothalamic-pituitary-adrenocortical (HPA) system, the noradrenergic system, and central oxytocin pathways (Ozbay et al., 2007). As a result, people with increased social support may feel less lonely, have increased optimism and self-efficacy which make them more resilient to stress (Southwick et al., 2005). Living with multimorbidity can be very challenging since individuals with multimorbidity have to cope with chronic strain (stress), which reduces quality of life, resulting in higher level of psychological distress. Social support may serve as an insulating factor, or buffer, between the stressor as having multimorbidity and depressive symptoms, to facilitate coping with stress and protect the receivers from the negative consequence of stress.

Although prior studies showed that social support (more instrumental help, more perceived satisfaction) moderated some depressive symptoms in prime care patients with functional disability (Travis et al., 2004), we did not detect a statistically significant interaction effect between multimorbidity and social support when conducting analyses stratified by functional status. A population-based study with 2012 Canadian Community Health Survey data indicated similar negative results that social support did not moderate the associations between major depressive symptoms and functional disability among those living with diabetes (Levy et al., 2017).

The implications of the results from present study include that clinicians providing care for older adults with multimorbidity should assess the presence of depressive symptoms, as well as perceived social support. Appropriate interventions or recommendations aimed at increasing social support should be considered to improve mental health of the aging population. Fortunately, the social environment is modifiable and it is never too late to make new connections to benefit from supportive social networks. For example, individuals can increase their social support and enhance resilience to stress through participation in support groups and activities in community organizations that promote social bonds and create networking opportunities. Also, behavioral therapists can help to increase an older individual's social support through teaching of skills directed at gaining support when needed.

5.5 Strengths and Limitations

This study has several strengths. A primary strength relates to the prospective nature and national representative sample used. This longitudinal study used the first follow-up data of CLSA of Canadians aged 65 above which allowed carrying out a longitudinal study to investigate multimorbidity, social support and depressive symptoms, in a large national representative sample while controlling for demographic variables, which minimizes the population bias. Also, the large sample size provided sufficient power to examine interaction effects between social support and multimorbidity. Additionally, CLSA includes validated instruments such as the CES-D to measure depressive symptoms and MOS to measure social support, which provides opportunities for future research to compare findings. In addition, relatively larger numbers (33) of chronic conditions were captured while measuring multimorbidity. In contrast, many of the previous studies were based on only a limited number of chronic conditions.

However, when interpreting the results of this study, several limitations should be considered. First, chronic conditions, and depressive symptoms were self-reported by participants, raising the possibility of misclassification due to recall bias. Moreover, the social support measure assesses perceptions of the availability of social support, which may differ from the actual support available. Second, the CLSA data does not include people living on First Nations reserves, full-time members of the Canadian Forces, and those living in long-term care facilities. In addition, the CLSA also does not include individuals who do not speak French or English and those with cognitive impairment, who may have lower social support, and may be more at risk for depression. Third, multimorbidity was assessed by simply counting the total number of conditions; CLSA does not include measures of disease severity. As such, all chronic conditions were treated equally and using a simple presence/absence of dichotomy. Fourth, CES-D was used, which is the most commonly used measure of depressive symptoms, but not a diagnostic tool, to assess depressive symptoms among participants. The CES-D measure is not the equivalent of having a diagnosis of major depression (Vilagut et al., 2016). Another concern is the issue of symptom contamination in the CES-D, although CES-D has acceptable screening accuracy in the general population or primary care settings. Clearly somatic symptoms of depressive symptoms overlap with disease-related symptoms, particularly decreased energy, concentration difficulties, sleep, and appetite disturbance. Additionally, among participants who exhibited depressive symptoms at follow-up, we do not know when the onset of symptoms occurred during the follow-up period. Future research on the incidence of depressive symptoms is warranted, which helps better understand the underlying biological mechanism at play.

