Examining the Mediating Role of Cardiovascular Disease Risk Factors on the Association Between Physical Activity and Global Cognitive Scores in Community-Dwelling Middle-Aged and Older Females

By

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Abstract

Cardiovascular disease (CVD) and cognitive decline are significant contributors to global mortality and morbidity. Physical activity (PA) has emerged as a modifiable factor with positive effects on various aspects of health across different age groups. While many studies has identified direct relationships between PA and cognition, PA and CVD risk factors, and cognition and CVD risk factors, limited research has investigated the potential mediating role of CVD risk factors in the relationship between PA and cognition, particularly among older adults. This thesis aimed to fill this gap by utilizing a cross-sectional study design and secondary analysis of data from the Women's Advanced Risk-Assessment in Manitoba (WARM) Hearts cardiovascular screening study. The study explored the mediating role of both composite and individual CVD risk factors on the association between PA and cognition in community-dwelling middle-aged and older females. Mediation analysis was conducted using the PROCESS macro (version 4.3) for SPSS. PA and specifically moderate to vigorous PA (MVPA) was associated with cognitive performance through body mass index (BMI) and frailty index (FI), but not through a composite CVD risk factor or other individual CVD risk factors, such as systolic blood pressure (BP), diastolic BP, arterial stiffness, and blood markers. The lack of significant mediating effects of CVD-specific risk factors suggests that the cognitive benefits of PA, particularly MVPA, may be more strongly linked to general health indicators such as BMI and FI rather than through CVD-specific pathways. These results imply that older females may see cognitive benefits through the maintenance of BMI and FI by engaging in PA and specifically MVPA. By investigating these relationships, this thesis provided insights into the mechanisms underlying the association between PA, cognition, and CVD risk factors in middle-aged and older females. The findings

may inform interventions aimed at promoting cognitive and overall health in this population, emphasizing the importance of regular engagement in PA.

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Chapter 1: Literature Review

In Canada, one person dies every five minutes due to heart conditions, vascular cognitive impairment, or stroke[1]. Cardiovascular disease (CVD) is the costliest disease in Canada, totalling $21.2 billion in direct and indirect costs[1]. Older adults are at increased risk of CVD due to the implications of aging on the entire body[2]. The implication of aging also occurs in the brain, as about 12% to 18% of individuals over the age of 60 develop mild cognitive impairment (MCI)[3]. Those with MCI have an increased risk of developing dementia, and it is estimated that 10% to 15% of MCI patients develop dementia each year[3]. Canada's older adult population (age 65+) is expected to grow by 68% over the next 20 years, with an estimated population of 10.4 million individuals by 2037; whereas in 2017 there were 6.2 million older adults in that age group[4]. With a growing number of older adults, it is essential to address research in the area of CVD and cognition pertaining specifically to older adults. This type of research could improve the lives of individuals and mitigate the impact that conditions such as CVD and MCI create on patients, families, and the healthcare system.

The underlying mechanisms that are activated by PA to affect the body is multifaceted. For example, PA improves cardiorespiratory fitness[5], cognitive functioning and psychological parameters [6–9]. However, it is not yet fully understood why PA influences both cardiovascular and mental function in humans. Since the heart and brain are closely connected[1], it is important to explore the role CVD risk factors plays in the association between PA and cognition.

PA, cognition, and CVD risk factors are closely associated. Numerous studies have examined the relationships between PA and cognition (Table 1a) and PA and CVD risk (Table 1b). Although some discrepancies exist in the findings, it is generally accepted that PA both positively affects cognition and has a critical role in reducing the severity of many CVD risk

factors, especially in older adults. Therefore, this literature review will provide a comprehensive overview of existing literature on the relationship of physical activity, cognition, and cardiovascular risk factors in older adults. Moreover, this literature review will consider evidence and data from multiple journal articles, systematic reviews and meta-analyses examining the association between PA and cognition; CVD risk factors and cognition; and the mediating role of CVD risk factors in the association between PA and cognition. This literature review will also investigate the methods and tools used, testing procedures, and participants to determine the connections between the articles, consensus among the research, and what are the points of disagreement about the relationship between PA and cognitive functioning among older adults. Lastly, this review will identify knowledge gaps in the literature.

Table 1a: Summary of notable studies examining the independent relationships between PA and cognition.

Author (year)	Tools used to measure PA	Tools used to measure cognition	Sample population	Findings
Weuve et al. (2004) Nurses' Health Study	Self-reported duration spent on different PA per week over 1 year	Over-the-phone assesement for Cognitive Status, East Boston Memory Test, category fluency test, Digit Span Backwards test	Community-dwelling older females from USA aged 70 to 81 years with no history of stroke (n=16,466)	Regular PA including walking, is associated with greater cognitive function and less cognitive decline in older females.
Aichberger et al. (2010)	Self-reported frequency of vigorous and moderate PA	Delayed word recall and semantic verbal fluency test	Community-dwelling adults 50 years or older from 11 European countries (n=17,333)	Engagement in moderate and vigorous PA protects against cognitive decline in older age.
Zhu et al. (2017)	Actical accelerometer. Cut-off points: SED (0–49 counts per minute (cpm)), LPA (50–1064 cpm), and MVPA (>1065 cpm)	Word List Learning and semantic fluency. Letter fluency, recall, and orientation items from the Montreal Cognitive Assessment	Community-dwelling African and Caucasian Americans aged 45 years and older (n= 6452)	Higher levels of MVPA is associated with better maintenance of memory and executive function, and lower risk of cognitive impairment in particularly Caucasian adults.
Stubbs et al. (2017)	Triaxial accelerometer monitor (GT3X+, ActiGraph, Pensacola, FL, USA). Cut-off points: light PA (100–1951 cpm), MVPA (>1951 cpm)	Chinese version of the Ascertain Dementia 8-item Questionnaire	Community-dwelling older adults from Taiwan aged 65 years or older (n=285)	Light PA and MVPA both significantly associated with reduced cognitive ability decline, independent from each other.

Table 1b: Summary of notable studies examining the independent relationships between PA and CVD risk factors.

Author (year)	Tools used to measure PA	Tools used to measure CVD risk factors	Sample population	Findings
Chudowolska-Kiełkowska & Małek (2020)	Pedometer (M2 Smartband) Cut-off points: MPA (between 7500–9999 steps per day) physical inactivity (<7500 steps per day)	Researcher assessed weight, waist circumference, SBP/DBP, resting HR, fasting glucose and TC concentration.	Community-dwelling older adults aged 50-75 years, with at least one or more CVD risk factor (n=199)	Subjects randomized to study group (daily goal of at least 7000 steps – and supporting phone calls) and control group (no goal or calls). Increased PA leads to improvement of CVD risk factors within 3 months.
Ramakrishnan et al. (2021)	Axivity AX3 triaxial accelerometer. Cut-off points: 100 milli-gravity to 400 milligravity as MPA, above 400 milligravity as VPA.	Incident CVD collected through corresponding hospital codes, self-reported age, sex, ethnicity, education, Townsend Deprivation Index, smoking, and alcohol consumption	Community-dwelling adults and older adults aged 40-69 years from UK (n=90,211)	Linear dose–response relationship between MPA, VPA, and risk of incident CVD.
Länsitie et al. (2022)	Wrist-worn uniaxial accelerometer. Cut-off points: 1.00-1.99 metabolic equivalent of task (MET) as sedentary time, 2.00-3.49 MET as LPA, all activity ≥3.50 MET as MVPA.	Framingham risk score	Community-dwelling older adults aged 67-70 years from Finland (n=660)	More time in PA regardless of intensity and less time being sedentary was associated with lower CVD risk and lower mortality rates in older adults.
Peter-Marske et al. (2023)	ActiGraph GT3X+ triaxial accelerometer. Cut-off points: time in SB as <19 VM per 15s epoch, LPA as 19-518 VM per 15s epoch, and MVPA as ≥519 VM per 15s epoch.	Self-reported	Community-dwelling women age 62 years and older, free of CVD (n=16,031)	Inverse association of total PA, MVPA with total CVD and ischemic stroke incidence, direct association of SB and total CVD.

1.1.1 Benefits of PA on health in the aging population

PA has positive effects on several domains of health regardless of age[2,5,10–18]. Examples such as the improvement of cardiorespiratory fitness[5], cognitive functioning[11,13,17–19], and psychological benefits are apparent[13]. These benefits are especially crucial as people age due to the physiological implications that occurs as a part of aging. The aging process affects the functioning of individual organelles to the entire organ systems, often making it challenging for older adults to engage in PA, and thereby leading to increased sedentary behaviour.

1.1.2 Defining PA

PA and exercise are terms often used interchangeably in common settings; however, there are distinct differences between the two. PA is defined as the use of energy caused by movements produced by skeletal muscles of the body[20]. This definition is used broadly to encompass all types, intensities, and domains of movement[21]. Exercise, on the other hand, refers to the performance of movements that are planned, structured, and repeated, with the intent to positively affect health[21]. Therefore, it can be understood that all exercises are PA, but not all PA is exercise. PA can be further categorized by the physiological effects, where the two predominant types of PA that are commonly examined in the literature are aerobic and anaerobic PA[21]. Aerobic PA involves activities that improves or maintains the cardiorespiratory fitness of an individual, for example, walking, jogging, or swimming[21]. Anaerobic PA refers to activities that are often high intensity, where the capacity to utilize oxygen to create adenosine-triphosphate (ATP) in contracting muscles is insufficient and, therefore, requires ATP from anaerobic metabolism to supply an increasing proportion of ATP for activities like power lifting and short distance sprinting[21].

PA can have different intensities, and this is often measured through absolute intensity, which refers to the rate of energy expenditure needed to carry out any PA[21]. Common ways to quantify absolute intensity include, metabolic equivalents (METs), oxygen consumption, joules, or kilocalories[21]. Among these, METs is used the most in the literature[21]. One metabolic equivalent of task (MET) equals to the energy expenditure rate while sitting at rest, which corresponds to an oxygen uptake of about 3.5 milliliters per kilogram per minute[21]. Intensity is then calculated in multiples of METs[21]. Using METs, PA can then be categorized into different intensities:

- Vigorous-intensity PA (VPA), which are intense PA that require 6.0 or more METs[21]. This means VPA must use six times more energy than compared to one sitting at rest. Examples of VPA include running, carrying heavy loads up the stairs[21].
- Moderate-intensity PA (MPA), which are activities that requires 3.0 to less than 6.0 METs[21]. This includes walking at a pace of 3 to 4 miles per hour (mph), mopping, or vacuuming[21].
- Light-intensity PA (LPA), which are activities requiring more than 1.5 to less than 3.0 METs[21]. For example, walking at a slow pace (less than 2 mph)[21].
- Sedentary behaviour (SB), which are activities requiring 1.5 or less METs[21]. Such as activities like sitting, reclining, or lying [21].

1.1.3 Measuring PA

Due to the complexity of PA, it is crucial to measure PA in an accurate and efficient manner. Over time, various tools have been employed in the field, each with its own advantages

and disadvantages. These tools can be categorized into two main types: indirect and direct measurements[22].

Indirect measurements, such as surveys, diaries, and questionnaires, are self-reported in nature and are widely used due to their ease of administration. Questionnaires, like the International Physical Activity Questionnaire (IPAQ), are validated and reliable tools that captures multiple domains of PA[23]. Advantages of indirect tools like the IPAQ are that they can be easily distributed, especially to larger sample sizes to reduce the cost and time commitment needed from both the researchers and participants[21]. Due to the ease of administering, questionnaires allow researchers to recruit larger samples, which can then increase the heterogeneity of the test cohort. Questionnaires are also able to capture information over extended time frames[24], allowing for a more wholesome establishment of PA patterns. Additionally, indirect measurements offer cost-efficiency, making it a popular choice among researchers [21,25,26]. Lear et al. conducted a study using the IPAQ and examined how PA affects mortality and CVD in 130, 000 people from 17 different countries[27]. This was feasible due to the aforementioned advantages of indirect measurement tools. However, due to the self-reporting nature of indirect measurements, they are prone to limitations such as recall errors, bias, and social desirability, despite efforts to minimize these issues[22,24–26].

Direct measurements, such as the triaxial accelerometer monitors (e.g., GT3X +, ActiGraph, Pensacola, FL, USA), targets the limitations of indirect measurements in providing objective data using assessments of acceleration and body position that may be used to estimate energy expenditure and identify pattens of movement that represent sleep[28,29]. This comprehensive approach more accurately captures PA and provides higher reliability, test-retest reliability, and validity when compared to indirect measurements[30]. However, accelerometers

also have disadvantages, such as increase in cost, difficulty of administration, and complexity of interpretation[22,24,30]. Direct measurements, such as the accelerometers, tend to be more expensive compared to indirect tools like questionnaires and surveys, both in the cost of the equipment and in their administration[30]. The distribution and collection of the accelerometers can be more challenging compared to indirect measurements, especially with large cohorts[30]. Although there present many recommendations for the choices regarding device specificity, there is not a standardized protocol among researchers[28–30]. This creates one of the major challenges in using accelerometers to measure PA, which is the difficulty in between-study and international comparability[30]. This includes choices such as the placement of the accelerometer, from the wrist, hip, thigh, to the ankle, the literature contains a mixture of the placements due to the type of data the researchers want to obtain [28,29]. This creates the challenge of inconsistency in interpreting the data collected and makes it difficult to rationalize the findings. Most studies in the literature agree on a wear-time of seven consecutive days, for at least 10 hours per day to capture habitual PA[24,29–31]. This places the burden on the participants as they are the ones in control of the quality of the data collected (e.g., wearing the device; remembering to wear the accelerometer again after it was removed), and thus compliance is presented as another challenge associated with the accelerometer.

1.1.4 How do accelerometers measure PA?

Accelerometers are wearable devices equipped with sensors that detect acceleration along the vertical, medio-lateral, and antero-posterior axes[28,29]. They are often worn on the wrist, hip, or thigh depending on the type of data the researcher wants to measure, as well as the participant cohort[28,29]. For example, wearing an accelerometer on the wrist is generally more effective in

capturing low-intensity activities in a free-living environment, as well as yields the most compliance among participants[29]. The non-dominant wrist is preferred to limit the accumulation of movements such as writing as PA[32]. Wearing the device on the hip has been traditionally adopted as it was the closest to the center of mass, and therefore was optimal in reflecting movements of the entire body[28]. Thigh placement provides information that better differentiates between body positions such as sitting and standing; activity type such as walking and running; and activity intensity of some activities like biking and climbing stairs[28]. Raw data collected by the accelerometer consists of the direction and magnitude of acceleration along each axis, measured in units of g, where 1 g corresponds to earth's gravity[28]. The sampling frequency is a crucial factor in determining how often the sensors record acceleration data[28]. To accurately capture movement signals, the sampling frequency should be at least twice the frequency of the movement signal[28,33]. Since human movement is generally under 10 Hz, even a minimum sampling frequency of 30 Hz is sufficient for capturing movement data[28,33]. Sampling frequency can be adjusted from 30-100 Hz to allow for the capture of finer details in the movement pattern and enables higher intensity activities to be recorded [28,29]. Migueles et al. recommends using 90 Hz in their systematic review of 235 studies that used the GT3X+ ActiGraph accelerometers, as it provided more accurate results while capturing an adequate number of details of human movement[29]. Acceleration data stored within the device can then be uploaded into its corresponding software for necessary data cleaning, such as using filters to remove trivial noise, this is the process of eliminating movement frequencies deemed to be outside of normal human movement range. For the GT3X+ accelerometer model, the standard filter excludes frequencies below 0.25Hz and above 2.5Hz[29,31]. ActiGraph provides different window lengths that the data can be analyzed in, this is called the epoch length, which can be selected from 1 to 60

second(s)[28]. Epoch length can be thought of as the magnifier, the shorter the epoch length, the more zoomed in the magnifier is, which results in more details in the data. Conversely, the longer the epoch length, the less detailed the data will be, but patterns can be detected more easily due to the visibility of the bigger picture. Data collected by the accelerometer are outputted in counts, which is a non-dimensional unit that is brand-specific and cannot be meaningfully interpreted[24,28]. Therefore, through the process of value calibration, the outputted data can be translated to more traditional measures of PA such as energy expenditure using MET values, or minutes spent at different PA intensities[28].

1.1.5 How are accelerometer data interpreted?

Accelerometer data have traditionally used cut-off points to categorize activity counts into intensity levels defined by MET values[34,35]. In a paper by Aadland and Ylvisåker[36] looking at the reliability of the GT3X+ accelerometers in free-living adults, the cut-off points chosen were:

a) less than 100 counts per minute (cpm) was considered sedentary;
b) 100 to 2019 cpm was considered LPA;
c) 2020 to 5998 cpm was considered MPA;
d) more than 5999 cpm was considered VPA; and
e) more than 2020 cpm was considered MVPA[36].

However, due to the various accelerometer brands that define a non-dimensional count unit differently than other brands and the lack of standardized protocol, cut-off points are inconsistent across studies, ranging from 191 to 3285 cpm for MVPA in adults[30]. The difference in cut-off points can significantly impact the association of estimated PA and health outcomes, resulting in

inaccurate findings[30,32]. The population also influences the selection of cut-off points significantly as movement patterns vary across different age groups[32,37]. For example, young adults will have considerably different movement patterns than compared with older adults, and therefore, the selection of cut-off ranges would need to be adjusted accordingly[32].

