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Sleep and Multimorbidity in the Canadian Longitudinal Study on Aging

Shreni Patel, *Western University*

Supervisor: Saverio, Stranges., *The University of Western Ontario*
Co-Supervisor: Speechley, Mark., *The University of Western Ontario*
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Abstract

Sleep health is a latent construct comprising various sleep measures such as duration, quality, initiation, maintenance, and daytime sleepiness. This thesis compared the association of two measures of sleep health, a conventional summary score and a pooled index, with incident multimorbidity over a 3-year follow-up in 30,097 middle- to older-aged adults from the Canadian Longitudinal Study on Aging. At baseline, approximately 26% and 29% of participants with multimorbidity displayed poor sleep patterns according to additive and pooled indexing methods. Longitudinal analysis indicated that those with additive scores of 4 to 5 at baseline had a 1.54 (95% CI: 1.18, 2.03) higher odds of multimorbidity compared to those with a score of 0, whereas 1-unit increases in pooled scores were associated with 1.32 (95% CI: 1.19, 1.47) odds after controlling for relevant confounders. Future research is suggested to understand the association better and inform public health and clinical guidelines.

Keywords

sleep, sleep health, multimorbidity, chronic disease, risk factors, older adults, Canadian Longitudinal Study on Aging

Summary for Lay Audience

Sleep problems affect a large segment of older adults in Canada and globally and contribute to an increased risk of chronic disease yet, are often neglected as a public health concern. Older adults are also more likely to develop multimorbidity, the co-occurrence of multiple chronic conditions. Emerging research has shown that sleep problems, similar to unhealthy diet or physical inactivity, may represent a modifiable behavioural risk factor that if improved could help lower the risk of multimorbidity in older adults. Sleep is often measured in terms of how long we sleep or how refreshed we feel in the morning, and then analyzed as separate components of sleep rather than together as overall 'sleep health'. A better understanding of sleep and its effect on health may come from examining sleep health, a concept that comprises these various facets of sleep into one holistic measure. The thesis aims to construct an index to measure sleep health, and then use this index to examine the association between sleep health and multimorbidity over time. The first study explored which sleep variables should be included in the index and compared two different methods of index development. The performance of these indices was compared to individual sleep measures by estimating the proportion of participants with multimorbidity experiencing poor sleep health. In the second study, a longitudinal analysis was conducted using the two indices to examine the association between sleep health and multimorbidity over time. The results revealed a significant relationship between poorer sleep scores and the development of multimorbidity, even after accounting for other health and lifestyle factors. A comparison of the two indices showed that the pooled indexing method performed better, particularly after age and sex stratification. These findings have practical implications for the health of Canadians by informing lifestyle changes and clinical interventions that may improve sleep health and thereby reduce the occurrence and burden of chronic conditions.

Co-Authorship Statement

The primary author of all chapters of this thesis is Shreni Patel. Shreni was involved in the conception and design of the study, data analysis, interpretation of data, writing, and editing of the papers. Shreni's supervisors, Dr. Saverio Stranges and Dr. Mark Speechley, were involved in the conceptualization and design of the study, analyzing and interpreting study results, writing, and editing the articles. This thesis relies on the health data collected and made available through the Canadian Longitudinal Study on Aging.

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Chapter 1

1 Introduction

The concept of 'sleep health' is broader than specific clinical diagnoses of sleep disorders, encompassing multiple dimensions of the sleep-wake function that affect health and wellbeing.[1] Sleep health is often neglected as a modifiable behavioural risk factor for multiple chronic conditions (multimorbidity) in older adults. Older adults are the fastest growing population segment and display a high prevalence of unhealthy sleep patterns and multimorbidity in Canada and globally.[2–7] Although aspects of unhealthy sleep have been associated with several chronic conditions in later life, fewer prospective studies have examined the relationship between sleep patterns and multimorbidity in older adults.[8–17] Thus, insight into the longitudinal impact of sleep health has on the risk of multimorbidity could further establish sleep health as a modifiable behavioural risk factor to be targeted in the aging population. A better understanding of this relationship would support clinicians, health promoters, researchers, and policymakers in decision-making to minimize the potential impact of poor sleep patterns on the health status of older adults.

Multimorbidity is commonly defined as the co-occurrence of two or more chronic conditions in an individual at one point in time.[18–20] There is no consensus among researchers on the operational definition of multimorbidity, with variations in the number of co-existing conditions (e.g. two or more (2+), three or more (3+)) and the particular conditions that should be included.[21] Despite these inconsistencies, it is evident that multimorbidity is becoming increasingly common amongst middle-aged and older adults. Findings from the Canadian Chronic Disease Surveillance System (CCDSS) showed a significant 10-year prevalence increase from 20.5% to 26.5% of Canadians who had two or more of five major chronic conditions: cardiovascular disease, respiratory disease, mental illness, hypertension, and diabetes.[22] The prevalence of multimorbidity is expected to continue rising as the population ages and risk factors accumulate, especially among older Canadians (65 years or older).[6] It should be noted that prevalence estimates of multimorbidity in Canadian populations vary greatly across studies due to

discrepancies in case definitions, data sources, reference populations, and samples.[21] Further, the combinations of specific chronic conditions vary across individuals with multimorbidity, which poses a unique healthcare challenge by increasing the complexity of disease prevention and management.[23,24]

Sleep health comprises multiple sleep dimensions such as duration, quality, initiation (sleep latency), maintenance (waking after sleep onset), and daytime sleepiness. Non-clinical sleep difficulties, such as insomnia symptomology (prolonged sleep latency or difficulty staying asleep), abnormal sleep duration, low sleep quality and daytime sleepiness, are common amongst older adults.[2,25–27] However, the decline in sleep health experienced by older adults cannot be solely attributed to age-related changes in sleep architecture.[2,25–27] Sleep is also affected by a bidirectional association with the accumulation of psychiatric disorders and physical illnesses with age. Bidirectionality signifies that poor sleep can negatively impact one's health, and poor health can negatively impact one's sleep. Beyond the detrimental effect on one's physical and mental health, inadequate sleep has been associated with cognitive decline, decreased quality of life, increased fall risk, and greater risk of mortality.[2] Despite the potentially substantive public health and policy implications of poor sleep, sleep health has received less research attention than other behavioural risk factors for multimorbidity, such as smoking, alcohol consumption, poor diet, and physical inactivity. Longitudinal information about the impact of poor sleep patterns on multimorbidity incidence in a Canadian population of middle-aged and older adults will provide valuable insights into the directionality and strength of the relationship.

Framing sleep as a risk factor for chronic disease suggests that significant improvements to health status and outcomes can be achieved through the early assessment of sleep health. Sleep's relationship with multimorbidity is less established in large population-based studies than sleep in relation to individual chronic conditions. Existing studies have consistently demonstrated that poor sleep health in older adults is associated with a higher likelihood of multimorbidity, but they have been limited mainly to cross-sectional designs.[8–11] As a result, the bidirectional relationship between sleep and chronic health conditions has not been adequately addressed. Complicating the

relationship further, there are age and sex specific differences in the prevalence, incidence, and management of both sleep health and chronic diseases.[3,4,8,28–31] There is a need to provide observational evidence with sex and age considerations in large nationally representative longitudinal studies of middle-aged and older adults to assess the relationship between sleep and multimorbidity.

There are methodological concerns when studying sleep health, as determining the appropriate measure to capture multiple sleep dimensions in population-based studies remains a challenge. Most studies assess sleep dimensions individually, without accounting for the complexity and interaction of the various aspects that quantify sleep health. Epidemiological studies using objective measures of sleep, such as actigraphy or polysomnography, are valuable but impractical in large health surveys due to high costs. The limitation on sample size when using these gold-standard measures hinders statistical power and generalizability of the findings. Widely used questionnaires, such as the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS), are not suitable to measure sleep health in the population of interest from the Canadian Longitudinal Study on Aging (CLSA). The PSQI is a widely used questionnaire to determine sleep quality, however, it is scaled with the purpose of assessing sleep disturbances rather than solely sleep health.[1,32] The ESS assesses only daytime sleepiness, limiting the content validity as a measure of general sleep health.[33,34] Attempts have been made to summarize self-reported sleep health as an index score; however, significant heterogeneity across these tools limits the ability to compare results.[34–37] Additionally, none of these composite scores incorporate the same set of sleep behaviours that are of interest and are available through the CLSA.

Overall, sleep health dimensions have been shown to impact the development of chronic conditions in older adults. This thesis encompasses sleep health into indices and utilizes the two-disease cut-off definition of multimorbidity to gain an understanding of the relationship. Research findings from this thesis, based on longitudinal data, will possibly corroborate the growing evidence on the role of sleep health as a modifiable risk factor for the development of multimorbidity in older adults.

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Chapter 2

2 Literature Review

2.1 Overview

The purpose of this chapter is to present a methodologically oriented review of the epidemiology of multimorbidity and the potential role of sleep as a contributing factor. This chapter also contains definitions of key terms used in this thesis.

2.2 Multimorbidity

2.2.1 Definition of Chronic Disease

Chronic diseases are long-term physical or mental health issues that persist over time and require ongoing management.[1] The term ‘chronic condition’ covers a broad range of health concerns, including communicable diseases (e.g. HIV/AIDS, chronic hepatitis), non-communicable diseases (e.g. cardiovascular disease, diabetes), mental disorders (e.g. anxiety, depression) and ongoing physical impairments (e.g. blindness, amputations).[1] Common features include multiple risk factors leading to onset, lengthy development period, long duration of illness that could lead to other health complications, and associated functional impairment or disability.[1,2] Chronic disease is a major global health burden that continues to grow at a concerning rate.[1] In 2012, chronic conditions were responsible for 38 million deaths worldwide and are projected to be responsible for 52 million deaths in 2030.[1] In Canada alone, about a third of the population lives with a major chronic disease.[3]

2.2.2 Definition of Multimorbidity

Multimorbidity is the co-occurrence of two or more (2+) or three or more (3+) chronic conditions in an individual at the same point in time.[4–6] There is limited generalizability of the findings from studies examining multimorbidity due to a lack of consensus on the operational definition amongst public health, research, and clinical sectors.

The variation in the literature arises from a multitude of sources. First, due to the limitations of information available from data sources about particular conditions, authors may choose to exclude certain conditions from their definition of multimorbidity.[7] Secondly, discrepancies are introduced when the definition of multimorbidity fails to differentiate between diseases (e.g. depression), risk factors or risk conditions (e.g. obesity) and symptoms (e.g. headache) of chronic conditions.[8] Third, depending on the information available and desired outcomes, study designs employ a variety of measures, limiting the comparability of findings. A systematic review found that over 35 different measures are employed by researchers across primary care and community health settings.[9] These methods can be broadly categorized into condition counts, physiological measurements, drug counts and diagnostic clustering.[9] Fourth, the exact number of co-occurring health conditions required to be deemed "multimorbid" differs across definitions.[10] The minimum number of chronic conditions ranges from 2 to 4, with the most widely applied cut-offs being two or more (2+) or three or more (3+) conditions.[7,8,11] The variation has been attributed in some cases to differences in the research target audience (e.g. public health or clinical), which leads to different research goals and operationalization considerations.[10] Lastly, the terms multimorbidity and comorbidity are often used interchangeably, as both refer to people with multiple co-occurring chronic conditions. Multimorbidity signifies that no single disease takes precedence over another, whereas comorbidity refers to chronic conditions in relation to an index disease.[4,6,12] Overall, this leads to considerable heterogeneity and misuse of the term multimorbidity across academic, public health and clinical settings.[4,6,12]

2.2.3 Prevalence of Multimorbidity

Acquiring exact prevalence estimates of multimorbidity is challenging due to the heterogeneity of the operational definitions.[11,13] A systematic review of 39 publications from 12 countries found prevalence estimates fluctuating between 13% to 95%.[13] A meta-analysis that combined multimorbidity estimates from 18 high-income countries (HIC) and 31 low and middle-income countries (LMICs) estimated a pooled random-effect prevalence of 33.1% (95% CI: 30.0, 36.3%).[14] A general trend observed across

populations is that the prevalence of multimorbidity increases with age, imposing a larger burden among middle-aged and older adults.[11,13,14]

Multimorbidity is a pressing concern due to the rapid growth of the older adult population in Canada. This demographic group is particularly vulnerable to the challenges associated with managing multimorbidity. In Canada, a retrospective cohort analysis found that of primary care patients aged 18 and older, 53.3% and 33.1% had two or three chronic conditions, respectively.[15] According to both cut-offs, there was an increase in the prevalence of multimorbidity until ages 85 years and older, with the largest proportion of patients experiencing multimorbidity between 45 and 64 years.[15] Similarly, the Canadian Longitudinal Study on Aging (CLSA) baseline data found a high prevalence of multimorbidity in participants between 45 and 64 years, with 39.6% (99% CI: 38.4, 40.7) reporting three or more chronic conditions.[16] Within this age range, the prevalence of multimorbidity increased considerably with age from 29.7% for those aged 45–49 years to 52% for those 60–64 years.[16]

Nicholson et al. (2020) conducted a cross-sectional analysis that provides an example of how the operationalization of multimorbidity can impact prevalence estimates.[17] In the same CLSA population, a primary care definition consisting of 17 chronic conditions and a public health definition of 9 chronic conditions was used in analyses.[17] Applying a primary care definition and two disease cut-off, 70% of the population lived with multimorbidity.[17] In contrast, when a public health definition was used at the same cut-off, only 30% were classified as living with multimorbidity.[17] The observed discrepancy highlights the influence the definition of multimorbidity has on results. Despite analysis being conducted using the same population at the same point in time, a wide range of prevalence estimates can be reported. Without standardized definitions of multimorbidity, reliable comparisons between populations and accurate assessments of its prevalence or incidence become challenging, limiting our understanding of its global burden and impact on health outcomes.

2.2.4 Risk Factors of Multimorbidity

Various sociodemographic, behavioural, and physical health-related factors influence the development of multimorbidity. The predominant factors contributing to multimorbidity are age and sex. Other sociodemographic factors such as ethnicity, annual household income and education may impact multimorbidity development. Potential behavioural and physical health risk factors include smoking and alcohol use, poor dietary patterns, low physical activity, high body mass index (BMI), and hypertension.[18–21]

Age: Age is a well-established multimorbidity risk factor across populations.[13] A systematic review found that across the human lifespan, there is a consistent pattern of two disease cut-off multimorbidity prevalence increasing sharply from about 20% to 75% between the ages of 40 and 70 years, forming an S-shaped curve.[11] The plateau at greater ages may be due to greater mortality or the two condition cut-off used, as applying the cut-off of three or more conditions retains a more linear association at ages 70 years and older.[11] A cross-sectional examination of the first follow-up CLSA data of a population aged 45 to 75 years or greater displayed that through middle to older ages, there is a variation amongst multimorbidity risk, as the odds continued to increase with age.[22] Due to the increasing prevalence with age, many multimorbidity studies are limited to older populations.