Also, the significant interaction effect detected between multimorbidity and social support in this study seems not very strong, and it is not clear what its clinical significance is. Furthermore, while there was a relatively low rate of deaths at follow-up, and the competing risk of death was likely low in the cohort overall, it could be high among older participants in the group of non-respondents in this study. However, non-respondents had higher rates of multimorbidity at baseline, indicating that these non-respondents might have contributed to strengthening the positively relationship between multimorbidity and depressive symptoms at follow-up if they were included.

5.6 Conclusions

In this population-based longitudinal cohort study we demonstrated a positive relationship between multimorbidity and depressive symptoms over a 3-year period, with social support acting as a protective buffering factor in this relationship among older adults aged 65 above living in a community setting. Our findings are important to health professionals who work with individuals having multimorbidity. It highlights the importance of assessing social support, and incorporating social support into therapies and treatment plans to reduce the negative impact of multimorbidity in this population, such as social support groups or connecting individuals with multimorbidity to community organizations that provide social engagement opportunities. There is a need of additional research focusing on increasing social support to improve mental health of aging people living with multimorbidity in the community.

CHAPTER 6: GENERAL DISCUSSION AND CONCLUSIONS

6.1 Summary of findings, implications and contributions

Multimorbidity, the coexistence of multiple chronic diseases within one individual, is becoming increasingly prevalent, particularly among older adults. Multimorbidity poses substantial challenges to healthcare systems worldwide in the presence of aging populations, urbanization, globalization, increasingly social economic disparity and undesirable lifestyle characteristics (The world health report, 2008; WHO, 2010, 2005). Although multimorbidity has attracted increasing attention, the existing evidence on multimorbidity is limited, especially longitudinal research (Fortin et al., 2005b; The Academy of Medical Sciences, 2015). Strong evidence and better understanding of health outcomes associated with multimorbidity, such as quality of life and mental health would be necessary for planning healthcare services and treatment guidelines to meet the needs of care for people living with multimorbidity. Therefore, the objective of this thesis was to investigate the longitudinal association between multimorbidity and health outcomes which included quality of life and depression. This was accomplished by conducting three studies in this dissertation research.

6.1.1 Multimorbidity and quality of life

Health-related quality of life (HRQoL) is a multidimensional concept covering significant functional, psychological, and social aspects of a patient's health (Centers for Disease Control and Prevention, 2000; Gandek et al., 2004; McHorney, 1999), and has become increasingly important in medicine assessed by patient-reported outcomes (PROMs) reflecting patient satisfaction in evaluation of quality of health care services, facilitating patient-focused care and medical decision making (Remick et al., 2020). However, research regarding the association of

multimorbidity and HRQOL is limited and longitudinal evidence is scarce (Kanesarajah et al., 2018; Makovski et al., 2019; Marengoni et al., 2011b).

Chapter 3 presents the study one in the dissertation research, which was a large population-based prospective cohort study on association between multimorbidity and HRQOL in a clinical setting. Using data from 14,573 patients who underwent elective THA or TKA for osteoarthritis, I examined the effect of multimorbidity on improvement in health-related quality of life (HRQoL) following joint replacement surgery. The results showed that almost two-thirds of patients had multimorbidity, which adversely affected improvements in HRQoL after joint replacement surgery. Mean improvements in HRQoL scores (OHS, PCS, and MCS) were all decreased in both THA and TKA patients. An increase in the number of chronic conditions was associated with increasing reductions in HRQoL improvements.

Study one adds to the existing literature by showing that multimorbidity has an adverse effect on pre- and postoperative HRQoL scores, and is associated with less improvement for patients one year after THA or TKA surgeries. These findings are more pronounced for general HRQoL measures than for condition-specific measures. This is not surprising, given that the OHS and OKS were designed to be relatively free of influence from factors other than the operation being examined (Dawson J, Fitzpatrick R, Carr A, 1996; Dawson et al., 1998). The findings of this study have relevance in several areas. First, they are important to care providers when counselling patients with multiple comorbidities about the outcome of THA or TKA. Patients with multimorbidity should be informed that having multiple chronic conditions may affect 1-year post surgery improvement of their quality of life. Second, they confirm the importance of, and potential need to control for, chronic conditions when analyzing measures of HRQoL for public reporting, quality assurance, or improvement initiatives. Third, they further

support the concept that Oxford scores alone cannot be used to determine appropriateness for surgery (Judge et al., 2011) as they are affected by the presence of multimorbidity.

