THE ASSOCIATION BETWEEN SEDENTARY BEHAVIOUR, MODERATE-VIGOROUS PHYSICAL ACTIVITY AND FRAILTY

by

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Dedication

To my father, for teaching me that when preparation meets opportunity, the sky is no longer the limit.

To my mother, who raised me with compassion, intelligence and determination. You knew I could well before I did. This is ours.

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Abstract

Background: As societies age, the health of their older people is a growing concern. Poor health is common in many older adults, whose high levels of chronic diseases and inability to function independently often result in high levels of frailty. One possible intervention to delay, avoid and manage frailty is physical activity. Frail older adults tend to be more inactive than non-frail individuals of the same age. Even so, it is necessary to examine whether the accumulation of physical activity is different across levels of frailty so that we understand where we need to target interventions. Additionally, research on physical activity and adverse health outcomes has focused mostly on moderate-vigorous intensity activity (MVPA; e.g. exercise). Previous studies have shown that sedentary behaviour is independently associated with various health outcomes such as cardiovascular problems, metabolic risk, depression and obesity. Even so, the direct association between frailty and sedentary behaviour has not yet been studied.

Objective: The purpose of the thesis was to examine the association between sedentary behaviour, MVPA and frailty. The specific objectives were to (1) examine whether the frailty index and phenotype demonstrate common characteristics of frailty scales, (2) examine the association between each definition of frailty and adverse health outcomes including disability, self-reported health, and healthcare utilization, (3) examine how sedentary behaviour and MVPA are each experienced during the day across different levels of frailty, (4) estimate and compare the extent to which high levels of sedentary behaviour and low levels of MVPA are associated with increased frailty and other domains of health including self-reported health, disability and healthcare utilization.**!**

Methods: This cross-sectional study examined adults aged 50+ from the 2003-2006 National Health and Nutrition Examination Survey. Frailty was measured both with the frailty index and the frailty phenotype. Sedentary behaviour and MVPA were measured using ActiGraph accelerometers. Descriptive statistics were used to compare measures of frailty. Relationships between frailty and physical activity patterns were evaluated with analysis of variance. Logistic and linear regressions were used to examine associations between sedentary behaviour, MVPA, frailty and other adverse health outcomes.

Results: The frailty index and the frailty phenotype each confirmed previously established characteristics of frailty scales. Even so, the frailty index may be a more sensitive measure of frailty due to its ability to discriminate at the lower to middle end of the frailty continuum. The overall sample engaged in about 8.5 hours of sedentary behaviour each day, with frail individuals being more sedentary than non-frail individuals. High sedentary behaviour and low MVPA were independently associated with higher levels of frailty, poor self-reported health, high ADL disability and higher healthcare usage.

Conclusions: Many people over the age of 50, and most of those who are frail, are highly sedentary with very few meeting the recommended weekly levels of MVPA. Despite this, sedentary behaviour and MVPA were independently associated with frailty and adverse health outcomes in middle to older aged adults. Future research should focus on a longitudinal study to determine the temporal relationship between sedentary behaviour and frailty.

List of abbreviations used

ACAPI	Audio Computer Assisted Self Interview (ACASI)
ACSM	American College of Sports Medicine
ADL	Activity of Daily Living
ANOVA	Analysis Of Variance
BMI	Body Mass Index
CDC	Centers for Disease Control
CHMS	Canadian Health Measures Survey
CI	Confidence Interval
CPAG	Canadian Physical Activity Guidelines
EQ	EuroQol
FI	Frailty Index
FRAIL scale	Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight
IADL	Instrumental Activity of Daily Living
IBM SPSS	International Business Machines Statistical Package for the Social Sciences
METS	Metabolic equivalents
MVPA	Moderate-Vigorous Physical Activity
NHANES	National Health and Nutrition Examination Survey
NHP	Nottingham Health Profile
OR	Odds ratio
PEI	Prince Edward Island
RAND	Research ANd Development
SAS	Statistical Analysis Software
SE	Standard Error
SF36	Short Form 36
TV	Television
UK	United Kingdom
US	United States

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Chapter 1. Introduction

As societies age, the health of their older people is a growing concern [1]. The impact on the healthcare system is forecast to increase significantly, especially now that the baby boomers have begun to reach 65 years of age [2]. Poor health is common in many older adults, whose high levels of chronic diseases and inability to function independently often result in high levels of frailty [3-5]. Conceptually, frailty is the state of increased vulnerability to adverse health outcomes, which is the result of an age-associated decline in multiple physiological systems [6-8]. Two commonly used measures to operationalize frailty are the frailty phenotype, which proposes frailty as a syndrome and the frailty index, which sees frailty as a state arising from deficit accumulation [9]. Previous studies have shown that a higher frailty score is associated with increased risk of falls, fractures and disability [10], poor health status [11], and a greater risk of mortality [12,13].