In the last decade, a new tool known as GGIR[38] has gained widespread acceptance among researchers in the field. GGIR is an R-package (http://cran.r-project.org) designed by Vincent van Hees and colleagues in an effort to establish an open-source method for processing multi-day raw accelerometry data in a transparent and customizable manner[32,39]. The traditional approach to processing accelerometry data required researchers to use proprietary software corresponding to the accelerometer's brand, limiting transparency and customizability[32]. The key advantage of GGIR over the traditional method is its direct utilization of raw accelerometry data, that is, gravitational acceleration (gravity or milligravity), rather than the non-dimensional unit counts. This approach enhances data accuracy by removing the reliance to convert raw acceleration into counts, which is a unit based on proprietary information that are not disclosed to researchers[32,38]. Another benefit of GGIR is its compatibility with multiple accelerometer brands, this allows for a consistent method for raw data to be processed from a wide range of devices and models, therefore enables inter-study comparability[39]. Moreover, GGIR is validated for processing wrist-worn accelerometer data and can detect abnormalities and automatically calibrate data[38]. Although GGIR continues to implement cut-off points to categorize PA intensity levels, its interpretation is not brand-specific and avoids the use of counts as a unit. Rather, GGIR defines cut-offs using milligravity. This milligravity approach facilitates consistency among researchers and improves comparability between studies[38,40]. The foundational paper by Hildebrand et al. established PA intensity cut-off points for ActiGraph accelerometers wore on the non-dominant

wrist, they defined 100.6 milligravity for MPA (3 METs) and 428.8 milligravity for VPA (6 METs)[37]. These thresholds have been validated for adults ages 21 to 61[37], and have been widely adopted in significant studies, including the UK Biobank study and the National Health and Nutrition Examination Survey (NHANES)[40]. For older adults over the age of 70, Migueles et al. derived specific PA intensity cut-off points for ActiGraph accelerometers worn on the non-dominant wrist, and they defined MPA as 60 milligravity or above[41]. Various cut-off points have been established for different age groups, as summarized in Table 2. Different accelerometer brands have been validated as comparable to each other[42] when using similar cut-off points. Therefore, cut-off points should be selected based on the age that most optimally aligns with the study cohort.

Table 2: GGIR cut-off points

Author	Device, attachment site	Age	Thresholds (milligravity)
Hildebrand 2014 **Hildebrand 2016**	ActiGraph, non-dominant wrist	21-61 yr.	Light: 44.8 Moderate: 100.6 Vigorous: 428.8
Hildebrand 2014 **Hildebrand 2016**	GENEActiv, non-dominant wrist	21-61 yr.	Light: 45.8 Moderate: 93.2 Vigorous: 418.3
Sanders 2019	GENEActiv, non-dominant wrist	60-86 yr.	Light: 57 Moderate: 104 Vigorous: N/A
Migueles 2021	ActiGraph, non-dominant wrist	≥70 yr. (mean: 78.7 yr.)	Light: 18 Moderate: 60 Vigorous: N/A

Table adapted from van Hees et al.[43]

The GGIR application comprises of five individual parts grouped based on functionality. Part one, also known as g.part1, initiates the process by detecting the accelerometer brand based on the selected file[38]. The function g.calibrate is then employed for auto-calibration and error detection[38,44]. Metrics extraction, such as PA and sleep, from the raw data follows[38]. Adjustments, such as data window size and time zone, can be made before g.part1 metrics are stored[38]. Next, g.part2 performs descriptive analysis on the output derived from g.part1, providing summaries for each measurement, each day of measurement, and separately for weekdays and weekend days, as well as for different segments of each day[38]. Modifications in the functions can be specified to suit the researcher's needs[38]. G.part3 and g.part4 are specific functions pertaining to sleep analysis, which are not relevant to this thesis project. G.part5

overlaps with g.part2; however, it allows for simultaneous cross-comparison of multiple parameters, such as sleep patterns with different thresholds of PA intensities[38].

1.1.6 24-Hour Movement Guidelines

In October 2020, Canada launched the 24-Hour Movement Guidelines (24HMG) for Adults (ages 18-64 years and 65 years and older)[45]. This replaced the historical Physical Activity Guideline[46], which exclusively advocated an evidence-informed PA recommendation, with an evidence-based recommendation for movement behaviours, integrating PA, sedentary behaviour (SB), and sleep into a single comprehensive guideline[45]. This change was driven by evidence indicating the interdependence of these movement behaviours, emphasizing the importance of addressing them collectively rather than creating separate, independent guidelines[47,48]. For example, the 24HMG recommends that adults aged 65 and older engage in at least 150 minutes of MVPA per week, perform muscle-strengthening activities involving major muscle groups at least twice a week, and include several hours of LPA, such as standing, each day[48]. It also recommend that adults in this age group should limit sedentary time to less than 8 hours per day and aim for 7-8 hours of quality sleep each night[48]. Adhering to the 24HMG is associated with various health benefits, including a reduced risk of CVD and improved cognitive function[48]. For example, Rollo et al. examined a sample of 8297 adults aged 18 to 79 and looked at the health associations of meeting all components, or partially meeting some of the components, of the 24HMG[47]. They compared a series of health indicators such as waist circumference, blood pressure, high-density lipoprotein (HDL), and C-reactive protein across the groups[47]. They reported that those individuals that met all three recommendations (PA, SB and sleep), compared to those that met two or fewer components of the 24HMG, had significantly better ($p<0.05$)

outcomes for 7 out of the 10 health indicators[47]. This included body mass index (BMI) (β (unstandardized beta coefficient) = -1.82), waist circumference (β = -0.06), aerobic fitness (β = 25.40), triglycerides (β = -0.19), C-reactive protein (β = -0.27), insulin (β = -0.35), and serum glucose (β = -0.32)[47]. Unstandardized beta coefficient represents the change in which meeting all three recommendations had compared with meeting two or fewer components of the 24HMG. For example, those that met all three recommendations were 1.82 units lower in BMI score than compared to those that met two or fewer recommendations. It was also reported that meeting no recommendations compared with meeting at least one recommendation was significantly associated ($p<0.05$) with the worsening of 5 out of 10 health indicators, which included BMI (β = 0.82), waist circumference (β = 0.02), aerobic fitness (β = -12.44), C-reactive protein (β = 0.11), and insulin (β = 0.11)[47].

1.2.1 Defining cognition

Cognition involves a broad range of activities that the brain controls, it is defined as all mental processes in which a person acquires information and uses the acquired information to implement resolutions[49]. Cognition consists of several domains, each domain involves specific cognitive functions, for example, reading and comprehension, fluency, and naming are all cognitive functions within the language/verbal skills domain; reasoning and problem solving are included in the executive functioning domain[50]. There are many other cognitive domains, including processing speed, memory, attention and concentration, motor skills and construction, perception, and sensation[50]. Global cognition refers to the collective performance across these domains[50]. Cognitive functioning is crucial in determining an individual's quality of life (QoL), as many activities of daily living rely on cognitive abilities[49]. A study by Pan et al. concluded

that as cognitive decline becomes more severe, its negative impact on an individual's QoL also intensifies[51].

1.2.2 Defining mild cognitive impairment

Cognitive decline, such as MCI, is the loss of cognitive abilities beyond that expected of normal aging[3,52]. MCI is not severe enough to cause functional ability changes that are associated with dementia, but the decline is enough to cause noticeable changes in one's cognition[3]. There are two classifications of MCI[3]. The first is amnestic MCI, which are cognitive issues related to memory; whereas the second classification is nonamnestic MCI, which are cognitive issues related to other cognitive functions such as language[3]. MCI becomes increasingly common among older adults as they age. About 12% to 18% of individuals over the age of 60 live with MCI[3]. Additionally, those diagnosed with MCI are at a heightened risk of progressing to dementia, with an estimated conversion rate of 10% to 15% among MCI patients each year[3]. Dementia costs over $10.4 billion on the Canadian economy and healthcare[53]. Therefore, being able to identify and intervene when an individual is in the MCI phase is important because it may delay the onset of dementia[54], which would significantly alleviate the burden on individual health as well as avoid cost incurred by the healthcare system. A study by Hussenoeder et al. involving 903 participants (110 with MCI) who were assessed for their perceived QoL, it was concluded that those with MCI had lower QoL across several aspects[55]. These aspects included autonomy, engagement in past, present, and future activities, social participation, and intimacy, compared to those without MCI[55].

1.2.3 How is cognition measured?

There have been many tools developed over the years that aim to measure cognitive impairment[56]. Among them, the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment (MoCA) are the two most widely used screening tools in both the clinical and research settings[54,56]. Both tools are designed to be a primary diagnostic assessment to quickly and efficiently detect cognitive impairment. The MMSE consists of eleven questions with a total score of 30 that assesses an individual's ability in orientation, registration, attention and calculation, recall, and language[57]. The MoCA is also a 30-point test that assesses visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation[58]. According to the original developers of the MoCA, a score below 26 indicates cognitive impairment[58]. Additionally, the official MoCA website suggests that a score between 19 to 25 to indicate MCI, and a score of 18 or lower is generally used to distinguish MCI from Alzheimer's disease[59]. To accommodate for different levels of education among individuals, the MoCA adds one point to the total score if an individual had less or equal to 12 years of education[58]. Both the MoCA and MMSE have been validated and proven reliable in the diagnosis of MCI[57,60]. However, several studies comparing the sensitivity of the two tools have shown that the MoCA is more sensitive in detecting MCI than compared to the MMSE[54,58,60–62]. The MoCA had a sensitivity rate of 90% compared to 18% for the MMSE in detecting MCI[58]. The reason why the MoCA has a superior sensitivity over the MMSE in detecting MCI is because of the more complex and demanding tasks involved with memory, executive functions, language abilities, and visuospatial processing that are tested in the MoCA than compared to the parameters tested by the MMSE[58].

1.2.4 Cognition and PA as people age

The relationship between PA and cognition as people age has received considerable attention in the literature. One of the foundational studies in this area is the Nurses' Health Study, which involved 18,766 community-dwelling females aged 70 to 81[63]. They were assessed using various cognitive tests, and their PA levels were measured through self-reported questionnaires[63]. Both cognitive function and PA levels were measured at baseline and then reassessed two years later[63]. It was concluded that higher levels of long-term PA were associated with better cognitive function over time, as shown by higher mean scores across all cognitive tests[63]. Specifically, those with the highest energy expenditure due to PA (>26.0 MET-hours/week) scored an average of 0.10 standard units higher on the cognitive test than those in the lowest quintile of PA (<5.2 MET-hours/week) (P<.001)[63]. Compared with individuals in the lowest PA quintile, those in the highest quintile of activity had a 20% lower risk of cognitive impairment, which was equivalent to having cognitive function being about three years younger in age[63]. It was also reported that walking at least 1.5 hours per week at a pace of 21-30 minutes per mile was associated with better cognitive performance[63]. Further supporting these findings, a systematic review and meta-analysis of 46 randomized control trials involving 5099 participants aged 68 to 86 reported that PA has protective effects on global cognition and can attenuate global cognitive decline in individuals with mild cognitive impairment or dementia[6]. The review highlighted that the duration and type of PA were key factors influencing the benefits of PA on global cognition, concluding that "the most pronounced effect on global cognition appears to arise from aerobic exercise at moderate or greater intensity with at least 24 hours of total training time"[6]. Additionally, a study by Buchman et al. conducted a cross-sectional analysis of 454 brain autopsies from community dwelling older adults with varying cognitive abilities, including those

with MCI and dementia. The study found that higher levels of total daily PA and better motor abilities were associated with better cognitive function in older adults[7]. This suggests that PA may help mitigate the harmful effects of brain pathologies on cognition in older adults[7]. Similarly, a systematic review and meta-analysis published in 2021 in the *Journal of Neurology* analyzed 122 studies involving 7231 participants. The review revealed that PA has a small but statistically significant effect (effect size = 0.12–0.24) on improving several cognitive domains, including attention and working memory, executive functions, memory, psychomotor speed, and global cognition across a wide range of populations[13]. Although the exact mechanisms through which PA attenuates cognitive decline are not fully understood, researchers suggest that increased blood flow and cerebral vascularization resulting from PA may enhance oxygen and nutrient delivery to the brain, thereby benefiting brain function[8,9]. Additionally, evidence suggests that PA can increase grey matter volume in the frontal brain regions and the hippocampus, and promote neurogenesis, which may help explain the attenuation of age-related decline in executive functions, particularly in older adults[8]. This evidence suggest that PA and cognition are positively associated as people age.

1.3.1 Defining cardiovascular disease

Cardiovascular disease (CVD) is a general term used to describe a number of pathologies associated with the heart and the circulatory system[64]. It is the leading cause of morbidity and mortality globally[64]. In 2016, CVD accounted for almost one-third of all deaths worldwide, and it is projected to cause over 23 million deaths annually by 2030[64]. In Canada, CVD claims the life of one person every five minutes due to heart conditions, stroke or vascular cognitive impairment[64]. It is also the costliest disease, with direct and indirect costs totalling $21.2 billion,

placing a significant burden on the healthcare system[1]. Early detection and intervention for CVD risk factors are crucial for improving individual health outcomes and alleviating the strain on healthcare systems worldwide. The most common causes of CVD include atherosclerosis, coronary artery disease (CAD), and arterial hypertension (AH)[64].

Atherosclerosis occurs when lesions in the arterial walls are aggravated by oxidative stress and inflammation, this can be triggered through a number of risk factors listed in Table 2[64,65]. Inflammation then causes endothelial dysfunction, resulting in the decrease of endothelial-derived nitric oxide (NO) bioavailability[64]. NO is critical vasodilator that also has anti-inflammatory and antioxidant properties[64]. Therefore, additional inflammation causes the retention of lipids and inflammatory cells at the site of damaged arterial wall, this accumulation of lipids and inflammatory cells creates clusters of unstable plaque that builds up inside the arterial walls, which when it ruptures, causes blood clots that blocks vessels that sends blood to different parts of the body such as the heart or the brain, resulting in adverse events such as myocardial infarction (MI), stroke, limb ischemia, and death[64].

CVD risk factors are commonly divided into modifiable and non-modifiable risk factors (Table 3). Modifiable risk factors include hypertension, dyslipidemia, diabetes, depression, smoking, excessive alcohol intake, poor nutrition, lack of PA, lack of sleep, excess SB, and obesity[2,12,66–68]. Non-modifiable risk factors include age, sex, ethnicity, and genetics[2].

Arterial stiffness is the stiffening of the artery walls, which can affect how pressure, blood flow, and arterial diameter respond with each heartbeat[69]. This stiffening can result in adverse hemodynamic effects, such as a decrease in shear stress rate, which is associated with an increased risk of CVD events[69]. Arterial stiffness can occur because of disease, aging, or exposures that reduces the elastic components and increases the collagen content of the artery

walls, causing stiffness[69]. Arterial stiffness is often measured using pulse wave velocity (PWV), which assesses the speed that the pulse wave travels through a segment of the blood vessel[69].

Table 3: CVD risk factors

MODIFIABLE RISK FACTORS	NON-MODIFIABLE RISK FACTORS
Hypertension	Age
Diabetes	Sex
Dyslipidemia	Ethnicity
Depression	Genetics
Smoking	
Excess alcohol	
Poor nutrition	
Lack of PA	
Lack of sleep	
Excess SB	
Obesity	
Arterial stiffness	

1.3.2 Framingham risk score

The Framingham risk score (FRS) is a multivariable function that calculates an individual's overall risk of developing CVD within the next ten years. It uses individual CVD risk factors, including sex, age, systolic blood pressure (mmHg), total cholesterol (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), smoking behaviour, diabetes status, and whether someone is on antihypertensive medications, to generate this composite risk score[70]. The FRS

was developed from one of the most seminal studies in the field of CVD research—the Framingham Heart Study, which commenced in 1948 and followed a cohort of 5,209 participants between the ages of 30 and 62 as they aged to study cardiovascular health and CVD risks[71]. Since then, several studies have branched out of the original study and continues to contribute to the understanding of CVD and its risk factors[71]. The FRS displayed high statistical significance ($p < 0.001$) in the relationship between all evaluated CVD risk factors and incident CVD[70].

1.3.3 Frailty index

Frailty is characterized by multisystem dysfunction, leading to a diminished physiological reserve against health stressors[72,73]. It is closely associated with aging, and it is known to increase the risk of CVD along with many other adverse health outcomes[72,73]. The frailty index (FI) serves as a commonly used tool to assess an individual's accumulation of deficits, incorporating a range of variables such as diseases, risk factors, syndromes, and laboratory measures[73,74]. A FI typically includes 30 to 40 health variables to produce a composite score that determines an individual's frailty status.

1.3.4 PA and CVD in older adults

The relationship between PA and CVD is well-established, especially for older adults who are more susceptible to CVD[2]. Evidence show that PA reduces activities of the sympathetic nervous system, therefore improves blood pressure and heart rate control[2]. PA also improves lipid profile, insulin sensitivity, as well as decreases the risk of coronary and peripheral artery disease[2,15,75]. PA as little as 30 minutes of walking can reduce the risk of cardiovascular events by 15-20% in a cohort of older adults with an average age of 70, compared to their sedentary

counterparts[2]. Cheng et al. examined multiple studies involving older adults, examining the relationship between PA levels and CVD risk. The findings consistently demonstrated that higher levels of PA are associated with a lower risk of CVD in individuals over the age of 60[12]. While there are various PA recommendations for older adults[21,45,76], the evidence-based 24HMG suggests that Canadian adults over the age of 65 should aim for at least 150 minutes of MVPA per week, along with muscle strengthening activities involving major muscle groups at least twice a week, as well as several hours of LPA such as standing[21,48]. However, given that older adults may experience more difficulty in meeting MVPA levels, studies have shown that any level of PA, compared to inactivity, is associated with a substantially lower risk of CVD[77].

1.3.5 CVD and cognition

CVD's impact on cognition in older adults is well-established[78]. Evidence suggests a bidirectional relationship where individuals with cognitive impairment have a higher risk of experiencing cardiovascular events[78], and those with CVD are at an increased risk of cognitive decline[67,78]. A study by Li et al. examined data from over 9000 participants to explore the association between cognitive function and CVD risk factors[78]. The study revealed that individuals with cognitive impairment had significantly more modifiable CVD risk factors, such as hypertension, diabetes, dyslipidemia (including elevated low-density lipoprotein and triglycerides), excess alcohol intake, smoking, and obesity, compared to those without cognitive impairment[67,78]. These risk factors are also commonly linked to risk factors associated with cognitive decline[66,78]. Furthermore, research indicates that cognitive impairment may result from toxins that damage the brain, which is associated with the activation of the renin-angiotensin system[78]. This is then associated with the development of abnormal cardiac structure and

function[78]. This abnormality can negatively affect the autonomic nervous system[78]. Therefore, Li et al. concluded that cognitive impairments are associated with increased biomarkers of cardiac damage and wall strain, which may contribute to the development of CVD[78]. Johansen et al. proposed of several mechanisms that links CVD to cognitive impairments such as dementia[67]. The first proposed mechanisms coincide with the findings by Li et al. suggesting that CVD and cognitive impairments have many shared risk factors, which might contribute to increased neurodegeneration due to the accumulation of brain toxins[67]. A second mechanism proposes that CVD could lead to stroke, which could induce cognitive impairment[67]. Lastly, it is suggested that CVD may alter cerebral perfusion, causing neuronal injury and aggravate cognitive impairment[67].