6.1.2 Multimorbidity and depressive symptoms

Depression is one of the most common mental disorders, affecting more than 322 million people worldwide (WHO, 2017a). It was projected that unipolar depressive disorder will be the leading cause of disease burden globally by 2030 (WHO, 2004). The clinical assessment of patients with both depressive symptoms and chronic medical conditions is complicated. Major depression in these patients frequently go undetected and untreated (Katon, 1984; Wang et al., 2007). However, there is limited research on the association between multimorbidity and depression, especially evidence based on longitudinal studies is lacking (Read et al., 2017).

Chapter 4 presents study two in the dissertation research which was a systematic review of literature on the longitudinal association between multimorbidity and depression among older adults aged 50 and above, assessing whether multimorbidity increases the risk of depression among older adults over time. A total of 20 studies involving 57,349 participants in community and clinical settings were included in the review. Seventeen studies provided information on change of depressive symptoms, three on both change of depressive symptoms and incidence of depression, and three on the incidence of depression only. Most studies demonstrated a positive association between multimorbidity and depressive symptoms later on and incidence of depressive symptoms, although four studies suggest that this relationship appears to depend on age, functional status, or time to death. The findings of the review suggest that it is important for clinicians to monitor the mental health of their patients with multimorbidity, and refer them to appropriate resources or interventions that can mitigate mental health problems.

To the best of my knowledge, chapter 4 presents the first systematic review to explore the impact of multimorbidity on both change of depressive symptoms and incidence of depressive symptoms over time among older adults, in a range of settings, countries and study sample sizes. Prior systematic reviews have examined the impact of chronic illness on depression (Hasan et al., 2014; Huang et al., 2009; Read et al., 2017). However, most of the work has either focused on single conditions (Hasan et al., 2014; Huang et al., 2009) or included only cross-sectional studies (Read et al., 2017) which could not assess the temporal association between chronic illness and depressive symptoms in the context of aging. The review also highlighted that there are relatively few longitudinal studies on the relationships between multimorbidity and depression. Therefore, additional longitudinal research regarding multimorbidity and mental health is warranted. Moreover, findings from this study indicate the need for further research on the prevention and treatment of depression in people living with multimorbidity. Collaborative care to older adults is especially warranted. For clinicians, raising awareness of the risk of subsequent depressive symptoms also supports early identification and treatment of depression in people with multimorbidity, which is a priority given the compounded decrements to overall health and mortality (Chang et al., 2010), and additional health care costs (Bhattarai et al., 2013).

Chapter 5 presents study three in the dissertation research, which was a large national population-based prospective cohort study following 16,919 CLSA participants age 65 or older from both the comprehensive and tracking cohorts of the CLSA for three years. In this study, I investigated the association between multimorbidity and depressive symptoms over time, and further explored if social support mitigates this association among older adults. The results showed that multimorbidity was associated with depressive symptoms; participants with multimorbidity had 1.3 times greater odds of having depressive symptoms at 3-year follow-up,

compared to those without multimorbidity. Furthermore, social support served as a protective factor in the association between multimorbidity and depressive symptoms.

With this large population-based prospective cohort study, I confirmed the findings of previous cross-sectional studies on the association between multimorbidity and depressive symptoms (Read et al., 2017), as well as longitudinal studies (see chapter 4). Furthermore, the results suggest that perceived social support can mitigate future depressive symptoms linked to multimorbidity. Most of participants in the sample (70.8 %) had multimorbidity, and the potential beneficial effect of social support could be considerable. The study also adds to the sparse research on the beneficial buffering effect of social support against the harmful physical and mental health impacts of chronic conditions in older adults (Ahn et al., 2017; Bennett et al., 2006; Dias et al., 2015; Hsu, 2015; Penninx et al., 1997).