Sex: Women are more likely to experience multimorbidity than men, but not all studies observe this difference.[13] The inconsistency could be attributed to a lack of adjustment or stratification for both age and sex, higher diagnosis rates in women, the inclusion of a differential number of sex-specific conditions, inadequate power to detect differences or a true lack of sex differences.[13,23] If sex does not biologically influence multimorbidity risk, it may be a context-dependent proxy for another modifiable characteristic that does influence risk or detection.[23] For example, women tend to engage in more healthcare-seeking behaviour, increasing detection rates of chronic conditions and, consequently, multimorbidity estimates.[23–25] Alternatively, sex could be interacting with other risk factors affecting multimorbidity risk or detection. In certain settings, women face greater

financial inequalities than men, which can contribute to adverse health outcomes and greater multimorbidity risk.[23,24]

***Ethnicity and race*:** Several studies have explored ethnicity or race in association with multimorbidity.[26–29] Reproducible differences about inter-ethnic differences in multimorbidity risk are difficult to observe due to a lack of representation and varied terminology usage across studies.[23] Further, many studies investigate ethnic groups within a single geographically defined population. Similar to sex, ethnicity potentially could act as a context-dependent proxy for other factors that increase the burden of disease that affect ethnic groups differentially, like financial inequality or migrant status.[23] Despite these issues, ethnicity should not be disregarded in the study of multimorbidity as it may still be influential to multimorbidity risk. For example, a study of an American population found that compared to White persons, Black persons have a higher prevalence of multimorbidity, while Asians displayed a lower prevalence.[28]

Education and Income: Education and income relationships to multimorbidity are environment dependent. In HIC, socioeconomic status (SES) often displays an inverse relationship with multimorbidity.[13] A cross-sectional analysis of 314 Scottish medical practices found that the onset of multimorbidity in young and middle-aged adults with lower SES status was 10 to 15 years earlier than in those living in more affluent areas.[30] In Dutch and German populations, those with a higher education were shown to be less likely to have multimorbidity.[31,32] Interestingly, this relationship is not consistent across all HIC; in CLSA baseline and follow-up cross-sectional analyses, only higher income was observed to be protective against multimorbidity.[16,22] In LMIC, the opposite relationship is typically seen due to an ongoing epidemiological transition, with those of higher income more likely to develop multiple chronic conditions due to an increasing prevalence of westernized lifestyle-related factors such as tobacco, alcohol consumption, high-calorie foods and sedentary behaviour.[23,33]

Smoking and Alcohol Use: Modifiable risk factors, such as smoking and alcohol consumption, contribute to various chronic conditions but have shown conflicting relationships with multimorbidity. At first follow-up, CLSA participants who never

smoked showed a protective effect against multimorbidity.[22] However, at baseline, there was no significant difference between the prevalence of multimorbidity between smokers and non-smokers.[16] Regarding alcohol consumption, both at baseline and follow-up in the CLSA, frequent alcohol consumption displayed decreased odds of multimorbidity.[16,22] These findings raise the possibility that individuals sampled or who chose to drink in the CLSA study are generally healthier. These results were not replicated in a separate cohort of Quebecois Canadians, in which alcohol consumption displayed no association with the presence of multimorbidity.[19] Inconsistencies could reflect different methodologies, varying selection of reference categories, confounding variables and study populations. Regardless, given the extensively studied relationship between substance use and chronic conditions, it is likely that the behaviours are relevant to multimorbidity risk.[23]

Physical Activity and BMI: A physically active lifestyle and healthy BMI are suggested to protect against multimorbidity. In the English Longitudinal Study of Ageing, self-reported physical activity levels displayed an inverse dose-response relationship with multimorbidity prevalence.[20] Similar results have been seen in large longitudinal studies of Irish and British populations.[34,35] However, two cross-sectional studies in Canada found that multimorbidity was not related to physical activity levels.[19,36] While the association between physical activity is biologically plausible, the evidence is currently limited and inconsistent. BMI has shown a more consistent relationship with the outcome in HIC, including Canada, with increases in BMI coinciding with multimorbidity prevalence increases.[19,37–40]

Hypertension: Persons with hypertension are more prone to multimorbidity. A study of over 200,000 Chinese individuals with hypertension found that multimorbidity was prevalent amongst the population (>40%).[41] Similar analyses of a population of individuals with hypertension in South Asia found that one in four participants had cardiometabolic multimorbidity, defined as the presence of two or more conditions from diabetes, chronic kidney disease, heart disease and stroke.[42] In Australian women aged 45-50 years, a greater accumulation of multimorbidity of diabetes, heart disease and stroke was observed in individuals living with hypertension.[43] Hypertension is

occasionally included in the definition of multimorbidity rather than viewed as a risk factor, limiting the number of studies available.

In summary, clarity is required in determining the etiology of multimorbidity through longitudinal studies, standardization of definitions and consideration of confounding factors. Research on the determinants of multimorbidity is mainly cross-sectional, limiting the ability to establish causality and discern temporal trends.[23] A better understanding of the possible determinants would aid in predicting multimorbidity trends and identifying populations that will benefit most from targeted interventions. Importantly, not all modifiable risk factors have been established in the literature, leaving room for further investigation into overlooked determinants and their broader public health implications.

2.3 Sleep

Sleep is a relatively neglected behavioural risk factor for multimorbidity. Sleep has been defined physiologically as a natural state of unconsciousness, characterized by the suspension of voluntary bodily functions and reduced metabolism, and defined psychologically as a complex process that includes various functions such as memory consolidation, emotional regulation, dreaming and restoration of physical and mental energy.[44,45] The idea of 'sleep health' covers various aspects of the sleep-wake cycle that impact an individual's health and is not specific to any particular clinical classifications of sleep disorders.[46] The upcoming section describes emerging evidence that sleep is associated with other sociodemographic factors, such as age, sex, chronic diseases, and multimorbidity.

2.3.1 Sleep, Age, and Sex

Physiological changes in sleep occur over the entire human life course; however, numerous studies have shown a higher prevalence of poor sleep patterns amongst older adults.[47–50] These adverse changes in overall sleep health are distinct from clinically defined sleep disorders. The National Institute on Aging found self-reported chronic sleep complaints in over 50% of older adults from a sample of over 9,000 participants aged 65 years and older.[51] The greater prevalence of sleep complaints with age is of concern, as

published literature links poor sleep patterns to greater mortality risk in the general population.[52–56] The disproportionately higher number of poor sleep health symptoms, such as nighttime awakenings, sleeping less, and taking longer to fall asleep, have been replicated in older populations using both self-report and polysomnography measures.[57]

Sex differences in sleep health have also been identified in the literature. An accumulation of biological, environmental and social factors influence the sex differences.[58] A consistent pattern seen across sleep literature is that women display objectively better sleep patterns than their male counterparts yet self-report poorer sleep health more frequently than men.[59–61] For example, when sleep parameters were measured using subjective and actigraphy methods in a sample of 956 older adults, sex-specific discrepancies in sleep health were observed.[61] Women tended to self-report a greater number of sleep problems, such as shorter duration, longer latency, worse efficacy and poorer quality than men.[61] However, these same issues were not exhibited when measuring sleep patterns using actigraphy as women had, on average, a longer duration of sleep, better efficiency, and less fragmented sleep patterns.[61] There is a need for more longitudinal information regarding sleep and health outcomes to explain the discrepancies between methodologies in the observed sex differences.

2.3.2 Sleep and Chronic Disease

The association between age-related physiological changes in sleep and chronic disease has been extensively studied. In older adults, approximately 40% of those with major chronic diseases perceived their sleep as fair or poor quality, whereas only 10% of those without comorbidity reported their sleep quality as fair or poor.[62] Chronic conditions frequently associated with sleeping difficulties include cardiovascular disease[63,64], cancer[65–67], chronic respiratory diseases (asthma[68–70] and/or chronic obstructive pulmonary disease[69,71]), diabetes[63,64,69,72], and mental illnesses (mood[68,72–78], and/or anxiety[68,72,74,79] disorders). Note that this is not an exhaustive list and is only meant to outline several chronic conditions commonly associated with sleeping issues in older adults.

Sleep and chronic disease exist in a bidirectional relationship, with poor sleep health being both a potential risk factor and a result of chronic disease accumulation.[17,80–82] First, changes in sleep patterns can result from age-related chronic disease accumulation.[83] In other words, a portion of the sleep health decline older adults experience can be attributed to physical and mental health declines rather than the aging process itself.[83] Secondly, poor sleep could be a risk factor for chronic disease incidence. The Swedish National Study of Aging and Care observed that baseline sleep disturbances in a population aged 60 years or older led to a higher rate of chronic disease accumulation throughout the 9-year follow-up period.[84] The findings suggest that sleep is a crucial health target for chronic disease prevention. Overall, the increased incidence of poor sleep health and chronic illnesses with age requires simultaneous consideration of both for proper disease management.

2.3.3 Sleep and Multimorbidity

Growing evidence suggests that sleep complaints are associated with the development of multiple chronic conditions later in life.[50] In the 2003 National Sleep Foundation survey, 53% of those aged 65 years and older without comorbid illness displayed a sleep problem.[85] In those with 2 to 3 comorbid conditions, this percentage increased to 68%, and in people with 4 or more comorbid conditions, it increased to 80%.[85] In a multi-national study of Finland, Poland, Spain, China, Ghana, India, Mexico, Russia, and South Africa, all nine countries displayed a linear dose-dependent relationship between the number of chronic conditions and sleep problems.[73] Similar patterns were seen in a study of 46 LMICs, where the odds of sleep problems increased alongside the number of chronic conditions an individual was experiencing.[86] These results suggest that sleep health is related to medical illness rather than solely the aging process.[59] A longitudinal examination of the relationship using data from a population-based sample is required to investigate the sleep's potential impact on multimorbidity.

2.4 Measures of Key Components of Sleep

The upcoming sections discuss measurable age-related changes in sleep that commonly occur and their relationship with multimorbidity.

2.4.1 Sleep Duration

Older adults often self-report a reduction in sleep duration as they age.[87] A study by Campbell and Murphy (2007) utilized a protocol in which young, middle-aged, and older adults were restricted from natural and artificial time of day cues for 72 hours.[88] Their results support the notion that aging causes reduced sleep durations, as the total sleep time over 24 hours was significantly shorter in older adults (8.13 hours) and middle-aged adults (9.06 hours) compared to young adults (10.53 hours).[88] These findings of normal age-related changes in sleep are reflected in the National Sleep Foundation's sleep duration recommendations of 8-10 hours for teens, 7-9 hours for young adults and adults, and 7-8 hours for adults over the age of 65.[89] Deviations from the recommended 7-8 hours per day can indicate and impact the presence of health risk factors and chronic conditions.[90]

Several longitudinal studies suggest a clear U-shaped association between short (<6 hours) and long (>10 hours) sleep hours and mortality, with the extremes of sleep increasing mortality risk.[52–55,91] In the Japan Collaborative Cohort Study of 104,010 subjects aged 40 to 79 years, sleep durations greater or less than 7 hours were associated with a greater risk of all-cause mortality.[92] In a prospective USA study, only elderly subjects (60 to 86 years), not middle-aged (32 to 59 years), displayed the U-shaped relationship between sleep duration and mortality.[55] A meta-analysis of prospective studies including over a million participants also determined that both extremes of sleep are significant predictors of death, making sleep duration a valuable behavioural risk factor.[53] There is contention with the biological feasibility of the U-relationship, as there is mixed evidence to indicate a mechanism in which sleeping longer results in adverse health effects.[93] Evidence suggests that sleep deprivation is a cause of poor health by triggering biological mechanisms, whereas long duration may be a marker of poor health.[53]

2.4.1.1 Sleep Duration and Multimorbidity

The sleep duration also exists in a U-shaped relationship with multimorbidity, although short sleep has shown a more consistent relationship with multimorbidity than

long sleep. In a sample of 1508 Luxembourg residents aged 25 to 64 years, short sleep duration was linearly associated with the number of chronic conditions independent of socioeconomic and behavioural factors.[81] Similarly, a longitudinal Chinese study of adults 45 years and over found that only short sleep during a four-year follow-up period increased the risk of incident multimorbidity.[94] Yet in another study of Chinese adults, long sleep duration in those aged 60 to 79 years was associated with multimorbidity.[95] This evidence may suggest that the association with sleep duration may differ from middle to older ages. Analysis of the Whitehall II cohort supports this notion, finding that short sleep was associated with higher multimorbidity risk at ages 50, 60 and 70 years, whereas long sleep duration displayed association at ages 60 and 70 years.[96] The inconsistency between the studies could result from different regions, study designs, multimorbidity definitions, age grouping, and sleep duration categorizations.

The association between sleep duration and multimorbidity has sex-specific facets. In community-dwelling Canadian adults, both extremes of sleep duration resulted in increased odds of multimorbidity in females, but only long sleep was significantly associated with odds of multimorbidity in males.[17] Sex-specific particularities have been seen in the German Cooperative Health Research in the Region of Augsburg (KORA) Age Study, in which neither short nor long sleep was significantly associated with multimorbidity in men, but short sleep was for women.[97] The sex specificity was also replicated in Brazil, where short sleep was correlated with an increasing number of chronic diseases in men, and long sleep was associated with three or more diseases in women.[98]

2.4.2 Sleep Quality

Sleep quality encompasses an individual's overall self-satisfaction with quantitative aspects (e.g. latency, duration, number of arousals) and qualitative aspects (e.g. depth or restfulness of sleep).[99] Sleep quality is commonly self-reported through either the Pittsburgh Sleep Quality Index **(**PSQI), comprised of 19 items of various aspects of sleep patterns to produce a global sleep quality score, or by asking participants to self-rate their sleep satisfaction.[99] Typically, sleep quality declines as a function of

normal aging, with the most substantial change in sleep efficiency characterized by more extended periods spent in bed while not asleep.[84,85]

2.4.2.1 Sleep Quality and Multimorbidity

In older adults, the number of chronic conditions present is associated with a decline in sleep quality. A recent cross-sectional analysis by Nicholson et al. (2020) of baseline CLSA national health survey data found a significant relationship between sleep dissatisfaction and odds of multimorbidity in Canadian adults over 45 years.[17] The association between poor sleep quality and multimorbidity prevalence has been replicated in cross-sectional studies of Japanese, Cyprus and multiple Chinese populations.[102–106] Studies of baseline CLSA data found that improved sleep quality was associated with greater multimorbidity resilience, the ability to cope and navigate with multimorbidity.[107,108] Despite the outcome definition not aligning with this paper's research interest, it provides valuable background linking sleep quality with attributes of multimorbidity and encourages further investigation into the direct relationship between the two.

2.4.3 Sleep Initiation and Maintenance

A declining ability to initiate sleep is reflected as an increased sleep latency (the length of time it takes to fall asleep). Issues in sleep maintenance are displayed by increased frequency of waking after sleep onset (WASO) and WASO duration.[109] Issues with initiation and maintenance are a chief complaint in adults over 65 years, with a study by Foley et al. (1995) finding that 43% of 9,000 participants reported difficulties with these aspects of sleep health.[51] The large number of complaints observed may even be an underestimation, as older adults often understate their decline of sleep initiation and maintenance in self-report measures compared to polysomnography.[109]

A meta-analysis published by Floyd and colleagues (2000) on the age-related changes in initiation and maintenance of sleep found a positive correlation between WASO duration (r=0.74, 95%CI= 0.71, 0.77), WASO frequency (r=0.38, 95%CI= 0.34, 0.42), and sleep latency (r=0.19, 95%CI= 0.14, 0.24) with age.[109] They concluded that age affects sleep maintenance more than the ability to initiate sleep, as WASO duration

and frequency displayed stronger correlations with age than sleep latency.[109] Further polysomnographic evidence agrees that while WASO frequency increases with age, reflecting issues with sleep maintenance, the ability to initiate asleep is largely unaffected.[110] Among older adults, high latency to initiate sleep and inability to maintain sleep are associated with increased morbidity and mortality.[111–113]

2.4.3.1 Sleep Initiation and Maintenance and Multimorbidity

The relationship between sleep initiation or maintenance and multimorbidity has not been extensively studied. Sex-stratified analyses of adults aged 65 years and older in the KORA study found greater odds of multimorbidity in women experiencing 'trouble falling asleep' and in both sexes experiencing 'difficulty staying asleep.'[97] In an older Eastern Chinese population, it was observed that 'prolonged sleep latency' and 'sleep disturbances' were associated with an increased likelihood of cardiovascular multimorbidity.[104] Overall, the lack of literature addressing the subject warrants further investigation.

2.4.4 Daytime Sleepiness

Daytime sleepiness is characterized by difficulty maintaining a desired level of wakefulness or alertness during waking hours.[114] The general level of daytime sleepiness is often evaluated by self-report using single-item questions or scales such as the Epworth Sleepiness Scale (ESS) and the multiple sleep latency test (MSLT).[114] Inconsistent work exists about whether daytime sleep propensity increases or decreases with age due to issues in consistently defining and quantifying sleepiness.

Age-related increases are suggested from prevalence estimates of sleepiness, which ranged from 5-10% in young and middle-aged adults and increased to 20-30% in older-aged adults.[114] A study of Australian adults aged 18 to 64 years observed that older age was a predictor of chronic daytime sleepiness, and middle-aged persons (41-50 years) have the highest prevalence of sleepiness.[115] The limitation of these findings is that older age was grouped too broadly, with the younger group comprising those aged 18 to 25 years and the older age group comprising ages 25 to 64 years.[115]

Alternatively, large epidemiological studies have suggested that daytime sleepiness declines with age. Canadian and Finnish population studies found a slight age effect, in which the risk of daytime sleepiness decreased with age.[116,117] Estimating daytime sleepiness in terms of daytime sleep propensity has also shown an age-related decrease. A 4-day laboratory study of healthy young, middle-aged, and older adults found that age-related reduction in daytime sleep propensity that was not attributed to increased time in bed, increased total sleep time or changes in sleep latency.[118] The authors conclude that decreased daytime sleepiness with age is a facet of healthy aging.[118]

2.4.4.1 Daytime Sleepiness and Multimorbidity

There is sparse research examining the relationship between daytime sleepiness and multimorbidity. In both sexes, the KORA study found that 'daytime tiredness,' defined as tiredness during the day caused by nighttime sleep issues, was significantly associated with multimorbidity, with the strongest associations with the disease dyads of joint and eye diseases in men and joint and heart diseases in women.[97] A cross-sectional of rural Chinese residents observed that excessive daytime sleepiness was not associated with cardiovascular multimorbidity.[104] Yet when researchers examined data from the UK Biobank, they found that people without frequent daytime sleepiness had a significantly reduced incidence of cardiometabolic multimorbidity, defined as the co-occurrence of two or more of hypertension, diabetes mellitus, coronary heart disease or stroke.[119] These studies provide promising new evidence that daytime sleepiness could exist in relation to multimorbidity.