1.4.1 Mediation analysis

Mediation analysis is a statistical method used to explore the causal relationship between a predictor variable X and an outcome variable Y through an intermediary variable M[79,80]. In other words, it uncovers how X influences Y, with X causing M, which subsequently affects Y[80]. Figure 1 illustrates a conceptual model for simple mediation. Mediation analysis is important as it examines the 'how' in a relationship, specifically uncovering the mechanisms by which X influences Y[79,80]. Hayes provides a simple example in his book which helps to unravel the concept of mediation; suppose an anti-smoking message that is framed in gains rather than loss better influences smokers to quit smoking, meaning, a message that provides the benefits of smoking cessation as opposed to the negatives if one does not quit smoking (X) correlates more strongly with smoking cessation (Y), is it because messages framed in gains triggers less anxiety (M), thus empowers smokers to quit[79].

When conducting a mediation analysis, researchers have the option of conducting single or multiple mediator analyses. The underlying mechanisms are identical however, slight differences arise when there appears to be more than one mediator. That is, when you test a single mediator, the analysis does not control for the influence of other potential mediators[79]. This means the mediator captures the entire indirect effect of the X on the Y[79]. Whereas in a multiple mediator model, the effect of each mediator on Y is measured while considering the influence of other mediators[79]. This helps to isolate the specific impact of each mediator[79]. In other words, multiple mediator model is more complex and can reveal how different mediators interact and collectively influence the dependent variable. See Figure 2 for conceptual model of multiple mediation.

In mediation analysis, key components to interpret include the direct effect, indirect effect, and total effect[79]. The direct effect (*c'*) denotes the relationship between X and Y while controlling for all mediators. The indirect effect (*ab*) reflects the influence of X on M and M on Y, again accounting for the presence of other mediators[79]. The total effect ($c=c'+ab$) represents the combined impact of both direct and indirect effects[79]. Established mediation effects can be categorized into complementary, competitive, or indirect-only mediation. Complementary mediation occurs when both the indirect effect and direct effects are present and point in the same direction[81]. Competitive mediation is when both indirect effect and direct effect exist but point in opposite directions[81]. Indirect-only mediation occurs when only the indirect effect is present, with no significant direct effect[81]. When neither the direct nor indirect effect is significant, it is considered non-mediation[81].

Bootstrapping is a resampling method that draws repeated samples from the data to compute confidence intervals without relying on distribution assumptions[79]. This allows

confidence intervals to be more robust to assumptions (normality, skewness, outliers), which is greatly useful since real-world data often deviate from the assumptions but may still pose significance[79]. Bootstrapping produces more valid and reliable results compared to using assumptions, which is commonly known as the Normal Theory Approach[79,82].

Figure 1: Conceptual model for simple mediation

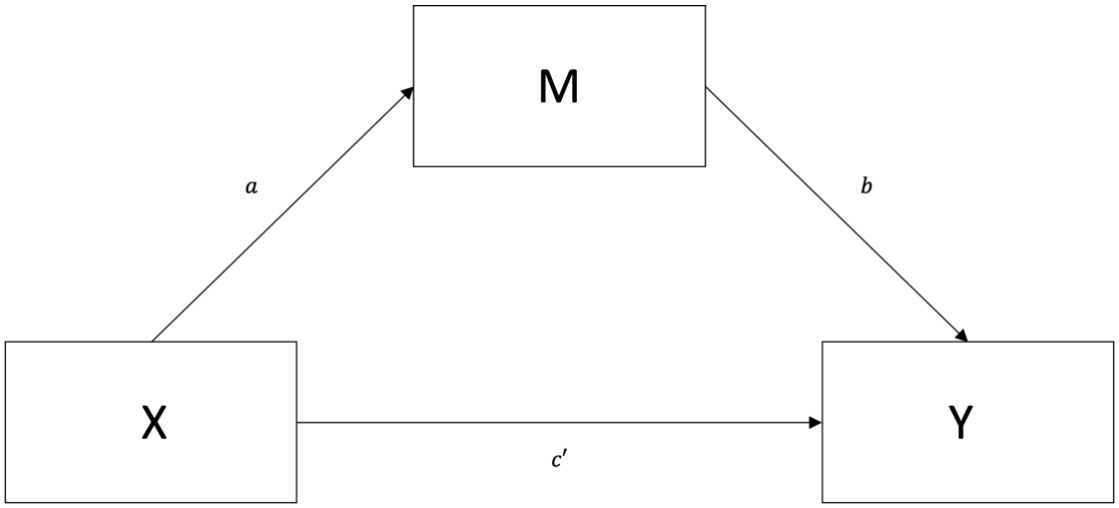


Figure adapted from Hayes (2022)[79]

Figure 2: Conceptual model for multiple mediation

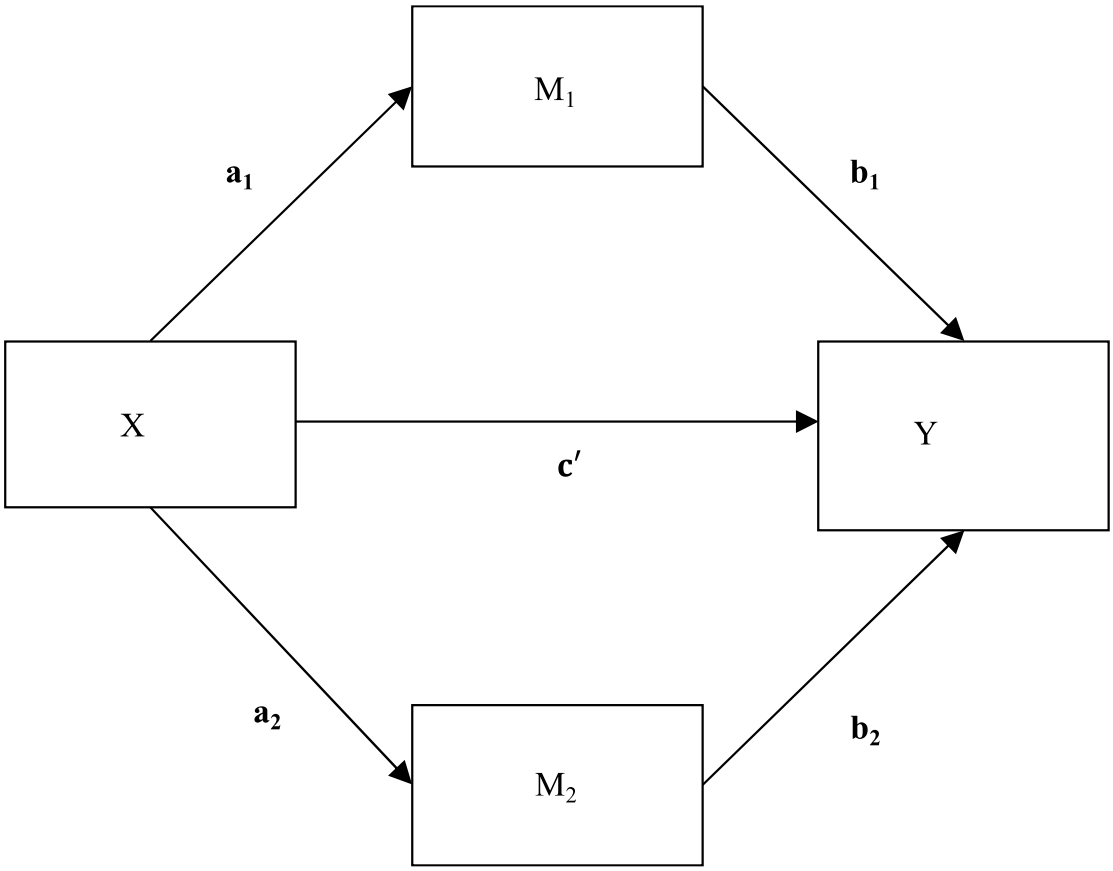


Figure adapted from Hayes (2022)[79]

1.5.1 Potential link between PA, cognition, and CVD risk factors

Although there has been extensive research into the relationship between any two parameters of PA, cognition, and CVD risk factors on their own, as highlighted throughout this literature review, there has not been much research that examines the relationship of all three (PA, cognition, and CVD risk factors) together. Even less research has delved into whether CVD risk factors mediate the relationship between PA and cognition in older adults.

Table 4 summarizes four studies that explore the mediating effects of CVD risk factors on the relationship between PA and cognition in older adults. The results generally demonstrate a positive relationship between PA and cognition[83,84], with evidence suggesting that PA is

associated with lower CVD risk factors, which is then associated with better cognitive function[14]. For example, Felisatti et al. published a study in 2022 that aligns closely with this proposed thesis project[14]. In their research, Felisatti et al. assessed whether CVD risk factors (insulin level, total cholesterol, HDL cholesterol, systolic blood pressure (SBP), BMI, and smoking status) mediated the relationship between PA and brain integrity markers in a sample of 134 cognitively unimpaired older adults[14]. It was reported that higher levels of PA were significantly associated ($p = 0.03$) with increased grey matter volume in the brain, and this relationship was mediated by insulin levels and BMI[14]. This meant that older adults who engage in more PA experience benefits of cardiovascular health, through the maintenance of insulin level and BMI, which is associated with greater structural brain integrity and better cognitive function[14].

Eggermont and colleagues assessed cross-sectional data from community-dwelling older adults aged 70 years and older ($n=544$)[84]. Participants had baseline MMSE assessments and were excluded if they had a score of less than 18, which was defined as moderate or severe cognitive impairment by the authors[84]. They primarily examined the relationship between PA and cognition, with an interest to identify the possible mediating role of CVD, CVD risk factors, chronic pain, and depressive symptoms[84]. The results showed that higher levels of PA were significantly associated with better cognitive performance ($p<.01$), and this association remained significant, particularly in the domain of executive function, even after controlling for CVD and CVD risk factors[84].

In a 2016 study, Castro et al. explored whether insulin sensitivity mediated the relationship between fitness and brain integrity[85]. Although this study did not explicitly examine CVD risk factors, but low insulin sensitivity is a known risk factor for the development of CVD[86]. Castro et al. estimated VO_{2max} using results from a 6-minute walk test in a sample of 84

adults aged 45-63 years[85]. Brain integrity was assessed with various neuroimaging methods such as MRI[85]. Mediation analyses conducted using the PROCESS macro revealed that insulin sensitivity was a significant mediator of the relationship between fitness and brain integrity[85]. It suggests that exercise may increase levels of insulin-like growth factor-1, which may then improve insulin sensitivity and promote brain health[85].

Minto et al. (2022) reported that higher PA levels were associated with better cognitive function in the domains of attention and verbal working memory at lower levels of CVD risk. However, at higher CVD risk levels, higher PA was associated with worse attention and verbal working memory[83]. Although this study does not specifically examine the mediation effect, it contributes to the broader understanding of the relationship among PA, cognition, and CVD risk factors. This study was collected from a sample of 62 non-cognitively impaired community-dwelling and institutionalized adults aged 45 years or older[83]. The inclusion of institutionalized adults among the cohort raises concerns as PA levels may be significantly skewed due to the differences in the engagement of daily PA. Research is consistent in that institutionalized adults have significantly less PA than their community-dwelling counterparts[87,88]. This poses as a risk to the validity and reliability of the findings as results may misrepresent the cohort.

The above studies, however, encompasses of limitations that impact the validity and reliability of their findings. The global limitation of the aforementioned studies is that almost all studies have relatively small sample sizes (n=64-544), which renders the findings less generalizable. In addition, all the studies except for Castro et al. rely greatly on self-reported data. This is evident in that at least one component of the variable is self-reported, whether it is the measure for PA, cognition, or CVD risks, this is susceptible to bias and recall error, especially for PA measurement as it may under-or overestimate participant PA levels, resulting in

inaccurate findings. Furthermore, only the study by Castro et al. utilized the PROCESS macro to conduct mediation analysis. This limits the inter-study comparability and interpretation of the data.

Table 4: Summary of the four identified studies examining the mediating effects of CVD risk factors on the relationship between PA and cognition.

Title	Author and year	Sample population	Tools used	Findings
Role of Cardiovascular Risk Factors on the Association Between Physical Activity and Brain Integrity Markers in Older Adults	Felisatti et al. (2022)	Cognitively unimpaired older adults aged 65 years and above (n= 134)	PA: self-reported questionnaire. CVD risk: insulin level, total cholesterol, HDL, SBP, BMI, smoking habits. Brain: neuroimaging	Changes in insulin level and BMI mediates the association between PA and gray matter volume in the brain.
Physical Activity and Executive Function in Aging: The MOBILIZE Boston Study	Eggermont et al. (2009)	Community-dwelling older adults aged 70 years and above (n= 544)	PA: self-reported questionnaire. CVD risk: mix of self-reported diagnoses of conditions and objective measures. Cognition: several cognitive domain tests.	PA participation was positively associated with cognitive tests focusing on executive functions in older adults, regardless of the presence of CVD risk factors.
Impact of cardiovascular risk factors on the relationships of physical activity with mood and cognitive function in a diverse sample	Minto et al. (2022)	Community-dwelling and institutionalized older adults aged 45 years and above (n= 62)	PA: self-reported questionnaire. CVD risk: self-reported diagnoses of conditions. Cognition: several cognitive domain tests.	Higher PA was associated with better cognition in the domains of attention and verbal working memory at lower levels of CVD. At higher levels of CVD, higher PA was associated with worse attention and verbal working memory.
Fitness, Insulin Sensitivity, and Frontal Lobe Integrity in Adults with Overweight and Obesity	Castro et al. (2016)	Community-dwelling adults aged between 45-63 years (n= 84)	PA: estimated VO_{2max} from 6 min walk test. CVD risk: insulin sensitivity index from blood collection. Brain: neuroimaging.	Significant mediation effect of insulin sensitivity on the relationship between fitness and brain integrity.

Chapter 2: Methods

2.1 Statement of the problem, objectives and hypotheses

Existing literature has identified independent associations between PA, cognition, and CVD risk[19,63,89–94]. However, limited research has investigated the potential mediating effect of CVD risk factors on the association between PA and cognition in older adults[14,83–85]. A study that aligns closely with this thesis identified that changes in insulin levels and BMI mediated the association between PA and gray matter volume in the brain[14]. However, that study was limited by self-reported PA, a relatively small sample size (n=134), and the use of a statistical approach to mediation that is no longer recommended due to flaws in the logic[95].

Mediation analysis aims to understand the extent to which a third variable transmits the effect of an independent variable on a dependent variable[79,80]. The interest in determining whether CVD risk factors mediate the relationship between PA and cognition arises from the observed co-existence of CVD risk factors and cognitive decline among adults, both of which impact their quality of life[3,55,64]. By examining the relationship between CVD risk factors and cognitive decline, it may enhance our understanding of how these variables interact to influence health outcomes. Therefore, this research may contribute to raising awareness about the importance of PA as a lifestyle intervention for older adults, and potentially stimulate the development of preventative and complementary strategies to delay age-related cognitive decline. This information could have significant implications for individual health outcomes as well as global health initiatives.

This thesis project aimed to address the limitations of existing research[14,83–85] by using objective PA data, a larger sample size, and a more comprehensive list of CVD risk factors. The main objectives of this thesis were to:

1. investigate the mediating effect of a composite CVD risk factor score (as measured by the FRS) on the relationship between PA and global cognitive score (as measured by the MoCA) in a cohort of older females; and,
2. determine the mediating effect of each CVD risk factor (SBP, DBP, arterial stiffness, BMI, LDL, triglyceride, glucose, and FI) separately on the relationship between PA and global cognitive score in a cohort of older females.

In regard to the objectives, the hypotheses were:

1. PA level will be positively associated with global cognitive score, and composite CVD risk factor score will be a mediator of this association.
2. BMI mediates the association between objectively measured PA and global cognitive score. This hypothesis is based on previous literature that has reported the significant mediating effects of BMI[14].
3. fasting glucose levels mediate the association between objectively measured PA and global cognitive score. This hypothesis is based on previous literature that has reported the significant mediating effects of insulin levels[14]. The WARM Hearts trial did not analyze blood data for insulin levels; however, insulin influences blood glucose levels in humans, and therefore, we will utilize fasting glucose as a surrogate marker of insulin levels.

The developed hypotheses do not specify a direction for the mediation. This choice was made because it is unclear if the mediation effect for each parameter tested was likely to increase/reduce the association between MVPA and cognition. Even so, the direction of change was examined and discussed in the results and discussion sections of this thesis. This approach enables us to do 2-tailed hypothesis testing.

2.2 Research design

This thesis was developed following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline. A copy of each checklist can be found in Appendix A. The research utilized a cross-sectional study design and was a secondary analysis of data collected during the Women's Advanced Risk-Assessment in Manitoba (WARM) Hearts cardiovascular screening study (ClinicalTrials.gov ***NCT03938155***)[74]. The WARM Hearts study was a prospective, observational study that employed a series of non-invasive assessments and biomarkers to identify measurements predictive of adverse cardiovascular events following a five-year period, specifically in community-dwelling older females aged 55 years or older[74]. A detailed protocol paper for the WARM Hearts cohort was published in the *British Medical Journal Open*[74]. The WARM Hearts study received ethical approval from the University of Manitoba Health Research Ethics Board (H2019:063) and the St. Boniface Research Review Committee (RRC/2019/1833)[74].