This study demonstrated that social support improves mental health, which makes it appealing to use this information to directly help older adults living with multimorbidity in the community. Health providers working with older adults with multimorbidity should assess the risk of depressive symptoms and consider the role of perceived social support in the treatment plans. Appropriate interventions and recommendations to mental health professionals and programs promoting social networking should be recommended to improve the mental health of the aging population. Future research is warranted to provide more evidence in this area.

6.2 Strengths and limitations

6.2.1 Strengths

The dissertation research has a number of strengths. Firstly, all three studies in this research project focused on the longitudinal association between multimorbidity and health

outcomes, including health related quality of life and depressive symptoms. The research therefore provides more definitive evidence on the detrimental consequences of multimorbidity than previous cross-sectional studies. Secondly, the empirical studies conducted in this research (study one and three) were both large population-based cohort studies, ensuring generalizability across the population. Furthermore, the two empirical studies were based on clinical and community samples, respectively, with the systematic review including clinical, institutional and community samples; this diversity adds to the generalizability of this dissertation research. Thirdly, well-validated and accepted measures for HRQoL, depressive symptoms, social support and functional limitations were used in the empirical studies. This not only adds scientific rigor to the research, but will also provide the opportunity for future research to be compared to results from this research. Finally, inclusive lists of many medical conditions were used to define multimorbidity in study one (14 conditions) and study three (31 conditions). The number of chronic conditions used to assess multimorbidity also varied widely in the systematic review. The fact that similar findings were obtained regardless of the number of conditions used, as well as the specific definition of multimorbidity (2+ condition in study one; 3+ in study 3), shows how consistent the findings are.

6.2.2 Limitations

The results of this dissertation research should be interpreted with a number of limitations in mind. Firstly, self-reported data was used to measure multimorbidity (in study one, the majority of studies included in the systematic review of study two, and study three) and depressive symptoms (in study three, the majority of studies included in the systematic review of study two), raising the possibility of misclassification due to recall bias. Secondly, in both empirical studies (study one and study three), multimorbidity was assessed by simply counting

the total number of conditions, as no indicator on levels of disease severity was available. Moreover, all chronic conditions were treated equally. Thirdly, none of the 3 studies conducted in the dissertation research looked at the effect of specific combinations of chronic conditions on HRQoL or depressive symptoms, which should be further explored in future research. Diseases belonging to common patterns of multimorbidity may interact, curtailing compensatory mechanisms and resulting in physical and mental health decline. Lastly, different predictors and outcomes were studied in the empirical studies (study one and study three) in this dissertation research, because databases used in these two studies did not contain the same variables. For example, the CLSA data did not include information on HRQoL measures, and the Winnipeg regional joint replacement registry did not collect data on social support or depressive symptoms. In addition, different statistical and analytical approaches were used in the two empirical studies of the thesis. In study one, a linear mixed-effects model was used to examine the impact of multimorbidity on improvements in HRQoL which were treated as continuous variables. This approach was acceptable and consistent with previous longitudinal studies testing the effect of multimorbidity on HRQoL (Luo et al., 2015; Tyack et al., 2016). In study three, multivariate logistic regression models were used to investigate the association between multimorbidity and depressive symptoms, which were treated as a categorical binary variable. This approach is also valid and frequently used in longitudinal research (Oslin et al., 2002; Vink et al., 2009).

6.3 Recommendations for future research, interventions and program planning

Given the findings of this dissertation research, the following recommendations are proposed for future research and policy planning:

Firstly, this dissertation research showed that multimorbidity predicted poor quality of life and depressive symptoms over time. However, additional studies considering the severity and duration of chronic conditions are required to further investigate these associations. Information about conditions used to define multimorbidity captured from sources of clinical data might provide a more accurate status of health of patients, would be less sensitive to measurement bias and might enable the assessment of the severity of chronic conditions. However, as patient registries may not be generalizable to the general population, further research based on surveys is important. In addition, the effects of other potential confounding variables recognized as having an effect on quality of life or depressive symptoms, such as health behaviors and medications should be explored in future research.