The benefits of physical activity have been primarily linked with increased physical resiliency [14-16], decreased disability [4,5,17], decreased chronic disease [18-20] and decreased frailty [21-24]; though research on frailty and physical activity remains limited. The arrival of the information age has resulted in decreased overall physical activity and increased sedentary behaviour [25-27] - behaviours that involve very limited energy expenditure such as sitting or lying down. These behaviours are especially common in older adults: older adults are the most sedentary age group, spending over 60% of their waking time sedentary [28,29]. The majority of research on sedentary behaviour has used measures such as self-report or TV viewing that do not fully capture levels of sedentary behaviour [30-36]. Accelerometers have emerged as an objective and reliable measure of physical activity that bypasses many of the limitations of self-reported data [37-41].

Research on physical activity and adverse health outcomes has focused nearly completely on moderate-vigorous intensity activity (e.g. exercise). Although many individuals may meet the 150 minutes/week recommendation for moderate-vigorous physical activity, they still spend the rest of their day in sedentary behaviours such sitting at a desk, driving, watching TV, etc. [42]. Previous studies have shown that sedentary behaviour is associated with various health outcomes such as cardiovascular problems, metabolism, depression and obesity [25,43-45]. This association remains, although attenuated, when levels of moderate-vigorous activity are considered [46-48]; in individuals who meet the recommended level of moderate-vigorous physical activity, sedentary behaviour is still associated with adverse health outcomes [44]. Even so, the direct association between frailty and sedentary behaviour has not yet been studied.

This thesis examined the association between sedentary behaviour, moderate-vigorous physical activity (measured with accelerometers) and frailty. Secondary associations between sedentary behaviour, moderate-vigorous physical activity and other measures of health including healthcare utilization, disability and self-reported health were also examined, as they are known indicators of individual health [49-51]. The thesis is divided into a background review (chapter 2), objectives (chapter 3), two manuscripts (chapters 4 and 5) and a general conclusion (chapter 6). The background review examines previous findings on frailty, levels of physical activity and associated adverse outcomes. The first manuscript describes the construction of a modified frailty phenotype and a frailty index for a US population over the age of 50, in the National Health and Nutrition Examination Survey (NHANES) and examines both their properties and the degree of convergence between the two measures. The second manuscript examines the association between physical activity and frailty including patterns of physical activity among frailty groups and the relationships between sedentary behavior, moderate-vigorous physical activity and adverse health outcomes. The concluding chapter summarizes the findings, considers strengths and limitations, and discusses the implications for both future research and policy.

Chapter 2. Background[1]

2.1 Health of the aging population

As the baby boomers begin to reach 65 years of age, the demographic distribution of the world's population continues to shift. The proportion of Canadian adults above the age of 65 has increased in the past 5 years, reaching nearly 15% of the country's population- 5 million Canadians- in the 2011 Census [(1)]. In the Maritimes, the proportion of seniors in Nova Scotia, New Brunswick and PEI are the highest in Canada at 16.5%, 16.2% and 15.8% respectively [(2)]. These growing numbers have caused many societies and governments to commission reports on the potential consequences [(52-54)]. The Government of Nova Scotia [(55)] and the Federation of Canadian Municipalities [(56)] estimated that adults over the age of 65 would make up approximately one quarter of the total population by 2036.

Whereas some older adults age successfully and meet or exceed life expectancy, many others experience a lower quality of life, and a higher proportion of chronic diseases [(3-5,57)], which inhibit their ability to function independently. Ninety-one percent of older adults have at least one chronic health condition and 50% have five chronic illnesses or more [(58)]. Chronic diseases are the leading cause of death in Canada [(15)]; an estimated 153 000 Canadians die each year due to one of the four main types: cardiovascular disease, cancers, pulmonary disease and diabetes [(17)]. The management of these chronic diseases places a heavy burden on Canada's healthcare system, yet Canada is not alone in the chronic disease epidemic; a report by the World Health Organization concludes that chronic disease is the leading cause of death worldwide [(59)]. While chronic diseases have often been used to quantify population and individual health, many other reliable health measures are also used. Individual health status is better regarded as a continuous measure that varies on a scale from full health to extreme illness [(60)]. A wide variety of health measurements capture this scaling issue of health, most commonly a) self-reported health [(19,61-64)], b) healthcare utilization c) disability scores [(24,30,31,65,66)]; and

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[1] Note that sections 2.2-2.7 of this chapter have been accepted as part of a review for publication in *Reviews in Clinical Gerontology (June 2014). See Appendix A (pg113) for Copyright Release Form.*

d) validated health outcome instruments [18,20,60,67].

