RELATIONSHIPS BETWEEN MOVEMENT BEHAVIOURS AND DEMENTIA

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Abstract

The primary objectives of this dissertation were three-fold: i) to evaluate the association of movement behaviors on incident dementia through a systematic review and meta-analysis; ii) to examine the association of movement behaviors on 3-year changes in memory among middle-aged and older adults, stratified by sex; and iii) to investigate the sex-specific association between movement behaviors on cognitive function changes over three years, including the mediation effects of cardiovascular disease on cognitive function. Data from population-based cohort studies, including the Canadian Longitudinal Study of Aging (CLSA), were utilized. A systematic review and meta-analysis (SRMA), as well as general linear regression, and mediation analyses, were employed.

In SRMA Study 1, regular physical activity was associated with a 28% reduction in the risk of incident dementia, while both short (<7 hours) and long (>8 hours) sleep durations were associated with an increased dementia risk (RR = 1.23 and 1.32, respectively). In CLSA Studies 2 and 3, 6-8 hours of sleep was associated with positive changes (z-scores) in immediate and delayed recall among males. Among females, the interaction of higher physical activity levels (≥10 MET-hours weekly) with 8+ hours of sleep and high sedentary time led to an increase in delayed recall. Increasing sedentary time was associated with positive changes in cognitive function in males, while excessive sleep duration was associated with a negative change in cognition. Sitting time was found to mediate the relationship between cardiometabolic components and cognitive changes over three years among males (*negatively*: systolic blood pressure, high-density lipoprotein, carotid intima-media thickness, glycosylated haemoglobin, and *positively*: waist circumference, diastolic blood pressure, and triglycerides) but not females. The relationship between sitting time and 3-year change in global cognition was further mediated

through waist circumference and high-density lipoprotein among both females and males, while glycosylated hemoglobin mediated the sitting time and cognition relationship among males but not females.

This dissertation highlights the importance of optimizing movement behaviors for cognitive health among older adults, emphasizing the opportunity for targeted interventions to reduce dementia risk and enhance overall cognitive functioning.

Keywords: Physical activity, sleep, sedentary behavior, dementia, cognition, memory, cardiovascular disease, older adults, movement behaviours

Dedication

To my mother, Adetoro Adeoba Oye-Somefun, I dedicate this work to you. Your infinite love, endless support, and incredible strength have been my guiding light and inspiration throughout this journey. Your prayers, wisdom, and unwavering belief in me have shaped every step I've taken. I am eternally grateful, and I want you to know that this achievement is as much yours as it is mine.

In loving memory of my father, David Akinwunmi Oye-Somefun, whose presence I deeply miss but whose spirit continues to guide me every day. He worked tirelessly, often sacrificing his own health and comfort, to provide for our family. His wisdom, love, and guidance remain a constant source of strength and inspiration in my life. Though he is no longer here, I take comfort in knowing he would have been so proud. Rest in Heaven, Dad, you are forever in our hearts. Your love, sacrifices, and devotion will never be forgotten.

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Chapter 1 Background

Subtle declines in cognitive function are considered a normal part of the aging process [1]. These changes can vary from person-to-person and can include changes in attention, comprehension, memory, and other cognitive abilities such as language [2]. Severe cognitive impairments, on the other hand, may indicate underlying health issues or clinical syndromes, such as dementia [3][4]. Accounting for 60-80% of all cases, Alzheimer's disease (AD) is the most common type of dementia in older adults [2][5][6][7]. AD is characterized by progressive neurodegeneration, a worsening of cognitive and functional status with overt behavioral symptoms such as severe memory loss and disability [2][7]. Currently, 50 million adults 60+ years are living with dementia [6][7] with direct medical expense and informal care [5][7][8] estimated to cost $1 trillion globally by 2050 [9]. There are ~100,000 new cases of dementia diagnosed annually among the older adult population (65+ years) in Canada, a higher proportion of which are women [5]. With nearly 10% of older Canadians living with dementia [10], the ongoing challenges to our healthcare system(s), caregivers, and society are substantial.

While related, mild cognitive impairment (MCI), has been characterized as an intermediate state between normal cognitive functioning and dementia, relative to age [8][11][12]. Although some individuals in the older adult population (65+ years) with MCI may go on to develop dementia, others may remain stable over time [8][11][12]. Research on the causes and treatments of MCI and dementia are multifactorial, and research is ongoing [8][11][13], but involve a host of genetic, environmental, and lifestyle factors [7][11][12][14] (**Figure 1.1)**. Certain risk factors, such as age and family history, are well-established; however, modifiable cardiovascular risk factors could play a considerable role in severe cognitive decline [8] [12] [13] [15] [16].

Many older adults are sedentary (8+ hours daily sitting time) [17], not engaged in sufficient amounts of moderate-to-vigorous physical activity (MVPA) [18][19], and have chronic sleep problems [20][21]. Investigation of how non-pharmacological, or "lifestyle" related interventions and behaviors, such as physical activity, sedentary time, and sleep, may impact brain health are of wide-scale importance. This includes a need to understand how these factors contribute to age-related cognitive decline and dementia risk among older adults in longitudinal analyses that account for variation by age, sex, and pre-existing health status / comorbidities. Long duration follow-up studies examining the effects of movement behaviours on cognitive outcomes can provide evidence-based recommendations for promoting active aging and ensuring sustainable healthcare systems capable of managing the growing number of dementia cases.

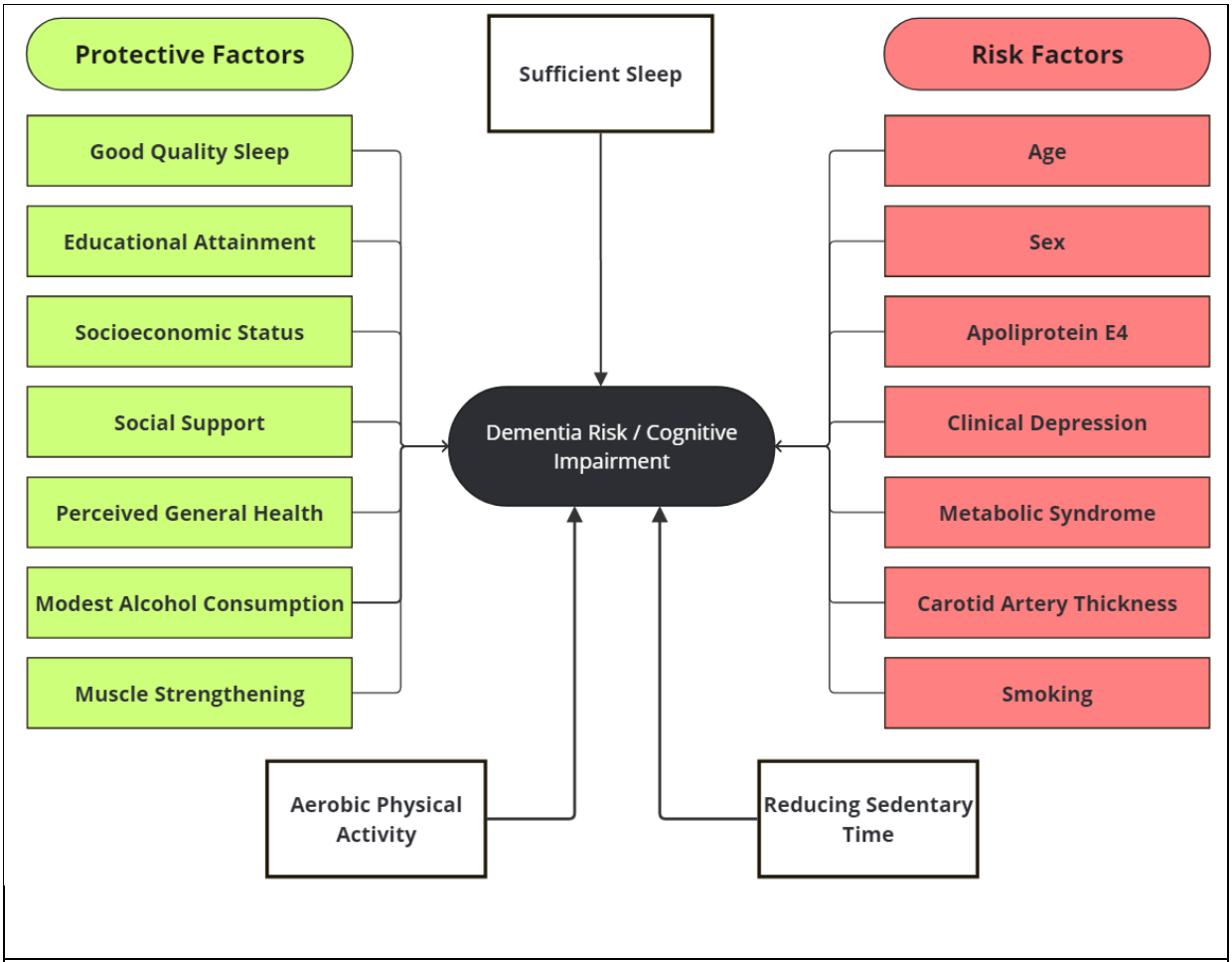

Figure 1.1. Characterization of factors in cognitive impairment and dementia.

Mechanisms

Although the mechanisms of action between movement behaviors, cognition, and dementia risk are not fully understood [8], several biological and physiological factors have been implicated in disorders of the brain that lead to neuroinflammation and neurodegeneration. These include blood-brain barrier permeability, neuroinflammation, hypo-perfusion (reduced blood flow), and hypoxia (lack of oxygen), which are common characteristics of neurodegenerative

disorders [4][22][23][24], to name a few. The blood-brain barrier is a complex of structures including endothelial cells, vascular smooth muscle cells, astrocytes, microglia and neurons involved in maintaining homeostasis of the brain and central nervous system [25]. Integrity of the blood-brain barrier is therefore crucial for brain health, as it regulates the passage of substances between the bloodstream and the brain [26]. A compromised blood-brain barrier allows entry of inflammatory agents [25], and inflammation due to injury, or infection, disrupts its integrity and promotes inflammatory markers and immune system responses across the barrier, that can contribute to secondary inflammation [25]. Resulting inflammatory processes within the brain activate immune cells to release cytokines and other inflammatory molecules, which creates cascades of chronic neuroinflammation, and a subsequent build up of toxins in the brain [22][23][24], which could weaken the blood-brain barrier integrity due to ineffective clearance of toxins. This can lead to a decrease in blood flow within the brain, which deprives neurons of oxygen and nutrients.

Accumulation of misfolded proteins in the brain has been highlighted a strong risk factor for progressing to dementia [27][28]. However, the presence of amyloid-β peptides or plaques in normal age-related cognitive change suggests that amyloid plaque is not necessarily a consistent model for dementia progression [28][29][30], and the trajectory of cognitive change may be differential; that is, a significant risk factor for one individual may not hold the same weight for another. Although pharmacological approaches may have potential benefits [31], non-pharmacological approaches (e.g., physical activity) have been shown to have positive benefits without the negative side effects on health. The onset of dementia may be delayed with early intervention to restore the balance between pro- and anti-inflammatory markers to prevent build-up of toxins in the brain and poor cerebral blood flow [22][23] [24], and may include physical

activity [32] [33]. The mechanisms behind this association are not fully understood. Although possible mechanisms include cardiovascular (i.e., small vessel changes), immunological (i.e., immune health and inflammation), and neurological factors (i.e., neuroendocrine and brain-derived neurotrophic factors). Moreover, uncontrolled blood sugar (diabetic autonomic neuropathy) and blood pressure problems are characteristics of autonomic impairment, and blood-brain barrier injury [34]. Optimal movement behaviours could play a significant role in restoring autonomic function that promote angiogenesis (e.g., vascular endothelial factor), and neurogenesis (e.g., brain-derived neurotrophic factor) [34].

Evidence to date suggests that physical activity, sedentary behavior, and sleep patterns may influence the blood-brain barrier permeability in different ways. Blood-brain barrier integrity can be altered by neuropathology, including brain injury, ischemic stroke, depression, and dementia [25]. Regular physical activity has been shown to improve cerebral blood flow and vascular function maintaining blood-brain barrier integrity [32] by stimulating anti-inflammatory pathways that regulate neuroinflammation and protects the blood-brain barrier from damage [35]. Physical activity in midlife has been shown to reduce the risk of incident dementia and Alzheimer's disease by 30-45 percent [6], with further benefit when additional modifiable behaviours are adopted. These effects are associated with improved cognition later in life and increased cognitive reserve [36].

The benefits of regular activity on brain health may extend to anatomical changes, as demonstrated by a reversal in age-related shrinkage of the hippocampus (i.e., the memory complex) [37] [38]. Among the explanations for this finding are increases in cerebral blood flow and oxygen delivery which enhance a cascade of factors (e.g., inducing fibroblast growth factors

in the hippocampus and cerebellum, reducing oxidative stress and inflammation), to stimulate increases in brain volume. Behaviourally, physical activity often increases social interaction. Older adults with less-than-ideal social support or social isolation are at increased risk of dementia [39], compared to those with ideal social support or social ties.

As individuals transition from working to retirement, sedentary behaviors could have negative effects on overall health. Given the potential for sedentary behaviours to increase with age [17][18][40], older adults may experience more memory complaints and cognitive decline [41]. The effect of prolonged sedentary behaviour correlates with low levels of cardiorespiratory fitness, impaired glucose metabolism, and reduced muscle activity over time [40]. This is supported by prospective studies of dementia deaths, wherein higher tertiles of cardiorespiratory fitness had improved survival rates (73% lower mortality risk) [38]. Thus, reductions in sedentary time have the potential to preserve cognitive function by promoting angiogenesis, cerebral blood volume, cerebral perfusion, and changes to brain structure and vasculature including hippocampal size, while lowering the number of important risk factors linked to cognitive decline [42]. Engagement in a variety of cognitive activities, such as reading, has the potential for improvements in executive functioning processing speed and memory, while reducing sedentary activity [32][33], which can be advantageous for older adults.

Optimal nightly sleep (i.e., seven to eight hours) plays a crucial role in overall health and is essential for maintaining brain health [43][44][45]. Suboptimal sleep impairs control of blood pressure, heart rate, and blood sugar levels, which contributes to insulin resistance and an increased risk of atherosclerosis [20]. Additionally, suboptimal sleep including poor sleep quality have been associated with poor blood-brain barrier integrity [46]. Although the exact mechanism is unclear, suboptimal sleep is associated with neuroinflammatory processes and oxidative stress

[47]. Moreover, suboptimal sleep is associated with dysregulated sleep-wake cycles and sleep duration, which can have detrimental effects on health [48]. Prospective studies focusing on measures aimed at prevention of chronic disease and improving quality of life of older adults, can inform care quality, development of innovative treatments, and policy research that significantly reduces the financial burden of dementia while enhancing the lives of those affected.

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Chapter 2 Literature Review

Although the exact underlying mechanisms of age-related cognitive decline and dementia are not fully understood, a number of potential pathways have been proposed including, increasing blood–brain barrier permeability, neuroinflammation, and oxidative stress [1], along with poor cardiac output that may contribute to cerebral hypo-perfusion and hypoxia [2]. Concurrently, low-grade chronic systemic inflammation may also contribute to micro-structural changes, and damage to the blood-brain barrier and cerebrovascular system [2]. Thus, information about the risks and ways to delay the onset of cognitive impairment are warranted due to the burden of health-care costs [3][4]. Scientific advancements in pharmacological interventions for severe cases include cholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist memantine, and may be used to manage symptoms [5], whereas gene therapy may be used to address underlying causes [6][7][8]. Non-drug therapies such as physical activity, quality sleep, and management of cardiovascular risk factors could help to preserve cognitive function and delay cognitive decline by maintaining cardiovascular health.

Physical Activity

Physical activity is a modifiable movement behaviour with beneficial effects on cognitive functioning and quality of life [Petersen]. Meta-analyses of prospective studies [9] and randomized controlled trials (RCTs) [10] have shown that physical activity may confer protection against cognitive decline in healthy older adults without diagnosed dementia. Indeed, higher amounts of physical activity are linked to lower risk of cardiovascular events and positive cognitive performance in a dose-response manner [9][11][12][13][14]. Physical activity also improves cerebral blood flow and endothelial function act to decrease the release of stress

hormones that increase the carotid intima-media thickness and cardiovascular disease risk [15][16][17][18]. Despite these benefits, one-third of world's population does not achieve the minimum recommended level of moderate-to-vigorous physical activity (MVPA) [19]. Moreover, older adults often face unique challenges that contribute to low levels of physical activity and exercise adherence; for example, about 55% to 70% of older adults 65 years and older are not engaged in sufficient amounts of MVPA [20][21]. Decreases in physical activity with age occur for various reasons, and may be related in part to changes in physical health, mobility limitations, and lifestyle factors, which has many implications for cognitive functioning and quality of life [22][23][24].

In older adult populations, research has shown positive associations between MVPA, memory, and global cognition [25][26] [27][28][29]. However, depression as well as overt neurological disorders, tend to decrease adherence to exercise or recreational physical activity [21]. Because most forms of physical activity are recreational, less is known about non-recreational physical activity [30][31][32], which encompasses a wide range of activities that vary in terms of physical intensity, such as occupational activities while sitting.

Sedentary Activity

Sedentary behaviour is defined as any non-exercise behaviour that is characterized by low energy expenditure (≤1.5 METs (metabolic equivalent of task) and is performed during waking hours, such as time spent sitting, reclining, and lying down [33][34]. Older adults spend as much as 9 to 10 hours of their waking day being sedentary [20][35], and such higher levels of sedentary behavior are associated with an increased risk of cognitive decline [36][37], and the negative effects of sedentary behavior on cognitive function are of a similar magnitude to the

negative effects of genetic risk factors associated with Alzheimer's disease or other forms of dementia [37].

In practical terms, sedentary behaviour is characterized by prolonged periods of sitting involving activities such as watching television, working at a desk, or driving for extended periods. To date, the full effects of a sedentary lifestyle on brain health remain unknown [38]. Research in this area is ongoing to explore the potential mechanisms, moderating factors, and long-term effects of sedentary activities on brain function across study settings and using differing measures of cognitive function and individual health status at baseline to account for study heterogeneity [39].

Sleep Activity

Sleep plays a crucial role in promoting brain health and overall well-being [40][41]. During sleep, the brain is consolidating memories and enhancing learning to improve processing speeds, which leads to better memory recall and cognitive performance [40][41]. Chronic sleep disorders or sleep disturbances, which have negative effects on sleep quality and sleep duration, have been identified as potential risk factors of poor cognitive function [42]. Sleep disturbances and sleep disorders tend to become more prevalent as individuals age, and they are associated with poor cognitive function in older adults [43][44]. Sleep disturbances and sleep disorders have been linked to cognitive impairment and decline in older adults and 70% of patients in early-stage dementia have sleep disturbances [45].

On the other hand, sleep duration – the total time someone reports or is objectively assessed to have been asleep - has been shown to follow a U-shaped curve in relation to various health outcomes [46][47]. This suggests that both low or insufficient sleep and excessive sleep

can be associated with negative health outcomes and worse cognitive performance, while moderate or sufficient sleep duration tends to be associated with optimal health [48][49][50] [51][52] [53]. Insufficient sleep duration has been linked to cognitive impairment and decreased cognitive performance, which may contribute to cognitive decline over time [48][49][50][51] [52]. Prolonged sleep duration in midlife may be a marker of underlying health conditions and is positively related to dementia in later life [54], but the relationship may be explained in part by other sleep disorders such as sleep apnea, or depression [55]. Variability among individuals, populations, and health conditions also warrants further study [42].

Other sleep disorders, such as insomnia, are characterised by persistent disturbances in sleep resulting in poor quality of sleep [56][57][58][59] that may worsen with age. About half of the older adult population report sleep problems [60], which increases their risk of other health problems such as cardiovascular disease risk factors [58][61][62] and could have adverse effects on the brain structure of older adults [63][64], including changes in the distribution of cerebral grey matter and decreases in volume or thickness of the certain brain regions (e.g., Hippocampus, prefrontal cortex, temporal lobes) [65][66][67][68], and hypertrophy in others (e.g., Amygdala) [69].

Effect of Sex/Gender

It is unclear whether women are at a higher risk than men for developing dementia or Alzheimer's disease at a specific age. Up until around 80 years old, the age at which dementia begins is similar for both men and women [70]. However, beyond age 80, the incidence rates of dementia and Alzheimer's disease tend to accelerate in women, and remain higher than men [70]. Women tend to outlive men, and as a consequence, cognitive impairment has a

disproportionate effect on women [71][72]. Of note, both the incidence and prevalence of dementia are higher in women than in men [71][72][73]. The implications of sex/gender differences in cognitive decline include years of life lost due to dementia, and lifetime risk for dementia [72]. A higher prevalence of cognitive impairment in women may be the result of both intrinsic (e.g., hormones), and extrinsic (e.g., environmental, psychosocial, and sociocultural) factors that could influence females and males differently [36], suggesting that all analyses should consider the intersection of age and sex/gender differences in cognitive function. Given the differential incidence of diagnosed dementia among Canadian seniors (65+, 14.3 new cases per 1,000; 15.8 for females, and 12.4 for males) [73], deliberate analysis of sex/gender in health research is necessary to inform ongoing surveillance efforts, and to identify opportunities for targeted interventions [71][73][74].

Sex differences in movement behaviour types are also apparent [75]. Representative accelerometer data suggest that U.S [76] and Canadian [77] men are engaged in higher amounts of total physical activity than women. The relationship is less clear for sedentary activity where there is considerable variability at older ages (60+) [78][79]; however, sex/gender differences are also observed in relation to sleep [80][81]. Women report more sleep problems [82][83], and are twice as likely as men to experience sleep disruptions and insomnia throughout their lifespan [83], and this remains a subject of investigation across a wide age range [80]. Sleep dysregulation is associated with an increased risk of diabetes, hypertension, and heart disease which might differ between females and males due to the impact of sleep on blood pressure regulation, inflammation, and metabolic disorders [42]. Sleep dysregulation is also linked to anxiety, depression, and cognitive decline due to the impact of sleep on changes in grey matter volume and cortical thickness [66][67][68]. Underlying these sex differences in the finding that

women may be more likely to experience depression associated with sleep disturbances [55] [42], whereas men may be more prone to cognitive decline related to poor sleep [48][49][50] [51][52].

Predictors of sex/gender differences in dementia risk include differences in both chronic disease factors such as depression [81], obesity [84][85], metabolic syndrome [86], diabetes [87], and hypertension [88], and social/cultural barriers to health-seeking behaviours [74][72][89] among men. A priority for the current dissertation is therefore to conduct a sex/gender analysis to evaluate differential risk for cognitive decline for females and males [84][90].

Rationale

Given the coinciding rise in the prevalence of dementia and increasing age of the world population, the investigation of the associations of modifiable risk factors to delay cognitive decline has wide-ranging implications. Knowing the associations and directionality of these risk factors on cognitive function is the first step in the development of primary prevention [91] strategies and the enhancement of quality of life of older adults [42]. Previous studies on cognitive deficits have shown that the interplay of risk factors deserves further study [92][93)]. There is also a paucity of data from midlife [91], longer-term [94][95][96], multi-site [97], and large-scale studies [98] [99][94]. As such, the longitudinal associations of integrated risk factors [96], such as the combined 24-hour movement behaviours (physical activity, sedentary behavior, and sleep) [100], on cognitive function in midlife and older adults is an area of research priority [91]. Because movement behaviours tend to change over time, investigating the longitudinal associations of movement behaviours, including the mediation effects of vascular risk factors [94][101] in adults at risk for severe cognitive decline, may help to elucidate changes in

cognitive function, and provide evidence for enhancing public health risk reduction strategies targeted towards the prevention and management of dementia **[**92**][**93**][**94**].**

Study Objectives

Study 1. The Relationships between Physical Activity, Sleep, and Dementia: A Systematic Review and Meta-Analysis of Population-Based Cohort Studies.

- Objective 1: To evaluate the association of movement behaviours (sleep, sedentary behavior, and physical activity) on incident dementia by performing a systematic review and meta-analysis of existing literature.

Study 2. Association of Movement Behaviours on 3-Year Changes in Memory: A Longitudinal Analysis.

- Objective 1: To examine the association of movement behaviours on 3-year changes in memory among adults 45+ years old; stratified by sex.

Study 3. Association of Movement Behaviours on 3-Year Changes in Cognition: An Analysis of The Mediation Effects.

- Objective 1: To examine the association of movement behaviours on 3-year changes in cognitive function among adults 45+ years old, stratified by sex, and; the mediation effect of cardiovascular disease, with movement behaviors, on cognitive function.

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Chapter 3 Study 1. The Relationships between Physical Activity, Sleep, and Dementia: A Systematic Review and Meta-Analysis of Population-Based Cohort Studies.

Abstract

Objective

To summarize the observational evidence from population-based cohort studies examining the relationship between regular physical activity and sleep duration on incident dementia in a systematic review and meta-analysis.

Methods

Systematic literature searches (1946 to September 2023) of CINAHL, EMBASE, MEDLINE, PSYCINFO, and SPORTDISCUS databases were performed without language restrictions. Random effects meta-analysis models pooled study results. Participants were community-dwelling adults aged 35+ years. Studies were excluded if they lacked valid measures of primary exposure or outcome, had <1 year follow-up, included baseline dementia diagnoses, or missed risk estimates for all-cause dementia. Grey literature was not considered. Incident all-cause dementia was the primary endpoint. Primary exposures were aligned with national movement behavior thresholds.

Results

Thirty-eight studies with physical activity (n=444 813 participants) and 14 studies with sleep duration (n=909,019 participants) were included in this systematic-review and meta-analysis. In all studies combined, physical activity was associated with reduced risk of incident dementia with a pooled risk ratio (RR) of 0.72 (95% CI = 0.64 to 0.81). Heterogeneity of study results overall was substantial; this improved in subgroup analyses involving 21 physical activity studies with older baseline age (65+ y) and shorter (<10 y) follow-up (0.72, 0.64 to 0.82). Both short (<7 hours; RR = 1.23, 95% CI = 1.11 to 1.39) and long (>8 hours; RR = 1.32, 95% CI = 1.16 to 1.51) sleepers were at greater risk of dementia than those with 7-8 hours of nightly sleep. Heterogeneity improved in sub-analysis involving 5 studies on both short- and long-sleepers with younger baseline age (< 65 y) and longer (10+ y) follow-up: <7 hours; (RR = 1.17, 95%CI = 1.06 to 1.29), and; >8 hours (RR = 1.09, 95%CI = 1.02 to 1.18).

Conclusion

Regular physical activity and sleep are protective, modifiable factors in the prevention or delay of dementia. Future studies with middle-aged adults and longer-term follow-up tracked for changes in movement behaviours are needed to better understand the relationship between sleep and physical activity in dementia risk.

Keywords: cohort studies, dementia, physical activity, sleep, systematic review, meta-analysis

Introduction

Dementia is a neurodegenerative disease and a leading cause of death in older adults [1]. Approximately 10 million new cases are diagnosed annually with Alzheimer's disease (AD), contributing to 60-80% of all cases [2]. There are currently 55 million people around the world living with dementia [3], which is estimated to triple by 2050, with 60% from low- and middle-income countries [4]. In 2018, the total (indirect and direct care cost) worldwide burden of dementia care was estimated at $1 trillion globally by 2050 [5].

Dementia results in severe worsening of cognitive function, disability, dependency, quality of life, and risk of death in individuals aged 65 and over [6]. The preclinical or prodromal period of dementia may occur decades before symptoms [7][8], and available pharmacological interventions have provided only limited success at preventing or treating dementia [9], despite the use of a wide range of medications with adverse side effects [10]. Research on modifiable risk factors including physical activity (PA) is important for informing evidence-based prevention strategies [11][12][13]. Older adults transitioning to retirement have low levels of regular physical activity [14], making this a period for accelerated health decline. Healthy movement behaviours, such as regular physical activity, limiting sedentary time, and sufficient nightly sleep, are important for management of dementia risk factors.

Physical activity has been linked with cognitive performance [15]; however, the relationship with dementia is less clear [16]. Epidemiological studies have shown that regular movement behaviours could lower the risk of cardiovascular disease including chronic inflammation [17][18][19] and are effective at lowering the risk of dementia and cognitive decline in older adult populations [20]. Sedentary behaviour is also a risk factor for cardiovascular disease.

Prolonged sitting has been linked to a wide range of problems including insulin resistance, inflammation, oxidative stress, which present an increased risk of neurodegenerative disease [21]. Prolonged sedentary activities may contribute to poor cognitive functioning and increased risk of cardiovascular disease [21][22][23][24]. Finally, sleep problems have also been associated with an increased risk of death [25], and dementia [26][27]; however, the effects of sleep duration and long-term sleep problems on the risk of dementia are not well known [28][29]. Because movement behaviours are independently related to cardiovascular health [21] [30], it is important to understand how these movement behaviours work together to maintain brain health [31].

Because the risk of developing dementia tends to accelerate in older age [32], it has been estimated that the management of risk factors through lifestyle intervention could delay or prevent up to 40% of cases worldwide [33]. Understanding the relationship between movements behaviors and dementia risk at an earlier age is needed to help inform risk reduction efforts in susceptible middle-aged and older-aged adult populations. We therefore aimed to build on previous literature to evaluate the relationships between established or recommended physical activity levels and sleep duration with incident dementia in a systematic review and meta-analysis of observational, prospective cohort studies. The growing interest in physical activity and sleep may complement existing approaches to improve brain health and delay dementia. However, few systematic reviews and meta-analyses have examined these relationships in community-dwelling adult populations across diverse ages [34][35] and follow-up duration [36][37].