Secondly, this dissertation research demonstrated that older adults have a high burden of physical multimorbidity, which adversely impacts mental health. However, the mechanisms underlying the association between multimorbidity and depressive symptoms are not well-understood. Future research is warranted to better understand pathogenic pathways linking chronic diseases and mental health disorders leading to health inequalities.

Thirdly, the finding of this thesis research indicated that multimorbidity predicts depressive symptoms among older adults suggests that future programs and treatment plans for older adults with multimorbidity should involve assessment of the risk of depressive symptoms to prevent a future cascade leading towards poor mental health outcomes. Clinicians need to carefully consider mental health, including depressive symptoms in patients with multimorbidity, especially in those with functional limitations. A Swedish study demonstrated that educational programs can have pronounced effects on collaborative care for patients with depression (Rutz et al., 1992). In the study, all the primary care physicians on the island of Gotland, Sweden, were

trained on diagnosis and treatment of depressive disorders, which resulted in an increase of diagnosed depression cases and subsequently decrease of suicide, three years after the program ended (Rutz et al., 1992).

Fourthly, findings from this dissertation research revealed the protective role of social support in the association between multimorbidity and depressive symptoms, which is important to those living with multimorbidity, their caregivers and health providers. Besides lessening multimorbidity, future research is needed to determine whether interventions focused on improving social support for older adults with multimorbidity are cost-effective and whether they help increase their mental health and quality of life.

Furthermore, living with multimorbidity can be stressful, restricting social interactions therefore, decrease social support. Additionally, older people are particularly vulnerable to losing established social connections due to other life changes such as retirement, and the death of a spouse. As a result, older adults are likely to become deprived of positive life styles and healthy behaviors which can eventually impact health status. Geriatric health professionals should make efforts to assess social relationships in older adults and help stimulate social support from relatives, friends, neighbors and significant others. Fortunately, the social environment is modifiable and it is never too late to make new connections to benefit from a supportive network.

Individuals can increase their social support and enhance resilience to stress through participation in support groups and activities in community organizations that promote social bonds and create networking opportunities. For example, Cancer Care Manitoba offers support programs, support groups and counselling services to people living with cancer (CancerCare

Manitoba, 2021). The Alzheimer society and Parkinson Canada have support groups to create opportunities to meet peers and support each other to cope with challenges of chronic diseases (Alzheimer Society, 2021; Parkinson Canada, 2021). Some community organizations such as A & O Support Services for Older Adults Inc. offer a variety of programs and provide a safe environment for isolated older adults to become socially engaged (A & O: Support Services for Older Adults, 2021). Health professionals should consider appropriate referrals or recommendations aimed at increasing social support to incorporate such support in the treatment plans for patients with multimorbidity to prevent future presence of depressive symptoms in this vulnerable population. On the other hand, clinical psychologists and therapists can also help older adults to increase their social support through teaching of psychosocial skills and capitalizing on support (e.g., cognitive behavioral therapy) within networks when needed. A randomized, controlled trial of enhanced social support services in the USA tested an intervention that helps caregivers of people living with Alzheimer's disease mobilize their social support network. The results showed that those in the treatment groups, who were taught support seeking skills had higher social support network satisfaction, in comparison to a usual-care control group (Drentea et al., 2006).

Lastly, few longitudinal studies have been conducted to investigate the negative health outcomes, such as quality of life and depressive symptoms associated with multimorbidity (Makovski et al., 2019; Read et al., 2017). More longitudinal studies as well as clinical trials are needed to examine this important association over time. Moreover, given that all three studies in the thesis provided quantitative evidence of the impact of multimorbidity, future qualitative research focusing on people's experiences living with multimorbidity would be warranted. A clear understanding of the relationship between multimorbidity and health outcomes including

quality of life and depressive symptoms will enable healthcare professionals to deliver more comprehensive care to people with multimorbidity in a clinical or a community setting.