Self-reported health is an easy and cost-effective way to measure health; however it has been controversial in its validity and reliability. Studies have demonstrated that self-reported health is not comparable across countries [42,68,69], gender [68-70], race [71], age [61] or education level [71]. Healthcare utilization has also been used as a measure of health, although it does not capture the actual health of the individual; it captures how frequently people use healthcare, for which health status is only one factor. Many health outcome instruments measure one area of health such as the RAND Social Health battery [72], the Beck Anxiety inventory [73], the Hamilton Depression Rating Scale [74], the Modified Mini-Mental State test [24] or the Barthel Activities of Daily Living Index [75] among others. Such measures do not adequately represent or measure the overall health status of an individual, as they do not encompass all aspects of health; this is something that has been stressed for decades [76]. An individual may not have extremely poor health in one specific measure but instead the additive effect of lower health levels across domains may yield poor overall health. Examples of measures that do encompass a wide range of health considerations include the Nottingham Health Profile (NHP) [77], the EuroQol EQ-5D Quality of Life Scale [78], the Health Utilities Index [79] and the Medical Outcome Study Short Form 36 (SF36) [80]. The strengths of these measures are their simplicity, sensitivity and wide coverage, yet they have not always been reliable in predicting adverse outcomes, specifically in predicting mortality or morbidity [81-83].

Another health approximation that encompasses many different domains of health is the frailty index, which quantifies one's level of health from extremely fit to managing well, vulnerable, mildly frail, moderately frail and eventually severely frail. It has been used to quantify the health status of younger individuals however it is most widely used in geriatric research where it has emerged as a useful tool to capture the frailty level both at a population and an individual level [8,12,84-86].

2.2 Defining and measuring frailty

Frailty is a term that has seen increasing use over the past two decades. Frail people have an increased vulnerability to adverse health outcomes, that is the result of an age-associated decline in multiple physiological systems [6,8,87,88]. The two most commonly used approaches to frailty differ in that Fried et al. [87] view frailty as a syndrome, while Rockwood and colleagues [6,8,89] see it as a state. Fried et al. [87] propose a continuous cycle of frailty arising with chronic malnutrition, sarcopenia (the loss of muscle mass and strength), poor resting metabolic rate and poor total energy expenditure. Fried et al. [87] suggest there is no single cause, but instead many different factors play a role in the emergence of each other, so that frailty can arise from any point in the cycle. The accumulation of deficits approach [89] sees frailty as a state that arises when damage (either environmental or intrinsic, the latter largely arising as byproducts of metabolism) goes either unrepaired or unremoved, resulting in deficits that affect the ability to repair damage [6,90]. Frailty is thus seen as a dynamic process of deficit accumulation; these deficits arise first at a subcellular level before consequently affecting tissues, organs and function [91,92]. A wide variety of deficits are associated with frailty, so that many different stochastic pathways lead to the multiply determined state of increased vulnerability. The deficit accumulation approach likewise recognizes grades of frailty.

Both approaches recognize that frail individuals are at greater risk of adverse health outcomes such as death, disability, and increased healthcare utilization including both hospitalization and institutionalization [9,87,93]. Being able to identify who is at increased risk of adverse outcomes can be very beneficial, consequently a lot of research has focused on the operational definitions of frailty [4,94-97]. The frailty phenotype and the frailty index are the two that have generated the most consideration [98], and are based on the syndrome versus state models respectively. Other operational definitions of frailty include the Groningen Frailty Indicator [99], the Tilburg Frailty Indicator [100], the Clinical Frailty Scale [101], the Edmonton Frailty Scale [102]and the FRAIL scale [103].

The most commonly used working definition of frailty was created by Fried et al. [87] by evaluating the prevalence, correlation and validity of their operational definition in relation to its ability to predict adverse outcomes including worsening mobility, increased disability, increased falls, hospitalization and death. They identified five features that correspond with frailty: unintentional weight loss, low energy, slow gait, reduced grip strength and reduced physical activity. Frailty was defined as being present when any three of the five criteria were met, whereas meeting only one or two of the criteria suggested that the individual was at a higher risk of becoming frail, and was labeled as "pre-frail" [87]. The Fried frailty phenotype, though widely cited, has also been subject to criticism, mainly on grounds of poor generalizability and limited clinical utility [104-107]. The phenotype does not include consideration of cognition despite a known association with functional decline [108]. An important but somewhat overlooked criticism is that the frailty phenotype may not be applicable to all individuals at increased risk. In the cohort in which the phenotype was developed, Fried et al. [87] excluded individuals with moderate to severe cognitive impairment, those with a history of Parkinson's disease or stroke as well as those taking antidepressants, thus there is some uncertainty surrounding the generalizability of the frailty phenotype to those individuals [109]. Although the phenotype can identify those who are at high risk of becoming frail, it discriminates less well between those who are fit and those who are at lower or moderate risk of becoming frail [110,111] and excludes many people who cannot participate in performance testing, but who remain at higher risk [112,113].