Methods

This systematic review and meta-analysis (SRMA) were registered in PROSPERO CRD42021272054. Systematic literature searches (1946 to September 2023) of CINAHL, EMBASE, MEDLINE, PSYCINFO, SPORTDISCUS databases were performed without language restrictions to identify relevant peer-reviewed journal articles related to reports of movement behaviours with dementia in community-dwelling adult populations. Search terms included (but were not limited to) the following: physical activity, walking, sedentary behavior, sleep, memory, cognition, dementia, alone or combined using Boolean operators in each database (see **Table 3.1** for the full electronic MEDLINE search strategy). References of retrieved articles were examined to locate additional relevant articles, and published studies were screened by title and abstract. Two independent reviewers (JGK and PM) were responsible for evaluating the full-text articles for study quality, and where necessary consensus with a third reviewer (CIA) was used to resolve discrepancies. Risk of bias was evaluated using the risk of bias in non-randomized studies of interventions (ROBINS-I tool) [38]; the assessment was performed by a single reviewer (PM). To mitigate potential biases and enhance the reliability of the evaluation, the assessments were confirmed by CIA.

Studies with appropriate definitions of incident dementia were included if their longitudinal cohort study designs involved measuring the outcome at the last time point. Participants were healthy, community-dwelling adults (35+ years at baseline). Studies were ineligible for inclusion if the study had any of the following: i) missing a valid measure of a primary exposure or outcome of interest; ii) less than 1 year of follow-up; iii) with clinical diagnosis of dementia at baseline, or; iv) missing a risk estimate of all-cause dementia at follow-up, and; v) duplication of cohort participants with other studies. In these instances, studies with

larger samples over subsets, higher quality and more interpretable measures of physical activity levels, and longer follow-up times were prioritized to enhance generalizability. Analysis of data and presentation of results were based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [39]. Ethics approval was not required from our host institution as there was no potential for participant identification from published summary data.

Risk of Bias Assessment

We assessed risk of bias, and representativeness of the current evidence. A comprehensive score of bias was assigned by aggregating sources of bias using the Risk of Bias in Non-randomised Studies - of Interventions or "ROBINS-I Assessment Tool" for observational study designs [38][40]. Evaluation of study bias was done across seven domains, including: risk of bias due to confounding, participant recruitment and selection, classification to (or deviation from) assigned interventions, missing data, measurement, and selection of the reported result. Overall bias was subsequently classified as "Low", "Moderate", or "Serious" as per the open-source ROBINS-I risk aggregation tool (.xls) developed by Marcolino (2020).

Outcome

The primary study endpoint was incident all-cause dementia according to neuropsychiatric evaluations, health registry data, and standardized clinical diagnostic criteria. We included studies where dementia was ascertained with or without dementia as the cause of death. Relevant data were extracted from individual studies including the most saturated (i.e., fully adjusted) primary outcome estimate (odds ratio (OR), risk ratio (RR), and hazard ratio (HR)) along with their 95% confidence intervals (CI) using a pre-specified format.

Exposures

The primary study exposures were based on self-report questionnaire and operationalized to approximate established movement behaviour thresholds used by national agencies [41]. For physical activity, the "active" group was defined as participating in 150 minutes or more per week of aerobic activity and compared to the "inactive" group (or approximations thereof in comparing the highest vs lowest active groups in a distribution) [41]. For sedentary time, the optimal time spent sitting per day was defined as engaging in fewer than 8 hours of sitting, compared to prolonged sitting (8+ hours) [41]. Although the search strategy was comprehensive, the records identified did not explicitly investigate or sufficiently describe sedentary behaviours for quantitative synthesis. For nightly sleep duration, shorter (<7 hours) and longer (>8 hours) sleep categories were compared to 7-8 hours of sleep per night [41].

Statistical Analyses

The main summary effect measures were individual study estimates with corresponding confidence intervals. Pooling of results of longitudinal cohort studies in a meta-analysis, included risk estimates that were adjusted for multiple risk factors to control for covariates. Studies were assumed to be heterogeneous and random effects were modelled to calculate pooled estimates (OR/RR/HR) under the rare disease assumption [42]. Risk estimates were log transformed for analysis purposes. The I^2 statistic was used to assess the heterogeneity between studies [42]. The analysis was carried out using R (version 4.1.3) [43] and the **metafor** package (version 3.4.0) [44].

Results

The PRISMA flow diagram (see **Fig. 3.1**) summarizes the studies selected for inclusion in this report consistent with the PRISMA statement [39]. Descriptive characteristics of each of the included studies are reported (see Table 3.2 and 3.3).

Quantitative synthesis

Forest plots of the pooled estimates for analysis are included by movement behaviour type: physical activity (see **Fig. 3.2**), and sleep (see **Fig. 3.3** and **3.4**). In terms of sedentary duration, there were no unique papers. The records identified did not explicitly investigate or sufficiently describe sedentary behaviours for quantitative synthesis. Funnel plots of the included studies are included by movement behaviour type: physical activity (see **Fig. 3.5**), and sleep (see **Fig 3.6** and **3.7**).

Physical Activity

A total of 38 articles met the criteria for quantitative synthesis as it relates to physical activity [**45-82**]. A total of 18 443 participants (4.2%) out of 444 813 in all studies were diagnosed with dementia at follow-up. The reported mean age was 66.8 y, with a mean length of follow-up of 12 y.

Overall, 17 (44.7%) of the 38 studies included in the meta-analysis reported a statistically significant reduction in risk of dementia in the physically active older adults (Yoshitake 1995 [45], Laurin 2001 [46], Abbot 2004 [48], Scarmeas 2009 [51], Bowen 2012 [54], Buchman 2012 [55], Elwood 2013 [56], Wang 2014 [59], Hessler 2016 [61], Tomata 2017 [65], Shakersain 2018 [67], Shaaban 2018 [70], Palta 2019 [73], Wu 2020 [78], Boongird 2020 [79], Feter 2021 [80], Yoon 2021 [81]). The overall (k = 38) random effects log risk ratio was calculated as −0.33

(95% CI = −0.45 to −0.21). The corresponding random effects risk ratio was 0.72 (95% CI = 0.64 to 0.81), which shows a statistically significant overall lower risk of dementia in older adults that engaged in regular (i.e., moderate-vigorous intensity) physical activity compared to their non-active counterparts (**Table 3.4**). Importantly, however, total heterogeneity between the studies was 81.39%, which suggests considerable between-study variation. To explore this further, subgroup analysis was performed using the prespecified subgroups of age and follow-up duration to assess heterogeneity, and results remained consistent (**Table 3.4**).

Sleep

A total of 14 articles met the criteria for quantitative synthesis as it relates to sleep **[83-96]**. A total of 43 621 participants (4.8%) out of 909 019 in all studies were diagnosed with dementia at follow-up. The reported mean age was 66.9 y, and length of follow-up was 14.5 y. Seven studies on *short* (Chen 2016 [85], Bokenberg 2016 [86], Sabia 2017 [87], Lutsey 2018 [90], Ohara 2018 [93], Uwaka 2022 [95], Wong 2023 [96]), and seven studies on *long* nightly sleepers (Benito-Leon 2009 [83], Virta 2013 [84], Bokenberg 2016 [86], Westwoood 2017 [89], Larsson 2018 [92], Ohara 2018 [93], Sindi 2018 [91]) reported a statistically significant higher risk of dementia compared to regular sleepers (7-8 hour of sleep). The random effects model revealed a statistically significant higher risk of dementia for short (< 7 hours) sleepers (k = 14; log risk ratio = 0.21, 0.10 to 0.33; risk ratio = 1.24, 1.11 to 1.39; I^2 = 54.8%) and long (> 8 hours) sleepers (k = 14; log risk ratio = 0.28, 0.15 to 0.41; risk ratio = 1.32, 1.16 to 1.51; I^2 = 66.5%), compared to regular sleepers (7-8 hour of sleep). Subgroup analysis was performed with age and follow-up duration to assess heterogeneity in short and long sleepers (see Table 3.5).

Risk of Bias: Robin's Risk of Bias assessment (**Supplementary Files S3.1, S3.2**) demonstrated low-to-moderate risk of bias for both physical activity (low: n=3; moderate: n=28, and; serious: n=7) and sleep studies (low: n=1; moderate: n=10, and; serious: n=3). Across all analyses, approximately 19% of sleep and physical activity studies (10/52) had a serious risk of bias, with similar rates observed among the sleep (21%, 3/14) than physical activity-specific analysis (18%, 7/38). When present, the primary risk of moderate or serious bias was the result of bias due to confounding, followed by bias due to missing data. As expected, the majority of studies had low risk of bias due to participant selection or missing data, whereas the greatest variability was found for bias due to confounding. Measurement of physical activity, sleep, and dementia classification were the larger contributors to overall risk of bias, with both mixed outcome studies (e.g., MCI/AD/dementia) or more fitness-based assessment of physical activity showing increased risk of bias.

Discussion

Results of this SRMA showed that adhering to established or recommended physical activity (PA) levels was associated with lower incidence (28% reduced risk) of all-cause dementia; however, considerable heterogeneity in the random effects model for physical activity suggests unexplained variability. While we have investigated potential sources including baseline age differences, and follow-up duration, as well as controlling for potential confounders using adjusted models, additional sources of heterogeneity cannot be dismissed. Our SRMA also found that either short or long nightly sleep duration was associated with a 24% and 32% higher risk of dementia, respectively, compared to recommended 7–8-hour levels, with only moderate heterogeneity between studies.

These results are consistent with previous meta-analyses that showed an association between PA and all-cause dementia, including a 38% reduced risk in the most physically active, compared to less active counterparts [34][35][36][97]. However, our SRMA expands these findings with more recent studies from larger, diverse populations, with longer follow-up times, and by focusing on middle- and older-age adults exclusively. Although heterogeneity was moderate-to-substantial, physical activity studies with older baseline ages and/or shorter follow-up periods had less heterogeneity. This was expected considering the challenges with long-term tracking of physical activity in older populations. As such, many studies examining physical activity in older age tend to have follow-up durations of less than 10 years [98][99][100].

For sleep, a recent meta-analysis found that only long sleep duration was associated with dementia [101]; however, in our study, nightly sleep both beyond and below 7-8 hours was associated with higher incidence of all-cause dementia, and the risk was higher with long sleep duration. Thus, our results support a U-shaped association between sleep duration and incident dementia, which was similar to studies assessing the relationship between sleep and broader cognitive disorders [85][90][102]. Of note, few longitudinal studies investigated the relationship between regular sleep and incident dementia [103], and future studies involving midlife and longer follow-ups are needed to better ascertain these relationships [36][37][95][104][105].

Lifestyle modifications are common public health interventions that could have durable effects in the prevention and delay of dementia [106][107]. Although the potential mechanisms and pathways are not fully understood, physical activity has been shown to improve physical function [106], and quality of life in older adults [108][109]. Indeed, regular physical activity stimulates antioxidative (protective) processes, which enhance blood flow, brain vasculature, and hippocampal volume [110]. Regular physical activity has also been found to increase brain-

derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1), which confer neuroprotection and neurotransmitter integrity [111][112]. Importantly, the proposed mechanisms of physical activity and sleep on brain health are not mutually exclusive, and may act through, or on other established chronic disease risk factors [113][114]. In the sleep-dementia relationship, the glymphatic system is most active during sleep to regulate inflammation in the brain [113][114], and the process of brain aging may be accelerated by sleep dysregulation [113]. When coupled with physical inactivity, sleep disruption can exacerbate the atrophy of brain structures [115].

Strengths and Limitations

Strengths of this study include: i) valid and reliable risk estimates of dementia using clinical diagnoses, ii) pooling of large community-dwelling population-based cohorts with long-term follow-ups increased statistical power to detect effects, iii) the breadth of countries, which allowed for a robust analysis of these effects and generalizability of results, and iv) low publication bias. Nonetheless, our approach also had some limitations. First, heterogeneity across PA studies requires further investigation into potential unexplained factors. While unlikely due to the exclusion of participants with dementia at baseline, reverse causation could not be ruled out due to the number of studies with short follow-ups. In these cases, participants may already have symptoms of dementia without formal diagnosis. Physical activity and sleep were self-reported, and sleep *quality* was not accounted for; therefore, interpretations of results should include careful consideration of recall bias. Objective measures (e.g., wearable devices) of sleep and PA could enhance internal validity of study findings by providing timely, accurate, and detailed understanding of movement behaviours in older adults with limitations in physical

fitness and recall. Comparison of our self-report findings should therefore be compared to a future SRMA with objective measures, as their use in cohort studies becomes more common.

Given that dementia could precede a clinical diagnosis by a decade [7], generalizability of evidence-based research on modifiable risk factors of dementia is a notable challenge [11]. Dementia has a long preclinical or prodromal period [7][8], which contributes to variability in the time to diagnosis of dementia. In the study of physical activity and sleep with dementia, this could contribute to reverse causation, particularly in light of our reliance on self-reported (behavioral) measures of physical activity and sleep [116]; however, decreases in PA across time would bias our results to the null. Our meta-analysis considered age (<65 or 65+ y) and follow-up (<10 or 10+ y), and results did not change substantially; however, heterogeneity between studies reinforced the influence of other unmeasured factors. Previous research reported significant results with short (below 10 years) follow-ups [36][37] or in older (65+ years) populations [35][34]. The analysis of sex differences in the included studies was limited by the small number of cohorts with exclusively female or male participants. Specifically, the physical activity studies were composed of two all-female cohorts, four all-male cohorts, and one study with 96% male participants. In the sleep studies, there were two all-female studies and one all-male study. Indeed, building on previous meta-analyses with incident dementia [97][117][118], more studies with mid-life changes in physical activity, sedentary time, and sleep, and longer follow-ups are warranted to ascertain the effects of changes in physical activity and sleep on dementia. To enhance representation, studies should include diverse cohorts and present results disaggregated by sex to provide a clearer understanding of sex differences.

Conclusion

Our study shows that the physical activity and sub-optimal sleep were associated with increased risk of dementia, adding to our understanding of the role of regular physical activity and sleep in cognitive health in a globally aging population. These findings suggest that more work is needed in future studies with longer-term follow-up and larger sample sizes to address issues of dose-response and alterability in the movement behaviour-dementia relationships. Taken together, our findings have important clinical implications that could inform guidelines across the life course, including implementation of tailored public health strategies. Whether changes in physical activity, sleep, or sedentary behaviour - a construct distinct from physical inactivity - is also related to dementia, and whether these associations are independent of risk factors such as pre-existing health risks, remain areas in need of future work.

List of Abbreviations

AD, Alzheimer's disease

CI, confidence intervals

CINAHL, cumulative index of nursing and allied health literature

EMBASE, *excerpta medica* database

HR, hazard ratio

MEDLINE, medical literature analysis and retrieval system online

MVPA, moderate- to- vigorous physical activity

PRISMA, preferred reporting items for systematic reviews and meta-analyses

OR, odds ratio

RR, risk ratio

ROBINS-I, risk of bias in non-randomized studies of interventions

SRMA, systematic reviews and meta-analyses

Declarations

Ethics approval and consent to participate.

Authors declare human ethics approval was not needed for this study.

Consent for publication.

Not applicable.

Availability of data and materials.

All data analysed during this study are available from the published articles or from their corresponding authors on reasonable request.

Competing interests.

The authors declare that they have no competing interests.

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Authors' Contributions.

AO had full access to the data and takes responsibility for the integrity and accuracy of all data analysis. AO and CIA conceived of the study. AO and CIA designed the study protocol and wrote the search strategy. PM and JGK undertook the literature searches and study screening. PM performed the quality assessment with CIA oversight. AO and PM undertook data extraction. AO performed the analyses, and MR and CIA oversaw the analyses. AO wrote the draft of the manuscript with inputs from all authors. JK, MR, and HT provided critical revisions to the article. All authors contributed to the interpretation of the findings and approved the final version of the article to be published.

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Table 3.1. Search Strategy Example: Medline search terms and results		
#	**Searches**	**Results**
1	Physical Activity.mp.	126263
2	exp Exercise/	224716
3	exp Exercise Movement Techniques/	9456
4	exp Exercise Therapy/	58083
5	Physical Exertion/	57156
6	Motor Activity/	99224
7	exp Sports/	201494
8	(sport$ or bicycl$ or swim$ or walk$ or run$ or jog$).tw.	473315
9	(physical$ adj2 activ$).tw.	133636
10	(aerobic adj2 (train$ or active$)).tw.	5291
11	or/1-10	881761
12	Sedentary Behavior/	12085
13	Screen Time/	819
14	(sitting or sedentar$).tw.	36089
15	low energy expenditure.tw.	191
16	(computer game* or video game* or television or tv).tw.	31515
17	(physical* adj2 inactivit*).tw.	8982
18	(Reading/ or Books/) and ((time* or duration*).tw. or Time/ or Time Factors/)	6104
19	or/12-18	82840
20	Sleep/	60729
21	(sleep adj3 duration).tw.	11449
22	20 or 21	65849
23	(cognit* or dement*).tw.	517487
24	(cogn* adj3 assess*).tw.	27360
25	(cogn* adj3 dis*).tw.	38394
26	(cogn* adj3 eval*).tw.	9258
27	(cogn* adj3 funct*).tw.	86146
28	(cogn* adj3 imp*).tw.	114859
29	(cogn* adj3 meas*).tw.	18656
30	(memory adj3 imp*).tw.	41791
31	or/23-30	540546
32	(11 or 19 or 22) and 31	42769
33	limit 32 to humans	31561
34	limit 33 to adult	10047
35	exp Child/	2043362
36	exp Infant/	1204271

37	exp Adolescent/	2153069
38	exp Students/	149554
39	or/35-38	3900395
40	34 not 39	7182
41	cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/	1532217
42	longitudinal studies.mp.	171890
43	follow-up studies.mp.	689792
44	cohort studies.mp.	327817
45	prospective studies.mp.	644218
46	or/42-45	1603919
47	41 or 46	1603919
48	40 and 47	1008
49	clinical trial/ or controlled clinical trial/ or randomized controlled trial/ or clinical trial protocol/ or clinical trial, veterinary/	905707
50	48 not 49	757
Note: Although the search strategy was comprehensive, the records identified did not explicitly investigate or sufficiently describe sedentary behaviours for quantitative synthesis.		

Table 3.2. Study Characteristics: Effect of Physical Activity on Dementia Risk.

Author and Country	Study and Sample	Design and Duration of Follow-up	Covariates	Physical Activity Measure	Incident Dementia	Risk Estimate (95%CI)
Yoshitake et al., 1995 [45] Japan	Hisayama study; n=828 (59.7% W, mean age: 73.6 y).	Prospective longitudinal design (average follow-up: 7 years).	Age, sex, physical activity, and Hasegawa's dementia scale.	Self-reported physical activity performed 3+ times per week.	Incident dementia cases (n=103) based on standard clinical evaluation criteria.	Highest PA level: RR, 0.20, 0.06 – 0.68
Laurin et al., 2001 [46] Canada	Canadian Study of Health and Aging; n=6,434 (60.3% W; mean age: 73.1 y).	Prospective longitudinal design (average follow-up period: 5 years).	Age, sex, and education.	Self-reported physical activity performed 3+ times per week.	Incident dementia cases (n=285) based on standard clinical evaluation criteria.	Highest PA level: OR, 0.63, 0.4 – 0.98
Verghese et al., 2003 [47] United States of America	Bronx Aging Study; n=469 (64.1% F; mean age: 79.1 y).	Prospective longitudinal design (average follow-up: 5.1 years).	Age, sex, education, chronic medical illness, baseline score on the Blessed Information-Memory-Concentration test.	Self-reported physical activity, based on a score (0-77) of 16+ points.	Incident dementia cases (n=124) based on standard clinical evaluation criteria.	Highest PA level: HR, 1.27, 0.78 – 2.06
Abbot et al., 2004 [48] United States of America	Honolulu-Asia Aging Study; n= 2,257 M (mean age: 76.8 y).	Prospective longitudinal design (average follow-up: 6 years).	Age, APOE, baseline Cognitive Abilities Screening Instrument score, decline in physical activity since mid adulthood, physical performance score, education, BMI, childhood years spent living in Japan, status as a skilled professional, hypertension, diabetes, prevalent coronary heart disease, and total and high-density lipoprotein cholesterol.	Self-reported physical activity at two time points, based on a physical activity index, resulting from the inverse of low PA.	Incident dementia cases (n=158) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.52, 0.3 – 0.9
Podewils et al., 2005 [49] United States of America	Cardiovascular Health Cognition Study (CHCS); n=3,375 (59.1% F, mean age: 74.8 y).	Prospective longitudinal design (average follow-up: 5.4 years).	Age, education, gender, ethnicity, APOE, baseline Modified Mini-Mental State Examination score, magnetic resonance imaging white-matter-grade score, activities of daily living impairment, instrumental activities of daily living	Self-reported physical activity based on the highest quartile resulting from metabolic equivalent of task (MET) per week.	Incident dementia cases (n=480) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.85, 0.61 – 1.19

			impairment, Lubben Social Network Score, and social support score.			
Ravaglia et al., 2008 [50] Italy	Conselice Study of Brain Aging (CSBA); n=469 (53.5% W; mean age: 79.1 y).	Prospective longitudinal design (average follow-up: 3.9 years).	Age, gender, education, APOE, cardiovascular disease, hypertension, hyperhomo-cysteinemia, comorbidity, basic activities of daily living.	Self-reported physical activity, based on 150+ minutes per week of moderate-to-vigorous PA.	Incident dementia cases (n=86) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.73, 0.46 – 1.15
Scarmeas et al., 2009 [51] United States of America	Washington Heights-Hamilton Heights-Inwood Community Aging Project (WHICAP); n=1880 (69% F; mean age: 77.2 y).	Prospective longitudinal design (average follow-up: 5.4 years).	Age, sex, ethnicity, education, APOE, caloric intake, BMI, smoking, depression, leisure activities, comorbidity index, baseline Clinical Dementia Rating score, and time between first dietary and first physical activity assessment.	Self-reported physical activity resulting from a score categorized into tertiles.	Incident dementia cases (n=282) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.63, 0.45 – 0.9
Chang et al., 2010 [52] Iceland	Reykjavik study; n=4,945 (57.7% F, mean age: 51.1 y).	Prospective longitudinal design (average follow-up: 25.7 years).	Age, sex, education, BMI, systolic blood pressure, smoking, and cholesterol.	Self-reported physical activity, performed 5+ hours per week.	Incident dementia cases (n=184) based on standard clinical evaluation criteria.	Highest PA level: OR, 0.76, 0.34 – 1.63
Sattler et al., 2011 [53] Germany	Interdisciplinary Longitudinal Study of Adult Development (ILSE); n=500 (49.3% F, mean age: 74.1 y).	Prospective longitudinal design (average follow-up: 12 years).	Age, gender, education, socioeconomic status, and depressive symptoms.	Self-reported physical activity performed 2+ hours per week.	Incident dementia cases (n=24) based on standard clinical evaluation criteria.	Highest PA level: OR, 0.93, 0.45 – 1.9
Bowen et al., 2012 [54] United States of America	Aging, Demographics, and Memory Study (ADAMS) from Health and Retirement Study (HRS); n=808 (58.5% F; mean age: 77.5 y).	Prospective longitudinal design (average follow-up: 5 years).	Age, sex, education, race, APOE, BMI, diabetes, hypertension, stroke, heart disease, smoking, and alcohol.	Self-reported physical activity performed 3+ times per week.	Incident dementia cases (n=277) based on standard clinical evaluation criteria.	Highest PA level: OR, 0.79, 0.64 – 0.97

Buchman et al., 2012 [55] United States of America	Rush Memory and Aging; n=716 (76% F, mean age: 81.6 y).	Prospective longitudinal design (average follow-up: 4 years).	Age, sex, and education, social, and cognitive activities, as well as current level of motor function, depressive symptoms, chronic health conditions, and APOE.	Physical activity was measured objectively using actigraphy.	Incident dementia cases (n=71) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.53, 0.29 – 0.95
Elwood et al., 2013 [56] United Kingdom	Caerphilly cohort study; n=2,235 M (mean age: 52 y).	Prospective longitudinal design (average follow-up: 30 years).	Age, social class, and National Adult Reading Test at baseline.	Self-reported physical activity performed 3+ times per week.	Incident dementia cases (n=79) based on standard clinical evaluation criteria.	Highest PA level: OR, 0.41, 0.22 – 0.77
Gray et al., 2013 [57] United States of America	Adult Changes in Thought (ACT) study; n=2,619 (60.1% F, mean age: 76.8 y).	Prospective longitudinal design (average follow-up: 6.5 years).	Age, sex, education, race, body mass index, depressive symptoms, antidepressant use, self-reported health, hypertension, diabetes, myocardial infarction, congestive heart failure, smoking, and baseline Cognitive Abilities Screening Instrument score.	Self-reported physical activity, resulting from the inverse of low PA.	Incident dementia cases (n=521) based on standard clinical evaluation criteria.	Highest PA level: HR, 1.03, 0.85 – 1.25
Tolppanen et al., 2014 [58] Finland	Cardiovascular Risk Factors, Aging and Dementia (CAIDE); n=1,511 (62.3% F, mean age: 50.6 y).	Prospective longitudinal design (average follow-up: 28.3 years).	Age, sex, education, midlife BMI, marital status, occupational physical activity level, smoking, and cardiorespiratory and musculoskeletal conditions.	Self-reported physical activity, resulting from the inverse of low PA.	Incident dementia cases (n=250) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.86, 0.69 – 1.08
Wang et al., 2014 [59] United States of America	Study of Osteoprotic Fractures (SOF); n=1,249 W (mean age: 83.3 y).	Prospective longitudinal design (average follow-up: 5 years).	Age, educational level, cognition, depressive symptoms, BMI, hypertension, smoking, and coronary artery disease.	Self-reported physical activity, resulting from the number of city-blocks or equivalent (10 blocks ≈ 1 mile) typically walked each day.	Incident dementia cases (n=212) based on standard clinical evaluation criteria.	Highest PA level: OR, 0.47, 0.33 – 0.69
Paganini-Hill et al., 2016 [60]	The 90+ study; n=587, (demographic data not available, mean age: 93 y).	Prospective longitudinal design (average follow-up: 3 years).	Age, sex, and education.	Self-reported physical activity performed 1+ times per week.	Incident dementia cases (n=268) based on standard clinical evaluation criteria.	Highest PA level: HR, 1.16, 0.83 – 1.62

United States of America						
Hessler et al., 2016 [61] Germany	Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg (INVADE-trial) study; n=3547 (59.2% F, mean age: 67.3 y).	Prospective longitudinal design (average follow-up: 6.7years).	Age, sex, and education.	Self-reported physical activity performed 3+ times per week, resulting from the inverse of physical inactivity.	Incident dementia cases (n=296) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.55, 0.41 – 0.76
Muller et al., 2017 [62] United States of America	Veterans Exercise Testing Study; n=6104 (3.5% F, mean age: 59.2y).	Prospective longitudinal design (average follow-up: 10.3 years).	Unadjusted (did not include covariates).	Self-reported physical activity performed 3+ times per week, resulting from the inverse of physical inactivity.	Incident dementia cases (n=353) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.94, 0.76 – 1.16
Tan et al., 2017 [63] United States of America	Framingham Study Original and Offspring; n=3,714 (54.4% F; mean age: 70.5 y).	Prospective longitudinal design (average follow-up: 7.5 years).	Age, sex, high school degree, APOE, log plasma homocysteine, systolic blood pressure, diastolic blood pressure, antihypertensive medication, total cholesterol, current smoking, prevalent cardiovascular disease, diabetes, stroke, and atrial fibrillation.	Self-reported physical activity, based on the highest quantile (a score resulting from oxygen consumption or metabolic equivalents).	Incident dementia cases (n=236) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.95, 0.63 – 1.41
Gross et al., 2017 [64] United States of America	Johns Hopkins Precursors study; n=646 (7.4% W, mean age: 47.1 y).	Prospective longitudinal design (average follow-up: 30 years).	Age, sex, smoking, diabetes, and hypertension.	Self-reported physical activity, based on metabolic equivalents (MET h/day).	Incident dementia cases (n=28) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.59, 0.19 – 1.87
Tomata et al., 2017 [65] Japan	Ohsaki cohort study; n=6,909 (55.6% W, mean age: 74.6 y).	Prospective longitudinal design (average follow-up: 5.7 years).	Age, history of disease (stroke, hypertension, myocardial infarction, diabetes or hyperlipidemia), education, smoking, alcohol, psychological	Self-reported physical activity at a two time points; based on 1+ hours per day.	Incident dementia cases (n=638) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.72, 0.53 – 0.97

			distress score, pain, and physical functioning level.			
Sabia et al., 2017 [66] United Kingdom	Whitehall II study; n=10,308 (33.1% F, mean age: 45 y).	Prospective longitudinal design (average follow-up: 26.6 years).	Age, sex, ethnicity, education, occupational position, marital status, smoking status, alcohol consumption, and fruit and vegetable consumption, hypertension, diabetes, body mass index, General Health Questionnaire score, cardiovascular disease, and cardiovascular disease drugs.	Self-reported physical activity, based on 2+ hours per week of moderate-to-vigorous PA.	Incident dementia cases (n=329) based on standard clinical evaluation criteria.	Highest PA level: HR, 1.07, 0.86 – 1.35
Shakersain et al., 2018 [67] Sweden	Swedish National study on Aging and Care-Kungsholmen (SNAC-K); n=2,223 (60.8% W; mean age: 70.6 y).	Prospective longitudinal design (average follow-up: 6 years).	Age, sex, education, civil status, total calorie intake, dietary vitamin/mineral supplement use, smoking, body mass index, vascular disorders, cancer, diabetes, depression, APOE, diet, and leisure activities.	Self-reported physical activity performed 3+ times per week.	Incident dementia cases (data not available) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.39, 0.22 – 0.67
Shih et al., 2018 [68] United States of America	Sacramento Area Latino Study on Aging (SALSA); n=1,438 (58.4% F, mean age: 70 y).	Prospective longitudinal design (average follow-up: 6.5 years).	Age, sex, education, smoking status, hours of standing or walking at work, history of stroke, hypertension, cardiovascular disease, depressive symptoms, BMI, smoking, alcohol, nativity, area of residence, and type of occupation.	Self-reported physical activity, based on the metabolic equivalent of task (MET) per day.	Incident dementia cases (n=136) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.7, 0.49 – 0.99
Larsson et al., 2018 [69] Sweden	Swedish Infrastructure for Medical Population-based Life-course Environmental Research (SIMPLER); n=28,775 (46.6% F, mean age: 71.6 y).	Prospective longitudinal design (average follow-up: 12.6 years).	Age, sex, education, BMI, healthy diet, smoking, hypertension, alcohol and coffee consumption, hypercholesterolemia, diabetes, and sleep duration.	Self-reported physical activity; resulting from walking/cycling 1.5+ hours per day, or leisure-time exercise 5+ hours per week).	Incident dementia cases (n=3,755) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.99, 0.83 – 1.17
Shaaban et al., 2019 [70]	Monongahela-Youghiogheny Healthy Aging Team (MYHAT); n=1,701	Prospective longitudinal design (average follow-up: 3 years).	Unadjusted (did not include covariates).	Self-reported physical activity performed 3+ times per week.	Incident dementia cases (n=109) based on standard	Highest PA level: HR, 0.65, 0.47 – 0.9