6.4 Conclusions

Multimorbidity is recognized widely as having negative impacts on health outcomes. This dissertation research demonstrates that multimorbidity adversely affects quality of life in clinical settings, and depressive symptoms over time among older adults living in the community. However, social support may buffer against the negative impact of multimorbidity on depressive symptoms. These findings can inform clinical practice, policy, and future research regarding the management of multimorbidity.

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Appendix A: Search strategy of electronic literature research

Database	**Date of search**	**Search strategy**
Pubmed	December 8, 2020	("longitudinal studies" [Mesh]) AND (("Comorbidity"[Mesh] OR "multimorbidity" OR "medical condition" OR "health condition" OR "chronic condition" OR " chronic illness" OR "physical condition" OR "Physical disease") AND ("Depressive Disorder"[Majr] OR "Depression/epidemiology"[Majr] OR "depressive symptoms")) Aged: 65+ years; English language
Psycinfo	December 8, 2020	1. exp major depression/ 2. depressive symptoms.ti,ab. 3. comorbidity/ 4. ("multimorbidity" or "medical condition" or "health condition" or "chronic condition" or " chronic illness" or "physical condition" or "Physical disease").ti,ab. 5. 1 or 2 6. 3 or 4 7. 5 and 6 8. limit 7 to english language 9. limit 9 to "380 aged <age 65 yrs and older>"

		10. limit 10 to "0450 longitudinal study" 11. from 11 keep 1-363
Embase	December 8, 2020	1. longitudinal study/ 2. comorbidity/ 3. multi-morbidity.ti,ab. 4. exp depression/ 5. major depression/ 6. ("multimorbidity" or "medical condition" or "health condition" or "chronic condition" or " chronic illness" or "physical condition" or "Physical disease").ti,ab. 7. 2 or 3 or 6 8. 4 or 5 9. 1 and 7 and 8 10. limit 9 to (english and article and journal and aged <65+ years>) 11. from 10 keep 1-472

Appendix B: Excluded articles after full-text screening

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Appendix C: Quality assessment of studies reviewed using the Newcastle–Ottawa Scale

First author, Publication year	**Representative-ness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**Total†**
Assari, 2017	*	*	*	**0**	**	**0**	*	**0**	**6**
Chou, 2008	*	*	*	*	**	**0**	*	*	**8**
Curyto, 1999	*	*	*	*	**	0	*	0	7
Dent, 1999	*	*	*	*	**	0	*	*	8

First author, Publication year	Representative-ness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total†
Eliyan, 2020	*	*	*	*	**	0	*	0	7
Fauth, 2012	*	*	*	0	**	0	*	0	6
Feng, 2013	*	*	*	0	**	*	*	*	8
Hsu, 2015	*	*	*	0	**	*	*	0	7

First author, Publication year	Representative-ness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total†
Marroig, 2019	*	*	*	0	**	0	*	0	6
Oslin, 2002	*	*	*	0	**	0	*	0	6
Rast, 2014	*	*	*	0	**	0	*	0	6
Roberts, 1997	*	*	*	*	**	0	*	*	8

First author, Publication year	Representative-ness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total†
Sachs-Ericsson, 2007	*	*	*	0	**	0	*	*	7
Stommel, 2004	*	*	*	0	**	0	*	*	7
Sutin, 2013	*	*	*	0	**	0	*	*	7
Tsai, 2013	*	*	*	0	**	0	*	0	6

First author, Publication year	Representative-ness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total†
Turuba, 2019	*	*	*	*	**	0	*	0	7
Vink, 2009	*	*	*	*	**	0	*	*	8
Wilson-Genderson, 2017	*	*	*	0	**	0	*	*	7
Wu, 2012	*	*	*	0	**	*	*	*	8

† The score range: 0-9.