In the frailty index, proposed by Rockwood and Mitnitski [6,89,114], health deficits are counted, such that the higher the number of deficits relative to all deficits considered, the frailer the individual [115,116]. Since its introduction in 2001, multiple groups around the world have used frailty indexes, constructed with a variety of different deficits [12,85,86,117-119]. Notably, the original frailty index meets a number of properties that appear independent of its construction. For example, as long as key criteria are met (see below), the frailty index has a characteristic distribution in community dwelling samples (right skewed) [120] and in clinical samples (closer to a normal distribution) [121]. Similarly, at any age, the mean values of the frailty index are higher in women than in men, whereas for any given level of the frailty index, mortality is higher in men [93]. The reproducibility of frailty across different frailty indexes suggests the number of deficits present, perhaps even more than their nature, is key, at least at the group level. While one study considers 40 variables for a frailty index, a separate study can consider 60 different variables and would yield similar frailty index findings. The index is considered to be both a sensitive measure of frailty as well as a reliable predictor of poor health outcomes [8,122]. The graded frailty index allows for dose-response relationships to be evaluated [84,123]. The greatest strengths of the frailty index are its ability to be created for nearly any dataset and its mathematical properties. The frailty index has also been used to quantify the health of younger populations as early as 15 years of age [120].

Searle et al. [116] outlined a standard protocol for creating a frailty index for any dataset. The frailty index is calculated as a ratio of deficits present out of the total number of possible deficits, giving a continuous score from total fitness to total frailty. For example, if 50 deficits are considered in a given frailty index and a patient has 10; the patient will have a frailty score of 0.2. Five criteria should be satisfied for a deficit to be included in a frailty index: the deficit should be related with health status, the deficit should become more prevalent with increasing age, the deficit should not saturate too early, the deficits should cover a range of systems and finally if a frailty index is to be compared for the same individual, the deficits used should be the same. Ideally, a minimum of 30 to 40 variables should be included in the frailty index [5,93,116]; the more variables included, the more precise the score will be [116]. It is not yet known if there is an upper limit or an optimal number of variables to be included. The overall validity and reliability of the frailty index is shown in its ability to predict death, health status, chronic disease outcomes, health decline and healthcare utilization [6,93,124,125].

2.3 Defining physical activity and sedentary behavior

As frailty is often associated with a loss of physical resiliency [95], this is an avenue relevant to prevention that warrants pursuit. First, it is important to define the constructs. *Physical activity* is defined as "any bodily movement produced by skeletal muscles that requires energy expenditure" [59], and can be differentiated by both type and intensity. Exercise, leisure activity and occupational activity are all examples of types of physical activity. *Exercise* is physical activity that is planned or structured with the objective of increasing or maintaining physical fitness [126]. Energy expenditure is often measured in METS or metabolic equivalents, as a measure of how hard the body is working. The more strenuous the activity is, the more oxygen the body must use for energy and thus the higher the MET level. A MET level of 1.0 is considered to be the reference level of an individual at rest [127]. Vigorous intensity activity refers to physical activity in which the individual exerts 6 METS or more. *Vigorous intensity* activities include running, swimming, bicycling >10km/hour, hiking uphill among others [81,128]. *Moderate intensity* activity refers to physical activities in which the individual exerts between 3 and 6 METS, such as brisk walking, water aerobics, bicycling <10km/hour or gardening [81,128]. Finally, *light intensity* activity refers to physical activities in which the individual exerts between 1.5 and 3 METS; examples of this are light walking, stretching, fishing or leisurely sports such as table tennis or playing catch [81,128]. See Figure 2.1.

The definition of *sedentary behaviour* has varied and as a result, measurement of sedentary behavior has been inconsistent. Operationally, sedentary behaviour has been defined as any waking activity characterized by an energy expenditure of less than 1.5 METS in a sitting or reclining position [42,128-131]. Common sedentary behaviors include watching TV, driving, screen time (video games, computers), and reading; essentially, anything done awake while sitting or lying down [128]. In the past, a number of studies have misconstrued sedentary behaviour- mostly defining it as a mere lack of moderate to vigorous activity [127,132]. For example, past research has defined sedentary behavior as levels of activity that fail to achieve the levels of moderate or vigorous physical activity [133], or those spending less than 2000 kcal·wk-1 through walking, climbing stairs and playing sports [134].

2.4 Associations between physical activity and frailty

The World Health Organization identified physical inactivity as the fourth leading risk factor for global mortality, after high blood pressure, tobacco use and high blood glucose [59]. There has also been a great deal of evidence surrounding its protective health benefits in the maintenance of physical resiliency [14,15,57,135]. Whereas lack of physical activity is known to be one of the major sources that lead to disability [4,5,17,136], there is also evidence of an inverse association between physical activity and frailty. Cruz-Jentoft et al. [137] demonstrated that physical activity could help slow down the age-related decline of muscle strength and muscle mass associated with frailty. Physical activity was also inversely associated with other components of frailty including physical disability [19,60,138-141], cognitive impairment [62,63], and depression [64,141]. Peterson et al. [24] examined the longitudinal relationship between physical activity and frailty, suggesting that physical activity had an independent, preventive effect against frailty as a whole; this effect held for both sexes and all ages. Despite this evidence on the positive impact of physical activity interventions on frailty, causality has yet to reliably established [30,31,65].