2.5 Study Rationale and Objectives

2.5.1 Study Rationale

Consistently, studies of sleep and multimorbidity have demonstrated that poor sleep health in older adults is associated with a higher likelihood of multimorbidity. Specifically, various aspects of sleep, such as duration, quality, initiation, maintenance, and daytime sleepiness, tend to decline in older adults with multimorbidity. This decline is partially suggested to be a consequence of the expected age-related changes in sleep. However, emerging evidence proposes that poor sleep health is not inherent in aging but

related to chronic disease development. This indicates that sleep health patterns could potentially predict multimorbidity incidence and management of sleep conditions could reduce the development of adverse health outcomes.

The literature pertaining to sleep and multimorbidity is sparse and limited. Primarily, the literature focuses on the relationship between a singular sleep measure and a singular chronic condition. Collectively examining the various facets of sleep health through an index score could yield a more accurate depiction of real-life conditions.[46] In the context of this thesis, the latent variable 'sleep health' is a function of causal indicators.[120,121] In other words, the various facets of sleep influence sleep health, with changes to any given measure of sleep resulting in a change in perceived sleep health.[120,121] These casual indicators can be combined to form an index.[122] Two index construction approaches are explored in this thesis, which we call additive and pooled, as there is no singular ideal approach. The additive approach is defined as the simple sum of the various items, whereas in the pooled approach, each item was standardized before summing.

Other limitations in sleep and multimorbidity research include that the few studies that directly address sleep health primarily have cross-sectional study designs, limiting the ability to discern potential reverse causation in the bidirectional association. Further, the generalization of the findings is limited due to inadequate adjustment of covariates and inconsistent multimorbidity definitions. There is a need for observational sleep evidence from a large population of middle-aged and older adults that addresses important health outcomes such as multimorbidity. The implications of the findings are likely to be substantial, as the growing segment of older adults in Canada is likely to face issues of poor sleep health and require informed public health initiatives and policies that address their concerns.

2.5.2 Objectives

The thesis aims to analyze baseline and first follow-up CLSA data to estimate the relationship between sleep and multimorbidity in community-dwelling Canadians. The primary objective is to discern the longitudinal impact sleep behaviours have on the risk

of multimorbidity in the middle-aged and older adult population. Another goal is to construct an index that quantifies sleep health while exploring whether the approach to index construction impacts the strength of the observed association. Lastly, we will examine whether age or sex-specific differences exist in the outcomes through stratification.

The specific objectives are to:

1. Estimate the prevalence of poor sleep health in the CLSA cohort at baseline.
2. Compare the relationship between sleep health and multimorbidity using individual dimensions of sleep health and novel sleep index approaches.
3. Estimate the association between poor sleep health at baseline and incident multimorbidity over a 3-year follow-up.
4. Test for age and sex differences in the association between baseline sleep behaviours and incident multimorbidity over a 3-year follow-up.

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Chapter 3

3 Sleep Index Approaches for Assessing the Prevalence of Poor Sleep Health among Middle and Older-aged Adults with Multimorbidity: Insights from the Canadian Longitudinal Study on Aging (CLSA)

3.1 Introduction

The complexity of sleep health is frequently unaddressed in the study of multimorbidity, as sleep factors are treated as independent outcome measures and uncorrelated with each other. The multidimensional nature of sleep health suggests that any single attribute of sleep does not sufficiently capture the construct.[1] A comprehensive understanding of sleep health requires the simultaneous assessment of multiple sleep factors in an efficient manner.[2] However, independently conducting multiple comparisons and tests on several factors inflates the Type I error, otherwise known as the false positive rate, and increases the likelihood of finding significant results purely due to chance.[3] A possible solution to the multiplicity problem is using a single composite measure, such as an index.

Recent evidence has shown that individuals with multimorbidity tend to report poorer outcomes across multiple dimensions of sleep.[4–8] For example, sleep duration and quality have shown a relationship with higher odds of multimorbidity in a Canadian population of older community-dwelling adults.[4] We hypothesize that sleep health comprehensively could reflect a modifiable risk factor for the development of multimorbidity. A single score capturing the latent variable sleep with an acceptable internal consistency that can be feasibly applied to the large cohort comprising the Canadian Longitudinal Study on Aging (CLSA) has yet to be developed. Sleep health measures such as the widely used PSQI or newly developed Sleep Health Index from the National Sleep Foundation were not implemented in the CLSA cohort, and the necessary sleep data is not available to retroactively apply these instruments to the cohort.[9,10] The lack of a standardized metric for assessing sleep health in the CLSA emphasizes the importance of developing an equivalent research tool.

The reduction in the variance of an index relative to the variance of the source variables yields higher statistical power to detect an effect (higher signal-to-noise ratio).[11–14] This is especially true for weakly intercorrelated items; as the pairwise correlation between items decreases, so does the index's joint variance relative to the individual items' variance.[11–14] The index approach covers important domains of sleep health while reducing measurement variability and increasing the statistical power to detect effects in a given sample size.[14] Therefore, to capture the latent variable of 'sleep health' in a singular numeric score and see whether the aggregate measure is associated with multimorbidity, two index construction approaches were explored, additive and pooled index, in a large cohort of Canadian adults. Both analytic approaches can provide a reproducible measure of a latent phenomenon and can develop valuable tools for predicting disease progression in older adults, making the comparison of the two methodologies of interest.

We hypothesize that combining multiple sleep outcomes for analysis improves the ability to detect statistical differences in sleep health among older adults with multimorbidity. The purpose of this chapter is to 1) develop indices that measure the overall sleep health of a community-dwelling Canadian population using additive and pooled techniques, 2) to estimate the prevalence of poor sleep patterns in the CLSA population using the indices, and 3) to compare prevalence estimates using individual sleep measures versus sleep indices scores.

3.2 Methods

3.2.1 Data Source and Study Setting

This chapter was based on a cross-sectional analysis of baseline data (2010-2015) from the CLSA. The CLSA is an ongoing national study of healthy aging and the factors that affect adult development composed of data on numerous biological, clinical, and health-related measures.[15] At the time of recruitment, over 50,000 community-dwelling adults aged 45 to 85 years were enrolled in the CLSA cohort.[15] Participants are anticipated to be followed over repeated waves of data collection every 3 years until 2033.[15] The sample excluded those living in the three Canadian territories, certain remote

areas or on federal First Nations reserves and settlements, full-time members of the Canadian Armed Forces, currently living in long-term care institutions (i.e. those providing 24-hour nursing care), unable to respond in either English or French or cognitively impaired.[16]

Stratified sampling by sex and age was used to recruit participants into the CLSA.[16] Several sampling frames were used, including provincial health registries, random digit dialling, and targeted sampling of underrepresented populations.[16] Participants were also drawn from the Quebec Longitudinal Study on Nutrition and Aging (NuAge).[16] Of the 51,338 participants, the CLSA Comprehensive cohort, consisting of 30,097 individuals located within 25–50 km of 11 data collection sites in seven provinces, was the focus of this thesis.[16] These participants gave their informed consent to provide complete physiological and psychosocial data in person, including information on sleep behaviours.[16] Approval to access data from the CLSA (Application 190247) and ethics approval from the Western University Health Sciences Research Ethics Board (Project 112140) was obtained.

3.2.2 Main Outcome

Multimorbidity was defined as having two or more chronic conditions from a list of major disease categories, including cardiovascular disease, cancer (ever had), chronic respiratory disease (asthma and/or chronic obstructive pulmonary disease), diabetes, and mental illnesses (mood and/or anxiety disorders), based on the latest definition suggested by the Public Health Agency of Canada (PHAC).[17,18] Participants self-reported their chronic conditions diagnosed by a healthcare professional lasting six or more months ("Has a doctor ever told you that you had…?"). A binary variable was generated to indicate multimorbidity using a cut-off of two or more diseases.

3.2.3 Sleep Measures

During the baseline assessment, participants were administered questionnaires to collect information on several sleep variables, including duration, quality, initiation, maintenance, excessive daytime sleepiness, and snoring. Sleep duration was measured using the self-reported average hours asleep per night over the past month. The duration

was categorized as Short (<7h), Normal (7-9h) and Long (>9h) for adults under 65 years or as Short (<7h), Normal (7-8h) and Long (>8h) for adults aged 65 years and over, following National Sleep Foundation guidelines.[19] Sleep quality was measured using the question "How satisfied or dissatisfied are you with your current sleep pattern?" with five possible responses of (i) Very dissatisfied, (ii) Dissatisfied, (iii) Neutral, (iv) Satisfied, or (v) Very satisfied. Information about insomnia symptoms, sleep initiation and maintenance, was obtained by asking, "Over the last month, how often did it take you more than 30 minutes to fall asleep?" and "Over the last month, how often did you wake in the middle of the night or too early in the morning and found it difficult to fall asleep again?", respectively. Excessive daytime sleepiness was assessed using the question, "Over the last month, how often do you find it difficult to stay awake during your normal waking hours when you want to?". The response options for the variables initiation, maintenance, and excessive daytime sleepiness were (i) Never, (ii) Less than once per week, (iii) Once or twice a week, (iv) 3-5 times per week, or (v) 6-7 times per week. Information about snoring was collected by asking, "Do you snore loudly? By 'loudly' I mean louder than talking or loud enough to be heard through closed doors." with responses of (i) Yes or (ii) No. Indicators of poor sleep health was as follows: short or long sleep duration, dissatisfaction with sleep quality, difficulties with sleep initiation, maintenance, or daytime sleepiness 3 times per week or more and snoring.

3.2.3.1 Variable Selection

The five items included in the sleep indices were duration, quality, initiation, maintenance, and excessive daytime sleepiness. Variable selection for the indices took into consideration the theoretical relevance of variables, correlation between variables and reliability of the assessment. The included sleep dimensions are relevant to the concept of sleep health as they have been implicated as risk factors for multimorbidity or the various chronic conditions comprising multimorbidity. Kendall's tau was used to examine the correlation between sleep measures. The original ordinal forms of sleep quality, initiation, maintenance, and excessive daytime sleepiness were used alongside binary snoring and sleep duration variables. The factors with low pairwise correlation coefficient ($\tau < 0.6$) were included in the index, as the inclusion of highly correlated

variables is redundant.[11–14] The reliability was measured using Cronbach's alpha, which quantifies the internal consistency of the items. Cronbach's alpha ranges from 0 to 1, with scores of 0.6 to 0.7 considered acceptable reliability, over 0.8 very good reliability and over 0.95 reflecting redundancy amongst items.[20]

3.2.3.2 Additive Index

The additive sleep index used recoded sleep components as binary variables, with 0 indicating behaviours as 'low risk' and 1 indicating 'high risk' behaviours. Low-risk factors were defined as a sleep duration of 6 to 8 hours per day, satisfaction with sleep quality (neutral, satisfied or very satisfied), and infrequent issues with sleep initiation, maintenance, or excessive daytime sleepiness (never, less than once per week). The index was a summed total of the five components ranging from 0 to 5, with lower scores indicating better sleep health. Poor sleep health was defined as scores of 3 or greater. Only participants with complete data on the component variables were included in the index calculation.

3.2.3.3 Pooled Index

The pooled index originated in studies of rheumatoid arthritis therapies by Smythe et al. (1977) and Goldsmith et al. (1993) and has been more recently seen in studies comparing the function of psychiatric clients or gait and cognitive function.[11–14] It is recommended that the pooled index contains only up to six component variables with low pairwise correlations because it ensures important measurement domains are covered and since there is little reduction in variability to be gained beyond this point.[11–14] The pooled approach combined the sleep factors into a single index score, with scores closer to negative one indicating better sleep health.[11–14] At baseline, each sleep measure's mean and standard deviation were calculated using the binary version of sleep duration and treating the ordinal variables as continuous. Then, each variable was standardized by calculating Z-scores. The arithmetic mean of the Z-scores was taken to produce a pooled sleep index score for each participant.[11–14] Poor sleep health was defined as scores in scores in the top quintile (highest 20% of scores). Only participants with complete data on the component variables were included in the index calculation.

3.2.4 Statistical Analysis

Analyses were performed using Stata Version 17, and figures were generated using R Version 4.1.0.[21,22] The CLSA has a complex sampling design; thus, descriptive analyses were weighted by inflation (trimmed) weights to obtain results representative of the Canadian population.[23] Characteristics also specified as part of the sampling design included the geographic strata, adjusted standard errors using Taylor series linearization and the "certainty" option to ignore strata with single observations in variance calculation.[23]

For the present study, of the 30,097 individuals enrolled in the CLSA Comprehensive cohort at baseline, 25,997 participants were included. Those included in analyses had complete data on sleep measures, multimorbidity, sex and age. Any responses as “Don’t know” or “Refused” were treated as missing values and excluded from analyses. Overall, 4100 participants were excluded due to missing data on sleep measures. Comparisons of the characteristics of the excluded individuals were conducted, and differences in proportions greater than 10% were considered potentially significant.

Descriptive statistics were presented as unweighted counts and weighted percentages. Baseline characteristics were computed for multimorbidity status and sleep variables by sex (male or female) and age group (45-54, 55-64, 65-74, 75-85 years) and compared using chi-squared tests. Histograms were used to visualize the distribution of index scores. The distribution of poor sleep measured using individual sleep factors and sleep indices by multimorbidity status was tabulated. Further, the indices were used in age and sex stratified analyses to classify poor sleep by multimorbidity status. All tests were two-sided, with a significance level of 0.05.

3.3 Results

3.3.1 Sample Characteristics

Compared to the analytic sample, the group excluded from the study tended to be older (20.2% vs. 10.3% in the 75 to 85 age group), but there were no significant differences in sex, multimorbidity, or sleep measure distributions (Appendix A). The

distribution of multimorbidity and sleep behaviours by sex and age is provided in Appendix B and C, respectively. While multimorbidity did not significantly differ between sexes ($p=0.047$), it varied significantly by age ($p<0.001$). Significant sex differences were observed in the distribution of sleep measures, except for sleep duration. Females reported being more dissatisfied with their sleep quality and experienced more issues with sleep initiation, maintenance, and daytime sleepiness than males. Conversely, males reported a higher frequency of snoring (34.9%) than females (21.8%). There were also significant differences in the distribution of sleep health across age groups, except for sleep initiation.

3.3.2 Index Construction

Pairwise correlations among sleep measures are shown in Table 3-1. The coefficients are all below 0.5, which is desirable for reducing redundancy among the items within an index. The highest correlations were between sleep quality and duration ($\tau = 0.40$) and sleep quality and maintenance ($\tau = 0.44$). The lowest correlations were observed amongst snoring and all other sleep measures, with correlations below 0.10. This raises concerns about whether snoring measures the same latent variable as the other variables. All correlations, except between snoring and sleep maintenance, had a statistically significant correlation ($p<0.001$).

Table 3-1. Kendall's Tau Correlations Between Sleep Measures.

	Duration	**Quality**	**Initiation**	**Maintena-nce**	**Daytime Sleepiness**	**Snoring**
Duration	-					
Quality	0.4043	-				
Initiation	0.1730	0.2835	-			
Maintenance	0.2768	0.4354	0.2484	-		
Daytime Sleepiness	0.1219	0.1633	0.0965	0.1307	-	
Snoring	-0.0329	0.0375	-0.0215	-0.0025	0.05654	-

The exclusion of snoring improved the internal consistency, as indicated by Cronbach's alpha. Snoring reduced the internal consistency of the index to 0.62, compared to an alpha of 0.69 with its exclusion. Daytime sleepiness also had low correlations amongst other sleep measures. However, it was retained due to low impact

on alpha values if excluded and expert opinion favouring the inclusion as an essential aspect of sleep health. Therefore, the five domains that composed the indices were duration, quality, initiation, maintenance, and excessive daytime sleepiness. The additive index ranged from 0 to 5, with higher scores indicating poorer sleep. As shown in Figure 3-1, only a small number of participants scored 5 on the additive index. The distribution of scores from the pooled index is illustrated in Figure 3-2, where higher scores again indicate unhealthy sleep.