United States of America	(62.3% F; mean age: 78 y).				clinical evaluation criteria.	
Hansson et al., 2019 [71] Sweden	Swedish Vasaloppet and participants in the Swedish population-based Malmo Diet and Cancer Study; n= 20,639 (60% W, mean age: 57.5 y).	Prospective longitudinal design (average follow-up: 15 years).	Age, sex, education, smoking, systolic blood pressure, BMI, alcohol, diabetes, cardiovascular disease, blood pressure-lowering medication, lipid-lowering medication, and physically heavy work.	Self-reported physical activity; resulting from the sum of the two assessments (5 years apart).	Incident dementia cases (n=1,375) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.9, 0.79 – 1.03
Najar et al., 2019 [72] Sweden	Gothenburg study; n=800 W (average: 47.2 y).	Prospective longitudinal design (average follow-up: 31.5 years).	Age, cognitive activity, smoking, and socioeconomic status.	Self-reported physical activity, performed 3+ times per week.	Incident dementia cases (n=194) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.72, 0.50 – 1.04
Palta et al., 2019 [73] United States of America	Atherosclerosis Risk in Communities (ARIC); n=10,705 (56% F, mean age: 60 y).	Prospective longitudinal design (average follow-up: 17.4 years).	Age, sex, education, race, APOE, smoking, household income, neighborhood socioeconomic status summary score at Visit 3, diabetes, hypertension, and BMI at Visit 4.	Self-reported physical activity at two time points; based on tertiles of metabolic equivalent of task (e.g., MET-min).	Incident dementia cases (n=1,063) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.71, 0.54 – 0.92
Zotcheva et al., 2019 [74] Norway	Nord-Trondelag Health (HUNT) study; n= 28,916 (50.2% W, mean age: 43.4 y).	Prospective longitudinal design (average follow-up: 25.2 years).	Sex, education, marital status, smoking, alcohol, longstanding physical illness, and distress.	Self-reported physical activity, based on moderate-to-vigorous PA.	Incident dementia cases (n=359) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.81, 0.62 – 1.06
Kunutsor et al., 2020 [75] Finland	Kuopio Ischaemic Heart Disease (KIHD) study; n=2,394 M (mean age: 53 y).	Prospective longitudinal design (average follow-up: 24.9 years).	Age, BMI, systolic blood pressure, smoking, alcohol, history of type 2 diabetes, total cholesterol, high-density lipoprotein cholesterol, history of coronary heart disease, and C-reactive protein.	Self-reported physical activity; based on the highest tertile resulting from the metabolic equivalent of task (MET) per day.	Incident dementia cases (n=208) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.97, 0.69 – 1.38
Rolandi et al., 2020 [76] Italy	Invecchiamento Cerebrale ad Abbiategrasso (InveCe.Ab) study;	Prospective longitudinal design (average follow-up: 6.9 years).	APOE, diabetes, heart disease, stroke, and delirium.	Self-reported physical activity, resulting from the inverse of physical inactivity.	Incident dementia cases (n = 111) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.75, 0.51 - 1.11

	n=1,100 (54.1% F, mean age: 53.7 y).					
Dupre et al., 2020 [77] France	Three-city cohort; n= 1,550 (63.6% F, mean age: 80 y).	Prospective longitudinal design (average follow-up: 4.6 years).	Age, center, sex, APOE, and education.	Self-reported physical activity performed 3+ times per week.	Incident dementia cases (n=117) based on standard clinical evaluation criteria.	Highest PA level: HR, 1.33, 0.72 – 2.44
Wu et al., 2020 [78] China	Shanghi Aging study; n=1,648 (54.5% F, mean age: 71.5 y).	Prospective longitudinal design (average follow-up: 5 years).	Age, sex, years of education, APOE, smoking, alcohol, hypertension, diabetes, and BMI.	Self-reported physical activity, based on the metabolic equivalent of task (MET).	Incident dementia cases (n=166) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.62, 0.44 – 0.89
Boongird et al., 2020 [79] Thailand	Health Check Ubon Ratchathani Project; n=206,073 (53.6% F, mean age: 62.5 y).	Prospective longitudinal design (average follow-up: 6 years).	Age, hypertension, diabetes, BMI, waist circumference, obesity, central obesity, and alcohol.	Self-reported physical activity performed 5+ days per week.	Incident dementia cases (n=480) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.41, 0.26 – 0.66
Feter et al., 2021 [80] United Kingdom	English Longitudinal Study of Ageing (ELSA); n=9,275 (56.2% F, mean age 63.8 y).	Prospective longitudinal design (average follow-up: 15 years).	Age, sex, ethnic group, education level, marital status, employment activity, and age x physical activity interaction, smoking, alcohol consumption, diabetes, emotional, nervous, or psychiatric problems, heart diseases (i.e., hypertension, angina, heart attack, heart murmur, abnormal heart rhythm, stroke), and cognitive function at baseline.	Self-reported physical activity performed 1+ times per week.	Incident dementia cases (n=631) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.22, 0.17 – 0.3
Yoon et al., 2021 [81] Korea	National Health Insurance Service (NHIS)–Senior database of Korea; n=62,286 (60.4% W, mean age: 73.2 y).	Prospective longitudinal design (average follow-up: 3.5 years).	Age, sex, body mass index, Hospital Frailty Risk score, annual income, smoking, alcohol, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, heart failure, vascular disease, prior ischemic stroke or transient ischemic attack, chronic obstructive pulmonary disease, and malignancy.	Self-reported physical activity, based on the metabolic equivalent of task (MET) per week.	Incident dementia cases (n=3,757) based on standard clinical evaluation criteria.	Highest PA level: HR, 0.73, 0.65 – 0.83

Nabe-Nielsen et al., 2021 [82] Denmark	Copenhagen Male Study (CMS); n=4,721 M (mean age: 49 y).	Prospective longitudinal design (average follow-up: 29.3 years).	Age, age at exposure assessment, marital status, socioeconomic position, calendar period, psychological stress, smoking, alcohol, BMI, and systolic and diastolic blood pressure.	Self-reported physical activity, performed 3+ times per week.	Incident dementia cases (n=697) based on standard clinical evaluation criteria.	Highest PA level: RR, 0.8, 0.6 – 1.08
Abbreviations: CI, confidence interval; W, women; F, females; M, males or men; y, years; PA, physical activity; APOE, apolipoprotein E ε4 allele; MET, metabolic equivalent of task.						

Table 3.3. Study Characteristics: Effect of Sleep Duration on Dementia Risk.

Author and Country	Study and Sample	Design and Duration of Follow-up	Covariates	Sleep Measure	Incident Dementia	Risk Estimate (95%CI)
Benito-Leon et al., 2009 [83] Spain	Neurological Disorders of Central Spain (NEDICES); n=3,286 (56.9% F; mean age: 73.2 y).	Prospective longitudinal design (average follow-up: 3.2 years).	Age, education, smoking, and alcohol.	Self-reported nightly sleep duration (hours) was categorized (≤ 5, 6, 7, 8, ≥ 9).	Incident dementia cases (n=140) based on standard clinical evaluation criteria.	Short Sleep: RR, 1.87, 0.85 – 4.15 Long Sleep: RR, 2.18, 1.09 – 4.37
Virta et al., 2013 [84] Finland	Finnish Twin study; n=2,336 (47.9% W; mean age: 73.6 y).	Prospective longitudinal design (average follow-up: 22.5 years).	Age, sex, education, APOE status, follow-up, life satisfaction, obesity, hypertension, physical inactivity, and alcohol.	Self-reported nightly sleep duration (hours) was categorized (< 7, 7 to < 8, ≥ 8).	Incident dementia cases (n=170) based on standard clinical evaluation criteria.	Short Sleep: OR, 1.5, 0.92 – 2.45 Long Sleep: OR, 1.75, 1.07 – 2.88
Chen et al., 2016 [85] United States	Women's Health Initiative Memory Study (WHIMS); n=7,444 W (mean age: 70.1 y).	Prospective longitudinal design (average follow-up: 7.3 to 7.7 y).	Age, race, socioeconomic status, smoking, alcohol, physical activity, depression, previous hormone therapy use, BMI, prior cardiovascular disease history, hypertension, DM, and hypercholesterolemia.	Self-reported nightly sleep duration (hours) was categorized (≤ 6, 7, ≥ 8).	Incident dementia cases (n=549) based on standard clinical evaluation criteria.	Short Sleep: HR, 1.36, 1.09 – 1.71 Long Sleep: HR, 1.27, 0.98 – 1.64
Bokenberger et al., 2016 [86] Sweden	Swedish Screening Across the Lifespan Twin (SALT); n=11,247 (56.4% W, mean age: 72.5 y).	Prospective longitudinal design (average follow-up: 14.3 years).	Follow-up time, sex, and education with age as the underlying timescale.	Self-reported nightly sleep duration (hours) was categorized (≤ 6, ≥ 9).	Incident dementia cases (n=1,850) based on standard clinical evaluation criteria.	Short Sleep: HR, 1.74, 1.19 – 2.55 Long Sleep: HR, 1.18, 1.01 – 1.38
Sabia et al., 2017 [87] United Kingdom	Whitehall II study; n=7,959, (32.8% F, mean age: 50.6 y).	Prospective longitudinal design (average follow-up: 25 years).	Age, sex, ethnicity, education, marital status, alcohol, physical activity, smoking, fruit and vegetable consumption, BMI, hypertension, diabetes, cardiovascular disease, depression, and central nervous system medications.	Self-reported nightly sleep duration (hours) was categorized (≤ 6, 7, ≥ 8).	Incident dementia cases (n=521) based on standard clinical evaluation criteria.	Short Sleep: HR, 1.22, 1.01 – 1.48 Long Sleep: HR, 1.25, 0.98 – 1.60
Luojus et al., 2017 [88] Finland	Kuopio Ischemic Heart Disease (KIHD) study; n=2,386 M (mean age: 53 y).	Prospective longitudinal design (average follow-up: 21.9 years).	Age, examination year, depression, physical activity, alcohol, smoking, systolic blood pressure, BMI, low-density lipoprotein and high-density lipoprotein cholesterol, high-sensitivity C-reactive protein,	Self-reported nightly sleep duration (hours) was categorized (≤ 6.5, 7 to <8, ≥ 8.5).	Incident dementia cases (n=287) based on standard clinical evaluation criteria.	Short Sleep: RR, 1.15, 0.85 – 1.56 Long Sleep: RR, 0.83, 0.55 – 1.23

			cardiovascular disease history, education, and living alone.			
Westwood et al., 2017 [89] United States	Framingham Heart Study; n=2,457 (57% F; mean age: 72 y).	Prospective longitudinal design (average follow-up: 10 years).	Age, sex, education, APOE status, and homocysteine	Self-reported nightly sleep duration (hours) was categorized (< 6, 6 to 9, > 9).	Incident dementia cases (n=234) based on standard clinical evaluation criteria.	Short Sleep: HR, 0.9, 0.58 – 1.38 Long Sleep: HR, 2.01, 1.24 – 3.26
Lutsey et al., 2018 [90] United States	Atherosclerosis Risk in Communities (ARIC); n=1,667 (53% F; mean age: 61.4 y).	Prospective longitudinal design (average follow-up: 15 years).	Age, sex, center, education, and APOE, BMI, smoking, and leisure time physical activity, diabetes, antihypertensive medications, C-reactive protein, and systolic blood pressure.	Self-reported nightly sleep duration (hours) was categorized (< 7, 7 to < 8, 8 to 9, ≥ 9).	Incident MCI/dementia cases (n=269) based on standard clinical evaluation criteria.	Short Sleep: RR, 1.89, 1.01 – 3.51 Long Sleep: RR, 1.53, 0.69 – 3.39
Sindi et al., 2018 [91] Finland and Sweden	Kungsholmen Project (KP), H70 study, Cardiovascular Risk Factors study, Aging and Dementia (CAIDE); n=1,446; late-life (60.4% W, mean ages: 70 y for CAIDE/H70).	Prospective longitudinal design (average follow-up: 5 to 9 years).	Age, sex, education, follow-up time, study, alcohol consumption, smoking, physical activity, cohabitant status, APOE status, cardio/cerebrovascular conditions and hypnotics, hopelessness.	Self-reported nightly sleep duration (hours) was categorized (≤ 6, ≥ 9).	Incident dementia cases (n=19, out of 437) based on standard clinical evaluation criteria.	Short Sleep: OR, 0.74, 0.36 – 1.53 Long Sleep: OR, 3.98, 1.87 – 8.48
Larsson et al., 2018 [92] Sweden	Swedish Infrastructure for Medical Population-Based Life-Course and Environmental Research (SIMPLER); n=28,775 (46.6% F, mean age: 71.6 y)	Prospective longitudinal design (average follow-up: 12.6 years).	Age, sex, education, BMI, healthy diet, smoking, hypertension, alcohol and coffee consumption, hypercholesterolemia, diabetes, and physical activity.	Self-reported nightly sleep duration (hours) was categorized (≤ 6, 6 to 7, 7 to 9, > 9).	Incident dementia cases (n=3,755) based on standard clinical evaluation criteria.	Short Sleep: HR, 1.05, 0.93 – 1.19 Long Sleep: HR, 1.44, 1.11 – 1.86
Ohara et al., 2018 [93] Japan	Hisayama study; n=1,517 (56% F, mean age: 70 y).	Prospective longitudinal design (average follow-up: 8.8 years).	Age, sex, education, systolic blood pressure, antihypertensive agent, diabetes mellitus, use of hypnotics, hypercholesterolemia, BMI, electrocardiographic abnormalities, history of stroke, smoking habits, alcohol intake, and regular exercise.	Self-reported nightly sleep duration (hours) was categorized (< 5, 5 to 6.9, 7 to 7.9, 8 to 9.9, ≥ 10).	Incident dementia cases (n=294) based on standard clinical evaluation criteria.	Short Sleep: HR, 2.64, 1.38 – 0.05 Long Sleep: HR, 1.57, 1.15 – 2.16

Lu et al., 2018 [94] Japan	Ohsaki Cohort study; n= 7,422 (55.9% F, mean age: 74.6 y).	Prospective longitudinal design (average follow-up: 5.7 years).	Age, sex, sleep duration in 1994, BMI, history of diseases (stroke, hypertension, myocardial infarction, diabetes, or hyperlipidemia), smoking, alcohol, education, pain, psychological distress score, and time spent walking.	Self-reported nightly sleep duration (hours) was categorized (≤ 6, 7 to < 8, ≥ 9).	Incident dementia cases (n=688) based on standard clinical evaluation criteria.	Short Sleep: HR, 0.98, 0.61 – 1.57 Long Sleep: HR, 1.01, 0.75 – 1.34
Uwaka et al., 2022 [95] Japan	New Integrated Suburban Seniority Investigation (NISSIN) project, Japan; n=1,954 (48.5% F; mean age: 64 y).	Prospective longitudinal design (average follow-up: 15.6 years).	Year of participation, sex, marital status, working status, education, smoking, alcohol, BMI, daily walking, depressive tendencies, and functional capacity.	Self-reported nightly sleep duration (hours) was categorized (≤ 6, 6 to 7.9, ≥ 8).	Incident dementia cases (n=260) based on standard clinical evaluation criteria.	Short Sleep: HR, 1.7, 1.02 – 2.83 Long Sleep: HR, 1.34, 0.84 – 1.95
Wong et al., 2023 [96] United Kingdom	Million Women Study; n=830,716 W (mean age: 60 y).	Prospective longitudinal design (average follow-up: 17 years).	Deprivation, education, exercise, BMI, smoking status, alcohol, menopausal hormones, paid work, marital status, depression/anxiety, diabetes, high blood pressure, and self-rated health.	Self-reported nightly sleep duration (hours) was categorized (< 7, 7 to <8, ≥ 8).	Incident dementia cases (n=34,576) based on standard clinical evaluation criteria.	Short Sleep: RR, 1.12, 1.06 –1.19 Long Sleep: RR, 1.08, 1.0 –1.16
Abbreviations: CI, confidence interval; W, women; F, females; M, males or men; y, years; APOE, apolipoprotein E ε4 allele; BMI, body mass index.						

Table 3.4. Meta-Analysis of Physical Activity studies.

Outcomes	No. of studies	Effect estimate (RR)	95% CI	I^2 (%)
Main analysis				
Overall	38	0.72	0.64 to 0.81	81.39
Subgroup analyses				
Below 65 years old	15	0.69	0.55 to 0.87	88.3
65 years and older	23	0.74	0.66 to 0.84	67.5
Short follow-up duration (under 10 years	23	0.71	0.62 to 0.80	66.3
Long follow-up duration (10+ years)	15	0.74	0.60 to 0.93	89.1
Below 65 years old with long follow-up (10+ years)	13	0.72	0.56 to 0.92	89.7
65 years and older with short follow-up (below 10 years)	21	0.72	0.64 to 0.82	65.6

Abbreviations: RR, risk ratio; CI, confidence interval

Table 3.5. Meta-Analysis of Sleep studies.

Outcomes	No. of studies	Effect estimate (RR)	95% CI	I^2 (%)
Main analysis				
Short Sleepers	14	1.24	1.11 to 1.39	54.8
Long Sleepers	14	1.32	1.16 to 1.51	66.5
Subgroup analyses: Short Sleepers				
Below age 65 years (with long follow-up (10+ years))	5	1.17	1.06 to 1.29	17.4
65 years and older	9	1.27	1.03 to 1.57	63.2
Short follow-up duration (under 10 years	5	1.35	0.92 to 1.97	62.3
Long follow-up duration (10+ years)	9	1.19	1.07 to 1.32	45.5
65 years and older with long follow-up (10+ years)	4	1.22	0.92 to 1.63	66.0
Subgroup analyses: Long Sleepers				
Below age 65 years (with long follow-up (10+ years))	5	1.09	1.02 to 1.18	1.1
65 years and older	9	1.48	1.22 to 1.80	66.4
Short follow-up duration (under 10 years	5	1.60	1.07 to 2.40	81.3
Long follow-up duration (10+ years)	9	1.25	1.09 to 1.42	55.5
65 years and older with long follow-up (10+ years)	4	1.44	1.15 to 1.82	55.7

Abbreviations: RR, risk ratio; CI, confidence interval

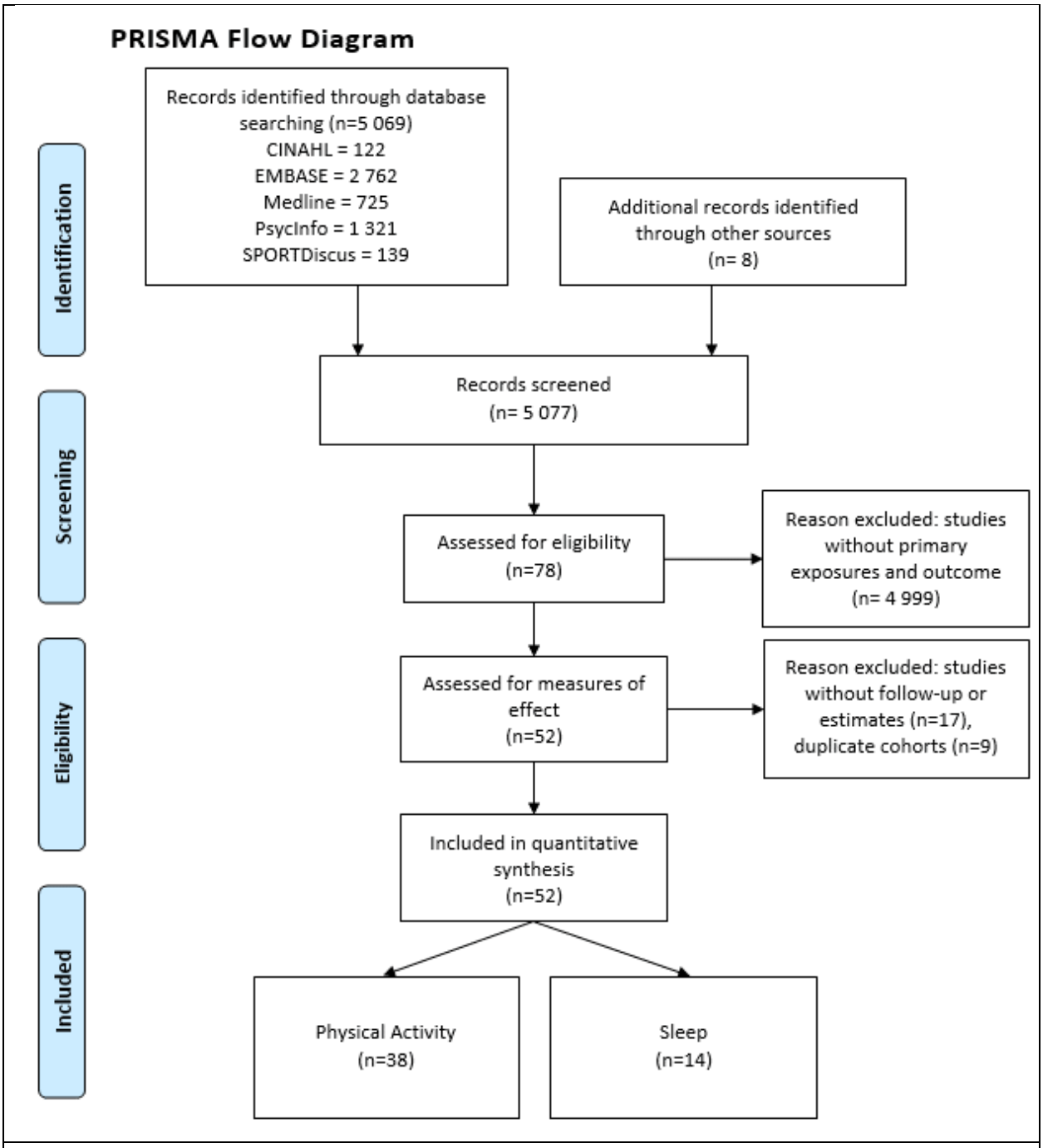

Figure 3.1. Figure showing a representation of the PRISMA flow chart.
Note: Although the search strategy was comprehensive, the records identified did not explicitly investigate or sufficiently describe sedentary behaviours for quantitative synthesis.

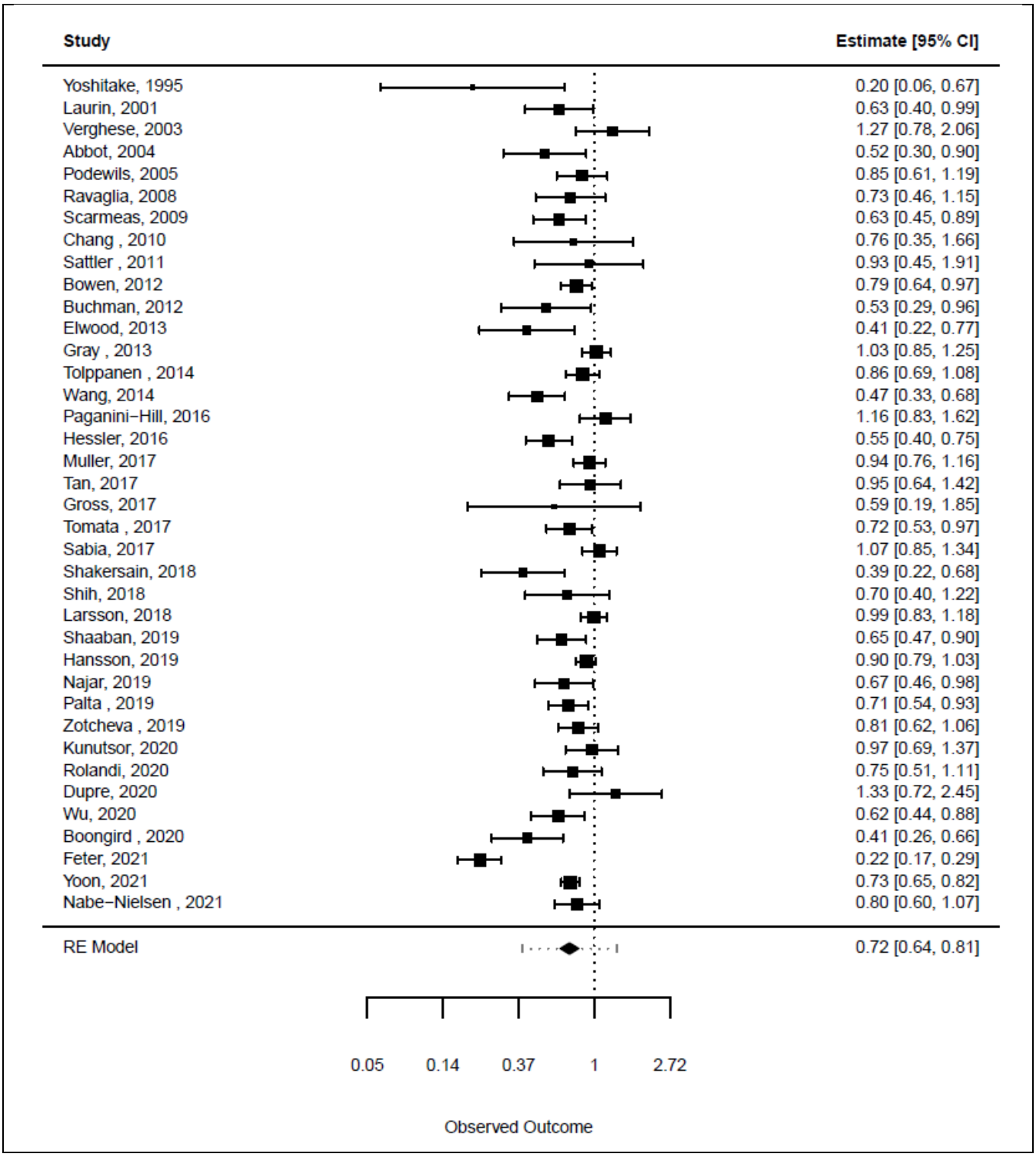
Study
Estimate [95% CI]
Yoshitake, 1995 0.20 [0.06, 0.67]
Laurin, 2001 0.63 [0.40, 0.99]
Verghese, 2003 1.27 [0.78, 2.06]
Abbot, 2004 0.52 [0.30, 0.90]
Podewils, 2005 0.85 [0.61, 1.19]
Ravaglia, 2008 0.73 [0.46, 1.15]
Scarmeas, 2009 0.63 [0.45, 0.89]
Chang , 2010 0.76 [0.35, 1.66]
Sattler , 2011 0.93 [0.45, 1.91]
Bowen, 2012 0.79 [0.64, 0.97]
Buchman, 2012 0.53 [0.29, 0.96]
Elwood, 2013 0.41 [0.22, 0.77]
Gray , 2013 1.03 [0.85, 1.25]
Tolppanen , 2014 0.86 [0.69, 1.08]
Wang, 2014 0.47 [0.33, 0.68]
Paganini−Hill, 2016 1.16 [0.83, 1.62]
Hessler, 2016 0.55 [0.40, 0.75]
Muller, 2017 0.94 [0.76, 1.16]
Tan, 2017 0.95 [0.64, 1.42]
Gross, 2017 0.59 [0.19, 1.85]
Tomata , 2017 0.72 [0.53, 0.97]
Sabia, 2017 1.07 [0.85, 1.34]
Shakersain, 2018 0.39 [0.22, 0.68]
Shih, 2018 0.70 [0.40, 1.22]
Larsson, 2018 0.99 [0.83, 1.18]
Shaaban, 2019 0.65 [0.47, 0.90]
Hansson, 2019 0.90 [0.79, 1.03]
Najar, 2019 0.67 [0.46, 0.98]
Palta , 2019 0.71 [0.54, 0.93]
Zotcheva , 2019 0.81 [0.62, 1.06]
Kunutsor, 2020 0.97 [0.69, 1.37]
Rolandi, 2020 0.75 [0.51, 1.11]
Dupre, 2020 1.33 [0.72, 2.45]
Wu, 2020 0.62 [0.44, 0.88]
Boongird , 2020 0.41 [0.26, 0.66]
Feter, 2021 0.22 [0.17, 0.29]
Yoon, 2021 0.73 [0.65, 0.82]
Nabe−Nielsen , 2021 0.80 [0.60, 1.07]
RE Model 0.72 [0.64, 0.81]
0.05
0.14
0.37
1
2.72
Observed Outcome

Figure 3.2. Figure showing a representation of the forest plot: associations between physical activity and incident dementia.

Forest plot, showing risk ratio with 95% confidence intervals (CIs), is a graphical representation of the random-effects model meta-analyses. The solid diamond shape at the bottom represents the estimated risk ratio (RR) along with its 95% confidence interval (CI), which indicates statistical significance when it does not cross 1. The dotted interval, which may cross 1, corresponds to the prediction interval, reflecting the variability of the risk ratio across different studies (i.e., how much the risk ratio can vary across studies).