For the WARM Hearts trial, a total of 1018 female participants aged 55 and older were recruited through a convenience sampling method[74]. Recruitment methods included radio interviews and media advertisements[74]. Interested individuals were instructed to contact the research team via email or phone, after which a screening process was conducted over the phone to determine eligibility[74]. A complete list of inclusion and exclusion criteria is reported in the WARM Hearts protocol paper[74] . Eligible participants were scheduled for two research appointments, 8-14 days apart, at the (1) Active Living Centre, University of Manitoba, Winnipeg, and (2) St Boniface Hospital Asper Clinical Research Institute, Winnipeg, Manitoba[74]. Recruitment for the WARM Hearts study commenced on October 10, 2019, and continued until March 23, 2020[74], when the COVID-19 pandemic led to the suspension of university research

activities. By this time, 480 individuals had been recruited into the WARM Hearts trial, with 240 of these individuals completed data collection[74]. The research remained on hold until September 16, 2020, and continued until November 10, 2020. Recruitment restarted in October 2021 and continued until December 20, 2021, bringing the cumulative total of 522 recruited participants, 330 of whom completed data collection. The COVID-19 Omicron variant then caused research to be suspended again. The research resumed on February 1, 2022, and continued until December 22, 2023, with a total of 1018 participants having completed data collection.

2.3 Inclusion and exclusion criterion

All participants who met the inclusion criteria of the WARM Hearts trial (as described in the *British Medical Journal Open*[74]) and completed both research appointments were included in this thesis. Exclusion criteria included incomplete or missing MoCA assessment; absence of accelerometer data, or accelerometer data with less than 16 hours of wear-time per day or worn for less than seven days; incomplete BMI measurement; and failure to provide a blood sample.

2.4 Measurements

2.4.1 Physical activity

PA was measured using the triaxial accelerometer monitors (GT3X, GT3X+, ActiGraph, Pensacola, FL, USA). Participants were instructed to wear the accelerometer on their non-dominant wrist for 24 hours each day over seven consecutive days in between the first and second research appointment, removing it only during water-based activities. Participants were also provided with a log to record any time frames when they removed the accelerometer. Research in both clinical practice and research settings highlighted that wrist placement

enhanced compliance among participants[28,29]. Wrist placement better captures low-intensity activities in a free-living environment[29]. Given that the cohort comprises of adults 55 years of age and older, it is reasonable to assume that low-intensity PA will constitute the majority of their total PA. The sampling frequency was set at 90 Hz, due to its accuracy in capturing movement patterns in older adults[28,29,31]. Data were considered valid for analysis if they contain 16 hours per day for seven days, this is to ensure consistency and coherence with existing literature such as those of the UK biobank in analyzing the data.

Raw accelerometry data were processed using the GGIR package version 3.0-3 in R (https://cran.r-project.org/web/packages/GGIR/). For this project, only "g.part1", "g.part2" and "g.part5" of the GGIR process were utilized. Accelerometry data were initially downloaded using ActiLife software version 3.13.3 (ActiGraph, Pensacola, FL) and saved as .gt3x files, which were then converted to .csv files containing x, y and z vectors[96]. GGIR auto-calibrates the raw data into a single omnidirectional measure of acceleration by calculating the vector magnitude (VM) of the three axes to determine the Euclidian norm minus one (ENMO) ($\sqrt{(x^2 + y^2 + z^2)} - 1$)[96,97]. Negative values were rounded to zero[96,97]. ENMO values were averaged over 5-second epochs for analysis. Data with errors greater than 0.02 g or with less than 16 hours of wear time were excluded from the analysis[42]. Non-wear was identified using default settings, which detect non-wear over 60-minute windows with 15-minute moving increments[42]. If standard deviation (SD) was less than 13 milligravity for two or more of the three axes, then the time window was considered as non-wear and was replaced with the averaged activity from the same time period on other measured days[42,98]. The time window was defined as midnight to midnight to retrieve data summarized over 24 hours[98]. The MVPA cut-off point was set at 104 milligravity, mean acceleration in a 5-second epoch (ENMO) must be at or over 104 milligravity

to be classified as MVPA[99]. This MVPA cut-off was chosen as it aligns optimally with the characteristics of the study cohort, where about 90% of participants were aged between 59 to 71 years. Time spent in MVPA was calculated across the monitoring period using the output variable [dur_day_mvpa_bts_1_min_pla] from part 5—person summary. This variable was selected because literature shows that using a bout criterion not only better captures sustained activities but also allows for the inclusion of short bursts of activity without counting all movements as MVPA[98,100]. This approach was validated by observing that when unbouted criterion was used, MVPA time/day doubled compared to when bouts were used[98]. Total PA was calculated by adding MVPA to the output variable [dur_day_total_LIG_min_pla] from part 5—person summary. This specific output variable was used because GGIR does not offer an option to process LPA in bouts. The output variable [dur_day_total_LIG_min_pla] was used independently when analysis focused on LPA. The standard operating procedure for the GGIR analysis in this thesis is included in Appendix B.

2.4.2 Cognition

A global cognitive score was obtained using the MoCA, which has been validated for adults ages 55 to 85[101]. Research staff were trained with MoCA-specific training course and administered the assessment following a strict script and protocol to minimize heterogeneity in testing procedures. Assessment was obtained during initial research appointment. One point was added to the total score if an individual had less or equal to 12 years of education[58]. The research staff then assessed the test and concluded a total score, this score was then reviewed and validated by another trained staff to ensure accuracy. A score of less than 26 on the MoCA indicates cognitive impairment[61]. The MoCA score was treated as a continuous variable in the

analysis within this thesis, not as a categorical variable. The scoring of the MoCA tests for all participants was reviewed by a senior research staff at the conclusion of the study to confirm the accuracy of the initial scoring. This secondary scoring was done independently to provide an impartial judgement.

2.4.3 CVD risk factors

Framingham Risk Score

The Framingham Risk Score (FRS) is a standard measure of composite CVD risk used widely in clinical settings. The FRS was calculated following recommendations by D'Agostino et al. using sex, age, systolic blood pressure (mmHg), total cholesterol (mg/dL), HDL cholesterol (mg/dL), smoking behaviour, diabetes status, and whether participant is on antihypertensive medications or not[70]. These values were inputted into a mathematical model based on the Framingham Heart Study[102]; the output value represents the risk percentage of an individual experiencing a cardiovascular event in the next ten years[70]. Variables were obtained over both research appointments.

Body Mass Index

BMI was obtained during the first research appointment using the bioelectrical impedance body composition analyzer (InBody 270) by inputting the height and mass of the participant[103,104]. The machine calculates BMI using mass in kilograms divided by height in meters squared (kg/m^2). Participants were instructed to stand still on the analyzer with bare feet, arms extended straight and away from the side of their body.

Blood pressure and arterial stiffness

SBP was measured in alignment with the Canadian Cardiovascular Society guidelines[74,76]. SBP were taken when participants were in a seated position on the left upper arm[74,76] except when the participant had implications such as recent surgical wounds on the left arm and the surrounding region, then SBP was taken on the right upper arm. A validated oscillometric device (Mobil-O-Graph) was used to measure SBP at the second appointment[74,76], which was extracted for this thesis. The Mobil-O-Graph is a validated ambulatory BP monitor that obtains non-invasive measurements of systolic, diastolic, and central BP[74,105].

Diastolic blood pressure (DBP) measurements were obtained in accordance with the SBP at the same time, following the Canadian Cardiovascular Society guidelines[74,76]. DBP were taken when participants were in a seated position on the left upper arm[74,76] except when the participant had implications such as recent surgical wounds on the left arm and the surrounding region, then DBP was taken on the right upper arm. The validated Mobil-O-Graph was used to obtain DBP[74,76].

The Mobil-O-Graph was used to measure arterial stiffness. The Mobil-O-Graph uses brachial oscillometry to assesses arterial stiffness, which measures brachial BP and brachial waveforms, then estimates central aortic pressure and carotid-femoral pulse wave velocity (cfPWV; measured in meters per second)[69]. This method of measure has been validated for healthy as well as hypertensive individuals[74,106,107]. The Mobil-O-Graph has been compared with intra-aortic measures[108], and cardiac magnetic resonance imaging[109], and has acceptable accuracy[74]. Variables were obtained in the second research appointment.

Low-density lipoprotein cholesterol (LDL), triglyceride and glucose

LDL, triglyceride, and glucose levels were obtained through a fasting blood sample, where a total of 15 mL were drawn into four separate tubes from each participant by a phlebotomist. The processing of the blood split the sample into a serum silica tube (1×4 mL), a lithium heparin tube (1×4 mL) and two EDTA tubes (2×3 mL)[74]. Blood then underwent processing procedures, were snap frozen in liquid nitrogen, and then stored at minus 80 degrees Celsius before later analyzed using standard lab procedures[74]. Variables were obtained in the second research appointment.

Frailty

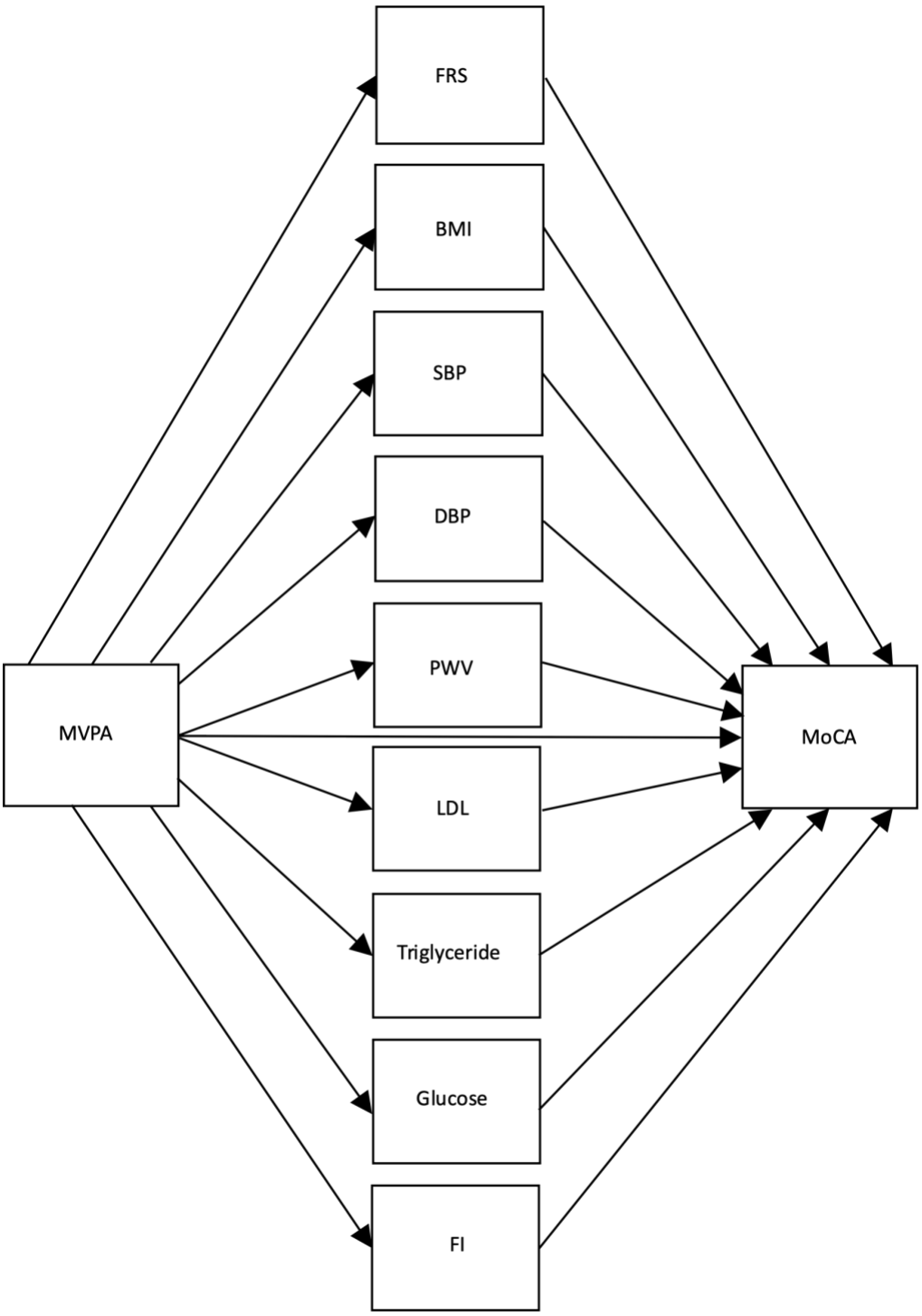
A FI was created with data collected from the WARM Hearts study following the recommendations of Searle et al.[110]. A total of 33 variables were used for this thesis (highlighted in Appendix C). The 33-variable FI included: grip strength, chair stand, gait speed, self-report PA, arm curls, back scratch, sit and reach, 8 feet up and go, 6 minute walk test, waist circumference, fat mass (kg), fat-free mass (kg), PHQ-9 score, clinical diagnosis of depression/anxiety, unintentional weight loss, decline in food intake, is biting or chewing food difficult, problems getting groceries, feel everything was an effort, could not "get going", mobility, self-care, usual activities, pain/discomfort, rate health today, arthritis, sleep apnea, cancer, irritable bowel disease (IBD), asthma, resting heart rate, Pittsburge Sleep Quality Index (PSQI), number of medications. Variables were obtained over both research appointments.

2.5 Statistical analyses plan

Data were obtained from stored database and underwent data cleaning in Microsoft Excel according to the exclusion criteria specific to this thesis. Normality testing was conducted for

each variable. Descriptive statistics were used to summarize the demographic data. For normal data, values were presented as mean plus or minus standard deviation (SD), and for non-normal data, values were presented as median and interquartile range (IQR). The variables tested included age, height, mass, education, PA (average minutes spent in MVPA per day in a week), waist circumference, MoCA, FRS, BMI, SBP, DBP, PWV, LDL cholesterol, triglycerides, glucose, and frailty index. Multiple mediation analysis was employed to examine whether PA influences cognition through various CVD risk factors, both as a composite CVD risk score and as individual factors. Overlap of variables among each risk factor was considered and avoided. The only overlap among all the variables exist for SBP, which is a part of the FRS, and analyzed as an individual CVD risk factor. Figure 3 illustrates the overall mediation model specific to this thesis project. The mediating effect of CVD risk factors on the relationship between MVPA and global cognitive score was performed using model four (multiple mediation) of the PROCESS macro (version 4.3) developed by Andrew F. Hayes (http://www.afhayes.com) for SPSS (version 29.0.2.0 IBM Corporation, Armonk, NY, USA). Data were reported using tables and figures. Bootstrapping (set at 5000) resampling technique was employed to estimate the confidence intervals (CI) (95% CI) for the direct and indirect effects. The significance of the mediation effect was determined based on the CI of the indirect effect. Mediation was supported if zero was not within the lower and upper bounds of the CI. Conversely, if zero fell within the lower and upper bounds of the CI, then the indirect effect was considered not significant. A p-value of 0.05 or less was considered statistically significant.

Figure 3: Mediation model specific to this thesis project



***MVPA**, moderate to vigorous physical activity; **FRS**, Framingham Risk Score; **BMI**, Body Mass Index; **SBP**, systolic blood pressure; **DBP**, diastolic blood pressure; **PWV**, pulse wave velocity; **LDL**, Low-Density Lipoprotein; **FI**, Frailty index; **MoCA**, Montreal Cognitive Assessment.*

Chapter 3: Results

3.1 Participant characteristics

Nine-hundred and sixty-five females had complete data and were included in the analyses. See Figure 4 for flow chart. A power analysis was not conducted, as post-hoc power analyses are generally considered uninformative and flawed[111–113]. However, the sample size was deemed sufficient based on similar existing studies, which have utilized sample sizes ranging from 64 to 544 participants. The full cohort reported an assigned sex at birth as female. The median age of the cohort was 64 (60-69) years. Body composition and anthropometric measures in this cohort consisted of a mean height of 163.2 ± 5.9 cm; median mass was 68.8 (60.7-79.3) kg; and median waist circumference was 92.9 (85.0-102.5) cm. About 79.5% of the participants received post-secondary education. The median time spent doing MVPA was 21(9-38) minutes per day, and MoCA scores had a median of 27 (25-28). CVD risk factors for this cohort included FRS 10-year risk, with a median of 6.3 (3.9-8.6); median BMI was 25.8 (23.2-29.7) kg/m^2; median systolic and diastolic blood pressure were 122 ± 14 mmHg and 77 ± 10 mmHg, respectively. Median PWV was 8.90 (8.30-9.80) mmHg; mean LDL cholesterol was 3.32 ± 0.86 mmol/L, median triglycerides was 0.98 (0.76-1.34) mmol/L, and median fasting glucose was 5.65 (5.35-6.01) mmol/L. Lastly, the median FI score was 0.15 (0.11-0.21). Baseline characteristics for the overall cohort are included in Table 5. A correlation matrix of all assessed variables is shown in Table 6.