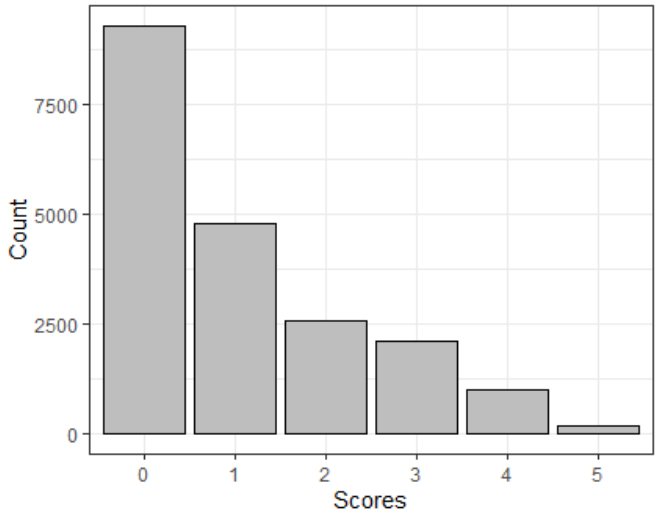

Figure 3-1. Distribution of Additive Index Scores

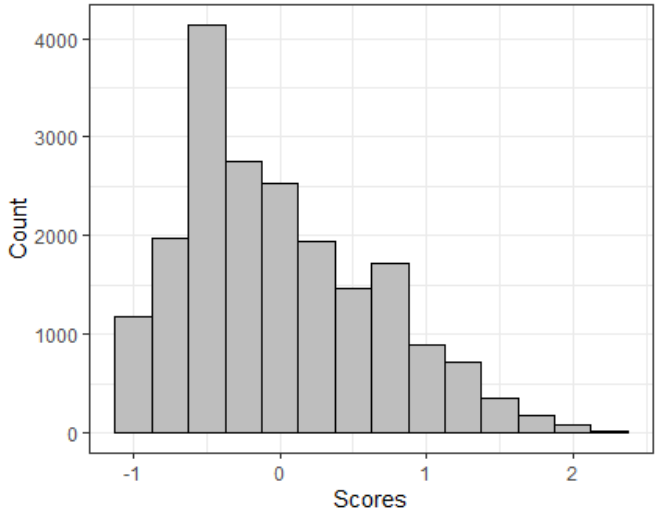

Figure 3-2. Distribution of Pooled Index Scores

3.3.3 Distribution of Sleep Measures by Multimorbidity Status

Table 3-2 displays the prevalence of poor sleep health among the CLSA population based on both individual sleep measures and indices. The results indicated that 26.3% and 28.8% of participants with multimorbidity had poor sleep patterns based on the additive and pooled indices, respectively. Notably, sleep duration, quality, maintenance, and snoring yielded higher prevalence estimates than the index measures. The greatest proportion of individuals experienced unhealthy sleep duration patterns, regardless of multimorbidity status. On the other hand, when poor sleep health was defined using measures of sleep initiation and daytime sleepiness, smaller prevalence estimates were obtained compared to the index measures**.** Appendix D presents age and sex specific prevalence estimates of poor sleep health by multimorbidity status, measured using the additive and pooled indices. The estimates for both sex and age groups were found to be comparable across the two indices. However, the pooled index identified a slightly higher number of participants with poor sleep patterns in the 45-54 age group (36.7% to 30.5%) and among females (32.3% to 28.7%) compared to the additive index.

Table 3-2. Prevalence of poor sleep health by multimorbidity status.

Variable	**Have Multimorbidity (n, %)**	**Do not Have Multimorbidity (n, %)**
Total	5181 (100.0)	20816 (100.0)
Additive	1271 (26.3)	3438 (14.6)
Pooled	1400 (28.8)	3796 (18.8)
Duration	2360 (45.8)	8133 (40.4)
Quality	1630 (34.1)	4934 (24.8)
Initiation	1113 (24.0)	2846 (14.9)
Maintenance	1452 (29.4)	4686 (23.4)
Daytime sleepiness	756 (14.0)	1486 (6.9)
Snoring	1695 (34.1)	5547 (26.8)

*Percentages (%) are estimated using inflation weights.

3.4 Discussion

Five sleep measures were combined into indices using two methods in this large prospective cohort of middle-aged to older Canadian adults. The indices incorporated sleep duration, quality, initiation, maintenance, and excessive daytime sleepiness.

Women displayed poorer sleep patterns, with significantly greater complaints across all sleep measures except snoring. A greater proportion of men tended to experience snoring; however, it was determined that snoring was a measure of a construct separate from sleep health. This is supported by the pairwise correlations, in which snoring displayed small correlations with the other sleep measures ($\tau < 0.10$) and improved Cronbach alpha value after snoring's exclusion. Ultimately, a total of 25,997 participants were included in each index. The indices are summarizing devices that provided more consistent prevalence estimates of sleep health in a population with multimorbidity than individual component measures.

The individual measures may be subject to measurement error and bias, contributing to the possible over- or underestimation of the true prevalence of poor sleep health. For example, using the self-reported average sleep duration over the past month, 46% of individuals with multimorbidity had poor sleep health. This value is highly subject to recall bias, leading to an overestimation of poor sleep health prevalence in the population if reliant solely on this measure. The potential volatility of using individual measures of sleep health compared to composite measures leads to greater variability in the prevalence estimates over time or across different populations. The variability can make it difficult to reliably compare estimates of sleep health across different studies or populations. Further, individual measures miss the broader context of sleep health compared to composite measures, which consider multiple aspects of sleep and provide a more comprehensive assessment.

The additive and pooled indexes are valuable tools for summarizing sleep health information with their respective strengths and weaknesses, making the comparison of the two methodologies of interest. The major differences in the indices are how they combine the sleep health variables and how they are interpreted. The additive index synthesizes the five source variables using each item's dichotomization, potentially losing information in the original measurement scales. Alternatively, the pooled index takes the source variables' Z-scores, retaining the original scales' content validity.[11–14] The simplicity of the additive approach is beneficial for interpretation and comparison purposes, as higher scores clearly indicate poorer sleep health. On the other hand, the

pooled index is specific to the population being measured, making the comparison across populations more difficult. The pooled index scores are a scale value interpreted as a participant's position in a distribution relative to other population members at the same moment in time.[11,12,14] A pooled index score could be conveyed as a percentile to address this and facilitate comparisons across populations, given that the scores are standardized to the Z distribution.[11,12,14] Despite their differences, both methods provide a reproducible measure of a latent phenomenon and could be valuable tools for predicting disease progression in older adults.

Various other sleep indices have been employed in research; however, none contain this combination of sleep health measures and have widespread acceptance. Commonly, additive approaches are taken in social sciences when developing indices. Fan et al. (2020) utilized an additive healthy sleep index to measure sleep health in regard to cardiometabolic multimorbidity in the UK Biobank cohort.[24] The internal consistency of this measure, as assessed by Cronbach's alpha or correlation with external measures, has not been reported for this score. Additionally, the authors did not clearly explain the selection of sleep behaviours out of all possible sleep measures. Alternative tools for assessing sleep health with fair reliability, validity and comparisons to external measures, such as the Sleep Hygiene Index, National Sleep Foundation's Sleep Health Index or Buysse's SATED, were not suitable for this study, as the CLSA did not have the necessary information available.[2,10,24]

There are several possible limitations to this study. Firstly, the development of the additive index relied on dichotomizing sleep measures, which may have led to a loss of information. Secondly, the analysis did not consider all sleep behaviours, such as sleep medication use and primary sleep disorders, which might also increase the risk of multimorbidity. The CLSA did not provide detailed information on these factors at the time of the study; further investigation is necessary to assess their potential impact on the findings. Third, the index cut-offs chosen for poor sleep health have yet to be validated. Identifying the ideal cut points depending on context and research questions warrants additional research. Fourth, this study investigated the association between sleep and multimorbidity cross-sectionally, meaning temporality and causality are not captured.

Longitudinal research is required prior to making any conclusions about causation. Lastly, research is required in other populations to replicate and validate the indices. For example, studies of populations with different ethnic backgrounds, age groups and geographical regions would all improve the generalizability of the index.

3.5 Conclusions

This study explored sleep measures suitable for combination into indices through additive and pooled approaches. The sleep measures included in the final indices included sleep duration, quality, initiation, maintenance, and excessive daytime sleepiness. The indices highlighted the greater risk of multimorbidity among people with poor sleep health. The prevalence estimates varied depending on the use of individual sleep measures versus indices, with indices providing an estimate more comprehensive of actual sleep health patterns in the population. The tools proposed in this study may provide a novel and concise method of quantifying Canadian sleep health that could be applied in other research and policy contexts to capture overall sleep health and its potential associations with health outcomes.

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Chapter 4

4 Association between Sleep Health and the Occurrence of Multimorbidity in Middle and Older-aged Adults: Results from the Canadian Longitudinal Study on Aging (CLSA)

4.1 Introduction

Older adults with multimorbidity have poorer health outcomes, decreased quality of life, and increased healthcare utilization compared to the general population.[1–3] Modifiable health factors, such as symptoms of poor sleep, have shown an association with physical and mental conditions in older adults.[4] However, the relationship between sleep health and multimorbidity has yet to be fully understood at the population level. There is scarce evidence examining sleep health in its entirety and not just as its components. Sleep health is a concept that holistically views the elements of the sleep-wake function that influence health, such as quality or duration.[5] The concept can be applied to and is particular to any individual, regardless of the presence of a clinical sleep disorder.[5] Clinical research and behavioural interventions largely aim to improve the health of individuals with clinical sleep disorders, neglecting the impact of non-clinical sleep problems on one's health.

Previous research has shown that the effects of sleep health on health outcomes, such as multimorbidity, differ by age and sex.[6,7] For example, older adults are likely to experience changes in their sleep architecture and medical comorbidity that result in poor sleep health characterized by abnormal sleep durations, poor sleep quality, sleepiness, and insomnia symptoms (difficulties falling or staying asleep).[8] Additionally, women have been shown to have a higher risk of poor sleep compared to men, possibly due to hormonal changes during the menopausal transition as well as differences in social roles and stressors.[9] The association between sleep and multimorbidity is made more complex by the bidirectional relationship between poor sleep health and multimorbidity. Individuals with multimorbidity are more likely to experience poor sleep, characterized by factors such as short sleep duration and poor sleep quality.[6] Conversely, poor sleep health could also increase the risk of multimorbidity by disrupting physiological and

immunological processes, contributing to the development and progression of chronic medical conditions.[10] However, most studies framing sleep as a risk factor for multimorbidity have been limited to a cross-sectional design.

The feasibility of longitudinal studies of sleep health using objective measures, such as actigraphy or polysomnography, is limited as these methods can be costly and impractical for large-scale studies.[6] Other options, such as the widely used questionnaires PSQI and ESS, have their place in sleep health measurement but cannot be applied to the CLSA cohort due to a lack of available information. Further, these measures have limitations, with the PSQI designed and scaled to access sleep disturbances alongside sleep health and the ESS designed to measure daytime sleepiness exclusively.[5,11,12] Indices for gauging sleep health that offer reasonable reliability and validity, such as the National Sleep Foundation's Sleep Health Index or Buysse's SATED, were not applicable for this study due to the unavailability of required information within the CLSA dataset.[5,13] The indices generated in Chapter 3 provide a solution to these issues by providing a comprehensive assessment of overall sleep health by including various sleep-related variables such as sleep duration, initiation, maintenance, and excessive daytime sleepiness. This allows for a better understanding of the relationship between sleep health and multimorbidity and can inform interventions and strategies to improve the overall health and well-being of individuals with multiple chronic conditions.

The objective of this chapter is to address sleep as a potential risk factor for multimorbidity using longitudinal population-based data from the CLSA and sleep health indices. Given the high prevalence of multimorbidity and poor sleep health among older adults, it is important to better understand the potential relationship between these two conditions. Exploring and comprehending this association can lead to the identification of effective interventions to improve sleep and related health outcomes, including multimorbidity.

4.2 Methods

4.2.1 Data Source and Study Setting

Baseline and first follow-up data collected between 2010 and 2018 were obtained from the CLSA, a research platform collecting data from a cohort of over 50,000 Canadian women and men aged 45 to 85 years.[14] The lower age limit of 45 years was chosen to enable the study of health trajectories across the adult lifespan and the identification of determinants that contribute to the aging process.[14] Participants will be followed through multiple rounds of data collection, which will occur every 3 years for 20 years or until death.[14] The sample excluded those living in the three Canadian territories, certain remote areas or on federal First Nations reserves and settlements, full-time members of the Canadian Armed Forces, currently living in long-term care institutions (i.e. those providing 24-hour nursing care), unable to respond in either English or French, or cognitively impaired.[15]

The CLSA utilized several sampling frames to ensure national representativeness, such as provincial health registries, random digit dialling, targeting sampling of underrepresented populations and the Quebec Longitudinal Study on Nutrition and Aging (NuAge).[15] Stratified sampling based on age and sex was used to recruit participants into either the Tracking (n=21,241) or Comprehensive (n=30,097) cohort.[15] The present study was a secondary analysis of only the Comprehensive cohort, which collected complete data on physiological, psychosocial and sleep health variables. Participants provided informed consent to an at home computer-assisted telephone and face-to-face interviews, physical assessments, and provision of biological samples at a data collection center.[15] Due to the required in-person assessments, this cohort only included individuals residing within 25 to 50 kilometres of one of the 11 data collection sites across 7 provinces.[15] The 7 provinces included in the Comprehensive cohort are Alberta, British Columbia, Manitoba, Newfoundland and Labrador, Nova Scotia, Ontario, and Quebec.[15] Approval was obtained from the CLSA for data access (Application 190247), and ethics approval was obtained from the Western University Health Sciences Research Ethics Board (Project 112140).

4.2.2 Definition of Multimorbidity

Multimorbidity, the primary outcome of interest, was operationalized using the public health definition as the co-occurrence of two or more (MM2+) chronic conditions from a list of 5 major disease categories. The classification system used in the current study is based on the definition previously implemented by Wilk et al. (2021) and established by the Public Health Agency of Canada (PHAC).[16–18] The public health definition included cardiovascular disease, cancer (ever had), chronic respiratory disease (asthma and/or chronic obstructive pulmonary disease), diabetes, and mental illnesses (mood and/or anxiety disorders).[16–18] The CLSA participants self-reported the presence of chronic conditions diagnosed by a healthcare professional that was expected to last or had lasted 6 or more months ("Has a doctor ever told you that you had…?"). A count variable was created to summarize the number of chronic conditions for each participant. The count variable was used to create a binary variable representing multimorbidity using the cut-off of two or more diseases. The resulting dichotomous multimorbidity variable classified participants as either with or without multimorbidity.

4.2.3 Factors Associated with Multimorbidity

4.2.3.1 Covariates

Sociodemographic variables with potential association with sleep or multimorbidity were examined. In any analyses of CLSA data, the CLSA recommends that the covariates sex, age, and highest education level are adjusted for in the analysis.[15] Sex is a binary variable coded as 'male' or 'female'. Participants were asked for their date of birth and then grouped into four age categories (45–54 years, 55– 64 years, 65–74 years, and 75-85 years). The reported highest education level attained was grouped into four categories: less than secondary school, secondary school, some post-secondary education, and a post-secondary degree and/or diploma. Other sociodemographic variables used were ethnicity and annual household income. The ethnicity was represented as a binary variable (White or Ethnic Minority) due to a large proportion of Canadians identifying as White. The racial identities captured by 'Ethnic Minority' include Aboriginal, Arab, Black, Chinese, Filipino, Japanese, Korean, Latin American,

South Asian, Southeast Asian, West Asian, multiple racial origins and others. The annual household income measured in Canadian dollars was recorded as an ordinal variable with 5 levels (<$20,000, $20,000-49,999, $50,000-99,999, $100,000-149,999, $150,000 or more).