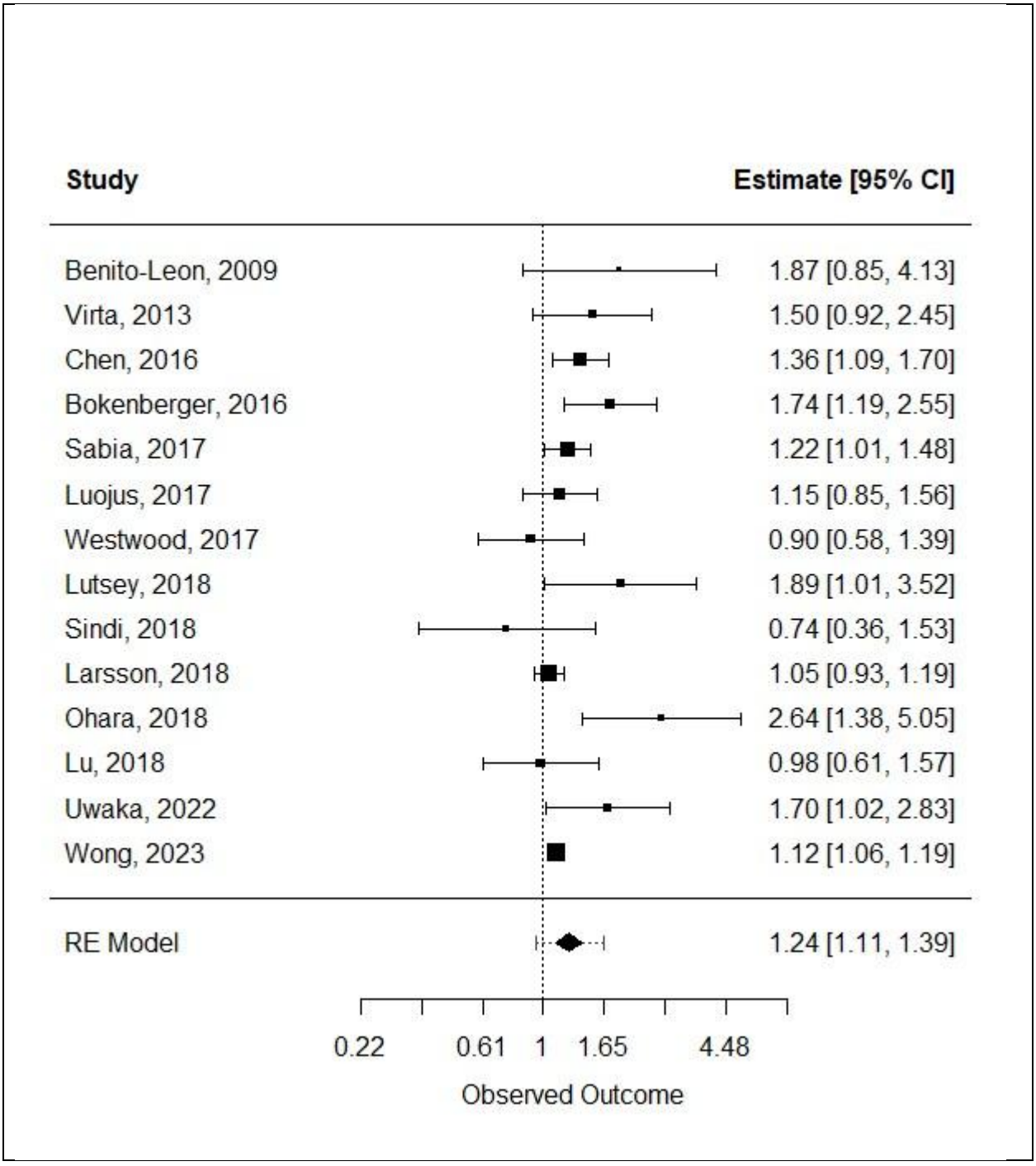
Study
Estimate [95% CI]
Benito-Leon, 2009
1.87 [0.85, 4.13]
Virta, 2013
1.50 [0.92, 2.45]
Chen, 2016
1.36 [1.09, 1.70]
Bokenberger, 2016
1.74 [1.19, 2.55]
Sabia, 2017
1.22 [1.01, 1.48]
Luojus, 2017
1.15 [0.85, 1.56]
Westwood, 2017
0.90 [0.58, 1.39]
Lutsey, 2018
1.89 [1.01, 3.52]
Sindi, 2018
0.74 [0.36, 1.53]
Larsson, 2018
1.05 [0.93, 1.19]
Ohara, 2018
2.64 [1.38, 5.05]
Lu, 2018
0.98 [0.61, 1.57]
Uwaka, 2022
1.70 [1.02, 2.83]
Wong, 2023
1.12 [1.06, 1.19]
RE Model
1.24 [1.11, 1.39]
0.22
0.61
1
1.65
4.48
Observed Outcome

Figure 3.3. Figure showing a representation of the forest plot: associations between short sleep duration and incident dementia.

Forest plot, showing risk ratio with 95% confidence intervals (CIs), is a graphical representation of the random-effects model meta-analyses. The solid diamond shape at the bottom represents the estimated risk ratio (RR) along with its 95% confidence interval (CI), which indicates statistical significance when it does not cross 1. The dotted interval, which may cross 1, corresponds to the prediction interval, reflecting the variability of the risk ratio across different studies (i.e., how much the risk ratio can vary across studies).

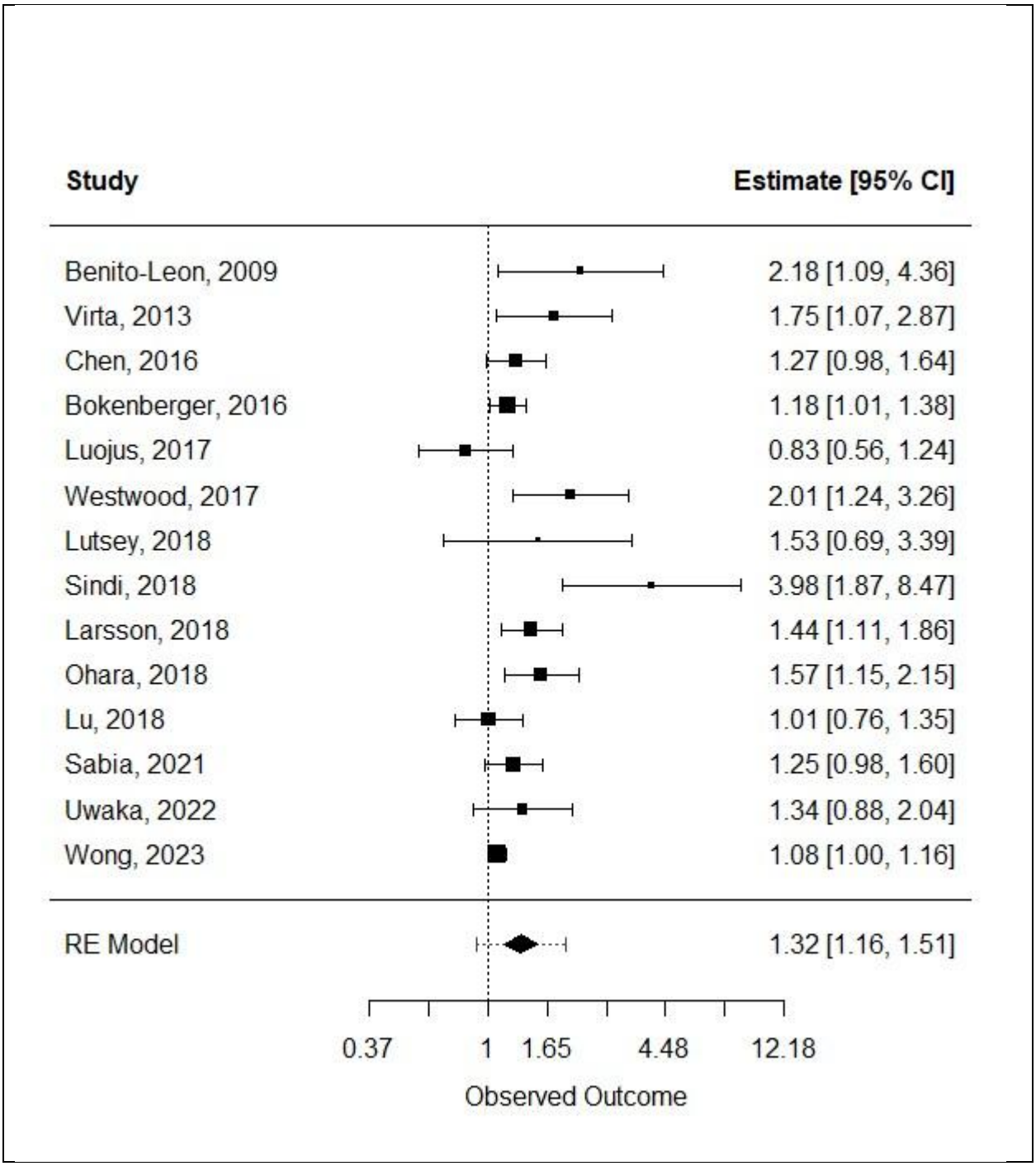
Study
Estimate [95% CI]
Benito-Leon, 2009
2.18 [1.09, 4.36]
Virta, 2013
1.75 [1.07, 2.87]
Chen, 2016
1.27 [0.98, 1.64]
Bokenberger, 2016
1.18 [1.01, 1.38]
Luojus, 2017
0.83 [0.56, 1.24]
Westwood, 2017
2.01 [1.24, 3.26]
Lutsey, 2018
1.53 [0.69, 3.39]
Sindi, 2018
3.98 [1.87, 8.47]
Larsson, 2018
1.44 [1.11, 1.86]
Ohara, 2018
1.57 [1.15, 2.15]
Lu, 2018
1.01 [0.76, 1.35]
Sabia, 2021
1.25 [0.98, 1.60]
Uwaka, 2022
1.34 [0.88, 2.04]
Wong, 2023
1.08 [1.00, 1.16]
RE Model
1.32 [1.16, 1.51]
0.37
1
1.65
4.48
12.18
Observed Outcome

Figure 3.4. Figure showing a representation of the forest plot: associations between long sleep duration and incident dementia.

Forest plot, showing risk ratio with 95% confidence intervals (CIs), is a graphical representation of the random-effects model meta-analyses. The solid diamond shape at the bottom represents the estimated risk ratio (RR) along with its 95% confidence interval (CI), which indicates statistical significance when it does not cross 1. The dotted interval, which may cross 1, corresponds to the prediction interval, reflecting the variability of the risk ratio across different studies (i.e., how much the risk ratio can vary across studies).

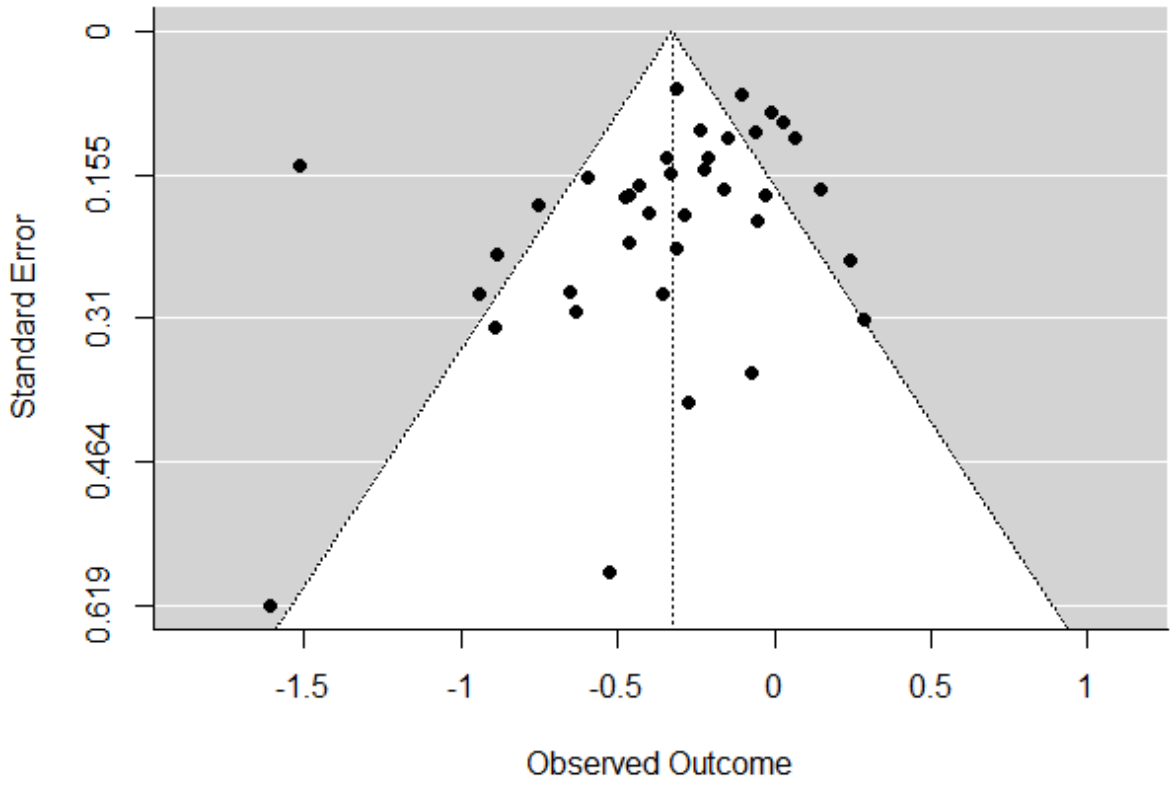

Figure 3.5. Figure showing a representation of the funnel plot: associations between physical activity and incident dementia. Funnel plot is a graphical representation of the publication bias.

Note: An uneven or asymmetrical cluster of dots with outliers far from the expected range suggests a higher chance of publication bias where studies with certain results (often positive) are more likely to be published..

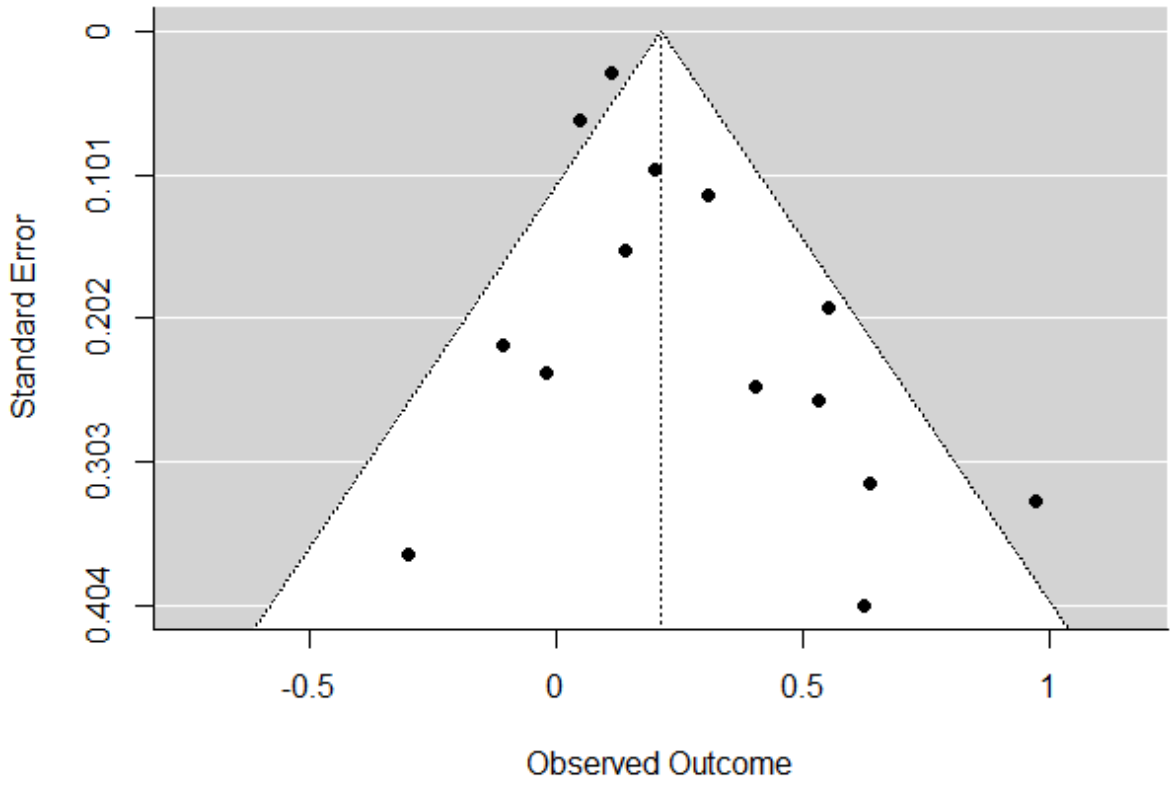

Figure 3.6. Figure showing a representation of the funnel plot: associations between short sleep duration and incident dementia. Funnel plot is a graphical representation of the publication bias.
Note: An even or symmetrical distribution of dots inside the funnel indicates consistency in the findings and publication bias is less likely to influence the results.

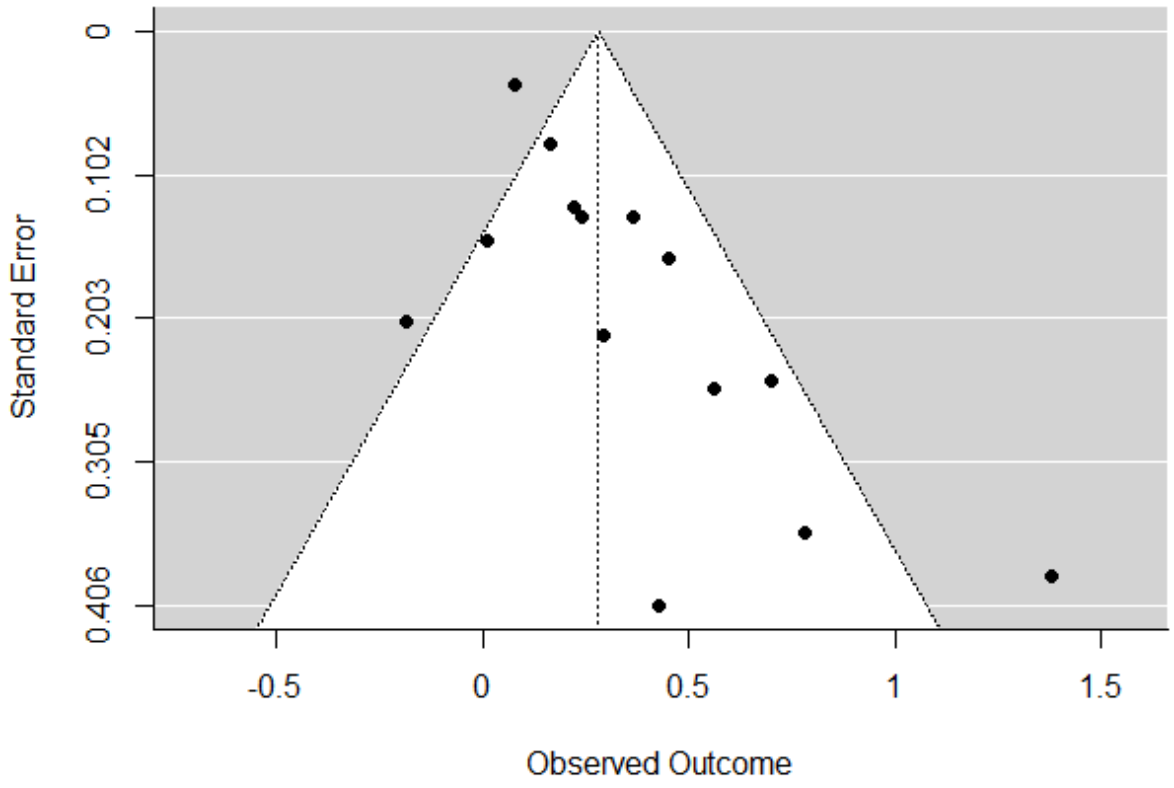

Figure 3.7. Figure showing a representation of the funnel plot: associations between long sleep duration and incident dementia. Funnel plot is a graphical representation of the publication bias.
Note: An uneven or asymmetrical distribution of dots inside the funnel indicates inconsistency in the findings and publication bias is more likely to influence the results.

Chapter 4 Study 2. Associations of Movement Behaviours on 3-Year Changes in Memory: Analysis of the Canadian Longitudinal Study on Aging (CLSA).

Abstract

Background: Building on evidence of the importance of modifiable risk factors in the prevention and management of dementia, this study examined the associations of movement behaviours on changes in immediate and delayed recall.

Methods: Data from the Canadian Longitudinal Study of Aging (CLSA) physical assessment cohort (n~30,000; 45y+) were used to examine the association between self-reported physical activity (PA), sedentary, and sleep duration, on 3-year changes (z-scores) in memory using age- and education-standardized immediate/delayed recall scores (Ray Auditory Verbal Learning Test).

Results: At baseline, participants engaged in 43.9±0.78 weekly MET-hours of PA (<10 MET-h: 35.83%; 10+ MET-h: 64.54%), 3.73±0.03 h (<8 h: 91.4%; 8+ h: 8.6%) of daily ST, and 6.78 h±0.02 (<6 h: 13.9%; 6-8 h: 80.7%, and 8+ h: 5.2%) of nightly sleep. Fully adjusted linear regression estimates revealed associations between 6-8 hours of nightly sleep and positive changes in immediate (0.114, 95% CI = 0.015 to 0.214) and delayed recall (0.114, 95% CI = 0.019 to 0.209) in males but not females. No significant interactions were found between baseline movement behaviors and immediate recall for either males or females. Among males, higher levels (8+ hours daily) of sitting were associated with negative change in delayed recall (unadjusted: -0.83, 95% CI = -1.64 to -0.024), and this association was dependent on higher levels of sleep (8+ hours), indicating an interaction. Among females, higher levels of PA (10+ MET-hours weekly) were associated with positive changes in delayed recall (adjusted: 1.09, 95% CI = 0.4 to 2.13), and this association was dependent on higher levels of sitting (8+ hours daily) and sleep (8+ hours nightly), indicating an interaction. After stratifying by sleep (< 6 hours, 6-8 hours, 8+ hours), PA (MET-hours weekly) was associated with positive changes in delayed recall (0.0007, 95% CI = 0.00008 to 0.0013) among females in the 6-8-hour sleep category, which was dependent on ST (hours daily). No significant associations were observed in the other nightly sleep categories (< 6 hours and 8+ hours).

Conclusion: Further longitudinal research including additional follow-up years could offer a unique opportunity to identify priorities for risk reduction efforts in susceptible middle-aged and older-adult populations.

Introduction

Normal aging is associated with subtle declines in cognitive function [1], but at the extreme, worsening of memory or cognition could indicate a neurodegenerative disorder, such as dementia, or mild cognitive impairment (MCI) [2][3][4]. MCI is characterized as difficulties with memory, or cognition, relative to age [3][5], whereas dementia is a severe worsening of memory, or cognitive status, with overt behavioral symptoms in adults [2][4][6]. Of note, 20% of older adults (65+ y) have MCI, and about 50% of older adult patients with MCI develop dementia within three to five years, compared with 3% of the age-matched general population [3]. Alzheimer's disease (AD) is the most common type of dementia, accounting for 60-80% of all cases in older adults [4][6].

In Canada, 76,000 older adults (65+ y) are diagnosed with dementia every year and about 7% are living with dementia [4] [7]. The etiology and pathophysiology are not well understood [3][6][8][9]. However, many risk factors have been identified including age, genetic susceptibility (apolipoprotein E gene isoform 4 (APOEε4)), and vascular diseases [3][6][10] [11]. Given that MCI and dementia are sequences of neurodegeneration, investigating modifiable risk factors, such as movement behaviours (e.g., physical activity, sleep, and sedentary time), may help to explain memory problems in preclinical and prodromal phases [3][5][12][13].

Several potential pathways have been proposed including blood–brain barrier permeability, neuroinflammation, oxidative stress, hypo-perfusion, and hypoxia [9][14], where movement behaviours have been shown to promote better health outcomes [15][16][17][18]. Thus, investigating non-pharmacological approaches that may delay the onset of neurological problems offer feasible public health strategies to address both the burden of disease and associated health-care costs [3][4][6]. Further prospective studies are therefore needed to

ascertain the independent and joint associations of movement behaviours on cognitive function in older adults, and in both men and women, where sex differences in the progression of neurodegeneration have been shown. The purpose of this study was to therefore investigate the associations of movement behaviours on 3-year changes in memory as an assessment of early risk identification.

Methods

Database

The Canadian Longitudinal Study on Aging [19] [20] is a strategic initiative of the Canadian Institutes of Health Research (CIHR), the Government of Canada, the Canada Foundation for Innovation, as well as the provincial governments of British Columbia, Alberta, Manitoba, Ontario, Québec, Nova Scotia and Newfoundland and Labrador. CLSA is a large, ongoing prospective study of health information (e.g., biological, medical, psychological, social, and lifestyle) for more than 50,000 individuals between the ages of 45 and 85 at the time of recruitment between 2010 and 2015. Individuals excluded from the study include residents of the Canadian territories, remote regions, Federal First Nations reserves, full-time members of the Canadian Armed Forces, those living in institutions, individuals unable to respond in English or French, and those who are physically or cognitively impaired.

Sample

A purpose-built physical assessment cohort sample (n=30 097) with baseline and initial follow-up assessments was used to explore participant health information. Exclusions were made for individuals with specific physician diagnosed conditions (dementia, Parkinson's disease, stroke, multiple sclerosis), those using mobility aids, individuals receiving dialysis, and pregnant individuals, resulting in 28 532 eligible individuals. Further exclusions for missing data on

physical activity, sitting duration, and sleep duration resulted in a baseline sample of 25 759 participants. From this group, 24 889 and 23 554 completed baseline assessments for Immediate and Delayed Recall. Finally, 20 662 and 19 060 individuals completed the 3-year follow-up assessment for Immediate and Delayed Recall. For further details, please refer to the flowchart (**Figure 4.1**).

Ethics and Data Access

This study received ethics review and renewal (Certificate Number: STU 2020-118) by the Human Participants Review Sub-Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines. This research was made possible using the data/biospecimens collected by the Canadian Longitudinal Study on Aging (CLSA). Funding for the Canadian Longitudinal Study on Aging (CLSA) is provided by the Government of Canada through the Canadian Institutes of Health Research (CIHR) under grant reference: LSA 94473 and the Canada Foundation for Innovation, as well as the following provinces, Newfoundland, Nova Scotia, Quebec, Ontario, Manitoba, Alberta, and British Columbia. This research has been conducted using the CLSA dataset [Comprehensive Cohort Version 1], under Application Number [2010021]. The CLSA is led by Drs. Parminder Raina, Christina Wolfson and Susan Kirkland.

Memory (Outcome)

The outcome for this study was the 3-year change from baseline in standardized immediate and delayed recall among CLSA participants. Participants in the CLSA completed a series of memory tests using the validated Rey Auditory Verbal Learning Test (RAVLT) for an immediate recall and a five-minute delayed recall [19] [21] [22] [23] [24]. The Rey Auditory Verbal Learning Test (RAVLT) is a popular neuropsychological assessment for evaluating

verbal learning and memory. It involves presenting a list of words for participants to recall immediately and after a delay. This test is valuable in clinical settings for assessing memory function, particularly in individuals with neurological disorders or cognitive impairments. The tests were administered in person by a trained interviewer. A full description of the tests is available in the CLSA protocol [20]. A score for each test was measured as a mean (SD) [19] [25], with higher scores indicating better performance. Continuous measures were age- and education-standardised (i.e., computed as a z-score) to both minimize floor and ceiling effects [26], and maintain variability in in predictors and outcomes.

Physical Activity (Exposure)

A modified version of the validated self-reported Physical Activity Scale for Elderly (PASE) captured information at baseline about the duration of physical activity over the past 7 days [27]. PASE demonstrated satisfactory validity [28][29][30] and reliability [28] [29] [30] as a measure of physical activity in healthy older individuals. Participants reported how often they did the following: walked outside, light, moderate, or strenuous sports, or recreational activities, and exercises specifically to increase muscle strength and endurance [31].

Sedentary Activity (Exposure)

Self-reported PASE at baseline also captured information about the duration of time spent in sedentary activity over the past 7 days [27]. Participants reported how often they engaged in reading, watching TV, computer activities or doing handicrafts, while sitting, over the past 7 days, and the average number of hours per day engaged in these sitting activities [31].

Sleep Activity (Exposure)

Self-reported total time asleep at night was collected by questionnaire at baseline, with satisfactory validity and reliability among adults [32]. Participants reported both hours of actual

sleep at night (e.g., 0 to 24 h), along with measures of sleep quality and satisfaction. Self-reported sleep duration was categorized as short (less than 6 hours), normal (6 to 8 hours), or long (more than 8 hours), and sleep quality reported as dissatisfied or very dissatisfied, neutral, and satisfied or very satisfied. The 6–8-hour sleep range was chosen to reflect variability in sleep durations observed in the population. Including 6 hours ensures the representativeness of our findings, and this range enhances statistical power by ensuring an adequate sample size across diverse sleep durations.

Covariates

Categorical covariates were selected at baseline based on previous research [25][26], which include age, body mass index, ethnicity, marital status, education, income, alcohol consumption, smoking, social support, self-rated health, sleep quality, and depression [33].

Statistical Analysis

The primary objective was to investigate the overall and sex-specific associations of daily movement behaviours (physical activity, sedentary activity, and sleep activity at baseline) on 3-year changes in memory (i.e., immediate, and delayed recall) in adults 45+ y. To investigate the associations of movement behaviours on 3-year changes in memory, each response variable was modelled using a change-score analysis for the difference between scores at baseline and first follow-up. A univariate analysis was performed to provide a summary of the frequency counts compared by chi-square and one-sample t-test. A bivariate analysis, including chi-square and two-sample t-test, was used to assess differences in characteristics between males and females. An analysis of 3-year changes in both immediate and delayed recall was subsequently performed using unadjusted repeated measures regression models. A fully adjusted repeated measures regression model was then used to examine 3-year changes in memory in relation to time for

correlation-structure repeated responses, with baseline covariates, to evaluate the associations of movement behaviour types on the change in the standardized memory scores. Movement behavior-by-sex interactions were then assessed, and analyses stratified where a differential risk in memory outcomes for females and males was observed [34][35]. Data analysis was performed with SAS software version 9.4 (Cary, NC, U.S.A.), weighted with the master survey inflation weights to ensure national representativeness of the data. Statistical significance was set at alpha = 0.05.