Figure 4: Study flow chart

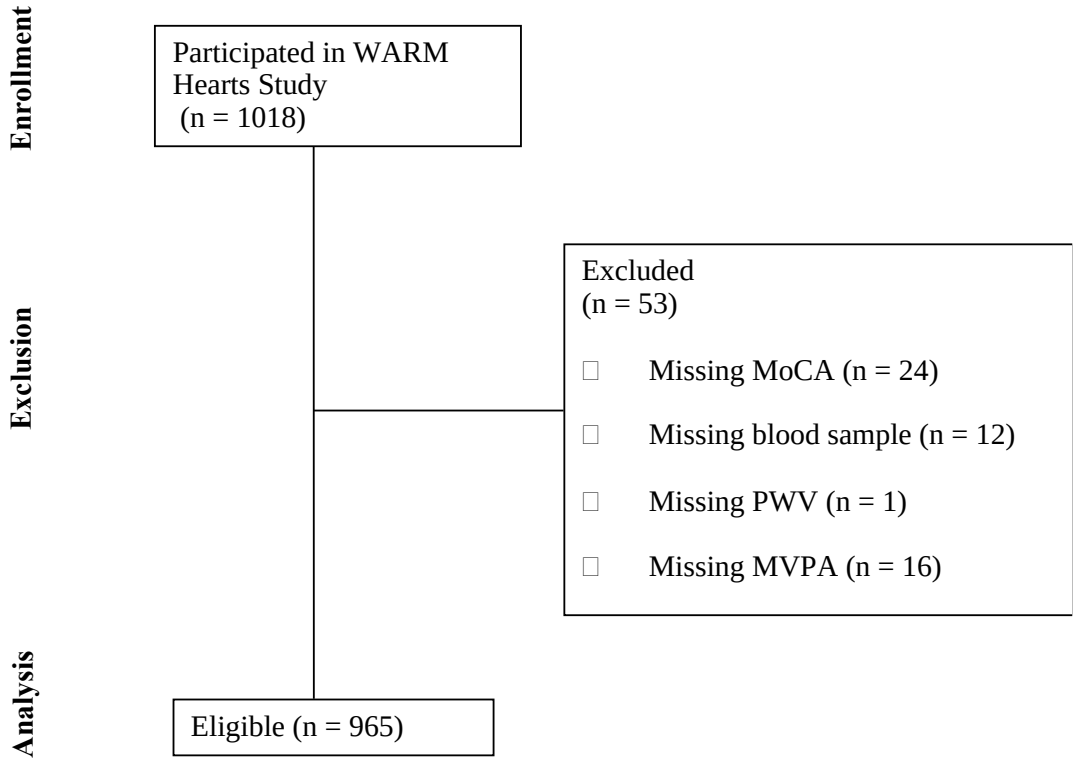


Table 5: Participant characteristics

Characteristic	Total cohort n=965
Age (years)	64 (60-69)
Height (cm)	163.2 ± 5.9
Mass (kg)	68.8 (60.7-79.3)
Waist circumference (cm)	92.9 (85.0-102.5)
Post-secondary education, n (%)	767 (79.5%)
MVPA (min)	21(9-38)
MoCA	27 (25-28)
FRS 10-year risk (%)	6.3 (3.9-8.6)
BMI (kg/m^2)	25.8 (23.2-29.7)
Systolic BP (mmHg)	121 (112-130)
Diastolic BP (mmHg)	76 (70-84)
Pulse wave velocity (mmHg)	8.90 (8.30-9.80)
LDL cholesterol (mmol/L)	3.32 ± 0.86
Triglycerides (mmol/L)	0.98 (0.76-1.34)
Fasting Glucose (mmol/L)	5.65 (5.35-6.01)
Frailty Index Score	0.15 (0.11-0.21)

Normal continuous variables expressed as mean ± standard deviation; non-normal continuous variables expressed as median (interquartile range); categorical variables expressed as n (%). ***MVPA****, moderate to vigorous physical activity;* ***MoCA****, Montreal Cognitive Assessment;* ***FRS****, Framingham Risk Score;* ***BMI****, Body Mass Index;* ***BP****, blood pressure;* ***LDL****, Low-Density Lipoprotein.*

Table 6: Correlation matrix

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	**Age**															
2	**MoCA**	-.183**														
3	**Height**	-.200**	.109**													
4	**Weight**	-.207**	.066*	.319**												
5	**BMI**	-.148**	0.03	-0.025	.934**											
6	**LDL**	-.110**	0.044	0.043	0.01	-0.001										
7	**Triglyceride**	-.072*	-0.023	-0.019	.321**	.348**	.143**									
8	**Glucose**	0.055	-0.051	-0.05	.228**	.261**	-.118**	.167**								
9	**Waist**	-.110**	0.043	.157**	.885**	.876**	-0.016	.361**	.237**							
10	**PWV**	.594**	-.106**	-.155**	-.069*	-0.018	-0.041	-0.007	0.062	-0.007						
11	**SBP**	.131**	-0.054	-.074*	.260**	.302**	0.005	.160**	.142**	.278**	.376**					
12	**DBP**	-.070*	0.008	-0.002	.253**	.270**	0.023	.149**	.104**	.251**	.147**	.708**				
13	**FRS**	.338**	-.096**	-.128**	.205**	.265**	.187**	.275**	.291**	.248**	.382**	.705**	.466**			
14	**FI**	.106**	-.173**	-.111**	.321**	.375**	-0.034	.177**	.183**	.370**	.083*	.172**	.078*	.255**		
15	**MVPA**	-.206**	.071*	0.041	-.209**	-.233**	.073*	-.109**	-.108**	-.249**	-.108**	-.121**	-0.04	-.182**	-.255**	

*** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed). **MoCA**, Montreal Cognitive Assessment; **BMI**, Body Mass Index; **LDL**, Low-Density Lipoprotein; **PWV**, pulse wave velocity; **SBP**, systolic blood pressure; **DBP**, diastolic blood pressure; **FRS**, Framingham Risk Score; **FI**, Frailty index; **MVPA**, moderate to vigorous physical activity.*

3.2 Composite CVD risk factors on PA and global cognitive score

A multiple mediation analysis was conducted to examine whether the relationship between MVPA and cognitive function, as measured by the MoCA, was mediated by composite and individual CVD risk factors. FRS was the composite mediator, and individual mediators included were BMI, SBP, DBP, PWV, LDL, triglycerides, glucose, and the FI. All mediators were put into one model and ran simultaneously. Mediation analysis summary is presented in Table 7.

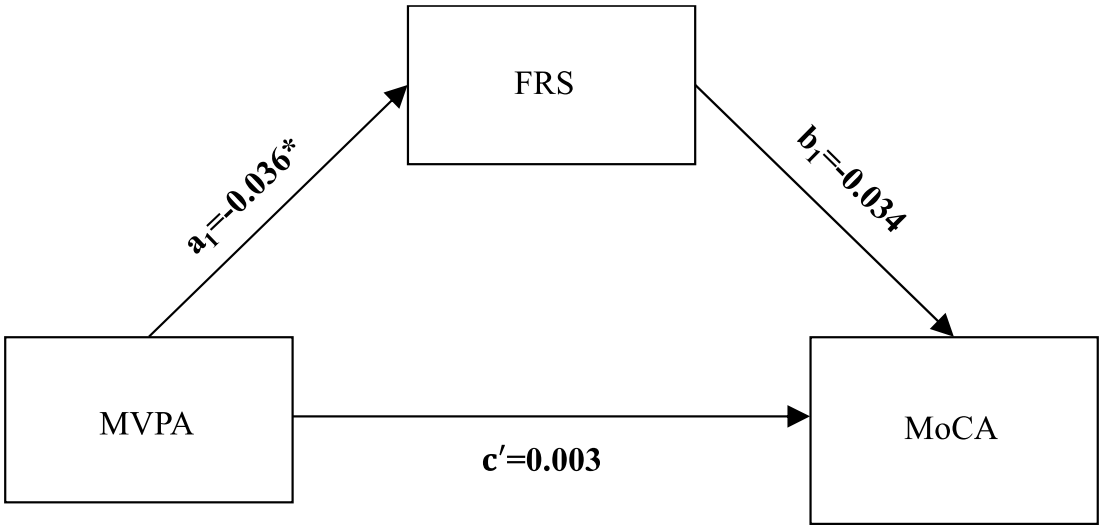
When the mediating role of the FRS on the relationship between MVPA and MoCA was assessed, the effect of MVPA on FRS (a1) was negative and significant ($b=-0.036$, $p<0.001$). This indicates that MVPA is inversely associated with CVD risk assessed using the FRS as a composite CVD risk score. However, the effect of FRS on MoCA (b1) was not significant ($b=-0.034$, $p=0.260$), which means that the FRS did not significantly associate with cognitive function when controlling for MVPA and other mediators. Furthermore, the direct (c') and indirect (a1*b1) effects were also not significant ($b=0.003$, $p=0.393$) and ($b=0.001$, 95% CI: [-0.002, 0.003]), respectively. Thus, indicating that there were no mediating effect by the FRS on the relationship between PA and cognitive function. These findings remained consistent even when total PA, (MVPA + LPA) replaced MVPA as the independent variable, and when LPA was analyzed alone Therefore, hypothesis #1 was not supported, composite CVD risk score by means of the FRS does not mediate the relationship between PA and cognitive function in this dataset. See Figure 5 for FRS-specific mediation model singled out from the complete multiple mediation model (Figure 3).

Table 7: Mediation analysis summary

Mediator	Path_a	Coefficient	SE	p-value_a	Path_b	Coefficient_b	SE_b	p-value_b	IE	Lower CI	Upper CI	DE_(c)	SE_c	p-value_c
FRS	a1	-0.036	0.006	<0.001	b1	-0.034	0.030	0.260	0.0010	-0.002	0.003	0.003	0.004	0.394
BMI	a2	-0.058	0.008	<0.001	b2	0.059	0.018	0.001	-0.0030	**-0.006**	**-0.001**	0.003	0.004	0.394
BP_SYS	a3	-0.079	0.021	<0.001	b3	-0.003	0.010	0.773	0.0002	-0.002	0.002	0.003	0.004	0.394
BP_DIA	a4	-0.019	0.015	0.209	b4	0.010	0.011	0.360	-0.0002	-0.001	<0.001	0.003	0.004	0.394
PWV	a5	-0.009	0.003	0.001	b5	-0.088	0.052	0.091	0.0008	0.000	0.007	0.003	0.004	0.394
LDL	a6	0.003	0.001	0.024	b6	0.124	0.096	0.194	0.0004	-0.0003	0.001	0.003	0.004	0.394
TRYG	a7	-0.003	0.001	0.001	b7	-0.095	0.147	0.517	0.0003	-0.0005	0.001	0.003	0.004	0.394
GLUCOSE	a8	-0.004	0.001	0.001	b8	-0.054	0.096	0.575	0.0002	-0.0009	0.002	0.003	0.004	0.394
FI	a9	-0.001	<0.001	<0.001	b9	-5.725	1.090	<0.001	0.0050	**0.003**	**0.008**	0.003	0.004	0.394

***FRS**, Framingham Risk Score; **BMI**, Body Mass Index; **BP_SYS**, Systolic Blood Pressure; **BP_DIA**, Diastolic Blood Pressure; **PWV**, Pulse Wave Velocity; **LDL**, Low-Density Lipoprotein; **TRYG**, Triglyceride; **FI**, Frailty Index; **Path_a**, X to M; **Coefficient**, unstandardized coefficient; **SE**, Standard Error; **Path_b**, M to Y; **IE**, indirect effect; **CI**, Confidence Interval; **DE_(c)**, direct effect (path c, X to Y).*

Figure 5: FRS-specific mediation model



Indirect effect= 0.001, 95% CI: [-0.002, 0.003]

***MVPA**, moderate to vigorous physical activity; **FRS**, Framingham Risk Score; **MoCA**, Montreal Cognitive Assessment.*

3.3 Individual CVD risk factors on PA and global cognitive score

When assessing the mediating role of individual CVD risk factors on the relationship between MVPA and MoCA, BMI and FI were the only significant mediators among the variables analyzed. The effect of MVPA on BMI (**a_2**) was negatively associated and significant (b=−0.058, p<0.001). This indicates that MVPA is inversely associated with BMI. Additionally, the effect of BMI on MoCA (**b_2**) was positive and significant (b=0.059, p=0.001), indicating that BMI has a positive association with cognitive function when controlling for MVPA and other mediators. The direct effect (**c'**) of MVPA on MoCA was not significant (b=0.003, p=0.393), this meant that when all mediators were present in the model, MVPA did not show a significant effect on MoCA, suggesting that the influence of MVPA on cognitive function is an indirect-only mediation by BMI. The indirect effect (**a_2*b_2**) was negative and significant (b=−0.003, 95%

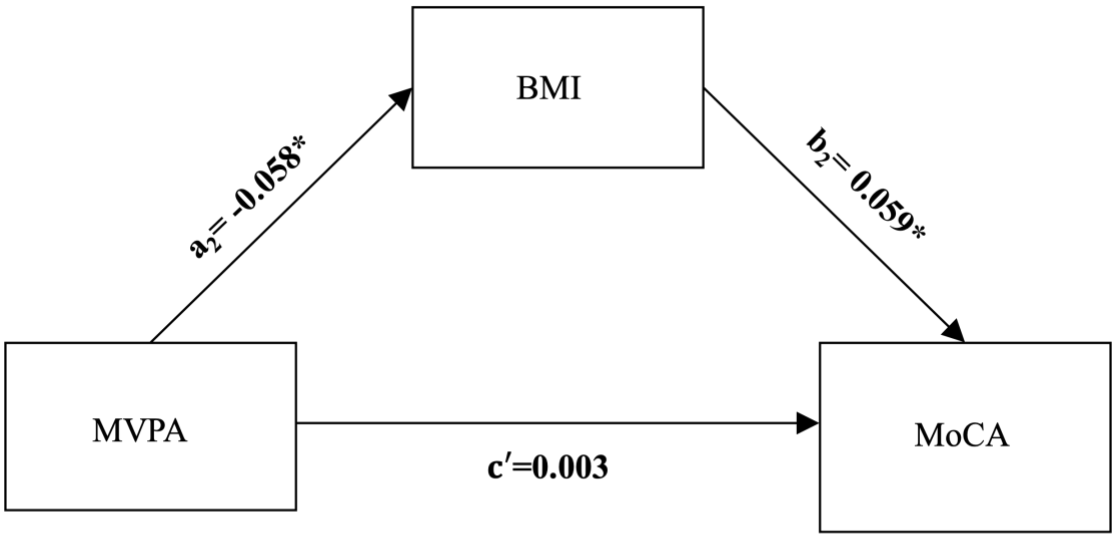
CI: [−0.006, −0.001]). This finding suggests that the overall effect of MVPA was negatively associated with cognitive performance through the effects of BMI. This was again consistent when total PA, (MVPA + LPA) and LPA alone replaced MVPA as the independent variable. Supporting the hypothesis #2 that BMI significantly mediates this association, but contrary to the previous literature that BMI acts as a synergist to improve cognitive function as MVPA increases. See Figure 6 for BMI-specific mediation model.

There was a significant negative association between MVPA on FI (**a_9**) (b=−0.001, p<0.001), suggesting that MVPA is inversely associated with frailty. Moreover, the effect of FI on MoCA (**b_9**) was negative and significant (b=-5.725, p<0.001), indicating that frailty negatively associates with cognitive function. Similar to BMI, the direct effect (**c'**) of MVPA on MoCA was not significant (b=0.003, p=0.394), while the indirect effect through FI (**a_9*b_9**) was positive and significant (b=0.005, 95% CI: [0.003, 0.008]), meaning that overall, cognitive performance saw positive effects from MVPA through its effects on frailty. Once again, the findings persisted even when total PA, (MVPA + LPA) and LPA replaced MVPA as the independent variable. Additionally, these results were consistent even when we recalculated a FI where the physical parameters (grip strength, chair stand, gait speed, self-report PA, arm curls, back scratch, sit and reach, 8 feet up and go, 6-minute walk test) were removed. We did this to determine if a FI that examined frailty independent of physical function would generate consistent results as those determined using a FI that included physical parameters. See Figure 7 for FI-specific mediation model.

Fasting glucose along with the remaining six other individual CVD risk factors did not exhibit significant mediation effects. The effect of MVPA on glucose (**a_8**) was negative and significant (b=-0.004, p=0.001), this indicates that MVPA level is inversely associated with

fasting glucose levels. However, the effect of glucose on MoCA (**b_8**) was not significant (b=-0.054, p=0.575), suggesting that fasting glucose levels did not significantly associate with cognitive function when controlling for MVPA and other mediators. The indirect effect of MVPA on MoCA through fasting glucose (**a_8*b_8**) was not significant (b=0.0002, 95% CI: [-0.0009, 0.0017]), and the direct effect (**c'**) was also not significant (b=0.003, p=0.394). These results suggest that no-effect (non-mediation) between fasting glucose level and the relationship between MVPA and cognitive function. Again, the findings persisted even when total PA, (MVPA + LPA) and LPA replaced MVPA as the independent variable. These results does not support hypothesis #3 that fasting glucose, as a surrogate marker for insulin level, mediate the relationship between PA and cognitive function. See Figure 8 for glucose specific mediation model.