The behavioural variables of alcohol consumption and smoking status were included in the model. Participants were categorized in terms of their alcohol consumption frequency in the past year as a Never Drinker (Lifelong abstainer), Former Drinker (Has consumed at least one drink but not during the past year), Infrequent Drinker (Less than once a month), Occasional Drinker (At least once a month and up to once a week), or Regular Drinker (At least 2-3 times a week and up to every day). Similarly, smoking status was classified as Never Smokers (Never smoked a whole cigarette), Former Smokers (At least 1 whole cigarette, but current Non-Smoker), Occasional Smoker (Less than 100 cigarettes in lifetime, either never or formerly a Daily Smoker), and Daily Smoker.

The physical health variables included physical activity measured using the Physical Activity Scale for the Elderly (PASE), body mass index (BMI) and hypertension. The PASE questionnaire is a valid and reliable instrument that combines information on older adults' engagement with leisure, household, and occupational activities to produce an overall physical activity score.[19] Participants were asked whether they engaged in a standardized set of activities over the past seven days and the frequency and time spent with said activity to generate a weighted score for each item.[19] The scores were summed to produce a total score, which was divided into quintiles, with higher scores indicating higher levels of physical activity.[19,20] The BMI, calculated using measured height and weight, was categorized into Underweight (BMI less than 18.5), Normal (BMIs 18.5 to 24.9), Overweight (BMIs 25 to 29.9) and Obese (BMI 30 and over), according to the Canadian Guidelines for Body Weight Classification in Adults.[21] Participants were classified as either with or without hypertension for regression analyses. Hypertension was defined as a self-report of physician diagnosis, a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg or taking medication for hypertension.[22] In descriptive tables, those with hypertension were further

categorized as aware or not aware. Participants who self-reported their hypertension status or took hypertension medication were classified as ‘aware.’ Among aware participants, those with a systolic of <140 mmHg and diastolic blood pressure of <90mm Hg were labelled as ‘controlled.’

4.2.3.2 Sleep Measures

Questionnaires were administered at baseline to collect data on several sleep variables, including duration, quality, initiation, maintenance, and excessive daytime sleepiness. Sleep duration was categorized based on self-reported average hours slept per night over the past month as Short (<7h), Normal (7-9h) and Long (>9h) for adults under 65 years and as Short (<7h), Normal (7-8h) and Long (>8h) for adults aged 65 years and over, in accordance with National Sleep Foundation guidelines.[23] Sleep quality was measured using the question “How satisfied or dissatisfied are you with your current sleep pattern?” with the possible responses of (i) Very dissatisfied, (ii) Dissatisfied, (iii) Neutral, (iv) Satisfied, or (v) Very satisfied. The frequency of issues with sleep initiation, maintenance and excessive daytime sleepiness was assessed using the questions “Over the last month, how often did it take you more than 30 minutes to fall asleep?”, “Over the last month, how often did you wake in the middle of the night or too early in the morning and found it difficult to fall asleep again?”, and “Over the last month, how often do you find it difficult to stay awake during your normal waking hours when you want to?”, respectively. The possible responses were: (i) Never, (ii) Less than once per week, (iii) Once or twice a week, (iv) 3-5 times per week, or (v) 6-7 times per week.

4.2.4 Sleep Indices

The five items included in the sleep indices were duration, quality, initiation, maintenance, and excessive daytime sleepiness. Only participants with complete data on the component variables were included in the index calculation. Specific details about the variable selection and index construction were provided in Chapter 3.

The additive index used binary variables, with 0 indicating 'low-risk' behaviours and 1 indicating 'high-risk' behaviours. Low-risk factors included 6-8 hours of sleep per day, satisfaction with sleep quality, and infrequent issues with sleep initiation, maintenance, or excessive daytime sleepiness. The index ranged from 0 to 5, with lower

scores indicating better sleep health. Participants with scores 4 and 5 were grouped together in subsequent analyses due to the low number of participants with these scores.

The pooled index combined the sleep factors into a single index score, with lower scores indicating better sleep health.[24–27] The ordinal and binary scales were treated as continuous in the calculation. Then at baseline, each sleep variable was standardized by calculating Z-scores, and the arithmetic mean of the Z-scores was used to calculate the pooled sleep index score for each participant.[24–27]

4.2.5 Statistical Analysis

4.2.5.1 Statistical Software and Survey Analysis

All analyses were performed using Stata Version 17.[28] The complex sampling design implemented by the CLSA suggests that the probability of selecting and including individuals from different population subgroups is unequal and must be accounted for to provide accurate estimates.[3] Thus, survey analysis using weighting was performed to reduce the effects of selection bias introduced by sampling procedures and improve generalizability. In accordance with CLSA recommendations, the descriptive and regression analyses were weighted by inflation (trimmed) and analytic (rescaled) weights, respectively.[15] The geographic strata representing each province included in the Comprehensive cohort were specified in the software.[29] The precise adjusted standard errors reflecting the complex survey design were computed using the Taylor series linearization method in Stata.[29] Lastly, single primary sampling unit (PSU) strata were assumed to have no contribution to the variance by specifying the “certainty” option.[29]

4.2.5.2 Data Analyses

Descriptive statistics were computed for all demographic and sleep variables. The categorical variables at baseline were expressed as unweighted counts and weighted percentages. The frequency of missing values for all variables of interest was also examined. Any responses for categorical or binary variables as “Don’t know” or “Refused” were treated as missing values and presented as unweighted counts and unweighted percentages. The characteristics of excluded and included individuals were

compared, and differences in proportions greater than 10% were considered potentially significant.

Weighted hierarchical multivariable logistic regression models were constructed to estimate odds ratios (ORs) with associated 95% confidence intervals (CI) for each model. Tests were two-sided with a significance level of 0.05 using adjusted Wald tests. Variables were hierarchically entered into the model. The pre-determined iterations in which predictor variables were entered into the model are listed in Table 4-1. The Crude Model contained the covariates age and sex, Model 1 added sociodemographic variables, Model 2 included behavioural and, and Model 3 incorporated physical health variables. The hierarchical models were repeated using the additive and pooled indexes as key predictors. In additive index models, tests for linear trend were conducted using ANOVA-style tests. Additional regression models using individual sleep measures and stratified analysis based on age and sex were conducted to compare the performance of the indices among different demographic groups.

Table 4-1. Hierarchical Models.

Crude	Age and sex
Model 1	Sociodemographic Factors (Ethnicity, annual household income, education)
Model 2	Behavioural Factors (Smoking status, alcohol consumption)
Model 3	Physical Health Factors (PASE score, BMI, hypertension)

Model assumptions for the multivariable logistic models were tested. Independence of errors was assumed, and linearity of the logit was not of concern as the model has no continuous variables. The absence of multicollinearity, otherwise known as redundancy amongst the independent variables, was tested using the Variance Inflation Factor (VIF). Variables with a VIF greater than 10 were not included in the analysis. Standardized Pearson residual plots were constructed to visualize any outliers, influential points were detected using beta coefficients, and no points of concern were detected. The model fit was assessed using Hosmer-Lemeshow goodness-of-fit tests.

4.2.5.3 Sensitivity Analyses

A sensitivity analysis was conducted in which participants with probable sleep disorders were excluded since this study aims to address the relationship between non-clinical aspects of sleep health and multimorbidity. The CLSA did not ask participants to self-report clinical sleep conditions or sleep medication use, so indicators for probable cases of clinical sleep disorders of insomnia and sleep apnea were generated and adjusted for in the present work. Probable insomnia disorder was classified as experiencing difficulties with sleep onset or maintenance >3 times per week with associated functional impairment (i.e. sleep problems were self-rated as interfering with daytime function "much" or "very much").[6] Participants were identified with possible sleep apnea if they responded 'Yes' to "Has anyone ever observed you stop breathing in your sleep?".[6]

4.2.5.4 Missing Data

Final models for the additive and pooled indices were rerun using multiple imputation to mitigate the potential for selection bias that may have resulted from the listwise exclusion of cases with missing data. The data were assumed to be missing at random (MAR), as the missingness of variables can be predicted using other variables within the dataset.[30] The multivariate imputation by chained equations (MICE) approach was taken for multiple imputation, using all covariates in the multivariable models as auxiliary variables.[31] The number of imputed datasets equalled the proportion of missing cases (11%). A total of 10 randomly imputed datasets were created to determine if missingness introduced bias into the results.[31]

4.3 Results

4.3.1 Sample Characteristics

There were 30,097 participants in the CLSA Comprehensive cohort baseline. The 6,226 cases with prevalent multimorbidity (MM2+) were excluded to create an inception cohort at risk for the outcome. Of these respondents, those who did not participate in the follow-up survey were excluded (n=1,612). After relevant exclusions and listwise deletion of those missing data on sleep and other variables of interest (n=2,361), 19,898

(66.1%) participants remained in the sample with complete data. Compared to the complete data group, the excluded group (n=10,199) had a lower proportion of younger individuals (45-54 years), regular drinkers, and those without hypertension and a greater number of obese individuals (Appendix E).

Table 4-2 displays participant characteristics of the analytic sample at baseline. After applying weights to the sample, most participants were in the 45–54 year age group (44.0%). An almost equal number of males and females were included. The majority identified as White (90.1%), had a post-secondary degree or diploma (66.2%), and had a household income above $20,000 (95.0%). Regarding substance use, most of the cohort self-identified as former smokers (57.8%) and regular drinkers (48.2%). After weighting, slightly more participants scored in the highest quintile of PASE (23.8%) compared to the lowest level (17.8%). Very few participants' BMI indicated they were underweight (0.9%), with most being overweight or obese (39.9% and 28.1%, respectively). Hypertension was prevalent (35.3%) in the cohort. Among 7657 participants with hypertension, 1287 (17%) were unaware they had hypertension. Of the 6338 aware of their hypertension status, only 4723 (74.5%) had controlled hypertension. At baseline, the most prevalent chronic condition was mental illness (13.6%), followed by respiratory disease (9.5%), diabetes (8.9%), cancer (7.3%) and lastly, cardiovascular disease (5.2%). At follow-up, 1,766 participants (8.9%) had developed two or more diseases and were living with multimorbidity.

Table 4-2. Characteristics of Included Participants.

Baseline Characteristics	**n**	**%**	**Missing, n (%)**
Total	19898	100	
Age (Years)			0
45-54	5745	44.0	
55-64	6785	30.2	
65-74	4539	16.7	
75-85	2829	9.0	
Sex			0
Female	9898	50.5	
Male	10000	49.5	
Ethnicity			176 (0.8)

White	18373	90.1	
Ethnic Minority Group	1525	9.9	
Annual Household Income			1,360 (6.1)
<20000	797	5.0	
20000-49999	3926	19.4	
50000-99999	7058	33.7	
100000-149999	4250	21.9	
>150000	3867	20.1	
Education			32 (0.1)
Less than secondary school	815	13.9	
Secondary school	1720	11.0	
Some post-secondary	1356	8.9	
Post-secondary degree/diploma	16007	66.2	
Smoking Status			120 (0.5)
Daily smoker	1172	8.5	
Occasional smoker	321	2.1	
Former Smoker	11837	57.8	
Never Smoker	6568	31.7	
Alcohol Consumption			5 (0.02)
Regular drinker	9947	48.2	
Occasional drinker	5476	26.0	
Infrequent drinker	2181	11.7	
Former Drinker	1881	11.7	
Never drinker	413	2.3	
PASE Score (Quintiles)			299 (1.3)
$P \leq 20$	3847	17.8	
$20 < P \leq 40$	3905	17.3	
$40 < P \leq 60$	3984	20.3	
$60 < P \leq 80$	4080	20.8	
$P > 80$	4082	23.8	
BMI			329 (1.5)
Underweight	138	0.9	
Normal	6292	31.1	
Overweight	8191	39.9	
Obese	5277	28.1	
Hypertension			0
No	12241	64.7	

Yes	7657	35.3	
Not Aware	1287	7.2	
Aware	6338	28.2	
Controlled	4723	20.4	
Not controlled	1615	7.6	
Chronic Conditions			
Cancer	1755	7.3	74 (0.3)
Cardiovascular Disease	1097	5.2	158 (0.7)
Diabetes	1754	8.9	85 (0.4)
Respiratory Disease	1799	9.5	152 (0.7)
Mental Illness	2451	13.6	103 (0.5)
Multimorbidity			0
Follow-up MM2+	1766	8.9	

*Unweighted n's and missingness, percentages (%) are estimated using inflation weights and may not total 100% due to rounding error.

4.3.2 Regression

The multivariable regression analyses for multimorbidity incidence at follow-up regressed on sleep indices are presented in Tables 4-3 and 4-4 for additive and pooled indices, respectively. Each index was tested in four hierarchical regression models, and all displayed a significant F-statistic ($p<0.001$).

The four hierarchical regression models consistently indicated that the risk of incident multimorbidity increased linearly with sleep scores. The sleep estimates remained stable across models, as additive index scores except 1 resulted in significantly higher odds of multimorbidity compared to a score of 0 in every model. However, adjusting for other variables independently associated with multimorbidity attenuated the initial association between sleep and multimorbidity, indicating that other factors may have confounded the observed relationship. The largest effect size was observed in the crude model at a sleep score of 4-5 of 1.88 (95% CI: 1.43, 2.47). As covariates were added to the model, the association was slightly reduced, with Model 1 and Model 2 reporting odds ratios of 1.73 (95% CI: 1.18, 2.03) and 1.64 (95% CI: 1.25, 2.15), respectively, for the highest scoring participants. In the final model (Model 3), those with a sleep score of 4-5 displayed 1.54 (95% CI: 1.18, 2.03) higher odds of multimorbidity compared to those with a sleep score of 0.

A notable change across the models is that after adjustment for physical health variables in Model 3, older age (65-74 and 75-85 years) was no longer strongly associated with multimorbidity. This finding suggests that PASE scores, BMI, or hypertension may have confounded the association between age and multimorbidity. Those in the third (OR: 0.61; 95% CI: 0.53, 0.82), fourth (OR: 0.72; 95% CI: 0.55, 0.93), and fifth (OR: 0.49; 95% CI: 0.37, 0.63) quartiles of PASE scores were less likely to develop multimorbidity compared to those with the lowest physical activity score. Those with overweight (OR:1.27; 95% CI: 1.06, 1.54) and obese (OR:1.98; 95% CI: 1.62, 2.42) BMIs were more likely to develop multimorbidity. Further, results showed that individuals with hypertension were more likely to develop multimorbidity (OR: 1.35; 95% CI: 1.16, 1.58) than those without hypertension. Lastly, in the fully adjusted model, smoking daily (OR: 2.20; 95% CI: 1.66, 2.91), occasionally (OR: 2.21; 95% CI: 1.15, 4.26), or formerly (OR: 1.31; 95% CI: 1.11, 1.53) was associated with multimorbidity.

Table 4-3. Hierarchical Regression Analysis of Multimorbidity using the Additive Index.