The recommendation that physical activity is beneficial for health is not novel; it has been repeatedly suggested for decades [18-20,60,66,67]. The Canadian Physical Activity Guidelines (CPAG) report that health benefits can be achieved by adults, aged 18 and older if they accumulate at least 2 1/2 hours of moderate to vigorous physical activity each week, in bouts of 10 minutes or more [142]. Hubbard et al. [143] found at 5 year follow up, older adults who exercised were more likely to improve their health status than those who did not. That study [143] also found that the more frail one was at baseline, the more likely they were to yield greater benefits. This relationship remained across all levels of frailty, suggesting the potential impact of exercise at the population level. Although it has been reported that greater health benefits can be obtained if the physical activity is of longer duration or more vigorous intensity [19,20,141], other studies have demonstrated that benefits can still be elicited with low to moderate activities [19]. The benefits of engaging in moderate-vigorous physical activity during daily life are well established, whereas the evidence on the importance of light activities and the harm of sedentary behaviors is limited.

2.5 Associations between sedentary behaviour and health

Research studies have examined the effect of sedentary behavior on a wide range of health domains such as body mass composition, cardiovascular disease, cancer and psychological disorders. Sedentary behavior has been identified as a risk factor for poor health, morbidity and mortality [23,43,45,68]. The odds of weight gain was higher in people whose daily sitting time was 8 hours or more per day compared to those who sat for less than 3 hours [144]. Similarly, a cross-sectional study demonstrated that the odds of being obese increased as weekly hours of TV viewing time increased [145]. TV viewing time and objectively measured sedentary behaviour with physical activity monitors were both associated with abnormal glucose tolerance [23,146], increased cardio-metabolic risk

[21,22,147,148], metabolic syndrome [146]and an increased risk of type 2 diabetes [149,150]. Increased risk of endometrial cancer in women and colon cancer in men were associated with high levels of TV watching [151,152], increased daily sitting time [152] and self-reported levels of sedentary behaviour [153]. Finally, a linear relationship was found between a sedentary index and the risk of developing a mental health disorder [154].

The relationship between sedentary behaviour and poor health outcomes persists even after controlling for moderate-vigorous activity. Camhi et al. [46] suggested higher levels of sedentary behaviour were associated with increased cardio-metabolic risk factors. Similarly, Healy et al. [44,47] found an association between high levels of sedentary behaviour and increased waist circumference, metabolic risks and risk for type II diabetes. Sedentary behaviour and all-cause mortality, independent of moderate-vigorous activity, were significantly associated in a population of men and women aged 45 to 75 years old [48]. One study proposed the 'Active Couch Potato' phenomenon in which there was a strong, significant dose-response association between TV watching time and waist circumference, systolic blood pressure and diabetes risk in a sample of men and women who reported at least 150 min a week of moderate-to-vigorous intensity physical activity-meeting the suggested guidelines [44].

Despite an abundance of research evaluating the effect of sedentary behaviour on an array of health outcomes, there is considerably less research on the effect of sedentary behaviour on aging and especially on frailty. Sedentary behaviors are particularly common in older adults, with evidence that older adults are the most sedentary age group [28,29]. In the 2003-2004 iteration of NHANES, the number of waking hours spent daily in sedentary behaviour increased in each 10 year age group from 7.24 hours at age 30-39, eventually reaching 9.28 hours at age 70-85 [28]. Dogra and Stathokostas [49] suggested that amongst 45-64 years old adults, those who were least sedentary were 43% more likely to age successfully than those who were most sedentary. Successful aging was measured using Rowe and Kahn's model of Successful Aging [155], which includes physical, psychological, and sociological components. This association had a dose-response relationship in older adults, aged 65 and above; those who were moderately sedentary were 38% more likely to age successfully and those who were least sedentary were 43% more likely. A short term association between decreasing sedentary activity and decreasing frailty has been proposed [156], with limited evidence suggesting exercise interventions and reduced sedentary behaviour can be used to either improve or maintain physical function and independence in frail, older adults [30,31,65,157,158]. The American College of Sports Medicine (ACSM) suggest that increasing physical activity may be more beneficial for frail people than any other intervention [30-32,159], however no recommendation currently exists about decreasing sedentary behavior.