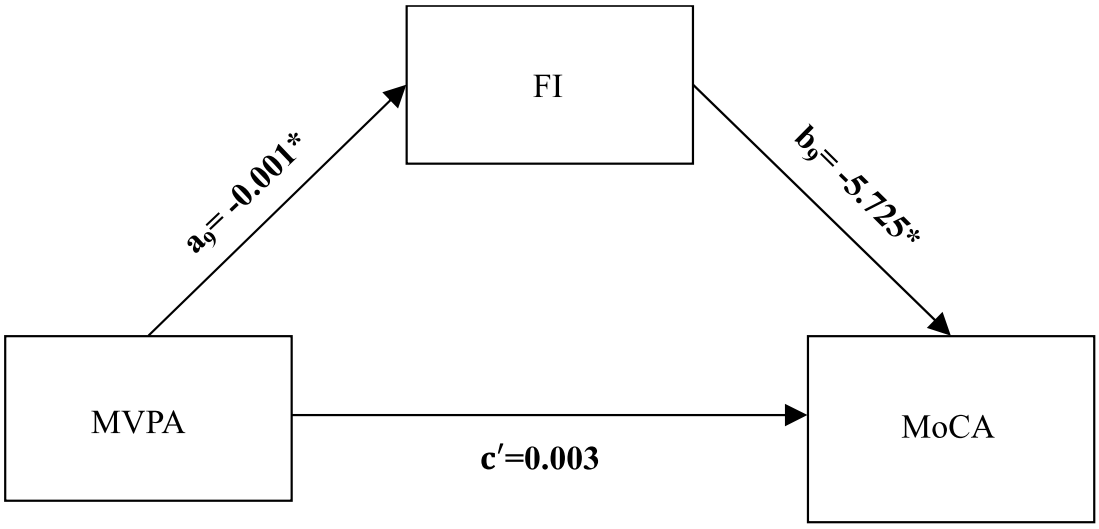
Figure 6: BMI mediation model



Indirect effect=−0.003, 95% CI: [−0.006, −0.001]*

***MVPA**, moderate to vigorous physical activity; **BMI**, Body Mass Index; **MoCA**, Montreal Cognitive Assessment.*

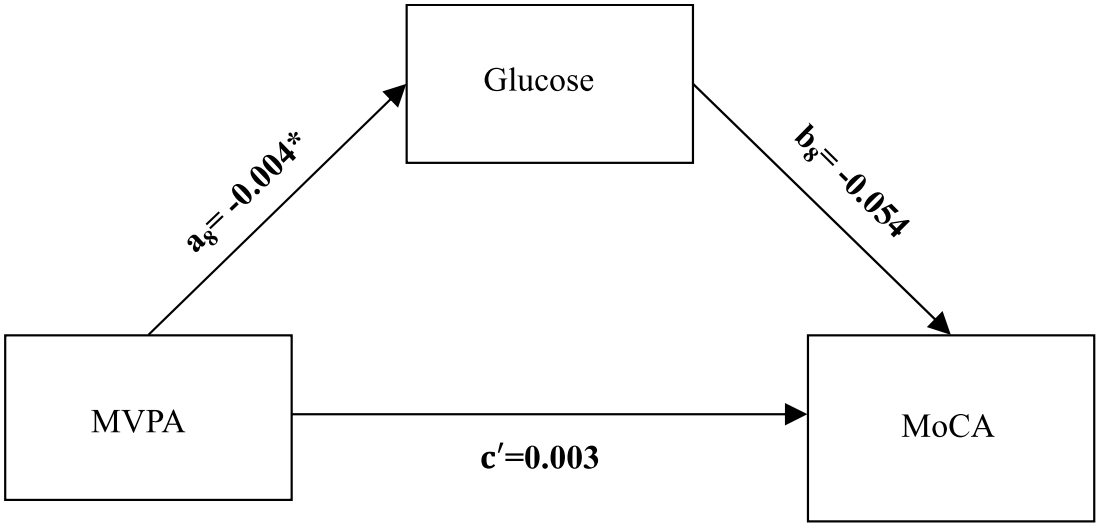
Figure 7: FI mediation model



Indirect effect= 0.005, 95% CI: [0.003, 0.008]*

***MVPA**, moderate to vigorous physical activity; **FI**, Frailty Index; **MoCA**, Montreal Cognitive Assessment.*

Figure 8: Glucose mediation model



Indirect effect= 0.0002, 95% CI: [-0.0009, 0.0017]

***MVPA**, moderate to vigorous physical activity; **MoCA**, Montreal Cognitive Assessment.*

Chapter 4: Discussion

4.1 Summary

Existing literature has identified independent associations between PA, cognition, and CVD risk factors[19,63,89–94]. However, limited research has explored the potential mediating effects of CVD risk factors on the association between PA and cognition in older adults[14,83–85]. Previous research have attempted to address this gap by conducting cross-sectional observational trials that examine the mediating effects of CVD risk factors on the association between PA and gray matter volume in the brain[14]. My thesis contributes to this body of knowledge by specifically focusing on an all-female cohort from the WARM Hearts study, adding and strengthening previous findings. First, my findings corroborate existing literature[14], but do so using more rigorous means of measurement, such as accelerometers, to obtain objective data. This approach contrasts with many prior studies that relied on self-reported PA and smaller sample sizes[14,83–85]. Additionally, my findings extend beyond prior knowledge by uncovering new information and providing alternative pathways to explore. For example, my data report the role of frailty and its specific associations with the relationship between PA and cognition in older females, which I will explore in detail its significance in the following discussion.

The main objectives of my thesis were to: (1) investigate the mediating effect of a composite CVD risk factor score (as measured by the FRS) on the relationship between PA and global cognitive performance (as measured by the MoCA) in a cohort of older females. The main finding was that MVPA was not associated with cognitive performance through a composite CVD risk factor or several individual risk factors, including SBP, DBP, arterial stiffness, LDL, triglyceride, and glucose. This suggests that while FRS and these individual risk factors are useful predictors of overall CVD risk, they may not be the most relevant targets for interventions

aimed at preserving or enhancing cognitive function in older females. Instead, these findings indicate that cognitive health may be more closely linked to general health indicators such as BMI and FI, rather than to specific cardiovascular health indicators. Given these results, health organization and policy makers might consider broadening their focus to include overall health indicators like BMI and frailty when thinking about strategies to maintain or improve cognition in aging populations. This broader approach could lead to more effective interventions that not only includes CVD risk management but also the promotion of overall health and wellbeing. The data also suggest that future initiatives aimed at maintaining or slowing the decline of cognitive function might be more effective if the focus was on improving overall health rather than solely targeting traditional CVD risk factors. This may include lifestyle interventions that incorporate PA, nutrition, and overall wellbeing, particularly tailored to the needs of aging populations.

Second, my thesis sought to determine the mediating effect of individual CVD risk factors (i.e.; SBP, DBP, arterial stiffness, BMI, LDL, triglyceride, glucose, and FI) separately on the relationship between PA and global cognitive performance in a cohort of older females. It was found that MVPA was associated with cognitive performance through specific individual CVD risk factors, namely BMI and FI. These findings were consistent when explored using total PA and LPA. Likewise, the data identify that cognitive performance saw positive effects from MVPA through its effects on frailty even when a modified FI index that had physical parameters removed was employed. This adds to the broader understanding of the relationships between PA, cognition, and CVD risk factors by highlighting the mediating roles of BMI and FI. Which implies that higher BMI and reducing frailty through regular PA could be crucial strategies for enhancing cognitive function in older females. This is also significant in the context of the aging population and the increasing prevalence of cognitive decline and CVD[114,115]. By identifying

specific mediators, this can provide insights that may inform targeted interventions aimed at promoting cognitive health. Clinicians should focus their efforts to support patients to increase their PA levels while understanding the nuanced role and protective effects of higher BMI. Moreover, clinicians should recommend interventions to reduce frailty, to ultimately contribute to better cognitive outcome and overall health in older females. The FI data extend the literature by indicating for the first time that frailty status, regardless of the physical function parameters being included or excluded from the measurement of frailty, mediate the relationship between PA and cognitive function. These findings emphasize the importance of a holistic approach to health that surrounds the relationship between PA, cognition, and CVD risk factors.

Overall, the data indicate that BMI and FI were the only mediators identified in this thesis. Both BMI and FI were indirect-only mediations on the relationship between PA and cognitive function. This suggests that although causality cannot be inferred, it is evident that BMI and FI play crucial roles in this relationship. Moreover, these findings also imply that simply examining the effect of PA on cognition alone may be insufficient without considering the mediating roles of BMI and FI.

4.2 BMI on PA and cognition

Results from this thesis corroborates existing literature indicating that BMI is a significant mediator in the relationship between PA and cognition. However, our results indicate a negative mediation, suggesting that reducing BMI through increased PA negatively influences cognitive performance. This finding is in the opposite direction than previously reported by Felisatti and colleagues, who conducted the only other published study that examines the mediating role of CVD risk factors[14]. In their study, BMI was identified as one of the significant

mediators among a list of CVD risk factors in the relationship between PA and grey matter volume in the brain[14]. They concluded a positive mediation effect, suggesting that PA is associated with greater cardiovascular health through the reduction of BMI, which could be associated with increased preservation of brain structure[14]. The difference between their findings (positive mediation, larger coefficient) and my findings (negative mediation, smaller coefficient) could be attributed to the differences in sample populations. The Felisatti et al. study was conducted among a smaller sample size of 134 older adults including both females and males, with an older mean age (69 ± 4) and a less active cohort (6 ± 5 average hour per week spent in total PA, measured using self-reported questionnaire[14], as compared to 15 ± 5 average hour per week spent in total PA in the WARM Hearts cohort). This raises questions about the specific role that BMI plays in the relationship between PA and cognition. Several mechanisms could underlie this mediation. BMI is associated with overall body mass, where higher body mass associate with various negative health outcomes[116,117]. In my cohort, participants had a median mass of 68.8 (60.7-79.3) kilograms and a median BMI of 25.8 (23.2-29.7). According to the World Health Organization, a BMI of 25 to 29.9 is categorized as overweight[118]. Therefore, most of the participants in the WARM Hearts cohort would be classified as overweight. This finding is consistent with other studies examining older females in a similar age group (62 years and older), where a cohort of 16,031 participants had an average BMI of 26.2[94]. When additional analysis was run with mass as one of the mediators (data not reported), similar results were shown in that FI was a significant mediator. However, BMI was no longer a significant mediator. Instead, mass replaced BMI as a significant mediator, showing a significant negative mediation. This indicates that when all mediators were considered, mass surpassed BMI as the variable that better explains the effect that MVPA had on cognitive performance, also suggesting that BMI is an indicator of

mass. Previous studies in children and adolescents have suggested that excess mass negatively affects cognitive performance[116,117]. This was said to be explained by factors such as negative impacts on executive functions, reduced grey matter volume and brain activity[116,117]. Other studies involving adults and older adults have also indicated that excess mass is associated with an increased risk of chronic diseases, such as CVD[119–121]. Several studies examining BMI and CVD, including data from the seminal Framingham Heart Study, have found that high BMI is an independent and significant predictor of increased risk of CVD[119–121]. BMI is also correlated with insulin resistance, which affects the brain and cognitive functions[85,86,122].

Additionally, BMI has been correlated with decreased mental health, which negatively impacts cognitive function[116,123]. Studies using data from the UK biobank have established strong associations between PA and brain structure in older adults through objective PA measures[124,125]. The studies highlight the importance of higher intensity PA for improving brain structure, noting that LPA did not display significance in their data[124]. This thesis did not find evidence of such a conclusion, when LPA was used as the independent variable, the results were largely similar to my initial findings for MVPA. PA is said to increase cerebral blood flow and upregulate the production of brain-derived neurotrophic factors (BDNF), which are associated with neurogenesis, synaptic plasticity, neuroprotection, learning, and memory[124]. Therefore, individuals may experience enhanced cognitive function through the maintenance of CVD risk factors, such as BMI, by maintaining a healthy body mass through increased PA participation.

Contrarily, other studies, varying in age range and ethnic backgrounds, have found no significant associations between high BMI and impaired cognitive functions[126,127]. Some studies have established a U- or J-shaped relationship between obesity and cognitive decline[127,128]. In a study by Han and colleagues, it was also found that a decrease in obesity over time was

associated with cognitive decline in older females who were obese (BMI⩾25.0) or normal (BMI 18.5-24.9) at baseline[129]. Many have brought up the concept of the "obesity paradox", although controversial due to potential biases and survival effects, it describes the paradoxical finding that overweight and obese individuals (typically categorized by BMI) in older age may have better health outcomes than normal or underweight individuals, especially in the face of disease[130–134]. This phenomenon has been especially studied in cardiac patients[130,132,133]. The idea is that higher BMI could reflect better nutritional status and adequate muscle reserves, which could be associated with greater robustness in the face of disease[131]. This is then positively related with cognitive function[127]. Adipokines produced by adipose tissue could also play a role in the mediation of cognition in adults who are physically active, as adipokines enhance cardioprotective properties by counteracting inflammation and endothelial dysfunction[135]. In my data, the majority of the cohort would be categorized as overweight, where malnourishment is unlikely.

In a large meta-analysis by Flegal and colleagues, which included over 2.8 million individuals, they found that when comparing the all-cause mortality among BMI groups, overweight individuals (BMI 25-<30) had significantly lower all-cause mortality compared to normal weight individuals (BMI 18.5-<25)[134]. However, BMI higher than overweight (BMI>30), was associated with higher all-cause mortality[134]. Another review published in The Lancet found that overweight (BMI 25-29.9) cardiac patients had the lowest risk for total and cardiovascular mortality compared to those with a normal BMI (20-24.9)[130]. They also explain that this finding could be due to the fact that BMI lacks the ability to differentiate between body fat and lean mass[130].

Although the "obesity paradox" does not specifically refer to cognitive functions, it is an apparent factor that contributes to all-cause mortality[130,131]. A study using data from the NHANES cohort found that overweight (BMI 25.0-29.9) and obese (BMI >30) individuals were associated with higher frailty. However, being overweight and having grade 1 obesity (BMI 30.0-34.9) were protective against mortality from frailty[136]. A similar study concluded that, for older adults with frailty, a higher BMI might be beneficial, potentially due to the increased energy reserves and muscle mass[137]. These findings help explain my results, as the majority of my cohort were considered as pre-frail (median FI score 0.15 [0.11-0.21])[138] and overweight (median BMI 25.8 [23.2-29.7] kg/m^2)[118]. Notably, none of the participants had a history of incident heart disease at the time of enrollment. Considering the literature, my findings may be explained by nutritional status and energy reserves. Some studies suggest that a higher BMI might indicate greater muscle mass, since BMI does not differentiate between body fat and lean mass[130]. In such cases, a higher BMI could provide protective benefits by offering greater muscle reserves, which are crucial in mitigating the effects of frailty and preserving cognitive function[130]. The loss of muscle is particularly critical in older adults because muscle mass is associated with frailty, which shares many risk factors with that of cognitive decline[139]. However, when lean body mass was analyzed as a mediator in this thesis, we did not come to the same conclusion (data not reported). The negative mediation effect suggests that increasing PA could influence BMI negatively, potentially due to the loss of adipose tissue. This reduction in BMI, while lowering body fat, might also diminish the protective benefits of adipokines, thereby negatively affecting cognition[137]. Therefore, examining my study cohort, where the median BMI falls within what most of the studies categorize as overweight, it is plausible to find that BMI negatively mediated the association between PA and cognition.

4.3 FI on PA and cognition

Frailty is characterized by multisystem dysfunction, leading to a diminished physiological reserve against health stressors[72,73]. Frailty is important to examine in this study because it is closely associated with aging, and it is known to increase the risk of CVD along with many other adverse health outcomes[72,73]. FI was also found to be a significant mediator in the relationship between MVPA and cognitive performance. The positive indirect effect indicated that MVPA was associated with better cognitive performance through its effects on frailty. This suggest that the positive effects elicited by MVPA mitigates the detriments of frailty, and since frailty and cognitive function share many risk factors[140], the positive effects then shows through onto cognition. The findings were consistent even when total PA, (MVPA + LPA) or LPA replaced MVPA as the independent variable. The findings were again true even when the physical components (grip strength, chair stand, gait speed, self-report PA, arm curls, back scratch, sit and reach, 8 feet up and go, 6-minute walk test) of the FI were removed from the index. This suggests that PA positively associates with cognitive performance through an overall measure of frailty, independent of the physical components of health. This creates an understanding that not only does PA have positive effects on the physical aspects of health, but it also has a holistic impact on frailty, positively affecting cognitive function. No study to date has examined frailty as a potential mediator in the relationship between PA and cognition, even though many have studied the direct influence of frailty on various domains of health.

Frailty encompasses a range of physical, psychological, and social markers that reflect an individual's overall health and vulnerability. Previous studies have found an association between frailty and decreased cognitive health[140]. Frailty often leads to diminished mobility and physical

functions, which limits individuals' ability to engage in activities that promote cognitive and mental health, further impairing cognitive functions and exacerbating cognitive decline117. Several mechanisms have been proposed, but one of the key mechanisms is high levels of inflammation[141]. Interleukin-6 (IL-6), a pro-inflammatory cytokine, is also higher in frail older adults compared to those who are not frail[141]. IL-6 is independently associated with pre-frailty and frailty[141,142]. The imbalance between pro-inflammatory and anti-inflammatory markers creates stress on the central nervous system, and therefore takes part in the pathophysiological mechanisms of frailty on cognitive functions[142]. The FI used in my thesis does not include specific pro- and anti-inflammatory markers, but this could be a future direction to explore as it will allow a direct examination of the root to frailty[143–145].

Frailty is also significantly related to cardiovascular health, studies have reported that frail and pre-frail older adults have a higher risk of developing CVD, major adverse cardiovascular events, and CVD-related mortality compared to non-frail older adults[146–149]. This can be explained by mechanisms such as elevated oxidative stress levels, increased inflammatory markers, which consequently results in higher markers of thrombosis, shortened telomere length, and endocrine dysregulation, all of which contribute to the risk of developing CVD[148].

PA has been found as an effective approach to mitigate and potentially reverse the effects of frailty on several domains of health[139,150–152]. A review which looked at objectively measured PA in community-dwelling older adults concluded that MVPA is consistently associated with reduced frailty[151]. This is consistent with the findings from this thesis suggesting that regular PA, particularly MVPA, could be an effective approach for improving cognitive functions by reducing or reversing frailty. The benefits of PA such as increased mitochondrial function and reduced inflammation, are key factors that combat the detrimental effects of frailty[10,11,151,153].

Since frailty shares many risk factors related with cognitive decline, by increasing MVPA and overall PA, it can enhance cognitive function by holistically reducing frailty. This not only improves physical health but also broader health benefits that collectively impact cognition.

4.4 Limitations

This study has a few limitations that must be acknowledged. First, the use of convenience sampling method for participant recruitment introduces the potential for sample bias. While convenience sampling was cost-effective and practical for recruiting a large target sample (n=1018), it is important to note that this method does not ensure a sample that is fully representative of the female population in Manitoba. The use of television and radio advertisements for recruitment may not have reached all parts of the population, potentially leading to a bias towards urban-dwelling, media-accessible participants over those from rural or remote areas with limited access. This sampling method also resulted in a predominantly Caucasian cohort, further limiting the generalizability of the findings to non-Caucasian populations. Participants in the WARM Hearts trial are likely health-conscious individuals since they chose to participate in health-related research studies, this could affect the external validity of the study. Data from the most recent health report of Manitoba show that 30.6% of Manitoban females over the age of 20 live with hypertension[154], whereas in this sample cohort only 21.3% have been diagnosed with hypertension. For this reason, the cohort likely underrepresented individuals in poorer health as they may have been less likely to participate.

This study is a secondary analysis of cross-sectional data from the WARM Hearts study. Therefore, the data collected were fixed, which limits the findings as it precludes any causal interpretation of the identified relationships that CVD risk factors have on the relationship

between PA and cognition. Since data collection occurred as a snapshot, the risk of capturing the evolving nature of conditions are limited, especially for conditions such as frailty since it is reversible[139,150–152]. Consequently, changes and longitudinal impacts were not captured.