	Crude			**Model 1**			**Model 2**			**Model 3**		
Variable	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Additive Index, 0 (Ref)												
1	1.18	0.98, 1.42	0.081	1.15	0.96, 1.39	0.137	1.11	0.93, 1.34	0.252	1.11	0.92, 1.34	0.281
2	1.53	1.21, 1.93	<0.001	1.50	1.18, 1.90	0.001	1.48	1.18, 1.87	0.001	1.42	1.13, 1.79	0.002
3	1.54	1.24, 1.92	<0.001	1.50	1.21, 1.87	<0.001	1.47	1.18, 1.82	<0.001	1.40	1.13, 1.74	0.002
4-5	1.88	1.43, 2.47	<0.001	1.73	1.32, 2.27	<0.001	1.64	1.25, 2.15	<0.001	1.54	1.18, 2.03	0.002
Age, 45-54 (Ref)												
55-64	1.27	1.05, 1.53	0.014	1.17	0.96, 1.43	0.112	1.20	0.99, 1.46	0.063	1.02	0.83, 1.25	0.839
65-74	1.84	1.51, 2.26	<0.001	1.52	1.21, 1.91	<0.001	1.67	1.34, 2.09	<0.001	1.28	1.00, 1.63	0.046
75-85	1.86	1.49, 2.33	<0.001	1.44	1.20, 1.87	0.008	1.64	1.27, 2.12	<0.001	1.24	0.94, 1.65	0.129
Sex, Female (Ref)												
Male	0.93	0.80, 1.07	0.317	0.97	0.83, 1.12	0.655	0.97	0.84, 1.12	0.674	0.98	0.84, 1.14	0.745
Ethnicity, White (Ref)												
Ethnic minority group				0.93	0.71, 1.22	0.599	0.89	0.68, 1.18	0.433	0.91	0.69, 1.20	0.497
Annual Household Income, <20000 (Ref)												
20000-49999				0.90	0.64, 1.28	0.572	0.97	0.69, 1.35	0.851	1.07	0.76, 1.49	0.700
50000-99999				0.73	0.51, 1.06	0.098	0.85	0.60, 1.21	0.368	0.98	0.69, 1.39	0.895
100000-149999				0.58	0.38, 0.88	0.010	0.70	0.47, 1.05	0.088	0.84	0.56, 1.25	0.384
>150000				0.55	0.37, 0.81	0.003	0.70	0.48, 1.03	0.073	0.87	0.59, 1.28	0.472
Education, Less than secondary school (Ref)												
Secondary school				0.79	0.55, 1.14	0.213	0.84	0.59, 1.20	0.339	0.90	0.64, 1.28	0.562
Some post-secondary				1.07	0.73, 1.56	0.733	1.15	0.80, 1.65	0.463	1.25	0.87, 1.79	0.222
Post-secondary degree/diploma				0.83	0.59, 1.17	0.286	0.93	0.68, 1.29	0.676	1.05	0.77, 1.44	0.771

Smoking Status, Never smoker (Ref)												
Daily smoker							2.17	1.64, 2.87	<0.001	2.20	1.66, 2.91	<0.001
Occasional smoker							2.17	1.11, 4.22	0.023	2.21	1.15, 4.26	0.018
Former smoker							1.35	1.15, 1.59	<0.001	1.31	1.11, 1.53	<0.001
Alcohol Consumption, Never drinker (Ref)												
Regular drinker							0.86	0.56, 1.33	0.491	0.95	0.62, 1.47	0.822
Occasional drinker							0.87	0.56, 1.35	0.538	0.90	0.58, 1.39	0.620
Infrequent drinker							1.38	0.88, 2.18	0.161	1.37	0.87, 2.15	0.176
Former drinker							1.34	0.84, 2.12	0.221	1.35	0.85, 2.13	0.208
PASE Score (Quintiles), $P \leq 20$ (Ref)												
$20 < P \leq 40$										0.87	0.71, 1.08	0.201
$40 < P \leq 60$										0.61	0.53, 0.82	<0.001
$60 < P \leq 80$										0.72	0.55, 0.93	0.010
$P > 80$										0.49	0.37, 0.63	<0.001
BMI, Normal (Ref)												
Underweight										2.10	0.96, 4.63	0.065
Overweight										1.27	1.06, 1.54	0.012
Obese										1.98	1.62, 2.42	<0.001
Hypertension, No (Ref)												
Yes										1.35	1.16, 1.58	<0.001

*Analytic sampling weights applied

The pooled index scores were consistently significantly associated with multimorbidity throughout the different models. Similar to the additive index, incremental adjustment for factors attenuated the relationship between the pooled index and multimorbidity. However, unlike the additive index, the reduction was slight across models. In the crude model, the odds of multimorbidity increased by 1.43 (95% CI: 1.29, 1.59) for every 1-point increase in the pooled index score. Models 1 and 2 displayed odds ratios of 1.38 (95% CI: 1.25, 1.54) and 1.36 (95% CI: 1.23, 1.51). Finally in Model 3, the odds of multimorbidity increased by 1.32 (95% CI: 1.19, 1.47) per corresponding increase in pooled index score. Other predictors exhibited consistent patterns in the additive index models, as no variation in which predictors remained significant in the fully adjusted model. Older age was no longer a strong predictor of multimorbidity after adjustment for physical health variables. Daily (OR: 2.18; 95% CI: 1.65, 2.89), occasionally (OR: 2.19; 95% CI: 1.13, 4.23) or formerly smoking (OR: 1.31; 95% CI: 1.11, 1.53) were associated with multimorbidity. Again, the third (OR: 0.66; 95% CI: 0.53, 0.82), fourth (OR: 0.72; 95% CI: 0.55, 0.93) and fifth (OR: 0.49; 95% CI: 0.38, 0.64) quantiles of PASE are negatively associated with the outcome. BMI indicating participants are overweight (OR: 1.27; 95% CI: 1.05, 1.53) or obese (OR: 1.99; 95% CI: 1.63, 2.43), and individuals with hypertension (OR: 1.35; 95% CI: 1.16, 1.58) had higher odds of having multimorbidity at follow-up.

Table 4-4. Hierarchical Regression Analysis of Multimorbidity using the Pooled Index.

	Crude			**Model 1**			**Model 2**			**Model 3**		
Variable	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Pooled Index	1.43	1.29, 1.59	<0.001	1.38	1.25, 1.54	<0.001	1.36	1.23, 1.51	<0.001	1.32	1.19, 1.47	<0.001
Age, 45-54 (Ref)												
55-64	1.27	1.05, 1.54	0.013	1.17	0.97, 1.43	0.103	1.21	0.99, 1.47	0.057	1.03	0.84, 1.26	0.784
65-74	1.86	1.52, 2.28	<0.001	1.54	1.23, 1.94	<0.001	1.70	1.36, 2.11	<0.001	1.30	1.02, 1.65	0.032
75-85	1.88	1.50, 2.35	<0.001	1.46	1.12, 1.90	0.005	1.66	1.29, 2.15	<0.001	1.27	0.96, 1.67	0.097
Sex, Female (Ref)												
Male	0.94	0.81, 1.08	0.370	0.97	0.84, 1.13	0.711	0.97	0.84, 1.13	0.721	0.98	0.84, 1.14	0.773
Ethnicity, White (Ref)												
Ethnic minority group				0.93	0.70, 1.22	0.591	0.89	0.67, 1.18	0.422	0.91	0.69, 1.20	0.486
Annual Household Income, <20000 (Ref)												
20000-49999				0.92	0.64, 1.30	0.622	0.98	0.70, 1.38	0.924	1.08	0.77, 1.51	0.651
50000-99999				0.74	0.51, 1.08	0.116	0.87	0.61, 1.24	0.427	0.99	0.70, 1.41	0.963
100000-149999				0.59	0.39, 0.90	0.014	0.72	0.48, 1.08	0.114	0.85	0.57, 1.27	0.435
>150000				0.56	0.38, 0.84	0.005	0.72	0.49, 1.07	0.104	0.89	0.60, 1.31	0.556
Education, Less than secondary school (Ref)												
Secondary school				0.80	0.56, 1.15	0.236	0.85	0.60, 1.21	0.374	0.91	0.65, 1.29	0.600
Some post-secondary				1.07	0.73, 1.56	0.733	1.14	0.79, 1.65	0.470	1.25	0.87, 1.79	0.227
Post-secondary degree/diploma				0.83	0.59, 1.17	0.295	0.94	0.68, 1.29	0.690	1.05	0.77, 1.44	0.757
Smoking Status, Never smoker (Ref)												
Daily smoker							2.16	1.63, 2.86	<0.001	2.18	1.65, 2.89	<0.001
Occasional smoker							2.14	1.09, 4.19	0.027	2.19	1.13, 4.23	0.020
Former smoker							1.35	1.15, 1.59	<0.001	1.31	1.11, 1.53	0.001

Alcohol Consumption, Never drinker (Ref)												
Regular drinker							0.86	0.55, 1.32	0.482	0.95	0.61, 1.47	0.815
Occasional drinker							0.87	0.56, 1.34	0.520	0.89	0.58, 1.38	0.604
Infrequent drinker							1.38	0.87, 2.18	0.169	1.36	0.87, 2.15	0.182
Former drinker							1.33	0.84, 2.12	0.225	1.34	0.85, 2.13	0.212
PASE Score (Quintiles), P ≤ 20 (Ref)												
20 < P ≤ 40										0.87	0.71, 1.08	0.216
40 < P ≤ 60										0.66	0.53, 0.82	<0.001
60 < P ≤ 80										0.72	0.55, 0.93	0.012
P > 80										0.49	0.38, 0.64	<0.001
BMI, Normal (Ref)												
Underweight										2.09	0.94, 4.62	0.069
Overweight										1.27	1.05, 1.53	0.012
Obese										1.99	1.63, 2.43	<0.001
Hypertension, No (Ref)												
Yes										1.35	1.16, 1.58	<0.001

*Analytic sampling weights applied.

The combined index scores were more strongly associated with incident multimorbidity than including each sleep factor separately in a regression model. The odds ratios from including the sleep measures simultaneously are shown in Table 4-5. Sleep quality and duration were not associated with the outcome ($p>0.05$). Those with issues with sleep initiation 6-7 times a week had greater odds of multimorbidity (OR: 1.47; 95% CI: 1.11, 1.93). Sleep maintenance showed a weak effect in those who experienced issues less than once per week (OR: 0.82; 95% CI: 0.67, 1.00) and 3-5 times a week (OR: 0.76; 95% CI: 0.58, 0.98). Daytime sleepiness had a positive association for 3-5 times a week (OR: 1.73; 95% CI: 1.25, 2.37) and 6-7 times a week (OR: 2.04; 95% CI: 1.47, 2.83).

Table 4-5. Regression Analysis of Multimorbidity using Individual Sleep Measures.

Individual Sleep Measures			
Variable	**OR**	**95% CI**	***P***
Duration, Normal (Ref)			
Short	0.99	0.66, 1.49	0.997
Long	0.99	0.67, 1.46	0.996
Quality, Neutral (Ref)			
Very satisfied	0.84	0.64, 1.11	0.215
Satisfied	0.88	0.69, 1.11	0.267
Dissatisfied	1.02	0.80, 1.32	0.851
Very dissatisfied	1.16	0.79, 1.71	0.451
Initiation, Never (Ref)			
Less than once per week	1.10	0.91, 1.32	0.352
Once or twice per week	1.11	0.88, 1.41	0.380
3-5 times per week	1.05	0.75, 1.48	0.778
6-7 times per week	1.47	1.11, 1.93	0.006
Maintenance, Never (Ref)			
Less than once per week	0.82	0.67, 1.00	0.049
Once or twice per week	0.95	0.74, 1.22	0.684
3-5 times per week	0.76	0.58, 0.98	0.035
6-7 times per week	0.92	0.70, 1.20	0.532
Daytime Sleepiness, Never (Ref)			
Less than once per week	1.19	0.98, 1.45	0.087
Once or twice per week	1.16	0.91, 1.46	0.206
3-5 times per week	1.73	1.25, 2.37	0.001
6-7 times per week	2.04	1.47, 2.83	<0.001

*Analytic sampling weights applied. Coefficients not shown but analyses adjusted for all variables included in fully adjusted models.

The sex-stratified analyses results are presented in Table 4-6. Males displayed a weak linear trend across the additive index (p=0.035) compared to females (p=0.0018). The odd ratios for females on the additive index ranged from moderate to strong effect sizes (Score 2: OR: 1.52; 95% CI: 1.09, 2.10 / Score 3: OR: 1.56; 95% CI: 1.18, 2.07 / Score 4-5: OR: 1.54; 95% CI: 1.08, 2.19). However, both sexes exhibited similar odd ratios when using the pooled index and displayed a strong effect (Males: OR: 1.37; 95% CI: 1.17, 1.60 / Females: OR: 1.30; 95% CI: 1.14, 1.50).

Table 4-6. Sex-Stratified Regression Analysis of Multimorbidity.

	Males			**Females**		
Variable	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Additive Index, 0 (Ref)						
1	1.14	0.88, 1.49	0.331	1.09	0.84, 1.42	0.502
2	1.36	1.00, 1.85	0.048	1.52	1.09, 2.10	0.013
3	1.20	0.87, 1.67	0.276	1.56	1.18, 2.07	0.002
4-5	1.62	1.05, 2.49	0.028	1.54	1.08, 2.19	0.017
Pooled	1.37	1.17, 1.60	<0.001	1.30	1.14, 1.50	<0.001

*Analytic sampling weights applied. Coefficients not shown but analyses adjusted for all variables included in fully adjusted models.

The results from age-stratified analyses are provided in Table 4-7. Following age stratification, a statistically significant relationship between additive index scores and multimorbidity, as indicated by p-values, was not consistently observed across all age groups. However, the additive index had significant linear trends present within the 55-64 and 65-74 year age groups. In contrast, the pooled index reported a strong association with multimorbidity across all age categories (Age 45-54: OR: 1.33; 95% CI: 1.07, 1.64 / Age 55-64: OR: 1.29; 95% CI: 1.09, 1.53 / Age 65-74: OR: 1.39; 95% CI: 1.15, 1.67 / Age 75-85: OR: 1.28; 95% CI: 1.04, 1.59).

Table 4-7. Age-Stratified Regression Analysis of Multimorbidity.

	45-54			55-64			65-74			75-85		
Variable	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Additive Index, 0 (Ref)												
1	1.45	0.98, 2.15	0.062	0.73	0.53, 0.99	0.040	1.10	0.79, 1.52	0.577	1.38	0.93, 2.06	0.114
2	1.31	0.80, 2.14	0.282	1.41	1.01, 1.97	0.045	1.32	0.92, 1.89	0.128	2.29	1.41, 3.73	0.001
3	1.53	1.00, 2.34	0.052	1.16	0.82, 1.64	0.401	1.74	1.15, 2.64	0.009	1.41	0.85, 2.33	0.185
4-5	1.37	0.77, 2.44	0.279	1.65	1.10, 2.48	0.015	1.48	0.89, 2.48	0.134	1.71	0.95, 3.06	0.073
Pooled	1.33	1.07, 1.64	0.009	1.29	1.09, 1.53	0.004	1.39	1.16, 1.67	<0.001	1.28	1.04, 1.59	0.021

*Analytic sampling weights applied. Coefficients not shown but analyses adjusted for all variables included in fully adjusted models.

4.3.3 Sensitivity Analysis

The regression results after excluding those with probable insomnia disorder (n=636) or sleep apnea (n=2559) are presented in Table 4-8. The additive index performed similarly for those with scores of 2 (OR: 1.42; 95% CI: 1.08, 1.87) and 3 (OR: 1.43; 95% CI: 1.11, 1.84) after exclusion. However, those in the highest scoring groups were no longer associated with multimorbidity (OR: 1.13, 95% CI: 0.79, 1.60), suggesting that scoring high on the additive index no longer indicated unhealthy sleep patterns but instead a sleep disorder. The pooled index remained significant after the exclusion, with an odds ratio slightly attenuated but consistent with odds ratio reported prior to exclusion (OR: 1.24; 95% CI: 1.09, 1.39).

Table 4-8. Regression Analysis of Multimorbidity Excluding those with Probable Sleep Disorders.

Probable Sleep Disorders			
Variable	**OR**	**95% CI**	***P***
Additive Index, 0 (Ref)			
1	1.15	0.93, 1.41	0.190
2	1.42	1.08, 1.87	0.013
3	1.43	1.11, 1.84	0.006
4-5	1.13	0.79, 1.60	0.512
Pooled	1.24	1.09, 1.39	0.001

*Analytic sampling weights applied. Coefficients not shown but analyses adjusted for all variables included in fully adjusted models.

4.3.4 Missing Data

The fully adjusted models using the additive and pooled indices were re-run with multiple imputation of missing cases due to listwise exclusion. The imputed parameter estimates are shown in Appendix F and were of similar magnitude and direction.

4.4 Discussion

In this longitudinal analysis of a large nationally representative cohort of Canadians, the association between baseline sleep health and incidence of multimorbidity

at follow-up was measured using two sleep indices. A total of 19,898 community-dwelling middle-aged and older adults were included in the analysis. At follow-up, 8.9% of the participants had developed multimorbidity, defined as having two or more chronic diseases. The results consistently showed that higher scores on the additive and pooled indices at baseline, indicating poorer sleep health, were associated with increased odds of developing multimorbidity over a 3-year follow-up. Participants with additive index scores of 1, 2, 3 and 4-5 had 1.11, 1.42, 1.40 and 1.54 higher odds of developing multimorbidity compared to those with scores of 0, respectively. Additionally, for every 1-point increase in pooled index score, participants had 1.32 higher odds of multimorbidity. These estimates remained stable after the imputation of missing data.

The literature increasingly supports the notion that various dimensions of sleep can serve as modifiable behavioural risk factors that influence health outcomes. Several previous studies have demonstrated that short and long sleep duration, poor sleep quality, difficulties in maintenance and initiation, and daytime sleepiness increase the risk of chronic conditions and multimorbidity.[6,7,32–35] Building upon these previous studies, the five dimensions of sleep health were combined into a comprehensive score. To the best of our knowledge, this is the first study framing sleep health as an index score in relation to multimorbidity. The indexing strategies aim to capture the complex interplay between different aspects of latent variables and their collective influence on health outcomes.