There is little information about the temporal relationship between sedentary behavior and frailty. The Health, Aging and Body Composition study followed the physical activity of an older cohort for five years [24]. Exercise activities were independently associated with delaying the onset and progression of frailty. Even so, there was no association between differing amounts or intensities of physical activity and the odds of transitioning to frailty [24], suggesting that any level of activity and thus reduction of sedentary behavior could decrease the odds of becoming frail. This finding is particularly important for older and frailer individuals, who might not necessarily be able to participate in vigorous physical activities. Of note, however, the study relied on self-reports of physical activity, which has been criticized [160-162]. Furthermore, the use of a phenotypic definition of frailty does not allow the degree of frailty to be graded and thus there was no observation of a dose-response relationship.

2.6 Patterns of physical activity

The positive relationship between physical activity and health has resulted in increases in physical-activity related consumerism [69-71]. In 2012, the global health and fitness club industry alone generated nearly 76 billion US dollars [71]. Global health and wellness sales are expected to reach a record high of US$1 trillion by 2017 [70]. The number of fitness and health clubs in the United States increased from 26,830 in 2005 to 30 500 in 2012. These numbers are expected to rise further as shown by the increase in the number of fitness memberships from 41.3 million in 2005 to 50.2 million in 2012 [71].

Even so, the relationship between fitness club membership and population physical activity is not clear as the latter appears to have decreased [163]. The reduction in overall physical activity has been associated with an increased number of health problems and the obesity epidemic [68]. For many reasons, the decrease in many types of physical activity has been associated with an increase in sedentary behaviors [26,27,68]. This combination is thought to be due to the transition from work-related physical labor to more sedentary, deskbound jobs [26], the conversion from physical domestic chores to labor saving technology in the home [27], the availability of motorized travel as opposed to previous non-motorized travel [26] and finally the shift from physical leisure activities to passive entertainment such as TV, computers or other electronic devices [68]. The rate of physical activity in Americans has decreased by approximately 8.5% from 1955 to 2005 [144]. A UK National Travel Survey reported that the average person now walks 304km each year; this is 106km less than the average 25 years ago [164]. This decrease in walking likely parallels an increase in sedentary behaviour. James et al. [165] reported that urbanization in China has reduced daily energy expenditure by up to 600 calories over the past 40 years.

Whereas some individuals participate in very little physical activity overall, others demonstrate both high levels of moderate-vigorous physical activity and high levels of sedentary behaviour [42]. Many individuals engage in 30-60 minutes of vigorous physical activity once a day while remaining largely sedentary otherwise [23,166]. Figure 2.2A demonstrates a typical daily pattern of sedentary behaviour in which the individual engages in purposeful exercise upon waking before participating in more than 15 hours of sedentary behaviour. This includes sitting for meals, transportation to and from work, sitting at a desk at work and watching TV or some other form of evening relaxation [42]. Figure 2.2B demonstrates a typical daily pattern of an active individual, one who does not participate in moderate-vigorous activity, yet remains active throughout the course of the day by walking to and from work, working an active job such as groundskeeper, nurse or carpenter and through active relaxation- playing with children or going for a light walk.

2.7 Measuring physical activity and sedentary behavior

Studies have differed in their measurement of physical activity and sedentary behavior- both objective and subjective measures have been used and there are differences within these two categories as well. Studies, which used subjective questionnaires to examine the benefits of physical activity, asked individuals to report on their engagement in various activities-mainly higher intensity activities. These questionnaires did not include questions about light activities such as cooking or washing dishes or questions about sedentary behaviours such as watching TV and reading [127]. This approach to the measurement of sedentary behaviour and physical activity could lead to misclassification bias. For example, one person could engage in sedentary behaviours for 20% of the day and in light activities for the other 80% (similar to the pattern described in Figure 2.2B); whereas another person could engage in sedentary behaviour for 75% of the day, in light activities for 20% and finally in moderate-vigorous physical activity for the remaining 5% (similar to the pattern described in Figure 2.2A). A questionnaire that only includes moderate-vigorous activities could wrongly classify the first individual as sedentary and the second as active. Further, if the total METS of these people were calculated, the first person would be likely to have the higher daily energy expenditure [127].

To avoid misclassification in the exposure, sedentary behaviour needs to be defined and measured [47,127,129,166]. As detailed above, an individual who is sedentary is not to be confused with an individual who does not meet the physical activity guidelines or more specifically, who performs insufficient amounts of moderate to vigorous activity [128]. Self-report of sedentary behaviour has been widely used to measure sedentary behaviour, due to its feasibility and low cost. Some studies simply ask participants to report the duration of a sedentary behaviour such as watching TV [21,44,133,147] whereas other studies have used questionnaires developed to estimate levels of sedentary behaviours such as the 7-day Sedentary and Light Intensity Physical Activity Log [167] or the Sedentary Behaviour Questionnaire [168]. Levels of one specific type of sedentary behaviour such as TV watching, talking on the phone, lying on the couch or driving to work are often generalized to represent sedentary behaviour as a whole [21-23,44,144-147,149-153,169]. Although sedentary behaviour does encompass these activities, one behavioural measure alone does not comprehensively assess sedentary behaviour throughout the day. Technology-related sedentary behaviours such as TV watching or computer use are the most commonly used measures of sedentary behaviour. While TV viewing is the most prevalent sedentary behaviour, with the average American watching 2.8 hours per day, this constitutes less than 50% [170] of the time spent in a sedentary state. In consequence, more than 50% of sedentary behaviour would not be accurately captured if TV watching was used as a proxy measure for sedentary behaviour [171]. Measures like reading, lying on the couch, driving to work, etc. contribute to total sedentary behaviour even less than TV watching and thus may be even less reliable as a proxy for sedentary behaviour.