Lastly, while the mediation analyses provided support statistically for hypotheses that were theoretically driven, they do not elucidate the biological mechanisms underlying these associations.

4.5 Future research directions

Future studies exploring the mediating effects of CVD risk factors on the association between PA and cognition should consider employing longitudinal or experimental study designs. Experts in the field call for such designs as it could delve into the biological mechanisms behind these theoretically driven hypotheses. This can help establish stronger relationships and identify the temporal sequence of these associations, which could be crucial for developing effective interventions and clinical applications.

Due to the limitations in the given sample cohort, future studies should aim to include more diverse populations to improve the generalizability of the findings. This includes variations in ethnic backgrounds, socioeconomic status, and geographic locations. A more diverse sample would strengthen the results and apply to a broader population.

Although BMI and FI have established associations as CVD risk factors, they are also correlated with multiple other health conditions. Since CVD-specific risk factors such as the FRS and PWV did not result in significant mediation effects in this thesis, future studies should examine this hypothesis considering other CVD-specific risk factors. For example, inflammation markers, it may provide more insights and have unique interactions with PA and cognition that

may not be captured by the FRS and PWV. This can help to elucidate whether the relationship between PA and cognition is truly mediated by CVD risk factors or if other pathways are involved.

Future studies could consider comparing the results of multiple groups of mediators by separating the mediators into smaller groups and conducting multiple mediation analyses for each group. This approach would help elucidate the specific associations that different mediators have within different groups. Such analysis could reveal unique pathways and interactions that might be overlooked when examining all mediators together, therefore offering deeper insights into the underlying mechanisms at play.

Lastly, exploring the role of moderators or moderated mediation analysis could provide an alternative perspective on how different factors influence the strength and direction of the mediation effects. This was not explored in my thesis because it was not deemed necessary. This was primarily due to the focus and scope of the research, which aimed to establish mediating effects of CVD risk factors. The existing data set and study design were adequate for addressing the current research questions. Future studies could build on these findings by incorporating moderators to explore additional layers of interactions and further progress intervention strategies.

4.6 Conclusion

The study explored the mediating role of both composite and individual CVD risk factors on the association between PA and cognition in community-dwelling middle-aged and older females. It was concluded that the protective properties of higher BMI and reducing frailty in the relationship between PA and cognition among community-dwelling older females highlight the

significance of promoting regular PA as a crucial strategy for enhancing cognitive function. This is particularly relevant in the context of an aging population and the increasing prevalence of cognitive decline and CVD[114,115]. The identification of specific mediators of the relationship between PA and cognition offers valuable insights that can inform targeted interventions aimed at promoting cognitive health. Composite and traditional CVD risk factors do not mediate the association of MVPA with cognitive function. This finding highlights the need for a more holistic approach that emphasizes the maintenance of general health rather than focusing solely on CVD-specific factors when promoting cognitive function in older females. The broader implications of these findings suggest that clinicians could focus on increasing PA levels in patients while understanding the nuanced role of BMI in considering the protective effects of higher BMI, and reducing frailty, to ultimately contribute to better cognitive outcome and overall health in older females. This holistic approach to health emphasizes the consideration of all of the three factors (PA, CVD risk factors and cognition) among the relationship, and how they each are connected and affect each other.

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Appendix A: STROBE Guideline

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	i
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	ii
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-31
Objectives	3	State specific objectives, including any prespecified hypotheses	32-33
Methods			
Study design	4	Present key elements of study design early in the paper	34-35
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	34-35
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	35
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	35-40
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	35-40
Bias	9	Describe any efforts to address potential sources of bias	35-40
Study size	10	Explain how the study size was arrived at	44
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	43
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	40-41
		(*b*) Describe any methods used to examine subgroups and interactions	41
		I Explain how missing data were addressed	n/a
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	41
		I Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	47-52
		(b) Give reasons for non-participation at each stage	n/a
		I Consider use of a flow diagram	44
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	43,45
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers of outcome events or summary measures	53-55

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	47-52
		(*b*) Report category boundaries when continuous variables were categorized	47-52
		I If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	47-52
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	47-52
Discussion			
Key results	18	Summarise key results with reference to study objectives	53-55
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	61-63
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	64-65
Generalisability	21	Discuss the generalisability (external validity) of the study results	61-62
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	i

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PloS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org

Appendix B: GGIR Standard Operating Procedure

GGIR SOP

Fall 2023/Winter 2024

1

Setting Up: Files & Software

Skip to next section if you already have raw .csv files, R, and R studio downloaded

2

Export raw data from ActiLife

- Open ActiLife
- File → Import/Export/Convert →raw to raw → .GT3X to .csv (batch)

3

Export raw data from ActiLife

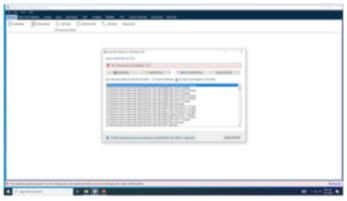
4

Export raw data from ActiLife

- ADD dataset
  - Add all .GT3X files
- 3 checkboxes
  - Create subfolders for exported CSV file(s) = recommended but optional, for convenience
  - Include timestamps = **DO NOT CHECK!!!!!!!**
  - Add column headers to CSV files = CHECK!!!!!

5

Export raw data from ActiLife



6

Export raw data from ActiLife

- Wait ☺

7

Download R

- https://cran.r-project.org/
- Pick the option that fits your computer

8

Download R Studio

- https://posit.co/download/rstudio-desktop/
- Pick the option that fits your computer

9

Setting up: GGIR

Skip to next section if GGIR package and dependencies are already installed on R & all converted .csv files are in one folder

10

Open R Studio

11

Open an R script

File → R script

12

You're ready when UI looks like this

13

You're ready when UI looks like this

14

Install packages

```
install.packages("GGIR", dependencies = TRUE)
```

Assuming you're using ActiGraph accelerometers/ActiLife software, you need this one too:

```
install.packages("read.gt3x")
```

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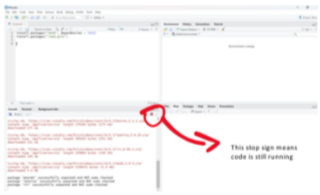
Installing will look like this



16

Prepare folder structure

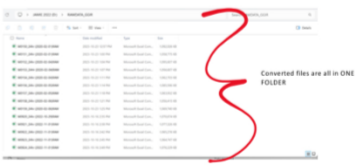
- Find LOCATION ON computer of exported ActiGraph .csv (or .gt3x) files

1. All accelerometer data that needs to be analysed should be stored in one folder, or subfolders of that folder.
2. Give the folder an appropriate name, preferable with a reference to the study or project it is related to rather than just 'data', because the name of this folder will be used later on as an identifier of the dataset.
   - E.g., "RAWDATA_GGIR"

17

Prepare folder structure

Example:



18

Running GGIR

Skip this section if you already have results files

19

What happens in GGIR?

- Part 1: preparing all data to be analyzed
  - REQUIRED
  - Longest step
- Part 2: physical activity analysis
- Part 3: preparing data to be analyzed for SLEEP
- Part 4: sleep analysis
- Part 5: summarizes physical activity and sleep data

20

What happens in GGIR?

- Part 1: preparing all data to be analyzed
  - REQUIRED
  - Longest step
- **Part 2: physical activity analysis**
- Part 3: preparing data to be analyzed for SLEEP
- **Part 4: sleep analysis**
- **Part 5: summarizes physical activity and sleep data**

Only these parts will generate an output file

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Outline of steps:

- Open R Studio
- Input code (see next slides) which specifies:
  - **Where .csv files are saved**
  - **Where you want to save GGIR output** } Bare minimum – GGIR can run just using this
  - Which acceleration intensity cut-offs to use
  - # of minutes a bout of
  - If you want one day to be considered midnight to midnight vs wake-up to next wake-up
  - Etc. → see GGIR data dictionary
- Wait

22

Open R Studio

It might look like this when it opens

23

Open an R script

File → R script

24

You're ready when UI looks like this

25

You're ready when UI looks like this

26

Base Code

- Replace datadir with location of accelerometer files
- Replace outputdir with location of where you want to save GGIR output
- Examples:

Generic Windows:

```
library(GGIR)
GGIR(datadir="C:/mystudy/mydata", outputdir="D:/myresults")
```

Example for Windows on my personal laptop:

```
library(GGIR)
GGIR(datadir="D:/RAWDATA_GGIR", outputdir="D:/OUTPUT_GGIR")
```

Example for LAB COMPUTER:

```
library(GGIR)
GGIR(datadir="W:/Duhamel Lab/Accelerometer Data/GT3X Raw Files_24hr/csv",
outputdir="W:/Duhamel Lab/Accelerometer Data/GGIR_OUTPUT")
```

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Base Code

- Replace datadir with location of accelerometer files
- Replace outputdir with location of where you want to save GGIR output

Use this path for datadir in lab computer
Outputdir should be changed if we run a new analysis
- make sure you make a new folder to direct output files to

Example for LAB COMPUTER:

```
library(GGIR)
GGIR(datadir="W:/Duhamel Lab/Accelerometer Data/GT3X Raw Files_24hr/csv",
outputdir="W:/Duhamel Lab/Accelerometer Data/GGIR_OUTPUT")
```

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Base Code:

- Input the base code into the R script and press run

When this appears, it's running

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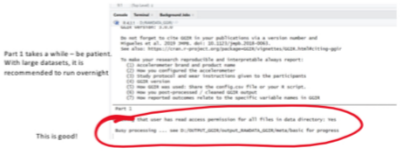
Base Code:

Running the base code will output all the default values for GGIR



Part 1 takes a while – be patient. With large datasets, it is recommended to run overnight

This is good!

30

GGIR Customizations

- See data dictionary for all possible ways to modify the code
  https://cran.r-project.org/web/packages/GGIR/vignettes/GGIRParameters.html#1_input_argumentsparameters_overview

  https://cran.r-project.org/web/packages/GGIR/index.html

- This SOP will cover some of the most relevant and useful modifications

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GGIR Input Customizations – SPECIFY FOR PART 1

Argument/Parameter	Recommended input(s) / Example input	GGIR Explanation	Lay Explanation
datadir	D:/RAWDATA_GGIR (example)	Character (default = c()). Directory where the accelerometer files are stored, e.g., "C:/mydata", or list of accelerometer filenames and directories, e.g. c("C:/mydata/myfile1.bin", "C:/mydata/myfile2.bin").	Pathway to the place on your computer where the raw .csv files are
outputdir	D:/OUTPUT_GGIR (example)	Character (default = c()). Directory where the output needs to be stored. Note that this function will attempt to create folders in this directory and uses those folder to keep output.	Pathway to the place on your computer where you want the output of GGIR (Results) to go
mode	c(1:5) c(1,2) c(2:5)	Numeric (default = 1:5). Specify which of the five parts need to be run, e.g., mode = 1 makes that g.part1 is run; or mode = 1:5 makes that the whole GGIR pipeline is run, from g.part1 to g.part5	Tells GGIR which parts (from 1-5) to run. You have to run part 1 the first time. If you're making minor adjustments to the code after, you can just run any or all of parts 2-5). PA analysis = 2, sleep = 3&4, summary of PA and sleep = 5
idloc	2	Numeric (default = 1). If idloc = 1 the code assumes that ID number is stored in the obvious header field. Note that for ActiGraph data the ID is never stored in the file header. For value set to 2, 5, 6, and 7, GGIR looks at the filename and extracts the character string preceding the first occurance of a "_" (idloc = 2), " " (space, idloc = 5), "." (dot, idloc = 6), and "-" (idloc = 7), respectively. You may have noticed that idloc 3 and 4 are skipped, they were used for one study in 2012, and not actively maintained anymore, but because it is legacy code not omitted.	Tells GGIR how to name (ID) each participant. Putting 2 means that it will read the filenames and call each participant whatever comes before an underscore (_)
maxdur	7	Numeric (default = 0). How many DAYS after start of experiment did experiment definitely stop? (set to zero if unknown).	Max number of days we want to analyze
dayborder	6	Numeric (default = 0). Hour at which days start and end (dayborder = 4 would mean 4 am).	Tells GGIR what hour to start each day (accelerometer programmed to start at 6 am so put 6)

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mvpathreshold	c(60, 100.6)	Numeric (default = 100). Acceleration threshold for MVPA estimation in GGIR g.part2. This can be a single number or an array of numbers, e.g., mvpathreshold = c(100, 120). In the later case the code will estimate MVPA seperately for each threshold. If this variable is left blank, e.g., mvpathreshold = c(), then MVPA is not estimated.	Magnitude of acceleration needed to be met for activity to be classified as MVPA. There are different thresholds for different age groups (older or younger than 70)
threshold.lig	c(18, 44.8)	Numeric (default = 40). In g.part5: Threshold for light physical activity to separate inactivity from light. Value can be one number or an array of multiple numbers, e.g., threshold.lig =c(30,40). If multiple numbers are entered then analysis will be repeated for each combination of threshold values. Threshold is applied to the first metric in the milestone data, so if you have only specified do.enmo = TRUE then it will be applied to ENMO.	Acceleration threshold for light activity
threshold.mod	c(60, 100.6)	Numeric (default = 100). In g.part5: Threshold for moderate physical activity to separate light from moderate. Value can be one number or an array of multiple numbers, e.g., threshold.mod = c(100, 120). If multiple numbers are entered then analysis will be replicated for each ombination of threshold values. Threshold is applied to the first metric in the milestone data, so if you have only specified do.enmo = TRUE then it will be applied to ENMO.	Acceleration threshold for moderate intensity activity
threshold.vig	428.8	Numeric (default = 400). In g.part5: Threshold for vigorous physical activity to separate moderate from vigorous. Value can be one number or an array of multiple numbers, e.g., threshold.vig =c(400,500). If multiple numbers are entered then analysis will be replicated for each combination of threshold values. Threshold is applied to the first metric in the milestone data, so if you have only specified do.enmo = TRUE then it will be applied to ENMO.	Acceleration threshold for vigorous intensity activity
boutdur.mvpa	10	Numeric (default = c(1, 5, 10)). Duration(s) of MVPA bouts in minutes to be extracted. It will start with the identification of the longest to the shortest duration. In the default setting, it will start with the 10 minute bouts, followed by 5 minute bouts in the rest of the data, and followed by 1 minute bouts in the rest of the data	Required duration for a bout of MVPA to be extracted
boutdur.in	60	Numeric (default = c(10, 20, 30)). Duration(s) of inactivity bouts in minutes to be extracted. Inactivity bouts are detected in the segments of the data which were not labelled as sleep or MVPA bouts. It will start with the identification of the longest to the shortest duration. In the default setting, it will start with the identification of 30 minute bouts, followed by 20 minute bouts in the rest of the data, and followed by 10 minute bouts in the rest of the data. Note that we use the term inactivity instead of sedentary behaviour for the lowest intensity level of behaviour. The reason for this is that GGIR does not attempt to classifying the activity type sitting at the moment, by which we feel that using the term sedentary behaviour would fail to communicate that.	Required duration for a bout of inactivity to be extracted
loglocation	enter pathway	Character (default = NULL). Path to csv file with sleep log information. See package vignette for how to format this file	Location of excel sleeping file in the correct format
timewindow	MM	Character (default = c("MM", "WW")). In g.part5: Timewindow over which summary statistics are derived. Value can be "MM" (midnight to midnight), "WW" (waking time to waking time), "OO" (sleep onset to sleep onset), or any combination of them.	Tells GGIR to look at data in days that start and end at midnight (i.e., normal calendar days)

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PART 1&2 CODE

Input this into the R script and run the code

```
library(GGIR)
GGIR(datadir="W:/Duhamel Lab/Accelerometer Data/GT3X Raw Files_24hr/csv",
outputdir="W:/Duhamel Lab/Accelerometer Data/GGIR_MARCH2024,
overwrite=FALSE,
f0=1, f1=0,
mode=c(1),
idloc=2,
maxdur=7,
dayborder=6
printsummary=TRUE,
boutdur.mvpa=10,
boutdur.lig=10,
boutdur.in=60,
mvpathreshold=104,
threshold.lig=57,
threshold.mod=104,
threshold.vig=104,
timewindow="MM")
```

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Other example:

```
GGIR(
datadir="D:/RAWDATA_GGIR",
outputdir="D:/GGIRDEC1",
mode = c(1:5),
idloc=2,
maxdur=7,
mvpathreshold=c(60,100.6),
threshold.lig=c(18,44.8),
threshold.mod= c(60,100.6),
threshold.vig=428.8,
boutdur.mvpa=10,
boutdur.in=60,
boutdur.lig=10,
timewindow="MM")
```

- GGIR(— necessary, tells R to use GGIR package
- mode — Specify which of the five parts need to be run; 1:5 makes that the whole GGIR pipeline is run
- idloc — how to name (ID) each participant. Putting 2 means that it will read the filenames and call each participant whatever comes before an underscore (_)
- maxdur — Max number of days we want to analyze
- mvpathreshold, threshold.lig, threshold.mod, threshold.vig — Acceleration thresholds for mvpa, lpa, mpa, and vpa
- boutdur.mvpa, boutdur.in, boutdur.lig — Required duration for a bout of mvpa or inactivity or lpa to be extracted
- timewindow — What is considered a day? MM = midnight to midnight (calendar day)

35

INTERPRETING GGIR OUTPUT

36

What will output from running base code:

- Part 2 Day Summary = PA levels for each day for each participant
- Part 2 Summary = summary of PA levels for each participant over the entire wear duration (i.e., ~7 days)
- Part 4 night summary sleep= summary of sleep for each night for each participant
- Part 4 summary sleep = summary of overall sleep for each participant

37

Where is the output?

- The same place you specified in code in `outputdir`

38

Where is the output?