Results

Data (weighted analysis) showing participant characteristics stratified by sex are reported in **Table 4.1**.

Covariates

Overall, the average age of participants at baseline was 59.19±0.12 y (females (F) 59.53 (SE=0.18) y vs males (M) 58.82 (SE=0.17) y; p=0.0035), with a significant proportion (40.7%) of the participants in the 45-54 age group (F: 39.5% vs. M: 41.9%; p=0.005). Approximately 5.98% identified as non-white (F: 5.2% vs. M: 6.8%; p=0.016), one-third reported a household income between $50,000 and $100,000 (F: 34.0% vs. M: 33.7%; p<0.0001), 74.6% reported regular alcohol consumption (F: 70.2% vs. M: 79.3%; p<0.0001), and 45.2% were never smokers (F: 48.2% vs. M: 42.1%; p<0.0001). A significant portion of the participants (41.5%) rated their general health as “very good” (F: 42.8% vs. M: 40%; p=0.0003), 16.2% reported a history of depression (F: 20.6% vs. M: 11.4%; p<0.0001), and 39.9% of participants had measured BMI within the overweight range (F: 34.3% vs. M: 46%; p<0.0001). In total, 39% reported satisfaction with their sleep quality (F: 36.9% vs. M: 41.3%; p<0.0001). There was no

difference in education (64.6% had attained post-secondary education (F: 63.7% vs. M: 65.6%; p>0.05)), or social support scores (80.95±0.22 (F: 81.29 (SE=0.31) vs M: 81.39 (SE=0.32); p=0.825)).

Movement Behaviors

Average weekly MET-hours of physical activity at baseline were 43.86 (SE=0.78 (females (F) 37.18 (SE=1.01) vs males (M) 51.08 (SE=1.19); p < 0.0001). Most participants spent 10+ MET-h in weekly physical activity (<10 MET-h: 35.5%; 10+ MET-h: 64.5%; 10+ MET-h for F: 60.8% vs M: 68.6%, p<0.0001 (**Table 4.2**)). On average, at baseline, participants spent 3.73 h (SE=0.03) per day sitting, with higher levels of sitting seen among males (F: 3.62 h (SE=0.04); M: 3.85 h (SE=0.05)). Overall sitting behavior was relatively low, with most participants (<8 h: 91.4%) reporting less than 8 hours of sedentary activity per day (F: 93.3% vs M: 89.33%, p<0.0001). Finally, average nightly sleep at baseline was 6.78 h (SE=0.02), with small differences in the percentage of participants who fall into three sleep duration categories: 13.9% had less than 6 hours (F: 14.8% vs M: 12.9%), 80.9% had between 6 and 8 hours (F: 79.2% vs M: 82.7%), and 5.2% had more than 8 hours (F: 6% vs M: 4.4%).

Immediate and Delayed Recall

Table 4.2 presents the primary outcomes related to the changes in immediate and delayed recall over a three-year period. At baseline, age and education standardized (z-score) immediate (F: 0.17 (SE=0.02), M: -0.28 (SE=0.02)) and delayed (F: 0.2 (SE=0.02), M: -0.3 (SE=0.02)) recall z-scores were both found to be higher (p <.0001) in females compared to males. At follow-up, a 3-year change (z-score) showed a decrease overall in both immediate (-0.03 (SE=0.01)) and delayed (-0.01 (SE=0.01)) recall; however, females (immediate recall:

0.02 (SE=0.02), p <.0001; delayed recall: 0.03 (SE=0.02), p = 0.0033) indicated higher number of correct responses (z-scores) than males (immediate recall: -0.09 (SE=0.02), delayed recall: -0.06 (SE=0.02)).

Table 4.3 (immediate recall) and **Table 4.4** (delayed recall) display the linear regression estimates.

In unadjusted linear regression estimates (z-score), among males, 8+ hours (vs less than 8 hours) of sitting (0.102, 95% CI = 0.010 to 0.195) and 6-8 hours (vs less than 6 hours of sleep) of sleep (0.132, 95% CI = 0.039 to 0.225) were associated with positive change (3-year) in immediate recall. Additionally, among males, 8+ hours (vs less than 8 hours) of sitting (0.136, 95% CI = 0.030 to 0.243) were associated with positive changes (3-year) in delayed recall. Finally, among males, each MET-hour of weekly physical activity (-0.0007, 95% CI = -0.0012 to -0.0002) was associated with negative changes in delayed recall but each hour of sitting (0.019, 95% CI = 0.007 to 0.031) was associated with positive changse in delayed recall. In fully adjusted linear regression estimates, 6-8 hours (vs less than 6 hours) of sleep were associated with positive changes in immediate recall (0.114, 95% CI = 0.015 to 0.214) and delayed recall (0.114, 95% CI = 0.019 to 0.209), in males but not females.

Interactions between baseline movement behaviours (entered the model as PA | Sitting | Sleep) were assessed in unadjusted and fully adjusted general linear regression models with respect to continuous-by-continuous and categorical-by-categorical interactions among females and males, separately. In the immediate recall models (unadjusted and adjusted), there were no significant interactions. In the unadjusted delayed recall model, a categorical-by-categorical interaction between baseline sitting (8+ hours daily vs less than 8 hours of sitting) and sleeping (8+ hours nightly vs less than 6 hours of sleep) was associated with negative changes (z-score)

in delayed recall (-0.83, 95%CI = -1.64 to -0.024), among males. However, a categorical-by-categorical interaction between baseline physical activity (10+ MET-h vs less than 10 MET-h weekly), sitting (8+ hours vs less than 8 hours daily), and sleeping (8+ hours vs less than 6 hours nightly), was associated with positive changes (z-score) in delayed recall, among females (unadjusted: 1.17, 95%CI = 0.15 to 2.19, and fully adjusted: 1.09, 95%CI = 0.4 to 2.13) but not males (unadjusted: 1.48, 95%CI = -0.08 to 3.03, and fully adjusted: 1.32, 95%CI = -0.27 to 2.91).

Interactions (entered the model as PA | Sitting) between 3-year changes in delayed recall (z-score), physical activity, and sitting time, were subsequently stratified by categorical hours of sleep (< 6 hours, 6-8 hours, 8+ hours). There was a statistically significant continuous-by-continuous interaction between physical activity (MET-h weekly) and positive changes in delayed recall (0.0007, 95%CI = 0.00008 to 0.0013), and this was depended on hours sitting (daily) among females getting enough sleep (6-8 hours nightly). The other categories (< 6 hours and 8+ hours) did not show significant associations (**Table 4.5**).

Discussion

This study investigated the associations of movement behaviours (defined as physical activity, and duration in sedentary, and sleep) and 3-year changes in memory (defined as immediate and delayed recall). For movement behaviours, recommended physical activity levels (10+ MET-hours per week) were higher in males than females, more females than males met current recommendations for sitting time (less than 8 hours daily), and more males than females met current recommended sleep levels (6-8 hours nightly). Among males, 6-8 hours of nightly sleep was associated with positive changes in both immediate and delayed recall z-scores.

Among females, higher levels of physical activity were associated with positive changes in delayed recall z-scores, and this association was dependent on higher levels of sitting and sleep, indicating an interaction between these movement behaviours. Additionally, among females getting 6-8 hours of nightly sleep, each MET-hour of weekly physical activity was associated with positive changes in delayed recall z-scores, and this association was dependent on each hour of daily sitting. While these findings indicate potential associations between movement behaviours and positive changes in recall, they do not definitively establish improvements in memory due to the short follow-up period.

The importance of studying changes in sedentary behavior and physical activity to reduce the risk of morbidity is well recognized [15][16][17][18][36][37][38], acting in part through improvements in inflammation and insulin resistance, among other factors [39][40][41][42]. Exploring additional mechanisms underlying these associations, such as cognitive reserve, or reductions in neuroinflammation, could further clarify how movement behaviours influence memory outcomes. However, the associations between physical activity, sedentary time, and changes in memory recall over a three-year period were inconsistent. While this study adjusted for educational attainment, the lack of data on cognitively engaging activities may have influenced these results. Cognitively stimulating activities such as reading, puzzles, or social engagement could potentially explain the observed associations with movement behaviours. Several factors, such as the subjective nature of physical activity and sedentary time measures, could also explain the findings. Additionally, the relatively short study follow-up likely limited statistical power, which is particularly important given the high prevalence of memory impairments that often precede the development of cardiometabolic disorders and dementia in middle-aged individuals. Larger sample sizes and longer follow-up periods could help confirm

these results and provide insights into the long-term impact of movement behaviours on memory function.

The health benefits of movement behaviours, including physical activity, on memory are well documented, and observed at all ages [43][44]. Adherence to recommended physical and sedentary activity levels has been shown to promote physical and mental health including improved brain health later in life [40][42][45][46][47][48]. Physical activity has also been shown to benefit executive functioning, processing speed, and memory among older adults [43][44]. However, only 30% to 45% of older adults engage in MVPA [36][49], a factor known to contribute to higher rates of depression and lower quality of life in those who are non-adherent [49][50][51][52]. This could potentially confound the observed associations of movement behaviours and memory outcomes, and future studies should examine these relationships further. The current study accounted for depression, sleep quality, and social support, as these factors may also be linked to health conditions such as cardiovascular disease risk [53][54][55][56][57][58][59], which warrant further study.

While guidelines recommend 7-8 hours for adults 65+ y [60], this study reinforced the health benefits of getting 6-8 hours of nightly sleep, which was associated with positive changes in both immediate and delayed recall after accounting for other factors, among males. Additionally, after examining different sleep categories with sex differences, physical activity (MET-hours weekly) was associated with positive changes in delayed recall among females in the 6-8-hour sleep category, with this association depending on sitting time (hours daily). These findings highlight the complex interplay between physical activity, sleep, and sitting time, suggesting that optimizing these behaviours may enhance memory. A longer follow-up period could provide further insights into how movement behaviors affect brain health.

Finally, dementia is more prevalent in women than men [4][6][61], which may in part be attributed to well-known differences in physical activity [62][63][64], sedentary time [65][66], and sleep quantity and quality [67][68][69][70]. The sex differences observed in this study highlight the need for a better understanding of brain health, as females may have more exposure to the impacts of inadequate movement behaviours. The extent to which intrinsic and extrinsic factors may interact with age and sex in our study is not fully known, and an area in need of further long-term study. Future research on the biological, psychological, and social mechanisms underlying these associations is needed to better understand the pathways linking movement behaviours to cognitive decline and ways to design effective prevention strategies.

Strengths and Limitations

A strength of this study is the large purpose-built Canadian cohort on which these relationships are investigated, and the inclusion of valid and reliable measures of immediate and delayed recall, which are risk factors of dementia. Potential limitations include insufficient follow-up, limited statistical power to detect smaller effect sizes, and the possibility of reverse causality where outcomes may influence exposures. Because movement behaviours were self-reported, potential self-report biases due to recall cannot be ruled out.

Conclusion

This study builds on previous research by examining the collective relationship between physical activity, sedentary time, and sleep with 3-year changes in memory. The results show that sufficient sleep (6-8 hours nightly) was associated with positive changes in both immediate and delayed recall among males. Among females getting sufficient sleep, increased physical

activity was associated with positive changes in delayed recall, as sitting time increased. Additionally, among females, staying physically active was associated with positive changes in delayed recall, even in the context of higher levels of sitting and sleep. These findings underscore the importance of adequate sleep and physical activity in memory preservation and highlight the potential for interventions aimed at enhancing movement behaviours to improve physical and mental health in an aging population. Future studies with longer follow-up periods and more comprehensive data on changes in movement behaviours are needed to further explore these associations and their impact on memory.

List of Abbreviations

AD, Alzheimer's disease

CIHR, Canadian Institutes of Health Research

CLSA, Canadian Longitudinal Study on Aging

MCI, mild cognitive impairment

MET, metabolic equivalent of task

MVPA, moderate-to-vigorous physical activity

PA, physical activity

PASE, physical activity scale for elderly

RAVLT, Rey Auditory Verbal Learning Test

Declarations

Ethics approval and consent to participate.

This study received ethics review and renewal (Certificate Number: STU 2020-118) by the Human Participants Review Sub-Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines.

Availability of data and materials.

All data analysed during this study are available from data/biospecimens collected by the Canadian Longitudinal Study on Aging (CLSA). This research has been conducted using the CLSA dataset [Comprehensive Cohort Version 1], under Application Number [2010021]. The CLSA is led by Drs. Parminder Raina, Christina Wolfson and Susan Kirkland.

Competing interests.

The authors declare that they have no competing interests.

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Authors' Contributions.

AO had full access to the data and takes responsibility for the integrity and accuracy of all data analysis. AO and CIA conceived of the study and designed the study protocol. AO performed the analyses, and CIA oversaw the analyses. AO wrote the draft of the manuscript with inputs from all authors. JK and HT provided critical revisions to the article. All authors contributed to the interpretation of the findings and approved the final version of the article to be published.

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Table 4.1. Participant Characteristics by sex; data (weighted analysis) derived from CLSA

	Sex			
	Female (N=12 969)	Male (N=12 750)	Total (N=25 719)	P-value
Age				0.0035[1]
Mean (SE)	59.53 (0.18)	58.82 (0.17)	59.19 (0.12)	
Age Group				0.0049[2]
45-54 (%, SE %)	39.49 (0.85)	41.93 (0.89)	40.66 (0.62)	
55-64 (%, SE %)	31.31 (0.73)	31.86 (0.77)	31.58 (0.53)	
65-74 (%, SE %)	18.13 (0.58)	17.27 (0.58)	17.71 (0.41)	
75+ (%, SE %)	11.07 (0.51)	8.94 (0.40)	10.05 (0.33)	
Ethnicity				0.0163[2]
Non-white (%, SE %)	5.22 (0.44)	6.80 (0.49)	5.98 (0.32)	
White (%, SE %)	94.78 (0.44)	93.20 (0.49)	94.02 (0.32)	
Education				0.3997[2]
Below secondary (%, SE %)	15.38 (0.92)	14.52 (0.98)	14.97 (0.67)	
Post-secondary (%, SE %)	63.66 (0.89)	65.62 (0.96)	64.60 (0.65)	
Secondary (%, SE %)	11.87 (0.47)	10.70 (0.52)	11.31 (0.35)	
Some post-secondary (%, SE %)	9.1 (0.42)	9.16 (0.46)	9.13 (0.31)	
Household Income				<.0001[2]
$100,000 - $150,000 (%, SE %)	19.119 (0.69)	22.91 (0.70)	21.01 (0.49)	
$150,000+ (%, SE %)	16.09 (0.56)	21.12 (0.65)	18.55 (0.43)	
$20,000 - $50,000 (%, SE %)	24.33 (0.80)	17.74 (0.72)	21.11 (0.54)	
$50,000 - $100,000 (%, SE %)	34.0 (0.80)	33.73 (0.84)	33.87 (0.58)	
Less than $20,000 (%, SE %)	6.40 (0.48)	4.50 (0.52)	5.47 (0.35)	
Missing (n)	982	575	1557	
Alcohol Use in Last 12 months				<.0001[2]
Non-drinker (%, SE %)	14.82 (0.69)	11.46 (0.59)	13.20 (0.45)	
Occasional drinker (%, SE %)	15.0 (0.62)	9.24 (0.57)	12.22 (0.43)	
Regular drinker (%, SE %)	70.17 (0.82)	79.30 (0.77)	74.59 (0.57)	
Missing (n)	365	220	585	
Smoking Status				<.0001[2]
Current smoker (%, SE %)	10.25 (0.59)	12.39 (0.65)	11.28 (0.44)	
Former smoker (%, SE %)	41.57 (0.82)	45.55 (0.87)	43.49 (0.59)	
Never smoker (%, SE %)	48.18 (0.83)	42.06 (0.84)	45.24 (0.59)	
General Health				0.0003[2]
Excellent (%, SE %)	20.64 (0.59)	18.22 (0.60)	19.48 (0. 45)	
Fair (%, SE %)	6.70 (0.48)	7.38 (0.51)	7.03 (0.35)	
Good (%, SE %)	28.96 (0.77)	33.20 (0.84)	31.0 (0.57)	
Poor (%, SE %)	0.88 (0.14)	1.20 (0.19)	1.03 (0.12)	
Very good (%, SE %)	42.83 (0.82)	40.0 (0.84)	41.47 (0.59)	
Missing (n)	8	8	16	
Social Support				0.8245[1]
Mean (SE)	81.29 (0.31)	81.39 (0.32)	80.95 (0.22)	
Missing (n)	209	202	411	

	Sex			
	Female (N=12 969)	Male (N=12 750)	Total (N=25 719)	P-value
Clinical Depression				<.0001[2]
No (%, SE %)	79.44 (0.69)	88.61 (0.53)	83.85 (0.45)	
Yes (%, SE %)	20.56 (0.69)	11.39 (0.53)	16.15 (0.45)	
Missing (n)	36	24	60	
Body Mass Index (BMI)				<.0001[1]
Mean (SE)	27.60 (0.09)	28.36 (0.08)	27.97 (0.06)	
Missing (n)	14	9	23	
Weight Status				<.0001[2]
Normal (%, SE %)	36.33 (0.80)	24.06 (0.75)	30.43 (0.55)	
Obesity (%, SE %)	28.09 (0.75)	29.68 (0.79)	28.85 (0.54)	
Overweight (%, SE %)	34.33 (0.78)	46.02 (0.86)	39.95 (0.59)	
Underweight (%, SE %)	1.25 (0.23)	0.25 (0.07)	0.77 (0.12)	
Missing (n)	14	9	23	
Sleep Quality (%)				<.0001[2]
Dissatisfied (%, SE %)	23.59 (0.70)	19.09 (0.65)	21.42 (0.48)	
Neutral (%, SE %)	15.22 (0.62)	15.43 (0.59)	15.32 (0.43)	
Satisfied (%, SE %)	36.92 (0.80)	41.29 (0.85)	39.02 (0.59)	
Very Dissatisfied (%, SE %)	5.31 (0.37)	3.83 (0.38)	4.60 (0.26)	
Very Satisfied (%, SE %)	18.96 (0.64)	20.37 (0.75)	19.63 (0.49)	
Missing (n)	4	9	13	

[1]Equal variance two sample t-test; [2]Chi-Square p-value;

Table 4.2. Movement Characteristics by sex; data (weighted analysis) derived from CLSA

	Sex			
	Female (N=12 969)	Male (N=12 750)	Total (N=25 719)	P-value
Sleep Duration (Hours Per Day)				0.5304[1]
Mean (SE)	6.78 (0.02)	6.76 (0.02)	6.77 (0.02)	
Sleep Status (6-8 Hours Per Night)				0.002[2]
6-8 hours (%, SE %)	79.18 (0.70)	82.67 (0.74)	80.86 (0.50)	
8+ hours (%, SE %)	6.03 (0.42)	4.39 (0.45)	5.24 (0.31)	
Less than 6 hours (%, SE %)	14.79 (0.61)	12.94 (0.63)	13.90 (0.44)	
Physical Activity (MET Hours Per Week)				<.0001[1]
Mean (SE)	37.18 (1.01)	51.08 (1.19)	43.86 (0.78)	
Physical Activity Status (10+ MET Hours Per Week)				<.0001[2]
10 or more MET hours (%, SE %)	60.78 (0.83)	68.60 (0.79)	64.54 (0.57)	
Less than 10 MET hours (%, SE %)	39.22 (0.83)	31.40 (0.79)	35.46 (0.58)	
Sitting Duration (Hours Per Day)				<.0001[1]
Mean (SE)	3.62 (0.04)	3.85 (0.05)	3.73 (0.03)	
Sitting Status (Hours per day)				<.0001[2]
8 or more hours (%, SE %)	6.70 (0.35)	10.67 (0.52)	8.60 (0.31)	
Less than 8 hours (%, SE %)	93.30 (0.35)	89.33 (0.52)	91.40 (0.31)	
RAVLT Trial 1 Score (z-score) at Baseline (Immediate Recall Standardized)				<.0001[1]
Mean (SE)	0.17 (0.02)	-0.28 (0.02)	-0.05 (0.01)	
Missing	413	417	830	
Change in RAVLT Trial 1 Score (z-score) at Follow-up (Immediate Recall Standardized)				<.0001[1]
Mean (SE)	0.02 (0.02)	-0.09 (0.02)	-0.03 (0.01)	
Missing	2719	2338	5057	

	Sex			
	Female (N=12 969)	Male (N=12 750)	Total (N=25 719)	P-value
RAVLT Trial 2 Score (z-score) at Baseline (Delayed Recall Standardized)				<.0001[1]
Mean (SE)	0.2 (0.02)	-0.3 (0.02)	-0.03 (0.01)	
Missing	937	1228	2165	
Change in RAVLT Trial 2 Score (z-score) at Follow-up (Delayed Recall Standardized)				0.0033[1]
Mean (SE)	0.03 (0.02)	-0.06 (0.02)	-0.01 (0.01)	
Missing	3304	3355	6659	

[1]Equal variance two sample t-test; [2]Chi-Square p-value;

Table 4.3. Associations between 3-year changes in immediate recall and movement characteristics by sex; data (weighted analysis) derived from CLSA.

	3-Year Changes (z-score) in Immediate Recall			
	Model 1		Model 2	
	Females β (95%CI)	Males β (95%CI)	Females β (95%CI)	Males β (95%CI)
Main Effects				
Immediate Recall (Standardized)				
Physical Activity Status (Weekly)				
Less than 10 hours	REF	REF	REF	REF
10 or more hours	0.047 (-0.021, 0.115)	0.021 (-0.043, 0.085)	0.027 (-0.042, 0.096)	0.016 (-0.047, 0.079)
Linear (each hour per week)	-0.00006 (-0.0007, 0.0006)	0.00013 (-0.0006, 0.0004)	0.0001 (-0.0006, 0.0009)	0.00006 (-0.0005, 0.0006)
Immediate Recall (Standardized)				
Sitting Status (Daily)				
Less than 8 hours	REF	REF	REF	REF
8 or more hours	-0.083 (-0.196, 0.030)	**0.102 (0.010, 0.195)**	-0.068 (-0.189, 0.052)	0.079 (-0.021, 0.179)
Linear (hourly)	0.0022 (-0.0117, 0.016)	0.0122 (-0.0004, 0.0248)	0.0006 (-0.015, 0.016)	0.009 (-0.005, 0.023)
Immediate Recall (Standardized)				
Sleep Status (Daily)				
Less than 6 hours	REF	REF	REF	REF
6-8 hours	0.067 (-0.027, 0.160)	**0.132 (0.039, 0.225)**	0.040 (-0.075, 0.154)	**0.114 (0.015, 0.214)**
8 or more hours	-0.079 (-0.236, 0.079)	-0.047 (-0.215, 0.121)	-0.038 (-0.218, 0.142)	-0.079 (-0.249, 0.091)
Linear (hourly)	-0.0008 (-0.026, 0.025)	0.011 (-0.015, 0.037)	0.0009 (-0.032, 0.033)	0.003 (-0.028, 0.034)
Interaction Effects				
Continuous-by-continuous interactions				
MET-h PA (weekly), hours sitting (daily)	0.0001 (-0.0021, 0.0023)	0.002 (-0.0006, 0.0036)	0.0009 (-0.0017, 0.0034)	0.0012 (-0.001, 0.0033)
MET-h PA (weekly), hours sleeping (nightly)	0.00005 (-0.0009, 0.0009)	0.0008 (-0.00002, 0.0016)	0.0006 (-0.0005, 0.0016)	0.0006 (-0.00018, 0.0014)
Hours sitting (daily), hours sleeping (nightly)	0.006 (-0.009, 0.020)	0.0008 (-0.015, 0.016)	0.007 (-0.0084, 0.0222)	-0.00014 (-0.015, 0.015)
MET-h PA (weekly), hours sitting (daily), hours sleeping (nightly)	0.00003 (-0.0003, 0.0004)	-0.00023 (-0.0006, 0.00009)	-0.0001 (-0.0005, 0.0003)	-0.00018 (-0.00052, 0.00015)
Categorical-by-categorical interactions				
10+ MET-h PA (weekly), 8+ hours sitting (daily)	-0.141 (-0.347, 0.629)	-0.145 (-0.682, 0.391)	0.056 (-0.465, 0.576)	-0.016 (-0.565, 0.532)

	3-Year Changes (z-score) in Immediate Recall			
	Model 1		Model 2	
10+ MET-h PA (weekly), 6-8 hours (nightly)	-0.006 (-0.217, 0.205)	0.147 (-0.108, 0.403)	0.044 (-0.168, 0.257)	0.194 (-0.004, 0.392)
10+ MET-h PA (weekly), 8+ hours sleeping (nightly)	-0.007 (-0.338, 0.325)	0.338 (-0.050, 0.727)	0.0820 (-0.256, 0.420)	0.200 (-0.132, 0.532)
8+ hours sitting (daily), 6-8 hours sleeping (nightly)	0.134 (-0.447, 0.178)	0.048 (-0.393, 0.489)	-0.076 (-0.411, 0.259)	0.156 (-0.297, 0.609)
8+ hours sitting (daily), 8+ hours sleeping (nightly)	-0.006 (-0.563, 0.55)	-0.138 (-0.789, 0.523)	-0.003 (-0.660, 0.655)	-0.072 (-0.699, 0.555)
10+ MET-h PA (weekly), 8+ hours sitting (daily), 6-8 hours sleeping (nightly)	-0.012 (-0.536, 0.560)	-0.114 (-0.685, 0.456)	0.057 (-0.523, 0.636)	-0.277 (-0.859, 0.3051)
10+ MET-h PA (weekly), 8+ hours sitting (daily), 8+ hours sleeping (nightly)	0.30 (-0.465, 1.064)	0.501 (-1.443, 2.445)	0.287 (-0.572, 1.147)	0.577 (-1.492, 2.646)

Model 1 unadjusted.
Model 2 adjusted for age, sex, ethnicity, education, income, alcohol, smoking, social support, movement behaviours (mutually for physical activity, sitting, and sleep status), body mass index, self-reported general health, depression, and sleep quality.
Subgroups: Females and Males were adjusted separately using Model 2 without sex variable.
In the categorical-by-categorical interaction models, the referent category (REF) is the lowest level (or least amount) of physical activity (less than 10 MET-hours weekly), sitting (less than 8 hours), or sleep (less than 6 hours) at baseline.

Table 4.4. Associations between 3-year changes in delayed recall and movement characteristics by sex; data (weighted analysis) derived from CLSA.

	3-Year Changes (z-score) in Delayed Recall			
	Model 1		Model 2	
	Females	Males	Females	Males
	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
Main Effects				
Delayed Recall (Standardized)				
Physical Activity Status (Weekly)				
Less than 10 hours	REF	REF	REF	REF
10 or more hours	-0.002 (-0.075, 0.071)	-0.06 (-0.133, 0.016)	0.005 (-0.071, 0.080)	-0.045 (-0.118, 0.027)
Linear (each hour per week)	-0.0004 (-0.001, 0.0004)	**-0.0007 (-0.0012, -0.0002)**	-0.0001 (-0.001, 0.0008)	-0.0004 (-0.001, 0.0002)
Delayed Recall (Standardized)				
Sitting Status (Daily)				
Less than 8 hours	REF	REF	REF	REF
8 or more hours	0.015 (-0.106, 0.136)	**0.136 (0.030, 0.243)**	0.013 (-0.106, 0.131)	0.074 (-0.029, 0.178)
Linear (hourly)	0.002 (-0.012, 0.016)	**0.019 (0.007, 0.031)**	-0.0002 (-0.016, 0.016)	0.009 (-0.004, 0.023)
Delayed Recall (Standardized)				
Sleep Status (Daily)				
Less than 6 hours	REF	REF	REF	REF
6-8 hours	0.010 (-0.093, 0.112)	0.068 (-0.034, 0.169)	-0.001 (-0.120, 0.118)	**0.114 (0.019, 0.209)**
8+ hours	-0.024 (-0.170, 0.122)	-0.035 (-0.313, 0.242)	-0.038 (-0.208, 0.131)	-0.055 (-0.317, 0.207)
Linear (hourly)	0.011 (-0.016, 0.039)	0.026 (-0.009, 0.062)	0.021 (-0.012, 0.054)	0.032 (-0.006, 0.070)
Interaction Effects				
Continuous-by-continuous interactions				
MET-h PA (weekly), hours sitting (daily)	0.032 (-0.106, 0.041)	0.0009 (-0.0014, 0.003)	0.0015 (-0.0011, 0.004)	0.001 (-0.0008, 0.0035)
MET-h PA (weekly), hours sleeping (nightly)	0.00003 (-0.0011, 0.0011)	0.0004 (-0.0006, 0.001)	0.0007 (-0.00038, 0.0018)	0.0005 (-0.0004, 0.0014)
Hours sitting (daily), hours sleeping (nightly)	0.012 (-0.003, 0.027)	0.008 (-0.010, 0.026)	0.013 (-0.0016, 0.028)	0.014 (-0.001, 0.030)
MET-h PA (weekly), hours sitting (daily), hours sleeping (nightly)	0.00001 (-0.0004, 0.0004)	-0.0002 (-0.0005, 0.0002)	-0.0001 (-0.0005, 0.00025)	-0.0002 (-0.0006, 0.00011)
Categorical-by-categorical interactions				
10+ MET-h PA (weekly), 8+ hours sitting (daily)	-0.04 (-0.73, 0.64)	-0.43 (-1.09, 0.23)	-0.08 (-0.78, 0.62)	-0.14 (-0.70, 0.42)

	3-Year Changes (z-score) in Delayed Recall			
	Model 1		Model 2	
	Females	Males	Females	Males
10+ MET-h PA (weekly), 6-8 hours (nightly)	-0.01 (-0.25, 0.23)	0.18 (-0.06, 0.41)	0.04 (-0.19, 0.28)	0.19 (-0.02, 0.40)
10+ MET-h PA (weekly), 8+ hours sleeping (nightly)	-0.22 (-0.53, 0.10)	-0.23 (-0.82, 0.35)	-0.14 (-0.47, 0.18)	-0.32 (-0.81, 0.17)
8+ hours sitting (daily), 6-8 hours sleeping (nightly)	0.10 (-0.26, 0.45)	-0.20 (-0.73, 0.34)	0.04 (-0.30, 0.39)	0.09 (-0.32, 0.50)
8+ hours sitting (daily), 8+ hours sleeping (nightly)	-0.39 (-1.13, 0.35)	**-0.83 (-1.64, -0.024)**	-0.34 (-1.09, 0.41)	-0.47 (-1.08, 0.14)
10+ MET-h PA (weekly), 8+ hours sitting (daily), 6-8 hours sleeping (nightly)	0.14 (-0.59, 0.87)	0.32 (-0.37, 1.01)	0.26 (-0.49, 1.01)	0.015 (-0.58, 0.61)
10+ MET-h PA (weekly), 8+ hours sitting (daily), 8+ hours sleeping (nightly)	**1.17 (0.15, 2.19)**	1.48 (-0.08, 3.03)	**1.09 (0.4, 2.13)**	1.32 (-0.27, 2.91)

Model 1 unadjusted.
Model 2 adjusted for age, ethnicity, education, income, alcohol, smoking, social support, movement behaviours (mutually for physical activity, sitting, and sleep status), body mass index, self-reported general health, depression, and sleep quality.
Subgroups: Females and Males were adjusted separately using Model 2 without sex variable.
In the categorical-by-categorical interaction models, the referent category (REF) is the lowest level (or least amount) of physical activity (less than 10 MET-hours weekly), sitting (less than 8 hours), or sleep (less than 6 hours) at baseline.