Using questionnaires to measure physical activity and sedentary behaviours has proven limitations. Klesges et al. [172] discovered that participants specifically tended to underestimate their level of sedentary behaviour and overestimate their aerobic activities by nearly 300%. In addition, there is not always coherence between self-reported and objectively measured sedentary behaviour using physical activity monitors such as accelerometers. Self-reports of physical activity in the NHANES dataset indicated that 60 to 63% of US adults between the age of 60 and 69 met the minimum US recommendations of physical activity [173,174]. However, objectively measured physical activity, using accelerometers, in the same dataset, indicated that only 9 to 26% of the designated population met the recommendations [174,175]. In short, self-report data may overestimate levels of physical activity; many factors could play a role in this. Social desirability bias is thought to contribute [161,176], as participants may intentionally provide false reports. There has also been evidence that sex [16] and weight can impact self-reporting of physical activity [177]. Difficulty recalling activities, cultural differences in interpretation and human error can influence self-reporting as well [162].

Accelerometers have emerged as useful instruments to measure levels of physical activity and sedentary behaviours. They provide an objective, reliable and accurate measure that overcomes many of the limitations of self-reported data [37-41]. Accelerometers measure the acceleration of an individual in specified planes [174] and can be used to describe how often and how long someone is sedentary in addition to the intensity, duration, frequency and patterns of movement [142,178]. Accelerometers have been used to measure physical activity and sedentary behaviours in both young [179] and older adults [180,181] and have consistently demonstrated a high degree of reliability in their measurement of physical activity, with very little variation over time [179,182]. Gardner and

Poehlman [183] compared doubly labeled water, the reference standard measurement of physical activity, with physical activity assessed by an accelerometer; the two measurements were highly correlated with an R of 0.83 and a p-value of less than 0.001. Doubly labeled water involves the ingestion of water labeled with isotopes of hydrogen and oxygen; as the body consumes energy, carbon dioxide and water are produced. Measuring these levels allows the exact total energy expenditure to be calculated [184].

Compared to other measures of physical activity such as self-report [185,186] and heart-rate measurements [187,188], accelerometers are more sensitive to the actual level of physical activity of the individual. The ongoing development of accelerometers has resulted in increased battery life and decreased cost leading to increased feasibility for use in epidemiologic studies [28,47]. Accelerometers can be worn around the wrist [189], thigh [190] or preferably the waist [142,189]. A 7 day accelerometer wear period is recommended in order to obtain reliable estimates of average behaviour [191], although others have suggested that a 5 day wear period is sufficient in older adults to obtain an accurate measure of average daily sedentary time [192]. While accelerometers can capture many different aspects of physical activity, they remain limited by their inability to capture the full energy expenditure of activities such as swimming (for non-water proof accelerometers) as well as walking, lifting weights or walking on an incline, as acceleration does not change under these conditions.

2.8 Frailty and physical activity in NHANES

2.8.1 United States National Health and Nutrition Examination Survey

The relationship between physical activity and health outcomes has been examined extensively in the National Health and Nutrition Examination Survey (NHANES). NHANES is a series of cross-sectional surveys that focuses on various population groups and health topics. The data provides information on the prevalence of major diseases, risk factors for these diseases, nutritional status, national standards for height, weight and blood pressure, etc. NHANES began in the 1960s, and in 1999 became a continuous study that examines a nationally representative sample each year. The survey combines both interviews and physical examinations. The interview portion includes demographic, socio-economic, dietary and other health related-questions, while the examination portion includes medical, dental and physiological measurements, as well as laboratory tests.

NHANES uses a complex statistical process to select the population sample to ensure that it is representative of the US population. Using the most up to date Census information, housing units are selected at random from pre-determined communities. These housing units are sent a letter introducing and explaining the study. NHANES interviewers subsequently approach these households to determine if they qualify to participate in the study. If the household is eligible, an in-home interview appointment is made followed by an examination appointment, which takes place at the Mobile Examination Center. All information collected is confidential and the privacy of all participants is protected. Participants receive a final report of test results as well as cash remuneration. All questionnaires, examination and laboratory components include information on a variety of different health measures. A complete list of topics can be found in Table 2.1. More sensitive topics that were considered inappropriate for the in-person questionnaire were covered with Audio Computer Assisted Self Interview (ACASI) questionnaires and included data on alcohol, bowel health, current health status, depression screen, drugs, kidney/urological health, pesticide use, physical activity, reproductive health, sexual behaviour, tobacco and volatile toxicants.