The finding that older adults with poor sleep patterns, as measured by additive or pooled approaches, are more likely to develop multimorbidity is consistent with existing evidence. A cross-sectional study based on CLSA baseline data found that short or long sleep duration and dissatisfaction with sleep quality lead to higher odds of multimorbidity.[6] Similar associations between short sleep duration and multimorbidity were observed in cross-sectional studies of Portuguese adults over 18 years and Luxembourg residents aged 25 to 64 years.[32,36] In a longitudinal study in China, short sleep duration increased the risk of incident multimorbidity during a four-year follow-up period among adults aged 45 years and above.[33] The lack of consistent associations

between long sleep duration and multimorbidity could be due to differences in population age or sleep duration categorizations within the studies. Cross-sectional studies conducted in Japanese, Cypriot, and Chinese populations have also replicated the association between poor sleep quality and increased odds of multimorbidity.[37–41] Insomnia symptoms and daytime tiredness have been shown to increase the odds of multiple chronic conditions in older adults from the KORA Age Study.[7] Similarly, a significantly reduced incidence of cardiometabolic multimorbidity was seen among participants who reported no frequent daytime sleepiness in the UK Biobank study.[35] Collectively, the evidence from these studies supports the selection of sleep factors included in the index scores.

Notably, the majority of these studies analyzed sleep health measures individually. It would be reasonable to suggest that all aspects of sleep health are synergistically important facets of multimorbidity across populations. However, including all sleep factors individually in the model did not yield consistent results in our study. Only sleep initiation issues (6-7 times per week) and daytime sleepiness (3-5 times a week or more) displayed a highly significant positive association with multimorbidity. This emphasizes the importance of employing indexing methods when investigating multidimensional concepts such as sleep health. The findings of this study support using comprehensive sleep measures to identify individuals at higher risk for the development of multimorbidity. Furthermore, the indices provide a standardized approach that can be implemented in other epidemiological studies, improving the ability to compare health across different populations.

Although both indices show promise in measuring multimorbidity, the pooled index consistently displayed more precise estimates across models that remained highly significant with sequential adjustment of other predictors. The difference in efficiency becomes more apparent when examining the results of age and sex-stratified analysis. In both sexes, the pooled index displayed highly significant associations with multimorbidity. Conversely, the additive index showed a relationship with

multimorbidity among women but a weak relationship in men. Some studies have shown that when using self-report, women report poorer sleep quality than men.[9] Also, it is plausible that poor sleep patterns may have a greater impact on health outcomes among women than men, as suggested by previous studies. For example, stronger associations between sleep deprivation and hypertension risk have been found among women.[42,43] Other studies have indicated that men and women report comparable sleep quality, with no clear sex differences in sleep.[44] These conflicting results in our study suggest that observed sex differences in sleep may partly depend on the methodology used to summarize sleep information.

Similarly, in age-stratified analysis, the pooled index showed that sleep was significantly and positively associated with multimorbidity across all age groups. On the other hand, the additive index did not observe any significant dose-response increases in sleep scores in relation to multimorbidity once age-stratified. The results from the pooled index align with existing literature, indicating that age alone does not fully explain the occurrence of multimorbidity in older adults.[4,45] This implies that stratification by age should not completely nullify the relationship between sleep and multimorbidity. Thus, the pooled effect of sleep provides a more accurate and reliable measurement of the odds of multimorbidity. While the additive sleep index is easier to interpret and may be more useful for identifying specific risk factors for multimorbidity, the pooled index offers a more comprehensive and integrated measure of sleep-related risk.

The exclusion of individuals with probable sleep disorders had a mixed impact on both index scores. The significant relationship with multimorbidity was no longer observed for those in the highest-scoring category of the additive index (scores of 4-5). This suggests that the poorest sleep scores likely reflect a clinical sleep disorder, and the exclusion of the majority of those in this category in sensitivity analyses led to the change in findings. The pooled index odds ratio was attenuated, indicating a weakened association when those with probable insomnia and sleep apnea were excluded. These findings highlight the importance of conducting additional assessments and diagnostic

tests for sleep disorders, particularly for individuals in the highest-scoring categories of both sleep indices. Individuals in these categories likely exhibit clinically defined sleep conditions that require specialized care.

4.4.1 Limitations

There are several limitations to this study. Due to the pre-existing nature of the health database utilized in this study, the secondary analyses were constrained in certain aspects. First, there was missing information on key variables that could confound the association between sleep and multimorbidity, such as information on sleep medication use and sleep disorders. The presence of sleep disorders was estimated to the best of our ability using the framework defined by Nicholson et al. (2020).[6] Further, information from widely employed measures of sleep, such as the PSQI, would have been beneficial for comparison to our sleep indices. Additionally, the sample recruited into the CLSA was predominantly White, highly educated and relatively wealthy. This may limit the generalizability of the results to the general population of middle-aged and older Canadians.

Next, a potential source of bias was the measurement of sleep and chronic conditions through self-report. While self-report methods for both variables have been established as valid and reliable across multiple settings, it is important to recognize the potential misclassification that may occur. Information about those unaware or undiagnosed with chronic conditions at the time of assessment is not possible, causing an underestimation of the disease prevalence in our sample. For example, the issue is evident in the assessment of covariates such as hypertension, where approximately 17% of individuals with hypertension were unaware of their hypertension status. The misclassification of sleep is likely non-differential in regard to multimorbidity status as recall bias affects both groups similarly, attenuating prevalence towards the null and underestimating the true effect of sleep on multimorbidity.

4.5 Conclusions

Overall, this longitudinal analysis of sleep health among approximately 20,000 Canadian middle to older-aged adults found an association between poor sleep health and the development of multimorbidity after statistically controlling several known confounders. Two indexing approaches were taken for sleep health measurement, additive and pooled, and both performed better than the use of sleep factors individually. The pooled index approach appeared to be the more efficient and consistent measurement tool of sleep health, with similar estimates across age and sex-stratified analysis and after sensitivity analysis by removing those with suspected clinical sleep disorders. This study provides a framework for the measurement of sleep health in large population-based studies and highlights the need to explore and bring awareness to the potential long-term health implications of poor sleep patterns.

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Chapter 5

5 Discussion

5.1 Overview

The objective of this chapter is to summarize the research goals, results, and interpretation of the two studies comprising this thesis. It provides a comprehensive discussion of the research and methodological strengths and limitations. This chapter also examines the implications of the findings and highlights future directions for research. Finally, the overall conclusions from this thesis are presented.

5.2 Overall Goal of Thesis

The overall goal of this thesis was to investigate the influence of sleep health on the development of multimorbidity in middle-aged and older Canadian adults. Sleep health, a multidimensional concept that views healthy sleep not as just the absence of a disorder, is a fundamental component of the health and well-being of all individuals.[1,2] Recent evidence indicates that sleep health may contribute as a risk factor for multimorbidity in older adults. Potentially, identifying and intervening in poor sleep health through clinical treatment and adopting lifestyle changes at an earlier stage of adulthood could mitigate harmful declines in health and chronic disease development. The two complementary studies conducted in Chapters 3 and 4 further this goal by developing a new tool to measure sleep health and providing longitudinal evidence that those with poor sleep health experience an increased risk of multimorbidity. In the first cross-sectional study in Chapter 3, two sleep health indices were developed using additive and pooled methods to quantify poor sleep health within the CLSA population effectively. This provided a methodology to estimate the prevalence of poor sleep patterns experienced by middle-aged and older adults at risk of developing multimorbidity more comprehensively than individual sleep factors. These newly developed indices were subsequently utilized in the analysis conducted in the second study. The second study, detailed in Chapter 4, is a

longitudinal analysis to assess whether sleep health may represent a modifiable risk factor for multimorbidity incidence over a 3-year follow-up and describe possible age and sex differences in this association.

5.3 Summary of Main Findings

In Chapter 3, a variable selection process was conducted among the sleep variables of duration, quality, initiation, maintenance, excessive daytime sleepiness, and snoring to determine which measure the latent construct of sleep health and should be retained during index construction. The pairwise correlations were all under 0.5, indicating a reduction in redundancy between index items. However, the correlations that snoring displayed were remarkedly small, with all correlations being less than 0.10. This raised doubt about whether snoring should be included in the index construction. The exclusion of snoring was further supported by an improved Cronbach alpha value from 0.62 to 0.69 with its exclusion. Therefore, the additive and pooled indices consisted of five sleep factors: duration, quality, initiation, maintenance, and daytime sleepiness. The additive index approach treated each factor as binary, with 0 and 1 representing healthy and unhealthy sleep behaviours, respectively. In the pooled index, measurements were combined using the mean of the Z-scores of each sleep factor. The scores for the additive index ranged from 0 to 5, and the pooled index ranged from approximately -1 to 2. Higher scores indicated poorer sleep health for both indices.

The index scores were compared to the use of individual sleep measures by estimating the prevalence of multimorbidity in the baseline CLSA sample. Participants with additive index sleep scores of 3 or greater and pooled index scores in the top quintile were defined as having poor sleep health. Regardless of the sleep measure utilized, individuals living with multimorbidity displayed a higher prevalence of poor sleep patterns. The additive and pooled indices yielded similar prevalence estimates. The additive index estimated that 26.3% of the participants identified with multimorbidity displayed poor sleep patterns, while the pooled index classified a slightly higher

proportion of individuals at 28.8% with poor sleep. The indices yielded more moderate estimates compared to the extremes provided by the individual measures of sleep health. This suggests that the indices could offer a more balanced and representative assessment of overall sleep health in relation to multimorbidity.

In Chapter 4, these indices were tested in a prospective cohort study to determine their association with multimorbidity, and which method is preferable. Hierarchical regression was used in which age and sex, sociodemographic, behavioural, and physical health factors were sequentially added to the model. The odds ratios for both additive and pooled indices were attenuated slightly with additions of covariates. In the fully adjusted model, those with additive index scores of 4-5 displayed 1.54 (95% CI: 1.18, 2.03) higher odds of multimorbidity compared to those with a sleep score of 0. In the fully adjusted pooled model, the odds of multimorbidity increased by 1.32 (95% CI: 1.29, 1.59) for every 1-point increase in the pooled index score. Both indices performed better than using individual sleep factors simultaneously in one model, as doing so resulted in inconsistent and largely insignificant relationships between sleep measures and multimorbidity. Exclusion of those with probable sleep disorders altered the relationship for both indices, with those scoring 4-5 on the additive index reporting an insignificant relationship (OR: 1.13; 95% CI: 0.79, 1.60) and the pooled index becoming attenuated (OR: 1.24; 95% CI: 1.09, 1.39).

Furthermore, in both Chapters 3 and 4, age and sex stratified analysis was conducted. Initial analysis of the sample characteristics in Chapter 3 revealed that multimorbidity varied significantly by age but showed no substantial variation between sexes. The distribution of sleep measures differed significantly by sex, except for sleep duration, and across age groups, except for sleep initiation. The pooled index estimated a slightly higher prevalence of poor sleep health among multimorbid participants in those aged 45 to 54 years (36.7% to 30.5%) and females (32.3% to 28.7%) compared to the additive index. In Chapter 4, the pooled index displayed more precise estimates across models, with narrower confidence intervals, that remained highly significant with sequential

adjustment of other predictors. However, the additive index also performed well in regression models. It was only during age- and sex-stratified analysis that it became more apparent that the pooled index might be the preferential method. The pooled index displayed strong relationships with multimorbidity after stratifying by age and sex. On the other hand, the additive index only detected a significant relationship in females and did not identify any significant dose-response increases in sleep scores in relation to multimorbidity once age-stratified.

5.4 Strengths and Limitations

There are several notable strengths of the studies in this thesis. The studies benefit from the large sample size of the CLSA, allowing for robust statistical analyses and potential generalizability of findings to the broader population of older Canadian adults. The longitudinal study design enables the examination of sleep health impact on multimorbidity incidence over time, providing valuable insights into the temporal relationship between these factors, unlike previous cross-sectional studies. A significant strength and the focus of the studies was the comprehensive measurement of sleep health through indices encompassing multiple sleep behaviours. The multidimensional approach is particularly important when measuring outcomes such as multimorbidity, as chronic conditions result from the cumulative effects of many co-occurring unfavourable factors. A composite score for sleep helps capture these individual variables while reducing the need for multiple testing and, thus, the potential for error. This is evident in the analysis comparing the composite scores with multiple individual components, in which aggregation consistently improved the efficiency and interpretability of the analysis. Lastly, this study provided a nuanced understanding of age and sex as important demographic factors influencing the relationship through stratified analysis.

There are certain limitations to both studies. The indices were constructed using data available from the CLSA about sleep behaviours, limiting the measurements accessible for study. Information on other key behaviours, such as medication use or sleep disorders,

could alter the components included in the composite scores. Additionally, the information was obtained through self-report, which may vary from information obtained through objective measures. The misclassification from self-report would likely be non-differential and underestimate the true effect of sleep health on multimorbidity. Further, the items included in the indices may vary across populations and study settings. The indices were developed based on the dependencies between the dimensions, measured using pairwise correlations and Cronbach alpha values, which could be particular to the sample or attributable to confounding factors.[2] A suggestion is to use the outlined framework to develop adaptations of the sleep health indices particular to the specific population.[2] However, context-specific indices would hinder the ability to standardize measures.

The indices themselves have some strengths and limitations to consider. The additive index dichotomized the measures, which may have led to a loss of information, whereas the pooled index uses Z-scores, retaining the content validity of the original scales.[3–6] However, the additive index is easily interpretable and has greater practicality in assessing sleep health, with clear cut-offs indicating poor sleep health. In public health applications, this would be advantageous for clinicians in decision-making, facilitating comparisons over time and populations, and setting public health targets.[2] The continuous pooled index provided greater statistical power. However, it is more difficult to interpret and compare, as a participant's score is their position in a distribution relative to other population members.[3,4,6] To improve interpretability, the pooled index scores can be treated as a percentile, but once again, this is specific to the population being studied.[3,4,6] Additionally, the index cut-offs for poor sleep health are yet to be validated. Determining the optimal threshold values for various contexts and research objectives requires further investigation. Lastly, the scores derived from either index are not informative about specific sleep dimensions an individual struggles with, which can inform intervention. A post hoc analysis must be conducted to obtain this information and determine a preventative strategy based on the individual's unique sleep patterns and needs.[2]

5.5 Directions for Future Research

The findings from Chapters 3 and 4 contribute to efforts to establish sleep as a behavioural modifiable risk factor for multimorbidity. Although research in this field is scarce, this thesis has highlighted that future studies should investigate sleep health and consider using indices when exploring this association. A key consideration for future research is to validate the indices by comparing scores to other established sleep instruments, such as the PSQI or ESS.[7–9] These instruments are effect indicators for the latent variable of sleep health.[9] If the indices are formative indicators of sleep health, one would expect a correlation with these external criteria.[9,10] These analyses were not possible in our studies due to limited sleep behaviour information. Further, the reliability of the indices can be tested in future studies as additional waves of CLSA are released. The repeated measurements of sleep measures can provide trajectories of decline, which can be used to delve deeper into the relationship with multimorbidity.

Another area for consideration is examining the indices' consistency in various settings and populations. While our study offers valuable insights into the sleep patterns of middle-aged and older Canadian adults, there are limitations regarding the generalizability of these findings to other cultural, social, and economic contexts. More culturally informed research steps need to be taken to address sleep health differences in ethnic minorities, which were underrepresented in the CLSA sample. Identifying potential disparities will aid in developing targeted interventions and promoting equitable health outcomes, as undertaking this approach could improve the indices' utility as descriptive tools and measures to detect early declines in health. Early detection of groups at risk for experiencing poor sleep health allows healthcare professionals to intervene at an earlier stage, mitigating the risk of developing multimorbidity and associated health complications later in life. These interventions may include lifestyle modifications, sleep hygiene education, or specialized treatments tailored to individual needs.