Table 4.5. Associations between 3-year changes in delayed recall, physical activity, and sitting time, by categorical hours of sleep (< 6 hours, 6-8 hours, 8+ hours); data (weighted analysis) derived from CLSA.

Categorical Hours of Sleep	3-Year Changes (z-score) in Delayed Recall		
	< 6 hours β (95%CI)	6-8 hours β (95%CI)	8+ hours β (95%CI)
FEMALES			
Continuous-by-continuous interactions			
MET-h PA (weekly), hours sitting (daily)	-0.0002 (-0.0011, 0.0007)	**0.0007** **(0.00008, 0.0013)**	0.0011 (-0.0008, 0.003)
Categorical-by-categorical interactions			
10+ MET-h PA (weekly), 8+ hours sitting (daily)	-0.02 (-0.79, 0.76)	0.18 (-0.08, 0.44)	0.94 (-0.11, 2.0)
MALES			
Continuous-by-continuous interactions			
MET-h PA (weekly), hours sitting (daily)	0.00006 (-0.0007, 0.0008)	-0.0001 (-0.0005, 0.0002)	0.00003 (-0.0012, 0.0012)
Categorical-by-categorical interactions			
10+ MET-h PA (weekly), 8+ hours sitting (daily)	-0.13 (-0.70, 0.43)	-0.12 (-0.33, 0.09)	0.43 (-0.87, 1.74)

All models were adjusted for age, ethnicity, education, income, alcohol, smoking, social support, movement behaviours (mutually for physical activity and sitting), body mass index, self-reported general health, depression, and sleep quality.
Subgroups: Females and Males were adjusted using covariates indicated above without sex variable.
In the categorical-by-categorical interaction models, the referent category (REF) is the lowest level (or least amount) of physical activity (less than 10 MET-hours weekly) or sitting (less than 8 hours) at baseline.

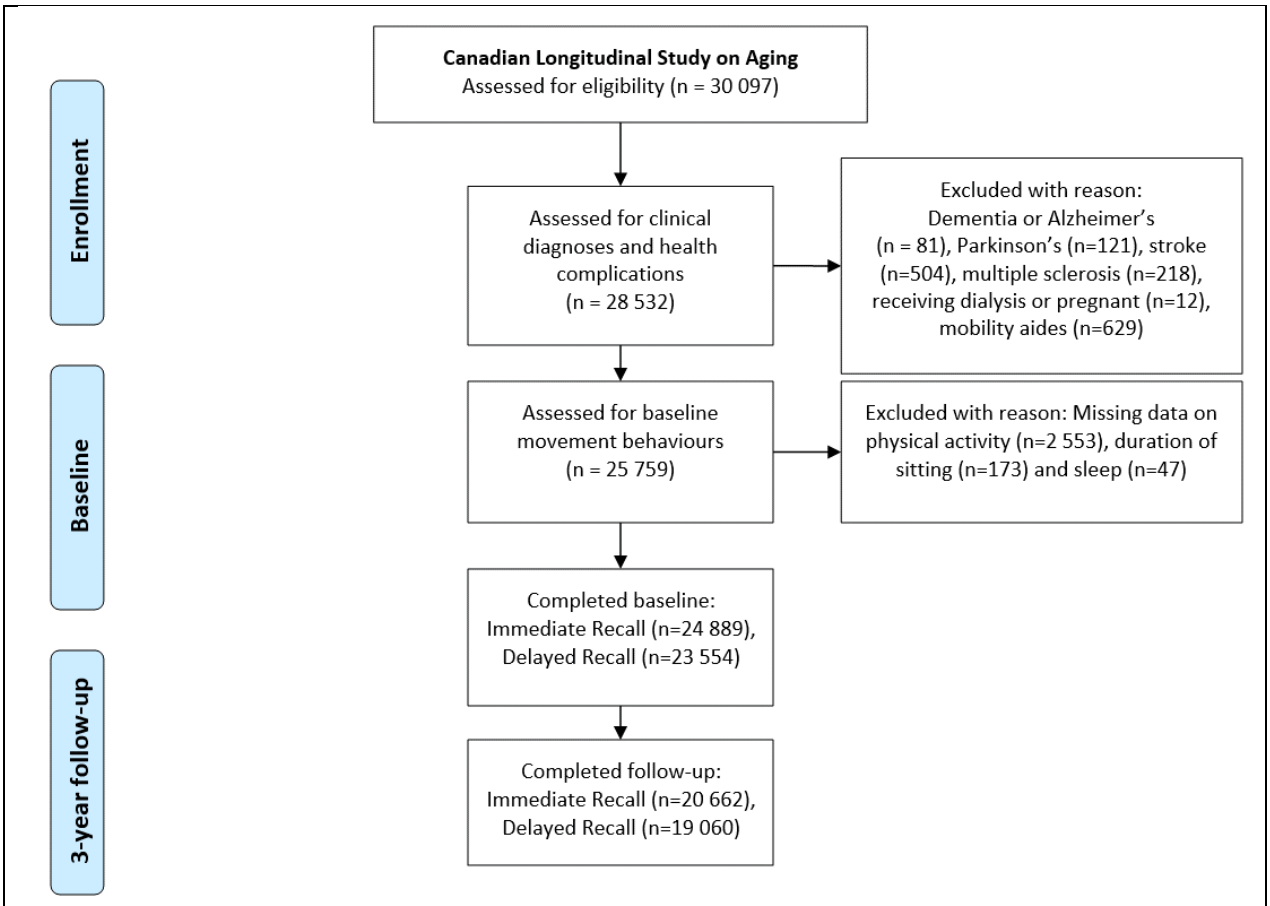

Figure 4.1. Figure showing a representation of the flow chart.

Chapter 5 Study 3. Association of Movement Behaviours with 3-Year Changes in Cognition: Mediation Analysis Using Data from the Canadian Longitudinal Study on Aging (CLSA).

Abstract

Background: The current study examined 3-year changes (and mediating effects of cardiometabolic risk) in global cognition with baseline movement behaviours (physical activity, sedentary habits, and sleep) for females and males.

Methods: Data were drawn from the Canadian Longitudinal Study of Aging (CLSA) physical assessment cohort (n~30,000; 45y+). General linear regression models were used to examine the association between physical activity, duration of sedentary, sleep activity, and 3-year changes in age- and education-standardized global cognition. Mediation analysis examined cardiometabolic components with movement behaviours for indirect effects on global cognition.

Results: At baseline, most participants engaged in more than 10+ MET-h per week of activity (61.2%), had <8 h of daily sitting (91.4%), and 6-8 h of nightly sleep (80.2%). General linear regression estimates revealed each hour of sitting associated with positive change in global cognition among males (unadjusted: 0.018, 95%CI = 0.004 to 0.032; adjusted: 0.021, 95%CI = 0.005 to 0.036); however, 8+ hours (vs less than 6 hours) of nightly sleep was associated with negative changes in global cognition among males (unadjusted: -0.218, 95%CI = -0.483 to 0.05; adjusted: -0.307, 95%CI = -0.576 to -0.039). Sitting time mediated the relationship between cardiometabolic components and 3-year change in global cognition among males but not females, while the relationship between sitting time and 3-year change in global cognition was mediated through waist circumference and high-density lipoprotein among both females and male, and; glycosylated hemoglobin among males but not females.

Conclusion: Future studies with changes in movement behaviours and longer-term follow-up are needed to better ascertain the interplay of physiological and lifestyle factors on global cognition, which can inform interventions aimed at enhancing the quality of life of older adults.

Introduction

Cognitive function encompasses mental processes involving thinking, learning, memory, and decision-making [1][2]. Dementia is a neurological disorder resulting from damaged brain tissues, which impacts cognitive function and causes a gradual decline in memory, language, judgment, and daily activities [3][4] 5]. In the early stages, mild cognitive impairment may progress to significant memory loss and impaired decision-making [4][5][6]. Prevention and management of dementia are an ongoing challenge for health-care systems around the world where the prevalence is expected to double in the next two decades [1][3][4][6]. Behavioural and psychological symptoms are common [7] and can be managed with both nonpharmacological and pharmacological options [8]. Although a variety of pharmacological agents exist, they increase the potential or risk for adverse events in older adults due to comorbid conditions, polypharmacy, and drug-drug interaction [7].

The early detection and management of cognitive decline may include lifestyle interventions, cognitive training, and social engagement to preserve and enhance cognitive function, potentially delaying the onset or slowing dementia progression [2][4][5][9]. However, the relationship between established modifiable risk factors and dementia is complex [2][4][5] [10]. Investigating the relationship between movement behaviours (physical activity, sedentary, and sleep) on negative health consequences including cognitive decline or impairment is therefore needed to optimize health and well-being across the lifespan.

In this study, our primary aim was to assess the associations of movement behaviors on the trajectory of cognitive function over a 3-year period, with consideration for potential sex differences in the progression of cognitive decline [11]. Examining sex differences is essential, as biological, psychological, and social factors may lead to varied responses to movement

behaviors, which could impact cognitive outcomes in females and males [12][13][14][15][16][17]. Recognizing the interconnected nature of movement behaviors with cardiometabolic risk factors, our secondary aim was to explore the mediating effects of movement behaviors on the relationship between cardiometabolic abnormalities (of carotid intima-media thickness [cIMT] and components of metabolic syndrome [MetS] such as waist circumference, systolic and diastolic blood pressure, triglycerides, high density lipoprotein cholesterol, and blood glucose) and global cognition.

Methods

This study extends findings from our earlier investigation on the relationships between movement behaviours and memory (immediate and delayed recall) using the Canadian Longitudinal Study on Aging database.

Database

The Canadian Longitudinal Study on Aging (CLSA) is a prospective study involving over 50,000 individuals aged 45 to 85, recruited between 2010 and 2015 [18]. The CLSA represents a collaborative initiative involving the Canadian Institutes of Health Research (CIHR), the Government of Canada, the Canada Foundation for Innovation, and provincial governments in British Columbia, Alberta, Manitoba, Ontario, Québec, Nova Scotia, and Newfoundland and Labrador. The aim of the study was to gather comprehensive health information, including biological, medical, psychological, social, and lifestyle data. Individuals excluded from the study include residents of the Canadian territories, remote regions, Federal First Nations reserves, full-time members of the Canadian Armed Forces, those living in institutions, individuals unable to respond in English or French, and those who are physically or cognitively impaired.

Sample

This study employed a purpose-built physical assessment cohort sample (n=30 097) with baseline and initial follow-up assessments to explore participant health information. Exclusions were made for individuals with specific conditions (dementia, Parkinson's, stroke, multiple sclerosis), individuals requiring mobility aids, those receiving dialysis, or pregnant individuals, resulting in a total available sample of n=28 532 individuals. Further exclusions were made regarding missing data on physical activity, duration of sitting and sleeping, resulting in a baseline sample of n=25 759. From this group, n=23 060 completed baseline assessments for Global Cognition and n=17 022 completed the 3-year follow-up assessment for Global Cognition. For further details, please refer to the flowchart (**Figure 5.1**).

Ethics and Data Access

This study received ethics review and renewal (Certificate Number: STU 2020-118) by the Human Participants Review Sub-Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines. This research was made possible using the data/biospecimens collected by the Canadian Longitudinal Study on Aging (CLSA). Funding for the Canadian Longitudinal Study on Aging (CLSA) is provided by the Government of Canada through the Canadian Institutes of Health Research (CIHR) under grant reference: LSA 94473 and the Canada Foundation for Innovation, as well as the following provinces, Newfoundland, Nova Scotia, Québec, Ontario, Manitoba, Alberta, and British Columbia. This research has been conducted using the CLSA dataset [Comprehensive Cohort Version 1], under Application Number [2010021]. The CLSA is led by Drs. Parminder Raina, Christina Wolfson and Susan Kirkland.

Cognitive Function

The outcome for this study was the 3-year change in standardized global cognitive function among CLSA participants. Comprehensive cognitive assessments were conducted across three domains (namely memory, executive function, and psychomotor speed) utilizing a battery of reliable and valid tests [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29]. Memory tests included the Rey Auditory Verbal Learning Test (RAVLT) for immediate recall, while executive function assessments comprised the Mental Alternation Test, Prospective Memory Test, Animal Fluency, Controlled Oral Word Association Test, and Stroop Test. Trained interviewers administered these tests in person, as detailed in the CLSA protocol [18]. Each test produced a score, reported as a mean (SD) [19] [30], with higher scores in memory and executive function tests indicating better cognitive function. A composite global cognitive function score was standardized (as a z-score) after averaging the standardized scores of individual cognitive tests [31]. The use of a composite z-score further mitigates floor and ceiling effects, enhancing the robustness of the analysis [31].

Exposure Variables

A modified version of the self-reported Physical Activity Scale for the Elderly (PASE) was used to gather information on the duration of physical activity in the past 7 days [32] [33]. Validity and reliability of PASE as a tool for assessing physical activity among healthy older individuals is well established [32] [34] [35]. Participants reported the frequency of engagements in various activities, including walking outside, light, moderate, or strenuous sports, recreational activities, and exercises specifically designed to enhance muscle strength and endurance [36].

The self-reported PASE was also used to record the duration of sedentary activity within the preceding 7 days [32] [33]. Participants provided information on the frequency (and average number of hours per day) of participation in sedentary activities such as reading, watching TV, engaging in computer activities, or doing handicrafts while seated [Dogra 36]. Finally, a self-reported sleep questionnaire contained the total time spent asleep at night. Participants provided details on the specific hours of actual sleep at night (0 to 24 hours) and sleep quality (very dissatisfied, dissatisfied, neutral, satisfied, very satisfied). Sleep measures consisted of self-reported sleep duration categorized as short (less than 6 hours), normal (6 to 8 hours), or long (more than 8 hours), and have demonstrated satisfactory validity and reliability among adults [37].

Categorical covariates were selected based on previous research [30][31], which includes age, body mass index, ethnicity, marital status, education, income, alcohol consumption, smoking, social support, self-rated health, sleep quality, and depression [38].

Metabolic Syndrome Components

Metabolic syndrome (MetS) was screened by adapting the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria [39]: i) triglycerides (≥ 150 mg/dl or 1.7 mmol/L) or pharmacologic treatment (Rx); ii) high-density lipoprotein cholesterol (≤ 40 mg/dl or 1.0 mmol/L [males] and ≤ 50 mg/dl or 1.3mmol/L [females]) or Rx; iii) glycosylated haemoglobin (A1c > 6.0%) in place of fasting plasma glucose (> 5.6 mmol/L); iv) blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg, or Rx), and; v) waist circumference (≥ 102 cm [males] and ≥ 88 cm [females]).

Carotid Intima-Media Thickness

Carotid Intima-Media Thickness (cIMT) was measured using the GE VIVID i® Carotid Doppler Ultrasound (87% to 98.6% sensitivity, and 59.2 to 75.7% specificity) [18]. Ultrasonography is a non-invasive and reliable method of measuring the intimal medial thickness of the carotid and femoral arteries [18]. The extent of carotid atherosclerotic vascular disease was determined using arterial thickness (continuous measurements).

Statistical Analysis

Initial analyses included a univariate approach to summarize frequency counts. To assess the impact of movement behaviors (namely physical activity, sedentary, and sleep) on 3-year changes in global cognition, a change score analysis was employed to calculate the difference between standardized global cognition scores at baseline and the first follow-up. Differences in sample characteristics between females and males were then assessed through a bivariate analysis utilizing chi-square and two-sample t-tests. Unadjusted repeated measures regression models were then employed to examine the association between movement behaviours and global cognition between sexes. Subsequently, a fully adjusted repeated measures regression model, incorporating relevant covariates, was used to evaluate the correlation structure of repeated responses (namely standardized global cognition scores) over time with different movement behavior types at baseline. A sex-based analysis, involving the assessment of interactions and stratification by sex, was used to ascertain differential effects for females and males.

A mediation analysis was subsequently performed to determine whether movement behaviours influence the relationship between cardiometabolic components (independent

variable, X) and 3-year change in global cognitive function (dependent variable, Y). A mediation analysis evaluates the influence of underlying mechanisms between an exposure and an outcome variable by a third mediator variable [40]. It will also explore whether some or all of the effect of X might result from an intermediary variable, M (movement behaviours), thought to mediate the effect of X on Y. As shown in **Figure 5.2**, X influences Y both directly (i.e., path c′) and indirectly (i.e., the combination of paths a and b) through the mediator M. For this study, the independent (X), mediating (M), and dependent (Y) variables were treated as continuous data. Covariates included baseline line global cognition (continuous data), and social support (continuous data); we adjusted for social support given its association with cognition [41]. The direct effect of X, and the indirect effect of X through M, on the outcome Y, were evaluated in multiple unweighted linear regression models (adjusting for covariates: social support, and baseline cognition), using PROCESS MACROS by Andrew Hayes (2013) [42]. Models were reproduced separately, as follows:(a) a regression between the exposure and mediator; (b) a regression between mediator and the outcome while adjusting for the exposure; (c) a regression between exposure and outcome, and a regression between exposure and outcome while adjusting for the mediator [40]. Regression estimates were computed, and indirect effects were standardized with the bootstrapping method (based on 1000 bootstrap samples) to yield bootstrapped standard errors and 95% confidence intervals. Data analysis was performed with SAS software version 9.4 (Cary, NC, U.S.A.), and where appropriate, weighted with the master survey weights to ensure national representativeness of the data. Statistical significance was set at alpha = 0.05.

Results

Similar to our previous work investigating the relationship between movement behaviors and memory (both immediate and delayed recall), the current study employed a similar subsample and methodology to examine changes in global cognition and mediating effects.

Baseline Characteristics

Characteristics of the sample were reported earlier **(Study 2: Table 4.1)**. In general, the sample consisted of middle-aged white individuals (average age 59.19 ± 0.12 years) who had post-secondary education, belonged to a middle-to-upper income bracket, had a low rate of current smoking, reported moderate to high levels of social support, and rated their health as good or very good. Few participants reported clinical depression, and over one-third were satisfied with their sleep quality. Similar to our previous work, participants reported 43.86 (SE=0.78) MET-hours of weekly activity, 3.73 h (SE=0.03) of sitting time per day and had an average nightly sleep duration of 6.77 h (SE=0.02).

Global Cognition

Table 5.1 displays the change (mean (SE)) in global cognition after age- and education-standardization. At baseline, global cognition (z-scores) was higher ($p < .0001$) in females (F: 0.01 (0.02), M: -0.11 (0.02)) compared to males. At follow-up, a 3-year change (z-score) showed no difference by sex (F: 0.03 (0.02), M: 0.02 (0.02); $p=0.594$). Sex differences were observed in all cardiometabolic components at baseline as follows: waist circumference (F: 87.44 (SE=0.22) cm, M: 100.24 (SE=0.24) cm; $p<0.0001$), systolic blood pressure (F: 118.39 (SE=0.28) mmHg, M: 121.83 (SE=0.26) mmHg; $p<0.0001$), diastolic blood pressure (F: 72.65 (SE=0.16) mmHg, M: 77.66 (SE=0.17) mmHg; $p<0.0001$), high density lipoprotein (F: 1.66 (SE=0.01) mmol/L, M: 1.29 (SE=0.01) mmol/L; $p<0.0001$), triglycerides (F: 1.66 (SE=0.02)

mmol/L, M: 1.98 (SE=0.02) mmol/L; p<0.0001), glycosylated hemoglobin (F: 5.53 (SE=0.01) %, M: 5.68 (SE=0.01) %; p<0.0001), and carotid intima-media thickness (F: 0.714 (SE=0.003) mm, M: 0.742 (SE=0.004) mm; p<0.0001).

Table 5.2 displays the linear regression estimates. In unadjusted general linear regressions, each MET-hour of weekly physical activity (females: -0.001, 95%CI = -0.0019 to -0.0001 z-score vs males: 0.00003, 95%CI = -0.0006 to 0.0007 z-score) and each hour of nightly sleep (females: -0.004, 95%CI = -0.07 to -0.01 z-score vs males: -0.005, 95%CI = -0.047 to 0.036 z-score) were associated with negative changes in global cognition among females but not males. Whereas 8+ hours of sitting was associated with positive changes in global cognition among males but not females (females: -0.076, 95%CI = -0.18 to 0.029 z-score vs males: 0.114, 95%CI = 0.004 to 0.224 z-score), each hour of sitting time was associated with positive changes in global cognition in both females and males (females: 0.017, 95%CI = 0.003 to 0.03 z-score vs males: 0.018: 95%CI = 0.004 to 0.032 z-score).

In fully adjusted models, analysis of sex differences showed each hour of sitting time was association with positive changes in global cognition among males (females: 0.007, 95%CI = -0.008 to 0.022 z-score vs males: 0.021, 95%CI = 0.005 to 0.036 z-score). Whereas 8+ hours of nightly sleep was associated with negative changes in global cognition among males (females: -0.151, 95%CI = -0.359 to 0.056 z-score vs males: -0.307, 95%CI = -0.576 to -0.039 z-score) (Table 5.2).

Interactions between movement behaviours (entered the model as PA | Sitting | Sleep) were assessed in a fully adjusted general linear regression model among females and males. In the first instance, with respect to continuous-by-continuous interactions ($p < 0.05$), each hour of daily sitting was associated with negative changes in global cognition among males

(unadjusted: -0.02, 95%CI = -0.03 to -0.0013 z-score, and fully adjusted: -0.019, 95%CI = -0.034 to -0.004 z-score) but not females (unadjusted: -0.0014, 95%CI: -0.02 to 0.013 z-score, and fully adjusted: -0.0015, 95%CI = -0.017 to 0.014 z-score); and this association was dependent on each hour of nightly sleep. In the second analysis with respect to categorical-by-categorical interactions, physical activity (10+ MET-hours vs less than 10-MET-hours weekly) was associated with positive changes in global cognition among males (unadjusted: 0.351, 95%CI = 0.004 to 0.698 z-score, and fully adjusted: 0.349, 95%CI = 0.053 to 0.646 z-score), but not females (unadjusted: 0.089, 95%CI = -0.158 to 0.337 z-score, and fully adjusted: 0.131, 95%CI = -0.140 to 0.406 z-score); and this association was dependent on sleep (6-8 hours vs less than 6 hours nightly). Additionally, with respect to categorical-by-categorical interactions, physical activity (10+ MET-hours vs less than 10-MET-hours weekly) was associated with positive changes in global cognition among females (unadjusted: 1.66, 95%CI = 0.48 to 2.84 z-score, and fully adjusted: 1.443, 95%CI = 0.330 to 2.557 z-score), and males (unadjusted: 1.34, 95%CI = -0.26 to 2.94 z-score, and fully adjusted: 1.919, 95%CI = 0.65 to 3.18 z-score); and this association was dependent on sitting (8+ hours vs less than 8 hours daily), and sleeping (8+ hours vs less than 6 hours nightly).

Sleep was subsequently stratified by categorical hours (< 6 hours, 6-8 hours, 8+ hours) among females and males in order to evaluate the interactions (entered the model as PA | Sitting). With respect to categorical-by-categorical interactions, among females getting too much sleep (8+ hours nightly), physical activity (10+ MET-hours vs less than 10-MET-hours weekly) was associated with positive changes in global cognition (1.18, 95%CI = 0.42 to 1.94 z-score) and this association was dependent on sitting (8+ hours vs less than 8 hours daily). Among males with excessive sleep (8+ hours nightly), a continuous-by-continuous interaction

showed that each MET-h of weekly physical activity was associated with positive changes in global cognition (0.0017, 95%CI = 0.00004 to 0.0034 z-score) and this was dependent on each hour of sitting, while categorical-by-categorical interaction showed that physical activity (10+ MET-hours vs less than 10-MET-hours weekly z-score) was associated with positive changes in global cognition (1.84, 95%CI = 0.46 to 3.21 z-score) and this association was dependent on sitting (8+ hours vs less than 8 hours daily).

Mediation Analysis

A mediation analysis was performed using continuous measures to examine the association of each baseline cardiometabolic component (continuous measures) on a 3-year change (z-score) in global condition through a mediator (e.g., continuous measures of physical activity, sitting, and sleep). Prior to formal analysis, the conditions for mediation were checked using general linear regression models [40]. These analyses (without inflation weights) confirmed a significant association (unadjusted and adjusted for each cardiometabolic component separately) between baseline sitting time (but not physical activity or sleep) and positive changes (z-score) in global condition among males (significant cardiometabolic component: waist circumference, systolic blood pressure, diastolic blood pressure, high-density lipoprotein, triglycerides, glycosylated hemoglobin, and carotid intima-media thickness), but not females. Among males, sitting time was also significantly associated with all cardiometabolic components (significant: waist circumference [positive], systolic blood pressure [negative], diastolic blood pressure [positive], high-density lipoprotein [negative], triglycerides [positive], glycosylated hemoglobin [negative], and carotid intima-media thickness [negative]); however, only waist circumference, high-density lipoprotein, and glycosylated hemoglobin were

associated with global cognition. Among females, sitting time was associated with a few cardiometabolic component (significant: waist circumference [positive], systolic blood pressure [negative], diastolic blood pressure [positive], high-density lipoprotein [negative], and carotid intima-media thickness [negative]); however, only high-density lipoprotein and glycosylated hemoglobin were associated with global cognition.

Sitting Time (Mediator)

Given the influence of sitting time on global cognition, we further explored its influence as a mediator among females and males. Baseline sitting time mediated the relationship between baseline cardiometabolic components and 3-year change in global cognition (z-score) among males but not females. Results of the mediation effect (i.e., the standardized indirect effect) of sitting time are shown in **Table 5.3 and 5.4**. Further estimates of the mediation model were presented in **Supplementary Files S5.1**.

In the unadjusted models (with baseline global cognition), there were significant *positive* indirect effects of sitting time on 3-year changes in global cognition (z-score) among males in relation to waist circumference, diastolic blood pressure, and triglycerides (see **Table 5.3)**. Conversely, there were significant *negative* indirect effects of sitting time on changes in global cognition among males in relation to systolic blood pressure, high density lipoprotein, glycosylated hemoglobin, and carotid intima-media thickness. After adjusting for social support, the relationships between changes in global cognition and cardiometabolic components were maintained among males (see **Table 5.4)**.

Cardiometabolic Components (Mediator)

The mediation effect (i.e., the standardized indirect effect) of baseline cardiometabolic components on the relationships between sitting time and 3-year change in global cognition was

explored in a subsequent analysis where it was shown that baseline cardiometabolic components mediated the relationship between baseline sitting time and change in global cognition (**Supplementary Files S5.1, S5.2, S5.3, and S5.4**).

In the unadjusted models (with baseline global cognition), the associations between **sitting time** and change in global cognition were *increased* with the indirect effect of glycosylated hemoglobin among males, but *decreased* with the indirect effects of waist circumference, and high-density lipoprotein, among females and males. After adjusting for baseline global cognition, and social support, the associations between sitting time and change in global cognition were maintained.

Discussion

Building on evidence of the importance of modifiable risk factors in the prevention and management of dementia, the current study examined the association (and mediating effects) between baseline movement behaviours (weekly physical activity, daily sedentary, and nightly sleep) and 3-year changes in global cognition This study highlights the influence of time spent sitting and sleeping on global cognition, as well as the interplay of physiological and lifestyle factors, which can inform future research and intervention aimed at enhancing the quality of life of older adults.

The findings of this study revealed associations of movement behaviours on global cognition with sex differences. Among males, each hour of sedentary activity was associated with positive changes in global cognition; longer sleep (8+ hours) was associated with negative changes in global cognition; each hour of nightly sleep was associated with negative changes in global cognition, an association that was dependent on depending on each hour of daily sitting.

Furthermore, among males, higher levels of physical activity were associated with changes in global cognition, an association that depended on sufficient nightly sleep.

For both females and males, higher levels of physical activity were associated with positive changes global cognition, and this association was dependent on longer sitting hours and longer nightly sleep. Among males with longer nightly sleep, each MET-hour of physical activity as associated with positive changes in global cognition, an association that was dependent on duration of sitting. Additionally, among both females and males with longer nightly sleep, higher levels of physical activity were associated with positive changes in global cognition, and this association depended on longer sitting hours. This suggests that staying physically active could be advantageous for individuals sitting for long hours.