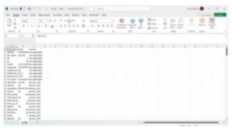
- The same place you specified in code in `outputdir`

39

Meta folder

40

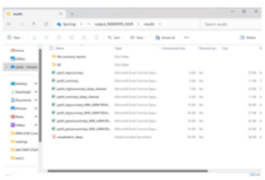
Configuration file



Essentially shows all the values used for all input options, including default values

41

RESULTS FOLDER



42

File summary reports

43

Results files:

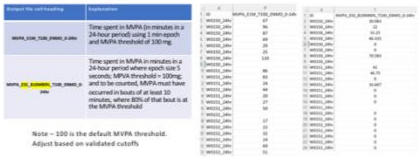
- For full interpretation, see data dictionary

44

Part2_daysummary

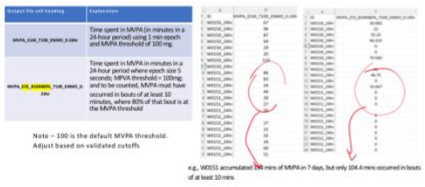
45

Part2_daysummary - Key results to look for (for 24hr movement guidelines:



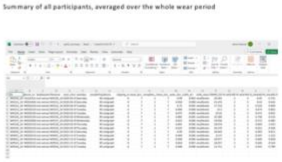
46

Part2_daysummary - Key results to look for (for 24hr movement guidelines:



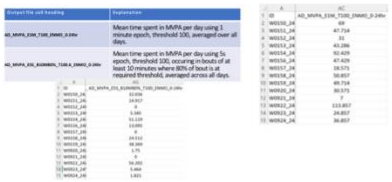
47

Part2_summary



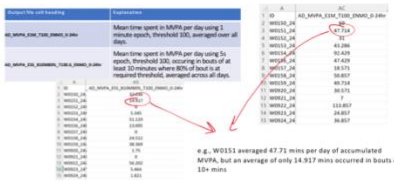
48

Part2_summary - Key results to look for:



49

Part2_summary - Key results to look for:

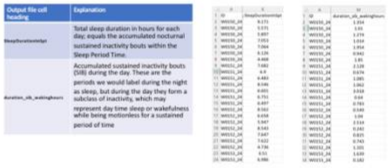


50

Part4_nightsummary_sleep_cleaned

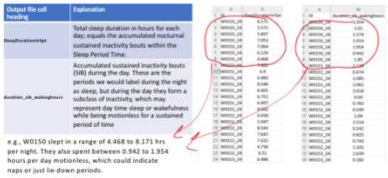
51

Part4_nightsummary_sleep_cleaned - Key results to look for (relevant to Canadian PA guidelines:



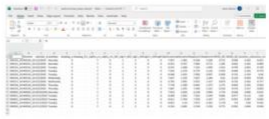
52

Part4_nightsummary_sleep_cleaned - Key results to look for (relevant to Canadian PA guidelines:



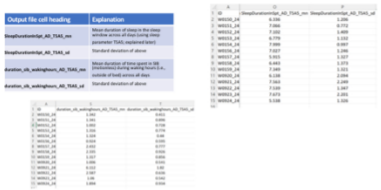
53

Part4_summary_sleep_cleaned



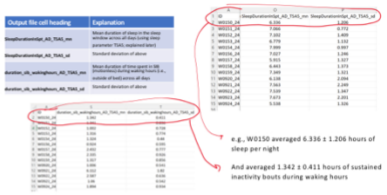
54

Part4_summary_sleep_cleaned - Key results to look for (for C24HMG):



55

Part4_summary_sleep_cleaned - Key results to look for (for C24HMG):



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Part 5 files:

Summarizes BOTH physical activity AND sleep data

- Part5_daysummary_MM_L40M100V400_T5A5
- Part5_daysummary_WW_L40M100V400_T5A5
- Part5_personsummary_MM_L40M100V400_T5A5
- Part5_personsummary_WW_L40M100V400_T5A5

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Part 5 files:

- Part5_daysummary_MM_L40M100V400_T5A5 "day" = data for every single day for each person (summary of all days)
- Part5_daysummary_WW_L40M100V400_T5A5
- Part5_personsummary_MM_L40M100V400_T5A5 "person" = average data across all days for each person
- Part5_personsummary_WW_L40M100V400_T5A5

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Part 5 files:

- Part5_daysummary_MM_L40M100V400_T5A5 MM = a day is considered Midnight to Midnight (this is what we want)
- Part5_daysummary_WW_L40M100V400_T5A5
- Part5_personsummary_MM_L40M100V400_T5A5 WW = a day is considered as the period from Waking to Waking (so a "day" could be +/- 24 hrs)
- Part5_personsummary_WW_L40M100V400_T5A5

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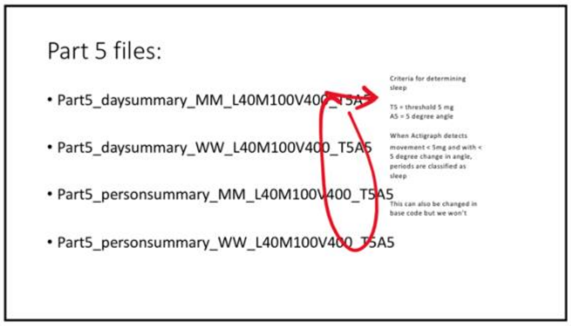
Part 5 files:

- Part5_daysummary_MM_L40M100V400_T5A5 Acceleration thresholds for light (L), moderate (M), and vigorous activity

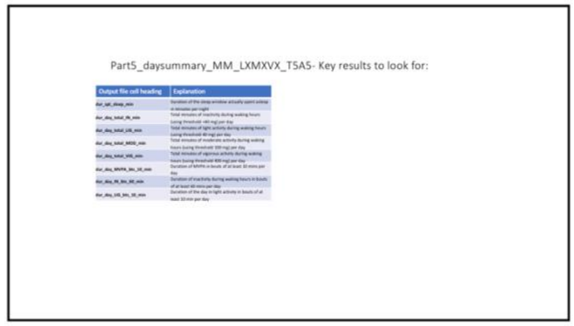
  In this example:
  L = 40 mg
  M = 100 mg
  V = 400 mg

  These can be changed by altering base code
- Part5_daysummary_WW_L40M100V400_T5A5
- Part5_personsummary_MM_L40M100V400_T5A5
- Part5_personsummary_WW_L40M100V400_T5A5

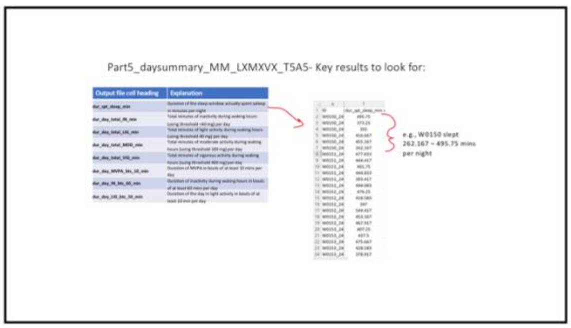
60



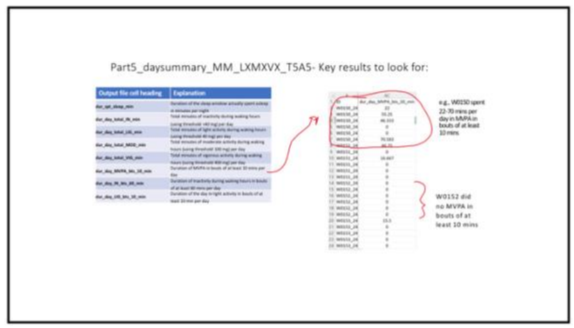
61



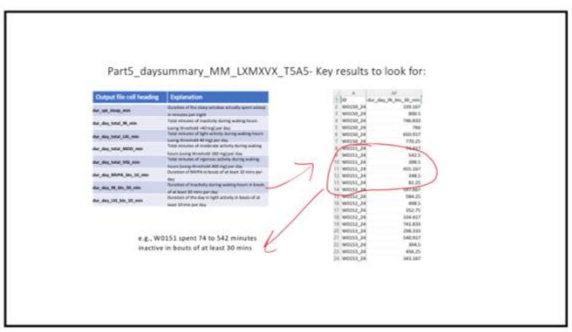
62



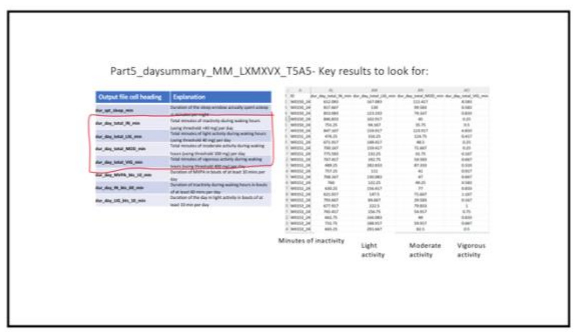
63



64



65



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sleepreg from GGIR

```
SRI_from_GGIR(outputdir = c(),
              alloutdir = c(),
              use.naps = TRUE,
              use.WASO = TRUE,
              use.miscal = TRUE,
              use.GGIRnonwear = TRUE,
              use.customnonwear = FALSE,
              nonWearInGGIRsleep = TRUE,
              wr.SWV = TRUE,
              wr.raster = TRUE,
              minSRIdays = 5)
```

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Appendix C: Frailty Index

Frailty Index - Version 11 (Final Version)

Number	Domain	Tool used in WARM Hearts	Variable	Cut Offs	References	Comments
1	Physical	Hand Dynamometer	Grip Strength	[BMI ≤ 23, 1=≤ 17 kg, 0=>17 kg], [BMI 23.1-26, 1=≤ 17.3 kg, 0=>17.3 kg], [BMI 26.1-29, 1=≤ 18 kg, 0=>18 kg], BMI >29, 1=≤21 kg, 0=>21 kg]	Fried (2001)	Stratified by BMI
2	Physical	Seniors Fitness Test	Chair Stand	[Age 50-64: 1=<12, 0=≥12], [Age 65-69: 1=<11, 0=≥11], [Age 70-74: 1=<10, 0=≥10], [Age 75-79: 1=<10, 0=≥10], [Age 80-84: 1=<9, 0=≥9], [Age 85-89: 1=<8, 0=≥8], [Age 90-94: 1=< 4, 0=≥ 4]	Rikli & Jones (2002)	Stratified by Age
3	Physical	5 M Gait Speed Test	Gait Speed	[Height ≤ 159 cm - 1=≤ 0.76 m/s, 0=>0.76 m/s], [Height >159 cm - 1=≤ 0.65 m/s, 0=>0.65 m/s]	Fried (2001)	Stratified by Height
4	Physical	Paffenbarger PA Questionnaire	Self-Report PA	1= < 270 kcal/week, 0= ≥ 270 kcal/week	Fried (2001)	
5	Physical	Seniors Fitness Test	Arm Curls	[Age 50-64: 1=<13, 0=≥13], [Age 65-69: 1=<12, 0=≥12], [Age 70-74: 1=<12, 0=≥12], [Age 75-79: 1=<11, 0=≥11], [Age 80-84: 1=<10, 0=≥10], [Age 85-89: 1=<10, 0=≥10], [Age 90-94: 1=<8, 0=≥8]	Rikli & Jones (2002)	Stratified by Age
6	Physical	Seniors Fitness Test	Back Scratch	[Age 50-64: 1=<-3, 0=≥-3], [Age 65-69: 1=<-3.5, 0=≥-3.5], [Age 70-74: 1=<-4.0, 0=≥-4.0], [Age 75-79: 1=<-5, 0=≥-5], [Age 80-84: 1=<-5.5, 0=≥-5.5], [Age 85-89: 1=<-7, 0=≥-7], [Age 90-94: 1=<-8, 0=≥-8]	Rikli & Jones (2002)	Stratified by Age
7	Physical	Seniors Fitness Test	Sit and Reach	[Age 50-64: 1=<-0.5, 0=≥-0.5], [Age 65-69: 1=<-0.5, 0=≥-0.5], [Age 70-74: 1=<-1, 0=≥-1], [Age 75-79: 1=<-1.5, 0=≥-1.5], [Age 80-84: 1=<-2, 0=≥-2], [Age 85-89: 1=<-2.5, 0=≥-2.5], [Age 90-94: 1=<-4.5, 0=≥-4.5]	Rikli & Jones (2002)	Stratified by Age
8	Physical	Seniors Fitness Test	8Ft Up and Go	[Age 50-64: 1=>6.0, 0=≤6.0], [Age 65-69: 1=>6.4, 0=≤6.4], [Age 70-74: 1=>7.1, 0=≤7.1], [Age 75-79: 1=>7.4, 0=≤7.4], [Age 80-84: 1=>8.7, 0=≤8.7], [Age 85-89: 1=>9.6, 0=≤9.6], [Age 90-94: 1=>11.5, 0=≤11.5]	Rikli & Jones (2002)	Stratified by Age
9	Physical	Seniors Fitness Test	6 Min Walk Test	[Age 50-64: 1=<498.35, 0=≥498.35], [Age 65-69: 1=<457.20, 0=≥457.20], [Age 70-74: 1=<438.91, 0=≥438.91], [Age 75-79: 1=<397.76, 0=≥397.76], [Age 80-84: 1=<352.04, 0=≥352.04], [Age 85-89: 1=<310.90, 0=≥310.90], [Age 90-94: 1=<251.46, 0=≥251.46]	Rikli & Jones (2002)	Stratified by Age

11	Weight	Tape Measure	Waist Circumference	1=>88 cm, 0=≤ 88 cm	Kehler (2020)	
12	Body Comp	InBody	Fat Mass (kg)	1=<18.2 or ≥36.1, 0=18.2-36.099	Kehler (2020)	
13	Body Comp	InBody	Fat-Free Mass (kg)	1=<40.9, 0.75=40,9-<43.3, 0.50=43.3-<45.8, 0.25=45.8-<49.3, 0=≥49.30	Kehler (2020)	
14	Mood/Depression	PHQ-9	PHQ-9 Score	1=20-27 (severe), 0.80=15-19 (moderately severe), 0.60=10-14 (moderate), 0.40=5-9 (mild), 0.20=1-4 (minimal), 0=0 (none)	Kroenke (2001)	
15	Mood/Depression	"Medical Conditions"	Clinical Diagnosis of Depression/ Anxiety	1=yes, 0=no		
16	Cognition	MoCA	MoCA	1= ≤ 25, 0= ≥ 26	Nasreddine (2006)	
17	Nutrition	Self-Report Questionnaire	Unintentional Weight Loss	1=yes, 0=no	Fried (2001)	
18	Nutrition	Self-Report Questionnaire	Decline in Food intake	1=yes, 0=no	Reber (2019)	
19	Nutrition/QOL	SCREEN II	Is biting or chewing food difficult for you?	1=Often or always, .6666=Sometimes, .3333=Rarely, 0=Never		
20	Nutrition/QOL	SCREEN II	Do you have any problems getting your groceries?	1=Always, .6666=Often, .3333=Sometimes, 0=Never or Rarely		
21	Exhaustion	CES-D	Feel everything was an effort	1=Most (3), .6666=Moderate (2), .3333=Sometimes (1), 0=Rarely (0)	Fried (2001)	
22	Exhaustion	CES-D	Could not "get going"	1=Most (3), .6666=Moderate (2), .3333=Sometimes (1), 0=Rarely (0)	Fried (2001)	
23	Quality of Life	EQ-5D-5L	Mobility	1=Extreme, 0.75=Severe, 0.50=Moderate, 0.25=Slight, 0=None	Janssen (2008)	
24	Quality of Life	EQ-5D-5L	Self-Care	1=Extreme, 0.75=Severe, 0.50=Moderate, 0.25=Slight, 0=None	Janssen (2008)	`
25	Quality of Life	EQ-5D-5L	Usual Activities	1=Extreme, 0.75=Severe, 0.50=Moderate, 0.25=Slight, 0=None	Janssen (2008)	
26	Quality of Life	EQ-5D-5L	Pain/Discomfort	1=Extreme, 0.75=Severe, 0.50=Moderate, 0.25=Slight, 0=None	Janssen (2008)	
27	Quality of Life	EQ VAS	Rate Health today	1-(EQ-VAS score/100)	Janssen (2008)	
28	Comorbidities	"Medical History"	Diabetes	1=yes, 0=no	Kehler (2017)	
29	Comorbidities	"Medical History"	Arthritis	1=yes, 0=no	Kehler (2017)	
30	Comorbidities	"Medical History"	Sleep Apnea	1=yes, 0=no	Kehler (2017), Kehler (2020)	
31	Comorbidities	"Medical History"	Cancer	1=yes, 0=no	Kehler (2017)	
32	Comorbidities	"Medical History"	IBD	1=yes, 0=no		

33	Comorbidities	"Medical History"	Asthma	1=yes, 0=no	Kehler (2020)	
34	Lab Values	Blood Pressure	Resting Systolic BP	1= <90 or >140 mmHg, 0= 90-140 mmHg	Kehler (2020)	
35	Lab Values	Blood Pressure	Pulse Pressure	1= <30 or >60 mmHg, 0= 30-60 mmHg	Kehler (2020)	
36	Lab Values	Heart Rate Monitor	Resting HR	1= <60 or >99 bpm, 0= 60-99 mmHg	Kehler (2017), Kehler (2020)	
37	Lab Values	Blood Draw	Glucose (Fasting)	1=<3.9 or >6.1 mmol/L, 0=3.9-6.1 mmol/L	Kehler (2017), Kehler (2020)	
38	Lab Values	Blood Draw	Total Cholesterol	1= > 6.2 mmol/L, 0= ≤ 6.2 mmol/L	Kehler (2020)	
39	Lab Values	Blood Draw	Triglycerides	1= ≥ 1.67 mmol/L, 0= <1.67 mmol/L	Kehler (2020)	
40	Lab Values	Blood Draw	HDL Cholesterol	1= < 1.03 mmol/L, 0= ≥ 1.03 mmol/L	Kehler (2020)	
41	Lab Values	Blood Draw	LDL Cholesterol	1= <0.98 or >3.36 mmol/L, 0= 0.98-3.36 mmol/L	Kehler (2020)	
42	Sleep Quality	PSQI	PSQI	1=5-21, 0=0-4	Tsai (2005)	
43	Medications	# of Medications	# of Medications	1=≥5, 0=0-4		