5.6 Conclusions

The main objective of this thesis was to explore the association between sleep health and multimorbidity. First, sleep health indices were developed using additive and pooled methodologies. The variables included in the indices were sleep duration, quality, initiation, maintenance, and excessive daytime sleepiness. The prevalence estimates reflected that both indices performed well in identifying poor sleep health in community-dwelling middle-aged and older Canadian adults. Secondly, these indices were compared in their association with multimorbidity in a prospective analysis of the same population. It was determined that those experiencing poorer sleep health were at a statistically significant greater risk of developing multimorbidity. Subsequent stratified analysis found that the pooled index had improved statistical power to detect multimorbidity compared to the additive index. However, the additive index may have better interpretability for public health and clinical purposes. This thesis reflects similar findings to existing literature while contributing insights into the temporal relationship between sleep and multimorbidity. Researchers and clinicians can translate these findings and indices into further research as well as evidence-based interventions and policies that promote better sleep health to prevent chronic condition development.

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Appendices

Appendix A. Comparison of Characteristics of Analytical sample and Individuals Excluded from Chapter 3 Analyses.

Variable	Complete Data (n, %)	Excluded Group (n, %)
Total	25997	4100
Age (Years)		
45-54	**6831 (40.4)**	**764 (30.6)**
55-64	8691 (31.6)	1165 (27.6)
65-74	6228 (17.8)	1074 (21.6)
75-85	**4187 (10.3)**	**1097 (20.2)**
Sex		
Female	12997 (51.5)	2323 (57.7)
Male	13000 (48.5)	1777 (42.3)
Multimorbidity		
Yes	5181 (18.7)	1045 (25.1)
No	20816 (81.3)	3055 (74.9)
Duration		
Short	9613 (38.2)	1628 (40.5)
Normal	15504 (58.6)	2216 (52.2)
Long	880 (3.2)	256 (7.2)
Quality		
Very satisfied	5142 (19.6)	732 (16.9)
Satisfied	10322 (38.9)	1547 (37.6)
Neutral	3969 (15.0)	633 (16.6)
Dissatisfied	5468 (21.5)	930 (22.7)
Very dissatisfied	1096 (5.0)	234 (6.3)
Initiation		
Never	12314 (46.2)	1842 (43.9)
Less than once per week	6648 (26.1)	917 (22.0)
Once or twice per week	3076 (11.1)	492 (11.5)
3-5 times per week	1958 (7.6)	337 (8.6)
6-7 times per week	2001 (9.0)	444 (14.0)
Maintenance		
Never	8547 (33.1)	1473 (35.2)
Less than once per week	7151 (27.7)	998 (24.8)
Once or twice per week	4161 (14.8)	538 (11.8)
3-5 times per week	3120 (12.3)	484 (11.3)

6-7 times per week	3018 (12.2)	572 (17.0)
Daytime Sleepiness		
Never	16084 (64.0)	2449 (63.0)
Less than once per week	5128 (18.8)	762 (17.3)
Once or twice per week	2543 (9.0)	402 (9.5)
3-5 times per week	1288 (4.7)	228 (4.3)
6-7 times per week	954 (3.5)	196 (5.9)
Snoring		
Yes	7242 (28.2)	40 32.2()
No	18755 (71.9)	124 (68.8)

*Proportions estimated using inflation weights.

*Bolded are groups with >10% difference in column proportion.

Appendix B. Distribution of Multimorbidity and Sleep Measures by Sex.

Variable	**Male (n, %)**	**Female (n, %)**	***P***
Total	13000 (100)	12997 (100)	
Multimorbidity			0.0047
Yes	2548 (17.4)	2633 (20.0)	
No	10452 (82.6)	10364 (80.0)	
Duration			0.4338
Short	4762 (38.3)	4851 (3802)	
Normal	7840 (58.9)	7664 (58.3)	
Long	398 (2.9)	482 (3.4)	
Quality			<0.001
Very satisfied	2682 (20.4)	2460 (18.8)	
Satisfied	5423 (40.6)	4899 (37.3)	
Neutral	2049 (15.2)	1920 (14.9)	
Dissatisfied	2438 (19.7)	3030 (23.2)	
Very dissatisfied	408 (4.1)	688 (5.9)	
Initiation			<0.001
Never	6967 (51.3)	5347 (41.5)	
Less than once per week	3255 (25.4)	3393 (26.8)	
Once or twice per week	1309 (9.7)	1767 (12.4)	
3-5 times per week	739 (6.4)	1219 (8.8)	
6-7 times per week	730 (7.3)	1271 (10.6)	
Maintenance			<0.001
Never	4694 (36.5)	3853 (29.8)	
Less than once per week	3669 (28.3)	3482 (27.0)	
Once or twice per week	1952 (13.6)	2209 (15.9)	

3-5 times per week	1365 (11.4)	1755 (13.2)	
6-7 times per week	1320 (10.2)	1698 (14.1)	
Daytime Sleepiness			0.0024
Never	7818 (62.1)	8226 (65.8)	
Less than once per week	2665 (19.4)	2463 (18.2)	
Once or twice per week	1341 (10.1)	1202 (7.9)	
3-5 times per week	650 (4.6)	638 (4.8)	
6-7 times per week	526 (3.8)	428 (3.3)	
Snoring			<0.001
Yes	4454 (34.9)	2788 (21.8)	
No	8546 (65.1)	10209 (78.2)	

*Percentages (%) are estimated using inflation weights and may not total 100% due to rounding error.

Appendix C. Distribution of Multimorbidity and Sleep Measures by Age.

Variable	**45-54 (n, %)**	**55-64 (n, %)**	**65-74 (n, %)**	**75-85 (n, %)**	***P***
Total	6831 (40.4)	8691 (31.6)	6288 (17.8)	4187 (10.3)	
Multimorbidity					<0.001
Yes	815 (11.4)	1688 (22.1)	1513 (23.5)	1165 (28.9)	
No	6016 (88.6)	7003 (77.9)	4775 (76.5)	3022 (71.1)	
Duration					<0.001
Short	2796 (42.1)	3288 (36.7)	2087 (34.1)	1442 (34.9)	
Normal	3981 (57.2)	5275 (61.2)	3828 (59.3)	2420 (55.0)	
Long	54 (0.7)	128 (2.1)	373 (6.7)	325 (10.1)	
Quality					<0.001
Very satisfied	1168 (17.2)	1642 (19.4)	1371 (21.9)	962 (25.4)	
Satisfied	2651 (37.9)	3361 (38.0)	2577 (43.0)	1733 (38.3)	
Neutral	1094 (16.1)	1361 (15.3)	937 (13.4)	577 (13.1)	
Dissatisfied	1590 (23.8)	1930 (21.6)	1176 (17.8)	772 (18.7)	
Very dissatisfied	328 (5.1)	398 (5.7)	227 (3.9)	143 (4.5)	
Initiation					0.0971
Never	3182 (46.0)	4025 (45.5)	3102 (48.5)	2005 (46.0)	
Less than once per week	1761 (26.0)	2240 (26.1)	1596 (25.8)	1051 (26.8)	
Once or twice per week	837 (11.0)	1046 (11.5)	703 (11.3)	490 (9.7)	
3-5 times per week	524 (7.9)	711 (8.6)	423 (6.2)	300 (6.2)	
6-7 times per week	527 (9.1)	669 (8.6)	464 (8.2)	341 (11.2)	
Maintenance					<0.001

Never	2104 (31.0)	2734 (32.0)	2184 (36.2)	1525 (38.6)	
Less than once per week	1908 (27.5)	2392 (28.2)	1765 (28.0)	1086 (26.1)	
Once or twice per week	1153 (15.5)	1458 (15.3)	944 (13.9)	606 (12.3)	
3-5 times per week	885 (14.0)	1085 (12.1)	667 (10.3)	483 (9.9)	
6-7 times per week	781 (12.0)	1022 (12.4)	728 (11.7)	487 (13.0)	
Daytime Sleepiness					<0.001
Never	4109 (62.6)	5378 (63.9)	4050 (67.3)	2547 (64.2)	
Less than once per week	1462 (20.0)	1716 (18.3)	1186 (18.5)	764 (16.6)	
Once or twice per week	744 (10.0)	899 (9.1)	517 (7.3)	383 (7.6)	
3-5 times per week	321 (4.7)	461 (5.2)	286 (3.6)	220 (5.2)	
6-7 times per week	195 (2.8)	237 (3.6)	249 (3.3)	273 (6.6)	
Snoring					<0.001
No	4889 (72.3)	5935 (67.7)	4584 (72.1)	3347 (82.1)	
Yes	1942 (27.7)	2756 (32.3)	1704 (27.9)	840 (17.9)	

*Percentages (%) are estimated using inflation weights and may not total 100% due to rounding error.

Appendix D. Age and Sex Stratified Prevalence of Poor Sleep Health by Multimorbidity Status.

Variable	**Additive**		**Pooled**	
	Multimorbid (n, %)	**Not Multimorbid (n, %)**	**Multimorbid (n, %)**	**Not Multimorbid (n, %)**
Age (Years)				
45-54	265 (30.5)	1045 (18.7)	296 (36.7)	1168 (20.5)
55-64	463 (29.2)	1206 (17.5)	508 (30.5)	1302 (18.3)
65-74	306 (19.0)	711 (14.8)	343 (20.3)	774 (16.1)
75-85	237 (23.2)	474 (17.2)	253 (24.8)	552 (17.5)
Sex				
Female	751 (28.7)	2013 (20.5)	826 (32.3)	2184 (21.0)
Male	420 (23.3)	1425 (15.0)	574 (24.6)	1612 (16.6)

*Percentages (%) are estimated using inflation weights.

Appendix E. Comparison of Characteristics of Analytical sample and Individuals Excluded from Chapter 4 Analyses.

Variable	Complete Data	Excluded and Missing Data Group
Total	19898	10199
Age (Years)		
45-54	**5745 (44.0)**	**1850 (29.0)**
55-64	6785 (30.2)	3071 (32.6)
65-74	4539 (16.7)	2823 (21.5)
75-85	2829 (9.0)	2455 (17.0)
Annual Household Income		
<20000	797 (5.0)	769 (11.6)
20000-49999	**3926 (19.4)**	**2434 (30.4)**
50000-99999	7058 (33.7)	2849 (32.1)
100000-149999	4250 (21.9)	1274 (15.5)
>150000	3867 (20.1)	932 (10.4)
Education		
Less than secondary school	**815 (13.9)**	**828 (24.4)**
Secondary school		
Some post-secondary	1720 (11.0)	1119 (12.4)
Post-secondary	1356 (8.9)	882 (9.4)
degree/diploma	**16007 (66.2)**	**7320 (53.8)**
Alcohol Consumption		
Regular drinker	**9947 (48.2)**	**4026 (37.0)**
Occasional drinker	5476 (26.0)	2790 (26.6)
Infrequent drinker	2181 (11.7)	1524 (15.1)
Former Drinker	1881 (11.7)	1546 (18.0)
Never drinker	413 (2.3)	300 (3.3)
BMI		
Underweight	138 (0.9)	79 (0.7)
Normal	6292 (31.1)	2303 (24.0)
Overweight	8191 (39.9)	3716 (36.1)
Obese	**5277 (28.1)**	**3652 (39.1)**
Hypertension		
No	**12241 (64.7)**	**4800 (50.7)**
Yes	**7657 (35.3)**	**5399 (49.3)**
Not Aware	1287 (7.2)	622 (7.4)
Aware	**6338 (28.2)**	**4763 (41.9)**

Controlled	**4723 (20.4)**	**3593 (30.7)**
Not controlled	1615 (7.6)	1170 (10.8)

*Proportions estimated using inflation weights.

*Bolded are groups with >10% difference in column proportion. Variables not shown had no significant differences between groups.

Appendix F. Regression Analysis of Multimorbidity with Imputed Missing Data.

Additive Model			
Variable	**OR**	**95% CI**	***P***
Additive Index, 0 (Ref)			
1	1.12	0.94, 1.33	0.223
2	1.37	1.10, 1.70	0.004
3	1.38	1.13, 1.70	0.002
4-5	1.55	1.20, 2.01	0.001
Age, 45-54 (Ref)			
55-64	1.06	0.87, 1.28	0.565
65-74	1.32	1.05, 1.65	0.017
75-85	1.21	0.93, 1.57	0.156
Sex, Female (Ref)			
Male	0.99	0.86, 1.15	0.888
Ethnicity, White (Ref)			
Ethnic minority group	0.89	0.69, 1.16	0.386
Annual Household Income, <20000 (Ref)			
20000-49999	1.06	0.77, 1.46	0.719
50000-99999	0.99	0.71, 1.38	0.944
100000-149999	0.90	0.62, 1.31	0.572
>150000	0.88	0.61, 1.26	0.475
Education, Less than secondary school (Ref)			
Secondary school	1.00	0.72, 1.38	0.980
Some post-secondary	1.27	0.90, 1.78	0.169
Post-secondary degree/diploma	1.09	0.81, 1.46	0.568
Smoking Status, Never smoker (Ref)			
Daily smoker	2.25	1.73, 2.92	<0.001
Occasional smoker	2.14	1.13, 4.03	0.019
Former smoker	1.33	1.14, 1.55	<0.001
Alcohol Consumption, Never drinker (Ref)			

Regular drinker	0.95	0.65, 1.41	0.813
Occasional drinker	0.88	0.59, 1.30	0.509
Infrequent drinker	1.39	0.92, 2.08	0.117
Former drinker	1.32	0.87, 2.00	0.197
PASE Score (Quintiles), P ≤ 20 (Ref)			
20 < P ≤ 40	0.86	0.71, 1.05	0.140
40 < P ≤ 60	0.66	0.54, 0.81	<0.001
60 < P ≤ 80	0.69	0.54, 0.89	0.004
P > 80	0.51	0.40, 0.65	<0.001
BMI, Normal (Ref)			
Underweight	2.06	0.95, 4.43	0.066
Overweight	1.27	1.07, 1.52	0.008
Obese	1.94	1.61, 2.34	<0.001
Hypertension, No (Ref)			
Yes	1.34	1.16, 1.54	<0.001
Pooled Model			
Variable	**OR**	**95% CI**	***P***
Pooled Index	1.30	1.18, 1.44	<0.001
Age, 45-54 (Ref)			
55-64	1.07	0.88, 1.29	0.509
65-74	1.34	1.07, 1.68	0.010
75-85	1.23	0.95, 1.60	0.113
Sex, Female (Ref)			
Male	0.99	0.86, 1.15	0.911
Ethnicity, White (Ref)			
Ethnic minority group	0.89	0.69, 1.16	0.380
Annual Household Income, <20000 (Ref)			
20000-49999	1.08	0.79, 1.49	0.638
50000-99999	1.02	0.73, 1.42	0.930
100000-149999	0.92	0.63, 1.34	0.647
>150000	0.91	0.63, 1.32	0.617
Education, Less than secondary school (Ref)			
Secondary school	1.00	0.73, 1.38	0.993
Some post-secondary	1.26	0.90, 1.77	0.179
Post-secondary degree/diploma	1.09	0.81, 1.46	0.577
Smoking Status, Never smoker (Ref)			
Daily smoker	2.23	1.71, 2.90	<0.001

Occasional smoker	2.13	1.13, 4.02	0.020
Former smoker	1.33	1.14, 1.54	<0.001
Alcohol Consumption, Never drinker (Ref)			
Regular drinker	0.95	0.65, 1.41	0.807
Occasional drinker	0.87	0.59, 1.29	0.496
Infrequent drinker	1.39	0.92, 2.09	0.118
Former drinker	1.32	0.87, 2.00	0.195
PASE Score (Quintiles), $P \leq 20$ (Ref)			
$20 < P \leq 40$	0.86	0.71, 1.05	0.144
$40 < P \leq 60$	0.66	0.54, 0.81	<0.001
$60 < P \leq 80$	0.70	0.55, 0.90	0.005
$P > 80$	0.52	0.40, 0.66	<0.001
BMI, Normal (Ref)			
Underweight	2.07	0.96, 4.45	0.064
Overweight	1.28	1.07, 1.52	0.007
Obese	1.95	1.62, 2.36	<0.001
Hypertension, No (Ref)			
Yes	1.34	1.15, 1.54	<0.001

*Analytic sampling weights applied.

Curriculum Vitae

Name:	Shreni Patel
Post-secondary Education and Degrees:	Western University London, Ontario, Canada 2021-2023 Msc. Epidemiology & Biostatistics The University of Toronto Toronto, Ontario, Canada 2017-2021 BSc. (Honours) Neuroscience
Honours and Awards:	Western Graduate Research Scholarship 2021-2023 University of Toronto Entrance Scholarship 2017-2021
Related Work Experience:	Graduate Teaching Assistant Western University 2023 Research Assistant Service Delivery Data Hub, Catholic Crosscultural Services 2022 Research Analyst Sleep and Brain Lab, Sunnybrook Health Sciences Centre 2020