Sedentary behavior encompasses activities with minimal energy expenditure, such as sitting, reclining, and lying down, during waking hours, typically characterized by an energy expenditure of ≤ 1.5 metabolic equivalent of task (MET) [43][44]. Studies have linked sedentary behavior to adverse effects on brain health [45] and have suggested that these associations may be modifiable through lifestyle interventions [46][47][48]. Notably, older adults spend a large portion of their day engaged in sedentary activities, estimated at approximately 9-10 hours [43] [44][45]. Despite its prevalence, the precise pathophysiological mechanisms by which a sedentary lifestyle affects brain health remain unclear, but its effect may be similar to other known risks for Alzheimer's disease [45] [47].

We evaluated causal associations to determine whether movement behaviours (physical activity, sitting time, and sleep) mediated the relationship between cardiometabolic components and 3-year change in global cognition among females and males. Sitting time, but not physical activity or sleep, mediated the cardiometabolic-global cognition relationship among males but

not females. The effects of sitting time were small but significant. Sitting time was associated with positive changes in global cognition from baseline, and its influence was noted across *all* cardiometabolic components in a mediation analysis among males but not females. When sitting time mediated the relationship between cardiometabolic components and 3-year change in global cognition from baseline, global cognition increased with waist circumference, diastolic blood pressure, and triglycerides, among males. While these cardiometabolic factors can negatively impact the brain, it is possible that their relationships with global cognition are curvilinear [49][50][51]. Conversely, global cognition decreased with systolic blood pressure, glycosylated haemoglobin, and carotid intima-media thickness, consistent with previous research [48][52][53][54]. Additionally, in the mediation model after adjusting for social support, there were non-significant direct effects between systolic blood pressure, diastolic blood pressure, triglycerides, and carotid intima-media thickness, with change in global cognition from baseline, which suggests that the relationship could be mediated to a larger extent through sedentary behaviour. The direct effects of waist circumference, high-density lipoprotein, and glycosylated haemoglobin were significant, indicating that the relationship between each of these cardiometabolic component and change in global cognition could be mediated to a lesser extent through sedentary behaviour.

It is also notable that, after accounting for social support, cardiometabolic components mediated the association between sitting time and 3-year change in global cognition, which decreased through waist circumference and high-density lipoprotein, among females and males, but increased through glycosylated haemoglobin among males but not females. This suggests that sex differences in cardiometabolic factors might influence how sitting time influences cognition. The indirect effect through waist circumference was consistent with previous research

[48][52][53][54]. High-density lipoprotein (HDL) is typically regarded as “good” cholesterol. However, increased HDL might have negative indirect effects on overall cognition due to underlying coexisting cardiometabolic abnormalities [55]. Increased glucose availability in males may mediate the relationship between sitting time and global cognition [56][57], as some cognitive tasks might be influenced by sedentary behaviors. Thus, the underlying mechanisms vary, and mediation plays a significant role in determining the associations between sitting time, cardiometabolic components, and global cognition. Other possible explanations may reflect differences in cognitive reserve to overcome cognitive deficits [58]. The direct effect of sitting time was significant with each cardiometabolic component among males but not females, which suggests that the path between sitting time and change in global cognition could be mediated to a lesser extent through cardiometabolic components.

Recommended hours of sitting have been shown to improve brain health including lowering risk factors, such as hypertension and diabetes, linked to heart disease [59], and time spent in prolonged sedentary activity could play a role in cognitive decline and risk of dementia. Sitting time (as a mediator) was linked to a decrease in global cognition in relation to systolic blood pressure, high-density lipoproteins, glycosylated haemoglobin, and carotid intima-media thickness. Prolonged sitting may contribute to changes in brain structure, influencing cognitive function through mechanisms such as cerebrovascular health [60][61]. Additionally, prolonged sitting may alter insulin sensitivity and body composition [62][54] among other risk factors of cognitive decline and neurodegenerative diseases [53].

Although depression and social support were accounted for in this analysis, other mental health issues such as anxiety and quality of life are also linked to sedentary activity [63][64] and were not adjusted for in this analysis. Movement behaviours may mediate blood flow and

engagement in certain sitting time activities may enhance overall brain health [29][65]. Further study into these mental health factors is needed to better understand their role in the relationships between sedentary behavior and cognitive decline. Thus, early interventions reducing cardiometabolic abnormalities that are associated with atherosclerosis and other pathophysiological heart conditions, may improve cognitive function and delay the onset of dementia [66][67][68][69][70]. Although the exact mechanisms are yet to be elucidated, dementia may be delayed with adherence to 24-hour movement recommendations including reducing sedentary time and achieving sufficient sleep [2][71]. Therefore, emphasis on movement behaviours remains an area of study for risk reduction efforts.

Regular nightly sleep is vital for brain health [72][73][74]. Sleep duration is a potential risk factor of brain health [73]; however, some variability may be explained in part by other problems involving the circadian system [75], cardiovascular system [76][77], depression [38], sleep quality [78][79], which warrants further study [73]. The recommended duration of sleep per night is 7-8 hours [80]; however, sleep problems tend to increase with age [75][81]. About 50% of older adults report sleep problems [82], which increases the risk of a stroke, heart failure [83][84], and is a risk factor for dementia.

The results of this study are consistent with previous studies on sleep patterns and brain health [72] [79] [85] [86] [87] [88]. Although the precise mechanisms and relationships are not yet fully understood, research suggests biological or physiological needs for sleep to allow the brain to recover [74] [89]. However, the impact on dementia risk may be based on complex interplay with physiological and lifestyle factors, which warrants research to gain further insight into the effects of sleep duration on dementia and its underlying mechanisms [79] [85].

Strengths And Limitations

A strength of this study is the large purpose-built Canadian cohort on which these relationships (direct, indirect, and total effects) were investigated, and the inclusion of valid and reliable measures of global cognition and bootstrapping to obtain robust estimates. However, limitations include the possibility of inadequate follow-up, reduced statistical power to detect smaller effect sizes, and the potential for reverse causality. Because all movement behaviours were self-reported, recall bias cannot be ruled out. Moreover, exploratory analysis of combined movement behaviors (of physical activity with longer sitting hours and longer sleep) was based on sparse cell sizes and requires confirmation in larger samples. Moreover, important lifestyle factors, such as engagement in cognitively stimulating activities, may be a source of confounding bias in the observed associations. Future studies should include cognitive stimulation as a covariate to reduce confounding. Confirmatory analyses are also needed to consider the broader impact of comorbid conditions, polypharmacy, time between movement behaviours, and age/sex effect moderation, with longer-term follow-up with additional endpoints to ascertain changes in cognition with changes in movement behaviours in middle-age and older-age adults.

Conclusion

This study examined the effects of movement behaviors on 3-year changes in global cognition. Positive changes in global cognition were associated with increased sitting time among males; however, longer nightly sleep negatively influenced cognition, in males. Sitting time and cardiometabolic components mutually mediated their effects on cognitive changes. Future longer-term research is needed to better understand the effects of changes in movement behaviors on changes in cognition.

List of Abbreviations

AD, Alzheimer's disease

CIHR, Canadian Institutes of Health Research

CIMT, carotid intima-media thickness

CLSA, Canadian Longitudinal Study on Aging

HbA1C, glycosylated haemoglobin.

HDL, high density lipoproteins

MCI, mild cognitive impairment

MET, metabolic equivalent of task

MVPA, moderate-to-vigorous physical activity

PA, physical activity

PASE, physical activity scale for elderly

RAVLT, Rey Auditory Verbal Learning Test

SBP, systolic blood pressure

TG, triglycerides

WC, waist circumference

Declarations

Ethics approval and consent to participate.

This study received ethics review and renewal (Certificate Number: STU 2020-118) by the Human Participants Review Sub-Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines.

Availability of data and materials.

All data analysed during this study are available from data/biospecimens collected by the Canadian Longitudinal Study on Aging (CLSA). This research has been conducted using the CLSA dataset [Comprehensive Cohort Version 1], under Application Number [2010021]. The CLSA is led by Drs. Parminder Raina, Christina Wolfson and Susan Kirkland.

Competing interests.

The authors declare that they have no competing interests.

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Authors' Contributions.

AO had full access to the data and takes responsibility for the integrity and accuracy of all data analysis. AO and CIA conceived of the study and designed the study protocol. AO performed the analyses, and CIA oversaw the analyses. AO wrote the draft of the manuscript with inputs from all authors. JK and HT provided critical revisions to the article. All authors contributed to the interpretation of the findings and approved the final version of the article to be published.

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Table 5.1. Health characteristics by sex; data (weighted analysis) derived from CLSA

	Sex			
	Female (N=12 969)	Male (N=12 750)	Total (N=25 719)	P-value
Waist Circumference (cm)				<.0001[1]
Mean (SE)	87.44 (0.22)	100.24 (0.24)	93.59 (0.18)	
Missing	53	59	112	
Systolic Blood Pressure (mmHg)				<.0001[1]
Mean (SE)	118.39 (0.28)	121.83 (0.26)	120.04 (0.19)	
Missing	133	84	217	
Diastolic Blood Pressure (mmHg)				<.0001[1]
Mean (SE)	72.65 (0.16)	77.66 (0.17)	75.06 (0.12)	
Missing	133	84	217	
High Density Lipoprotein (mmol/L)				<.0001[1]
Mean (SE)	1.66 (0.01)	1.29 (0.01)	1.48 (0.01)	
Missing	1401	1075	2476	
Triglycerides (mmol/L)				<.0001[1]
Mean (SE)	1.66 (0.02)	1.98 (0.02)	1.81 (0.01)	
Missing	1401	1075	2476	
Glycosylated Haemoglobin (%)				<.0001[1]
Mean (SE)	5.53 (0.01)	5.68 (0.01)	5.60 (0.01)	
Missing	1515	1063	2578	
Carotid Intima-media Thickness, Left (mm)				<.0001[1]
Mean (SE)	0.714 (0.003)	0.742 (0.004)	0.73 (0.002)	
Missing	2317	1791	4108	
Global Cognitive Score at Baseline (Standardized)				<.0001[1]
Mean (SE)	0.01 (0.02)	-0.11 (0.02)	-0.05 (0.01)	
Missing	1289	1370	2659	

	Sex			
	Female (N=12 969)	Male (N=12 750)	Total (N=25 719)	P-value
Change in Global Cognitive Score (Standardized) at Follow-up				0.5942[1]
Mean (SE)	0.03 (0.02)	0.02 (0.02)	0.03 (0.02)	
Missing	4469	4228	8697	

[1]Equal variance two sample t-test; [2]Chi-Square p-value;

Table 5.2. Associations between 3-year changes in global cognition and movement characteristics by sex; data (weighted analysis) derived from CLSA.

3-Year Changes in Global Cognition				
	Model 1		Model 2	
	Females β (95%CI)	Males β (95%CI)	Females β (95%CI)	Males β (95%CI)
Main Effect				
Global Cognition (Standardized)				
Physical Activity Status (Weekly)				
Less than 10 MET-hours	REF	REF	REF	REF
10 or more hours	-0.026 (-0.099, 0.047)	-0.033 (-0.051, 0.117)	-0.033 (-0.107, 0.042)	0.019 (-0.068, 0.105)
Linear (each hour per week)	**-0.001 (-0.002, -0.0001)**	0.00003 (-0.0006, 0.0007)	-0.0007 (-0.0016, 0.0003)	-0.0002 (-0.0006, 0.0009)
Global Cognition (Standardized)				
Sitting Status (Daily)				
Less than 8 hours	REF	REF	REF	REF
8 or more hours	-0.076 (-0.180, 0.029)	**0.114 (0.004, 0.224)**	-0.104 (-0.224, 0.015)	0.109 (-0.008, 0.227
Linear (hourly)	**0.017 (0.003, 0.030)**	**0.018 (0.004, 0.032)**	0.007 (-0.008, 0.022)	**0.021 (0.005, 0.036)**
Global Cognition (Standardized)				
Sleep Status (Daily)				
Less than 6 hours	REF	REF	REF	REF
6-8 hours	-0.010 (-0.122, 0.101)	0.092 (-0.029, 0.212)	0.019 (-0.111, 0.149)	0.036 (-0.093, 0.165)
8 or more hours	-0.179 (-0.362, 0.004)	-0.22 (-0.48, 0.05)	-0.151 (-0.359, 0.056)	**-0.307 (-0.576, -0.039)**
Linear (hourly)	**-0.04 (-0.07, -0.01)**	-0.005 (-0.05, 0.036)	-0.037 (-0.074, 0.0005)	-0.031 (-0.074, 0.012)
Interaction Effect				
Continuous-by-continuous interactions				
MET-h PA (weekly), hours sitting (daily)	0.001 (-0.0016, 0.0035)	-0.0011 (-0.003, 0.0008)	0.0015 (-0.0012, 0.0041)	0.0016 (-0.0035, 0.0004)
MET-h PA (weekly), hours sleeping (nightly)	0.0002 (-0.001, 0.0015)	0.0001 (-0.0011, 0.0008)	0.0008 (-0.0006, 0.0021)	-0.0003 (-0.0013, 0.0006)
Hours sitting (daily), hours sleeping (nightly)	-0.0014 (-0.02, 0.013)	**-0.02 (-0.03, -0.0013)**	-0.0015 (-0.017, 0.014)	**-0.019 (-0.034, -0.004)**
MET-h PA (weekly), hours sitting (daily), hours sleeping (nightly)	0.0001 (-0.0001, 0.0003)	0.0002 (-0.0001, 0.0005)	-0.0002 (-0.0006, 0.0002)	0.0003 (-0.00005, 0.0005)
Categorical-by-categorical interactions				
10+ MET-h PA (weekly), 8+ hours sitting (daily)	-0.421 (-1.01, 0.166)	-0.094 (-0.898, 0.71)	-0.472 (-1.096, 0.152)	-0.250 (-1.026, 0.526)
10+ MET-h PA (weekly), 6-8 hours (nightly)	0.089 (-0.158, 0.337)	**0.351 (0.004, 0.698)**	0.131 (-0.140, 0.406)	**0.349 (0.053, 0.646)**

3-Year Changes in Global Cognition				
	Model 1		Model 2	
	Females	Males	Females	Males
10+ MET-h PA (weekly), 8+ hours sleeping (nightly)	0.066 (-0.313, 0.446)	0.53 (-0.05, 1.11)	0.486 (-0.446, 0.351)	0.486 (-0.046, 1.018)
8+ hours sitting (daily), 6-8 hours sleeping (nightly)	0.092 (-0.467, 0.284)	0.018 (-0.56, 0.60)	-0.048 (-0.748, 0.419)	-0.164 (-0.748, 0.419)
8+ hours sitting (daily), 8+ hours sleeping (nightly)	-0.163 (-0.961, 0.634)	0.40 (-0.34, 1.14)	0.165 (-0.667, 0.996)	0.331 (-0.417, 1.079)
10+ MET-h PA (weekly), 8+ hours sitting (daily), 6-8 hours sleeping (nightly)	0.34 (-0.30, 0.97)	-0.045 (-0.88, 0.79)	0.336 (-0.333, 1.004)	0.098 (-0.709, 0.904)
10+ MET-h PA (weekly), 8+ hours sitting (daily), 8+ hours sleeping (nightly)	**1.66 (0.48, 2.84)**	1.34 (-0.26, 2.94)	**1.443 (0.330, 2.557)**	**1.919 (0.65, 3.187)**

Model 1 unadjusted.
Model 2 adjusted for age, ethnicity, education, income, alcohol, smoking, social support, movement behaviours (mutually for physical activity, sitting, and sleep status), body mass index, self-reported general health, depression, and sleep quality.
Subgroups: Females and Males were adjusted separately using Model 2 without sex variable.
In the categorical-by-categorical interaction models, the referent category (REF) is the lowest level (or least amount) of physical activity (less than 10 MET-hours weekly), sitting (less than 8 hours), or sleep (less than 6 hours) at baseline.

Table 5.3. Associations between 3-year changes in global cognition, physical activity, and sitting time, by categorical hours of sleep (< 6 hours, 6-8 hours, 8+ hours); data (weighted analysis) derived from CLSA.

	3-Year Changes in Global Cognition		
Categorical Hours of Sleep	< 6 hours β (95%CI)	6-8 hours β (95%CI)	8+ hours β (95%CI)
FEMALES			
Continuous-by-continuous interactions			
MET-h PA (weekly), hours sitting (daily)	-0.0004 (-0.0014, 0.0006)	0.00045 (-0.00007, 0.00098)	-0.0001 (-0.0027, 0.0025)
Categorical-by-categorical interactions			
10+ MET-h PA (weekly), 8+ hours sitting (daily)	-0.47 (-1.13, 0.20)	-0.14 (-0.38, 0.10)	**1.18** **(0.42, 1.94)**
MALES			
Continuous-by-continuous interactions			
MET-h PA (weekly), hours sitting (daily)	0.00006 (-0.00074, 0.0006)	-0.00001 (-0.00053, 0.00051)	**0.0017** **(0.00004, 0.0034)**
Categorical-by-categorical interactions			
10+ MET-h PA (weekly), 8+ hours sitting (daily)	-0.23 (-0.85, 0.40)	-0.16 (-0.39, 0.07)	**1.84** **(0.46, 3.21)**

All models were adjusted for age, ethnicity, education, income, alcohol, smoking, social support, movement behaviours (mutually for physical activity and sitting), body mass index, self-reported general health, depression, and sleep quality.
Subgroups: Females and Males were adjusted using covariates indicated above without sex variable.
In the categorical-by-categorical interaction models, the referent category (REF) is the lowest level (or least amount) of physical activity (less than 10 MET-hours weekly), or sitting (less than 8 hours), at baseline.

Table 5.4. Unadjusted model showing the total, direct, and indirect effects of each cardiometabolic component (X) on 3-year changes in global cognition (Y) among females and the influence of baseline sitting time (M) as a mediator in the relationship; data (unweighted analysis) derived from CLSA.

IV	Effects, X (IV) → M (sitting) → Y (cog)	beta	SE	t	p	LL	UL
WC	Total	-0.0014	0.0008	-1.8843	0.0596	-0.0029	0.0001
	Direct	-0.0015	0.0008	-2.0205	0.0434	-0.0030	-0.0000
	Indirect*	0.0001	0.0001			-0.0000	0.0002
	Standardized Indirect*	0.0015	0.0008			-0.0001	0.0032
SBP	Total	-0.0011	0.0006	-1.7578	0.0788	-0.0023	0.0001
	Direct	-0.0011	0.0006	-1.7397	0.0820	-0.0023	0.0001
	Indirect*	-0.0000	0.0000			-0.0000	0.0000
	Standardized Indirect*	-0.0002	0.0002			-0.0008	0.0002
DBP	Total	-0.0003	0.0011	-0.2691	0.7879	-0.0025	0.0019
	Direct	-0.0004	0.0011	-0.3393	0.7344	-0.0025	0.0018
	Indirect*	0.0001	0.0001			-0.0000	0.0002
	Standardized Indirect*	0.0007	0.0005			-0.0002	0.0018
HDL	Total	0.0567	0.0223	2.5379	0.0112	0.0129	0.1005
	Direct	0.0583	0.0224	2.6062	0.0092	0.0144	0.1021
	Indirect*	-0.0016	0.0011			-0.0040	0.0003
	Standardized Indirect*	-0.0008	0.0005			-0.0020	0.0002
TG	Total	-0.0172	0.0124	-1.3912	0.1642	-0.0415	0.0070
	Direct	-0.0172	0.0124	-1.3941	0.1633	-0.0415	0.0070
	Indirect*	0.0000	0.0003			-0.0006	0.0006
	Standardized Indirect*	0.0000	0.0002			-0.0005	0.0005
HbA1c	Total	-0.0760	0.0184	-4.1281	0.0000	-0.1121	-0.0399
	Direct	-0.0760	0.0184	-4.1274	0.0000	-0.1121	-0.0399
	Indirect*	-0.0000	0.0004			-0.0008	0.0007
	Standardized Indirect*	-0.0000	0.0002			-0.0005	0.0005
CIMT	Total	-0.0810	0.0600	-1.3486	0.1775	-0.1987	0.0367
	Direct	-0.0793	0.0601	-1.3198	0.1869	-0.1970	0.0385
	Indirect*	-0.0017	0.0016			-0.0056	0.0010
	Standardized Indirect*	-0.0003	0.0003			-0.0010	0.0002

Global cognition (z-score) data were age- and education- standardized. Covariates included baseline global cognition (z-score). * 95% CI based on 1000 bootstrap samples. Abbreviations: IV, independent variable; SE, standard error; t, t-test; p, p-value; LL, lower limit of 95% CI; UL, upper limit of 95% CI; WC, waist circumference; SBP, systolic blood pressure; HDL, high density lipoproteins; TG, triglycerides; HbA1C, glycosylated haemoglobin; cIMT, carotid intima-media thickness.
Note: The influence of the effect of the mediator is assessed using the total, direct, and indirect effects. The direct effect is the effect of the exposure on the outcome. The indirect effect is the effect of the exposure on the outcome through the mediator. The total effect is the sum of the direct and indirect effects, which determines the overall impact on the outcome after accounting for the mediator.

Table 5.5. Adjusted model showing the total, direct, and indirect effects of each cardiometabolic component (X) on 3-year changes in global cognition (Y) among females and the influence of baseline sitting time (M) as a mediator in the relationship; data (unweighted analysis) derived from CLSA.

IV	Effects, X (IV) → M (sitting) → Y (cog)	beta	SE	t	p	LL	UL
WC	Total	-0.0014	0.0008	-1.8186	0.0690	-0.0029	0.0001
	Direct	-0.0015	0.0008	-1.9604	0.0500	-0.0030	-0.0000
	Indirect*	0.0001	0.0001			-0.0000	0.0002
	Standardized Indirect*	0.0015	0.0008			-0.0000	0.0031
SBP	Total	-0.0010	0.0006	-1.5834	0.1134	-0.0022	0.0002
	Direct	-0.0010	0.0006	-1.5645	0.1177	-0.0022	0.0002
	Indirect*	-0.0000	0.0000			-0.0000	0.0000
	Standardized Indirect*	-0.0002	0.0002			-0.0007	0.0002
DBP	Total	-0.0004	0.0011	-0.3250	0.7452	-0.0025	0.0018
	Direct	-0.0004	0.0011	-0.4003	0.6889	-0.0026	0.0017
	Indirect*	0.0001	0.0001			-0.0000	0.0002
	Standardized Indirect*	0.0008	0.0005			-0.0001	0.0019
HDL	Total	0.0564	0.0224	2.5172	0.0119	0.0125	0.1004
	Direct	0.0581	0.0224	2.5903	0.0096	0.0141	0.1021
	Indirect*	-0.0017	0.0011			-0.0041	0.0002
	Standardized Indirect*	-0.0008	0.0005			-0.0020	0.0001
TG	Total	-0.0182	0.0124	-1.4639	0.1433	-0.0425	0.0062
	Direct	-0.0182	0.0124	-1.4662	0.1426	-0.0425	0.0061
	Indirect*	0.0000	0.0003			-0.0005	0.0006
	Standardized Indirect*	0.0000	0.0002			-0.0005	0.0005
HbA1c	Total	-0.0713	0.0185	-3.8637	0.0001	-0.1075	-0.0351
	Direct	-0.0713	0.0185	-3.8607	0.0001	-0.1075	-0.0351
	Indirect*	-0.0001	0.0004			-0.0009	0.0007
	Standardized Indirect*	-0.0000	0.0002			-0.0005	0.0004
CIMT	Total	-0.0566	0.0605	-0.9356	0.3495	-0.1753	0.0620
	Direct	-0.0548	0.0606	-0.9049	0.3656	-0.1735	0.0639
	Indirect*	-0.0018	0.0017			-0.0060	0.0009
	Standardized Indirect*	-0.0003	0.0003			-0.0011	0.0002

Global cognition (z-score) data were age- and education- standardized. Covariates included baseline global cognition (z-score) and social support. * 95% CI based on 1000 bootstrap samples. Abbreviations: IV, independent variable; SE, standard error; t, t-test; p, p-value; LL, lower limit of 95% CI; UL, upper limit of 95% CI; WC, waist circumference; SBP, systolic blood pressure; HDL, high density lipoproteins; TG, triglycerides; HbA1C, glycosylated haemoglobin; cIMT, carotid intima-media thickness.
Note: The influence of the effect of the mediator is assessed using the total, direct, and indirect effects. The direct effect is the effect of the exposure on the outcome. The indirect effect is the effect of the exposure on the outcome through the mediator. The total effect is the sum of the direct and indirect effects, which determines the overall impact on the outcome after accounting for the mediator.

Table 5.6. Unadjusted model showing the total, direct, and indirect effects of each cardiometabolic component (X) on 3-year changes in global cognition among (Y) males and the influence of baseline sitting time (M) as a mediator in the relationship; data (unweighted analysis) derived from CLSA.

IV	Effects, X (IV) → M (sitting) → Y (cog)	beta	SE	t	p	LL	UL
WC	Total	-0.0020	0.0008	-2.4854	0.0130	-0.0037	-0.0004
	Direct	-0.0022	0.0008	-2.6389	0.0083	-0.0038	-0.0006
	Indirect*	0.0001	0.0001			0.0000	0.0002
	Standardized Indirect*	0.0016	0.0006			**0.0006**	**0.0029**
SBP	Total	-0.0003	0.0007	-0.4355	0.6632	-0.0016	0.0010
	Direct	-0.0002	0.0007	-0.3332	0.7390	-0.0015	0.0011
	Indirect*	-0.0001	0.0000			-0.0001	-0.0000
	Standardized Indirect*	-0.0010	0.0005			**-0.0021**	**-0.0003**
DBP	Total	0.0003	0.0010	0.3076	0.7584	-0.0017	0.0024
	Direct	0.0001	0.0010	0.1218	0.9031	-0.0019	0.0022
	Indirect*	0.0002	0.0001			0.0001	0.0004
	Standardized Indirect*	0.0019	0.0007			**0.0007**	**0.0034**
HDL	Total	0.0668	0.0268	2.4922	0.0127	0.0142	0.1193
	Direct	0.0693	0.0268	2.5856	0.0097	0.0168	0.1218
	Indirect*	-0.0025	0.0012			-0.0052	-0.0004
	Standardized Indirect*	-0.0010	0.0005			**-0.0020**	**-0.0002**
TG	Total	-0.0056	0.0097	-0.5740	0.5660	-0.0246	0.0135
	Direct	-0.0066	0.0097	-0.6802	0.4964	-0.0257	0.0125
	Indirect*	0.0010	0.0005			0.0002	0.0021
	Standardized Indirect*	0.0011	0.0005			**0.0003**	**0.0023**
HbA1c	Total	-0.0581	0.0138	-4.1980	0.0000	-0.0852	-0.0310
	Direct	-0.0563	0.0138	-4.0645	0.0000	-0.0834	-0.0291
	Indirect*	-0.0018	0.0008			-0.0035	-0.0006
	Standardized Indirect*	-0.0014	0.0006			**-0.0027**	**-0.0004**
CIMT	Total	-0.0195	0.0544	-0.3585	0.7200	-0.1261	0.0871
	Direct	-0.0074	0.0545	-0.1351	0.8925	-0.1141	0.0994
	Indirect*	-0.0121	0.0041			-0.0208	-0.0048
	Standardized Indirect*	-0.0024	0.0008			**-0.0041**	**-0.0010**

Global cognition (z-score) data were age- and education- standardized. Covariates included baseline global cognition (z-score). * 95% CI based on 1000 bootstrap samples. Abbreviations: IV, independent variable; SE, standard error; t, t-test; p, p-value; LL, lower limit of 95% CI; UL, upper limit of 95% CI; WC, waist circumference; SBP, systolic blood pressure; HDL, high density lipoproteins; TG, triglycerides; HbA1C, glycosylated haemoglobin; cIMT, carotid intima-media thickness.
Note: The influence of the effect of the mediator is assessed using the total, direct, and indirect effects. The direct effect is the effect of the exposure on the outcome. The indirect effect is the effect of the exposure on the outcome through the mediator. The total effect is the sum of the direct and indirect effects, which determines the overall impact on the outcome after accounting for the mediator.

Table 5.7. Adjusted model showing the total, direct, and indirect effects of each cardiometabolic component (X) on 3-year changes in global cognition (Y) among males and the influence of baseline sitting time (M) as a mediator in the relationship; data (unweighted analysis) derived from CLSA.

IV	Effects, X (IV) → M (sitting) → Y (cog)	beta	SE	t	p	LL	UL
WC	Total	-0.0020	0.0008	-2.3878	0.0170	-0.0036	-0.0004
	Direct	-0.0021	0.0008	-2.5505	0.0108	-0.0037	-0.0005
	Indirect*	0.0001	0.0001			0.0000	0.0003
	Standardized Indirect*	0.0017	0.0006			**0.0006**	**0.0031**
SBP	Total	-0.0003	0.0007	-0.3974	0.6911	-0.0016	0.0010
	Direct	-0.0002	0.0007	-0.2836	0.7767	-0.0015	0.0011
	Indirect*	-0.0001	0.0000			-0.0001	-0.0000
	Standardized Indirect*	-0.0012	0.0005			**-0.0022**	**-0.0003**
DBP	Total	0.0003	0.0011	0.2495	0.8030	-0.0018	0.0023
	Direct	0.0001	0.0011	0.0534	0.9574	-0.0020	0.0021
	Indirect*	0.0002	0.0001			0.0001	0.0004
	Standardized Indirect*	0.0020	0.0007			**0.0007**	**0.0034**
HDL	Total	0.0667	0.0269	2.4790	0.0132	0.0140	0.1195
	Direct	0.0693	0.0269	2.5739	0.0101	0.0165	0.1221
	Indirect*	-0.0026	0.0012			-0.0053	-0.0005
	Standardized Indirect*	-0.0010	0.0005			**-0.0021**	**-0.0002**
TG	Total	-0.0043	0.0097	-0.4455	0.6560	-0.0234	0.0148
	Direct	-0.0054	0.0097	-0.5522	0.5808	-0.0245	0.0137
	Indirect*	0.0010	0.0005			0.0002	0.0022
	Standardized Indirect*	0.0011	0.0006			**0.0003**	**0.0024**
HbA1c	Total	-0.0566	0.0139	-4.0800	0.0000	-0.0838	-0.0294
	Direct	-0.0547	0.0139	-3.9397	0.0001	-0.0819	-0.0275
	Indirect*	-0.0019	0.0008			-0.0037	-0.0006
	Standardized Indirect*	-0.0015	0.0006			**-0.0028**	**-0.0005**
CIMT	Total	-0.0114	0.0545	-0.2092	0.8343	-0.1182	0.0954
	Direct	0.0012	0.0546	0.0223	0.9822	-0.1058	0.1082
	Indirect*	-0.0126	0.0043			-0.0215	-0.0053
	Standardized Indirect*	-0.0025	0.0008			**-0.0043**	**-0.0010**

Global cognition (z-score) data were age- and education- standardized. Covariates included baseline global cognition (z-score) and social support. * 95% CI based on 1000 bootstrap samples. Abbreviations: IV, independent variable; SE, standard error; t, t-test; p, p-value; LL, lower limit of 95% CI; UL, upper limit of 95% CI; WC, waist circumference; SBP, systolic blood pressure; HDL, high density lipoproteins; TG, triglycerides; HbA1C, glycosylated haemoglobin; cIMT, carotid intima-media thickness.
Note: The influence of the effect of the mediator is assessed using the total, direct, and indirect effects. The direct effect is the effect of the exposure on the outcome. The indirect effect is the effect of the exposure on the outcome through the mediator. The total effect is the sum of the direct and indirect effects, which determines the overall impact on the outcome after accounting for the mediator.

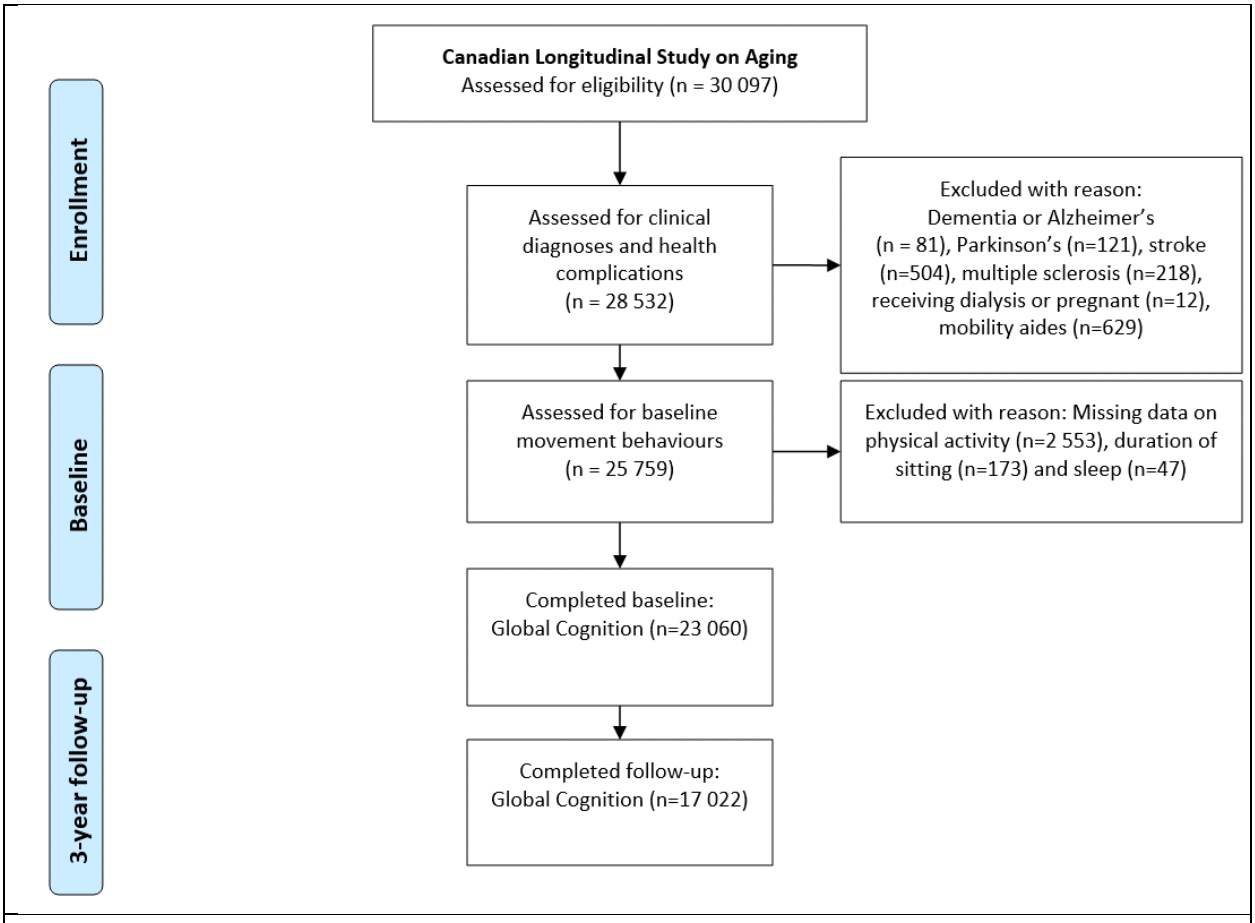

Figure 5.1. Figure showing a representation of the flow chart.

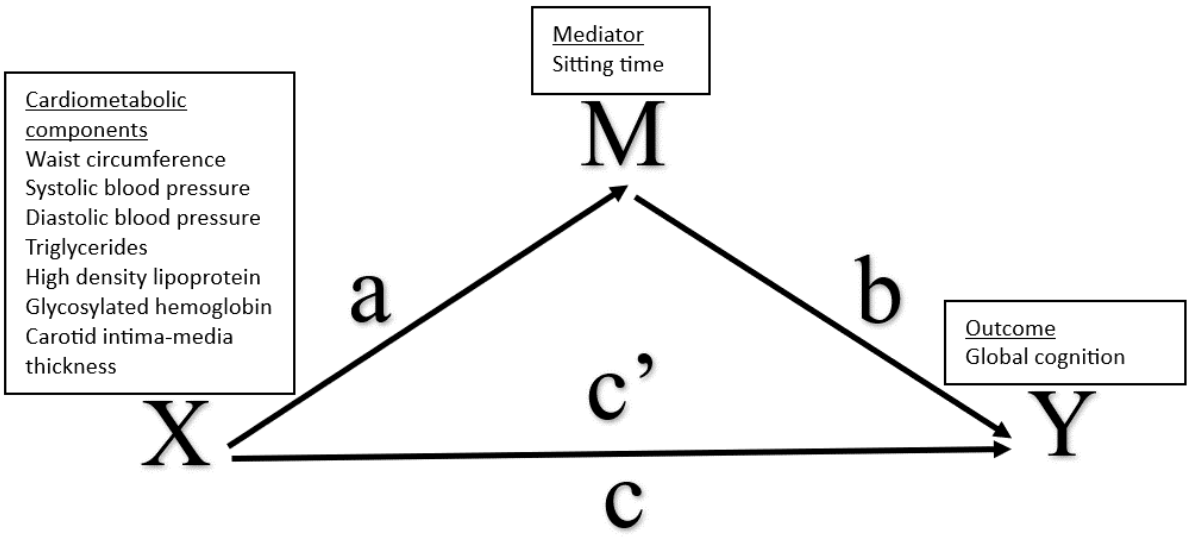

Figure 5.2. Figure showing a representation of the mediation model.

Note: The total effect (c) measures the overall relationship between each baseline cardiometabolic component (X) and 3-year change in global cognition (Y), encompassing both direct (c`) and indirect (*a* * *b*) influences through baseline sitting time (M). Path *a* measures the effect of X on M. Path *b* measures the effect of M on Y after accounting for X. Path *c`* measures the effect of X on Y after accounting for M. Path *c* measures the total effect of X on Y without accounting for M.

Chapter 6 Extended Discussion

6.1. Systematic Review and Meta-Analysis (Chapter 3)

Dementia is a progressive impairment comprised of many diseases, with Alzheimer's disease accounting for most cases [1]. For many individuals living with dementia, changes in behavior can manifest in different ways and vary in severity and by stage. The resulting variability and complexity of behaviours in individuals living with dementia highlights the need for comprehensive assessment and management strategies.

While the relationship between movement behaviours and brain health is complex; evidence from meta-analyses and systematic reviews are widely considered to be the gold standard design of literature syntheses, used here to quantify the relationship between physical activity, sleep, and sedentary time with dementia. Results of the SRMA (Study 1) showed that higher levels of physical activity were associated with a 28% reduction in the risk of incident dementia; an inverse association that varied with age (i.e., < 65 and 65+ years) and follow-up duration (i.e., < 10 and 10+ years). Both short and long nightly sleep duration were associated with increased risk of dementia: 23% and 49% respectively. However, there was a limited number of sleep studies and variability in optimal sleep duration across studies.

A familiar U-shaped relationship between sleep and dementia was observed. Although there is strong evidence on relationship between physical activity, sleep, and brain health, there has been limited longitudinal or prospective studies on sedentary behaviours. One relevant issue involves the difficulties in quantifying sedentary behaviours: many population-based studies rely on self-reported questionnaires which may not be reliable [2]. Self-reported questionnaires are prone to recall bias and may not always capture all instances of sedentary behavior, which involve low energy expenditure and encompasses a wide variety of activities (e.g. reading,

watching television, using a computer, or tasks involving manual dexterity, such as handicrafts, while awake and sitting, reclining, or lying down). Therefore, studies involving sedentary behavior and its relationship with dementia or mild cognitive impairment may be prone to recall and reporting bias, due to the multitude of behaviors that must be studied.

6.1.1. Operationalization of Sedentary Time

Compared to the physical activity, the concept and operationalization of sedentary behavior in its current form - as distinct from physical *in*activity - has been in use for less than two decades. As such, the conflation of physical inactivity and sedentary behavior represents a methodological problem. Whereas physical inactivity refers to insufficient engagement in moderate-to-vigorous physical activity, sedentary behavior refers to prolonged periods of low energy expenditure, independent of overall physical activity levels. Because our SRMA relied on historical cohorts, there was a lack of clarity about the measurement of sedentary behaviours, and no studies with an assessment of both physical activity and sedentary behaviours using validated tools for this intent. Indeed, most studies that were identified did not distinguish between physical inactivity and sedentary behaviours; therefore, little is known about the relationship between sedentary behaviours and dementia, and no studies were included in our SRMA. Future studies using objective measures (e.g. accelerometers or inclinometers), or other wearables capable of capturing both the duration and patterns of sedentary behavior and cardiometabolic health (e.g. blood pressure) throughout the day, are necessary to provide new insight. Whereas accelerometers are considered within the epidemiological literature as valuable objective measures of physical activity, there have been challenges with accurately distinguishing between sitting and standing postures.

6.2.1 ***CLSA Analyses (Chapters 4 and 5) – Assessment of Dementia and Cognitive Function***

Importantly, more than half of the CLSA sample had some form of cognitive impairment at baseline and there were significant changes in the distribution of cognitive impairment over time, which was consistent with the literature [3][4][5]. Potential transitions between cognitive states over time were notable for most categories except for "Single Domain Non-Memory Cognitive Impairment" and "Dementia". The prevalence of dementia was very low (rare) over time, consistent with previous research [6]; however, the absolute number of individuals with dementia increased by 67% (unweighted percentage of the total sample) at the initial follow-up assessment, compared to the baseline assessment. This aligns with previous research on the high risk of progression from MCI to dementia within three years [7]. Using a variety of cognitive screening test scores at baseline and initial follow-up (at 3-year) assessment, underlying dementia (i.e., not doctor diagnosed) was screened to distinguish severity of impairment as opposed to normal age-related cognitive change [1]. Participants (n=16 444) at baseline and initial follow-up assessments were classified into one of five discreet groups (see **Fig. 6.1**): "Normal" (43.7%, 39.9%), "Multiple Domain Cognitive Impairment – Not Dementia" (14.6%, 17.6%), "Amnesic Cognitive Impairment" (5.2%, 6%), "Single Domain Non-Memory Cognitive Impairment" (36%, 36%), and "Dementia" (0.5%, 0.5%). Overlap between categories could not be ruled out due to challenges of categorizing participants into discrete groups. Supplementary files (**Fig. S6.1** and **S6.2**) contain visual representations of the distribution of dementia and cognitive impairment across different age groups for females and males. Variations in the prevalence of dementia and other forms of cognitive impairment underscores challenges in establishing accurate prevalence rates [3][5]. Future research should investigate the potential for overlap between the different categories of cognitive impairment.

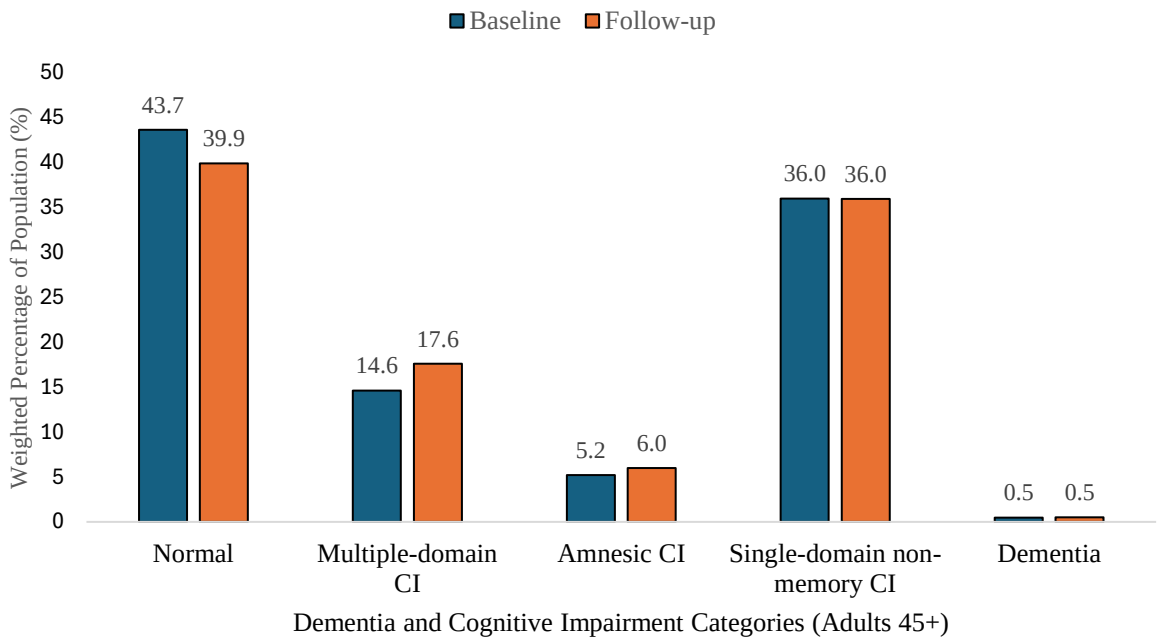

Figure 6.1. Distribution of Normal, Cognitive Impairments (CI), and Dementia in Adults 45+ y: data derived from CLSA.
Note: In Amnestic CI, memory is significantly impaired, while other cognitive domains are not significantly impaired [Rapp]. In Single Domain CI Non-Memory, one other cognitive domain is impaired. In Multiple domain CI, more than one other cognitive domains are impaired [8].

6.2.2 Associations of Movement Behaviours On 3-Year Changes in Memory (Chapter 4).

Standardization of CLSA Cognitive Function Outcome Variables

The benefits of movement behaviours are well established [9][10][11], with evidence of a positive associations between movement behaviours and brain health [12][13][14][15][16][17][18][19][20][21]. Movement behaviours as public health strategies may delay the onset of dementia and reduce the burden of health-care costs [7][22].

CLSA – Self-Report Questionnaires

Although self-report questionnaires are susceptible to recall and social desirability bias [23][24][25], in population-based studies and cohorts, they are often regarded as reliable and valid approaches for longitudinal study [23]. In the CLSA database, a modified version of the validated self-reported Physical Activity Scale for Elderly (PASE) was used to quantify the duration of physical activity and sedentary activity over the past 7 days [26], while a sleep questionnaire captured information about the total time asleep at night. Participants self-reported the frequency of engaging in various activities, including walking outdoors, participating in light, moderate, or strenuous sports or recreational activities, and muscle strength exercises. PASE has demonstrated validity [27][28][29] and reliability [28][29]. While PASE is a common tool for assessing physical activity in older adults, it has important limitations. First, it relies on self-reported data, which could skew our results compared to actual physical activity levels measured by more objective methods [30]. Second, if individuals misclassify their activities, physical activity levels could be over- or under-estimated. Sex differences and motivations for physical activity in older adults are also not well understood [31] and could distort our assessment of sex-differences in the main analysis. The strength of the association may differ between females and males with different activity levels, particularly those that involve social interaction. In addition, our results show that cardiometabolic components could influence both how much a person sits and sleeps.

6.2.3. Operationalization and Measurement of Cognitive Function and Memory

Longitudinal assessment of memory recall provides valuable insights into cognitive health and potential indicators of dementia, assessed in the current CLSA analysis at two points in time over 3 years. Although a second CLSA follow-up became available after approval of the proposal, we were constrained for this analysis by the available data. Memory task performance

can change over time and may be influenced by baseline biological and environmental factors, which presents challenges for studies where the available data may not be sufficient to fully characterize variability in memory recall at 3 years. Finally, although i) individuals with overt clinical conditions were excluded from the analysis, and ii) the prevalence of amnesic cognitive impairment in the sample was low), rapid declines in memory due to disease progression could not be ruled out.

6.3.1. Associations of Movement Behaviours On 3-Year Changes in Global Cognition (Chapter 5)

Role of Cardiometabolic Health as a Mediatory of Cognitive Decline

Cardiometabolic abnormalities are associated with brain health [32][33][34] and are essential in disease risk assessment. High waist circumference, high blood pressure, low good cholesterol (high density lipoprotein), high total triglycerides, high glycosylated haemoglobin, and high carotid intima-media thickness are associated with atherosclerosis [35][36], heart disease, insulin resistance and diabetes [37][38], and various aspects of cognitive health [39]. Given the multifaceted nature of dementia, assessment of cardiometabolic health could provide additional information to support optimal decision making. Mediation analysis may be used to provide more fulsome understanding of cognitive health by considering a wide range of cardiometabolic factors in the evaluation of cognitive function. To this end, identification of intermediate (and modifiable) cardiometabolic risk factors is an important step in patient care and help to provide an estimate of changes in cognitive function, mild cognitive impairment, and dementia.

When sedentary time acted as a mediator, the results of the mediation approach suggest that increasing waist circumference, diastolic blood pressure, and triglycerides were associated with a higher global cognition. This seems counterintuitive, given presence of these three components also increases the risk for type 2 diabetes, heart disease, and stroke. However, *higher* waist circumference, diastolic blood pressure, and triglycerides in older adults might be protective against cognitive decline [40][41], a finding that may be explained by inflammation [42]. Conversely, increasing systolic blood pressure, high-density lipoprotein, and glycosylated haemoglobin were associated with a *decline* in global cognition when sedentary time mediated these relationships. Here again, higher systolic blood pressure, high-density lipoprotein, and glycosylated haemoglobin in older adults might be indicators of underlying metabolic dysfunction, which could be deleterious to cognitive health [43][44][45]. Indeed, metabolic syndrome is a known risk factor for cardiovascular disease, but its influence on cognitive health is not clear [42][46]. These findings therefore highlight the importance of considering the mediating role of movement behaviours and metabolic factors in the assessment of cognitive changes.

Recent research suggests that focusing solely on the amount of time spent on certain behaviors, like physical activity, sitting, or sleep, may not fully capture their impact on health [47]. For example, guidelines often recommend 150 minutes of exercise per week, no more than 8 hours of sitting per day, and 7-8 hours of sleep at night. However, other factors, such as how regularly someone sleeps or the type of sedentary activities they do (like reading versus watching TV), may be just as important. Research suggests that having a consistent sleep schedule might be a stronger predictor of health outcomes, like heart disease, diabetes, and even longevity, than

just the amount of sleep [47]. This suggests that looking beyond duration to include other aspects of behavior could provide a clearer picture of their effects on health.

6.5. Limitations

Results of this dissertation build on existing knowledge of the interaction between movement behaviors, cardiometabolic risk, and cognitive function and dementia. Detailed information on specific types of dementia and potential mechanisms underlying the association between movement behaviours and assessments of memory and global cognition furthered the understanding of the dementia risk. In study 1, the systematic review and meta-analysis provided a comprehensive evaluation of large-scale prospective cohorts of movement behaviours and dementia risk including use of objective assessments for dementia diagnoses. However, there were some limitations. Further work is needed to validate our findings, as the measurement of predictors was limited by self-report data, while the outcomes were drawn across multiple validated cognitive assessment tools. For the CLSA analyses (Study 2 and 3), a logical next step would involve examining self-reports of 3-year *changes* in movement behaviours in relation to changes in cognitive assessments, specifically memory and global cognition. Additionally, the CLSA population was not diverse; therefore, external validation may be needed using participants from more ethnically and culturally diverse populations. Future studies should examine the dose-response relationship with respect to movement behaviours and their role in dementia prevention to better understand the impact of movement behaviours during midlife, which could provide valuable insights on protective effects in brain function and structure in individuals older than 65 years.

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Additional Materials

Extended Methods, page 159-164 from:

1. Raina P, Kirkland S, Wolfson C. Canadian Longitudinal Study on Aging (CLSA): Protocol. (https://www.clsa-elcv.ca/doc/511) (Accessed July 11, 2020)
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Study Design

Full descriptions of the methods are outlined in the CLSA protocol [1], and detailed administrative and scoring procedures for cognitive tests can be found in Tuokko, Griffith, Simard & Taler (2017, 2020) [2][3]. The CLSA is a national, stratified random sample of 50,000 Canadians aged 45 to 85 years at recruitment, followed for at least 20 years or until death [1][3]. Data collection occurs every 3 years to capture significant health changes with minimal loss to follow-up. The baseline age of 45 includes individuals from the baby boom cohort (born 1946–1964), allowing for the study of mid-life transitions and their impact on later-life outcomes.

A comprehensive set of demographic, social, clinical, psychological, economic, and health service data was collected via computer-assisted telephone interviews (CATI) [1][3]. Of the 50,000 participants, 30,000 were asked for additional in-depth data through physical exams and biological specimen collection (blood and urine), while the remaining 20,000 provided data for provincial-level health estimates.

At baseline, the CLSA included non-institutionalized adults aged 45 to 85 years, without cognitive impairment, who could read and speak French or English [1][3]. Participants who became institutionalized were followed through proxy interviews. The 30,000 participants undergoing physical exams were selected near data collection sites (DCS), with oversampling for individuals living within a 25-kilometer radius of one of the 10 DCS locations (Vancouver, Victoria, Calgary, Winnipeg, Hamilton, Ottawa, Montréal, Sherbrooke, Halifax, and St. John’s).

Sampling

The CLSA's sampling frame was informed by the Canadian Community Health Survey (CCHS) version 4.2, in collaboration with Statistics Canada [1][3]. The CCHS, a biennial cross-sectional survey, provides demographic data on health determinants, health status, and system

utilization across Canada's health regions. It served as the recruitment vehicle for the telephone interview cohort and allowed for comparisons between participants and non-participants to identify potential selection bias. Provincial health registration databases were used for the in-depth cohort and to address any recruitment gaps. However, challenges in obtaining contact information due to varying provincial data requirements may have limited their use [1][3].

Sample Size

The CLSA used simulations to assess sample size adequacy for detecting outcomes like chronic diseases [1]. The minimum detectable odds ratio (MDOR) for conditions such as hypertension ranged from 2.1 for rare exposures to 1.3 for common exposures with 90% power. Simulations indicated that detecting rarer outcomes, like Parkinson's disease, would require additional data from later waves. Continuous outcome measures like cognition were used to enhance statistical power [1]. For illustration, the formula [5] used to estimate the sample size required to perform a test of hypothesis is shown below:

$$n = \left(\frac{Z_{1-(\frac{\alpha}{2})} + Z_{1-(\beta)}}{ES = \frac{\mu_d}{\sigma_d}} \right)^2$$

Where:

$\alpha = 0.05$, indicates the level of statistical significance

$Z_{(1-\alpha/2)} = 1.96$, indicates 95% confidence level from the standard normal distribution

$Z_{(1-\beta)} = 0.842$, indicates 80% power from the standard normal distribution

μ_d represents the mean difference expected under the alternative hypothesis.

σ_d represents the standard deviation of the <u>difference</u> in the outcome (i.e., the difference based on cognitive measurements over time); assume the covariance is 0.5 [5].

ES indicates the effect size.

Null Hypothesis: There is no significant association between sleep duration and 3-year change in global cognition among adults aged 45 and above.

Alternative Hypothesis: There is a significant association between sleep duration and 3-year change in global cognition among adults aged 45 and above.

Assuming data from each additional hour of nightly sleep (Manuscript 3: Model 2) showed an absolute change in the standardized global cognition ($d = 0.03$) across time (3-year), after adjusting for covariates (age, sex, ethnicity, education, income, alcohol, smoking, social support, movement behaviours (mutually for physical activity, sitting, and sleep status), body mass index, self-reported general health, depression, and sleep quality).

Therefore, using the effect size of 0.03, the sample size need can be calculated as:

$$n = \left(\frac{1.96 + 0.842}{0.03}\right)^2$$

$$n = 8\,723$$

A sample size n = 8 723 achieves 80% power using a two-sided Z-test with a significance level (alpha) of 0.05 to detect a clinically significant difference in the 3-year change in global cognition.

Data Collection

All CLSA participants provided questionnaire data via Computer-Assisted Telephone Interviews (CATI) [1][3]. At baseline, 30,000 participants also underwent home interviews, physical examinations, and biological specimen collection [1][3]. Subsequent waves included

CATI followed by face-to-face interviews using Computer-Assisted Personal Interviewing (CAPI) software at Data Collection Sites (DCS), where trained health assessors gathered measurements and samples according to strict protocols [1][3]. Quality control systems ensured data validity and reliability. Data were linked with health databases, including medication use and disease registries, with participant consent [1][3]. Further details on CLSA data collection and storage procedures can be found in the CLSA combined-protocol (version 3) at https://clsa-elcv.ca/doc/511.

Biobanking and Data Storage

Biological samples were processed and stored at the Biological Processing Centre (BPC) using liquid nitrogen and tracked with barcode identifiers [1][3]. Confidentiality was maintained, and samples were linked for potential identification purposes. A unique study ID was assigned to each participant for data and sample tracking. Data linkage and quality control were overseen by the National Coordinating Centre (NCC) at McMaster University [1][3]. All data were stored securely at the Statistical Analysis Centre (SAC), following agreements with Statistics Canada to ensure integrity [1][3].

Cognitive Assessment Protocols

Cognitive tests were administered at participants' homes and DCS [1][2][3]. At home, the Rey Auditory Verbal Learning Test (RAVLT), Animal Fluency (AF), and Mental Alternations Test (MAT) were conducted through CAPI [1][2][3]. The RAVLT assesses verbal learning and memory; Trial 1 of the RAVLT was used to assess immediate memory recall, followed by a delayed recall trial conducted roughly 5 minutes later. The AF evaluates verbal fluency and executive function; it involves naming as many animals as possible within a brief period, usually 1 minute. The MAT is a brief, or 30-second, cognitive switching task that evaluates mental

flexibility and processing speed, generating a score based on the total number of correct alternations between paired letters and numbers (e.g., 1-A, 2-B). For detailed administrative and scoring procedures of the RAVLT, AF, and MAT, refer to Tuokko, Griffith, Simard & Taler (2017, 2020).

Participants provided informed consent, and tests were audio-recorded for accuracy [2]. At DCS, additional tests were administered: the Miami Prospective Memory Test (MPMT), Stroop Test (Victoria Version), Controlled Oral Word Association Test (COWAT), and Choice Reaction Time (CRT) task [1][2][3].

The **Miami Prospective Memory Test** (MPMT) includes two tasks: an Event-based task and a Time-based task [1][2][3][4]. In the Event-based task, participants are given an envelope with currency and instructed to give ten dollars to themselves and five dollars to the examiner when a timer goes off after 30 minutes. In the Time-based task, participants are shown a clock set at 8:00 and an envelope with numbered cards. At 8:15, they must open the envelope and hand the card numbered "17" to the examiner. Scores for both tasks are based on three components: Intention to perform (0-3), Accuracy of response (0-3), and Need for Reminders (0-3) [2][3][4].

The Victoria version of the **Stroop Test** was administered following specific instructions for each card [2][3][6]. It consists of three off-white cards with six rows of four items. The first card, the "Dots" card, contains coloured dots in blue, green, red, and yellow ink, with each colour appearing once per row in pseudorandom order. Participants quickly name the colour of each dot while their performance is timed. In French adaptations, participants use French colour names [7]. The second card, the "Words" card, features neutral words printed in the same-coloured ink as the first card [2][3][6]. Participants name the ink colours while ignoring the word content. The examiner records the time taken to complete the task. The third card, the "Colour"

card, features colour names printed in incongruent ink colours (e.g., “blue” printed in red ink). Participants name the ink colours while disregarding the words, with performance measured in seconds. In French adaptations, participants use French colour names for this task [7].

The **Controlled Oral Word Association Test** (COWAT) consists of three subtasks using the letters “F,” “A,” and “S,” where participants generate as many words as possible starting with each letter, excluding proper nouns and words with different endings [2][3]. Responses were audio-recorded for scoring, with each subtask discontinued after 60 seconds. Scoring was based on master dictionaries and electronic algorithms to identify homophones, sister words, and repeated words. One point was awarded for each admissible word per letter, and scores were tallied accordingly [2][3].

The **Choice Reaction Time** (CRT) measure in the CLSA consists of 56 trials organized into seven blocks, with scoring automatically generated by computer software [2][3][8]. Each block contains eight stimulus presentations with varying millisecond differences [8]. The test begins with a warm-up of four trials. The CLSA baseline dataset includes variables such as the mean time to complete the entire test (including the warm-up and 56 trials) and the percentage of correct answers. Scoring is automatically generated through the touchscreen computer [2][3][8].