2.8.2 Physical activity in NHANES

NHANES collected objective data on physical activity using ActiGraph AM-7164 accelerometers. Objective physical activity data is only available in the 2003-2004, 2005-2006 and 2009-2010 (data not yet released) cohorts. Pregnant women, those taking insulin and those who were unable to walk were not given an accelerometer. Participants were instructed to wear the monitor on an elastic waist belt on the right hip, underneath the clothing during waking hours for 7 consecutive days. As the monitors were not waterproof, participants were instructed to remove the monitors during any bathing or swimming activities. The accelerometers do not display the data immediately and thus respondents were blind to the data collected while wearing the monitor. Participants returned the accelerometers by mail in postage-paid padded envelopes that were provided and received $40 remuneration.

The ActiGraph AM-7164 detects and records the intensity of a movement and stores this data according to one-minute time intervals known as epochs. To summarize the accelerometer data of each subject, NHANES researchers created a component variable, which examined if the activity monitor results were thought to be reliable based on a preliminary review of the raw data. Another variable noted if the monitor was still in calibration after the subject returned it. For each individual, there were 10 080 consecutive minute-by-minute data epochs that provided information on intensity value and step counts.

2.8.3 Frailty in NHANES

Although frailty was not directly measured in NHANES, a limited number of studies have identified frailty in the NHANES population. These studies used different operational definitions of frailty including slow gait speed [(193)], the Steverink-Slaets model [(194)] and the Puts model [(194)]. The majority of studies that examined frailty [(195-200)] in NHANES used a modified frailty phenotype proposed by Wilhelm-Leen et al. [(201)]. Wilhelm-Leen et al. [(201)] adhered to the five frailty domains established by the Fried et al. (2004) criteria, but customized it for use in the NHANES dataset. The five adapted criteria are as follows [(201)]:

- slow walking speed, defined as the slowest quintile adjusted for gender in a timed 8 foot walk .
- exhaustion, defined by "some difficulty", "much difficulty", or "unable to do" when asked how much difficulty they have "walking from one room to the other on the same level".
- low physical activity, defined as "less active" when asked "Compared with most (men/women) your age, would you say that you are more active, less active, or about the same?"
- grip strength , defined by "some difficulty, "much difficulty", or "unable to do" when asked how much difficulty they have "lifting or carrying something as

heavy as 10 pounds [like a sack of potatoes or rice]".

- unintentional weight loss , defined by BMI≤18.5 kg/m^2.

Beginning in 2003-2004, NHANES no longer assessed walking speed in individuals over the age of 50 and thus, Wilhelm-Leen et al.'s [201] frailty phenotype can no longer be used. No study has examined frailty in NHANES since the 2001-2002 dataset; as such, there is a need for a valid and reliable measure of frailty in the NHANES population. Previous studies, in other populations, have used modified 4-item versions of Fried et al.'s [87] phenotype that excluded gait speed [202,203]; these smaller versions of the phenotype were still able to accurately measure the construct of frailty. Furthermore, no previous studies have identified frailty in NHANES using the frailty index approach.

Tables

Individual level questionnaire:

- acculturation;
- allergy;
- audiometry;
- blood pressure;
- cardiovascular disease;
- demographics;
- dermatology;
- diabetes;
- dietary supplements;
- prescription medication
- dietbehavior;
- nutrition;
- early childhood;
- health insurance;
- hospitalization and access to care;
- immunization;
- kidney conditions;
- medical conditions;
- occupation;
- oral health, osteoporosis;
- physical activity and physical fitness;
- physical functioning;
- respiratory health and disease;
- sleep disorders;
- smoking and tobacco use;
- social support;
- vision;
- weight history

Family questionnaire:

- demographics;
- occupation;
- food security;
- housing characteristics;
- income;
- smoking;
- future contact information.

Examination component:

- audiometry;
- body composition;
- body measurements;
- cardiovascular fitness;
- ophthalmology;
- oral health;
- physical activity monitor;
- physician's exam and vision

Laboratory component:

- blood&urine;
- venipuncture;
- urine collection;
- bone markers;
- diabetes profile;
- infectious disease profile;
- laboratory assays;
- kidney disease profile;
- nutritional biochemistries &hematologies;
- STD profile;
- tobacco use;
- blood lipids.

Table 2.1 List of content of questionnaires, examination and laboratory components in the NHANES 2003-2004 and 2005-2006 datasets

Figures

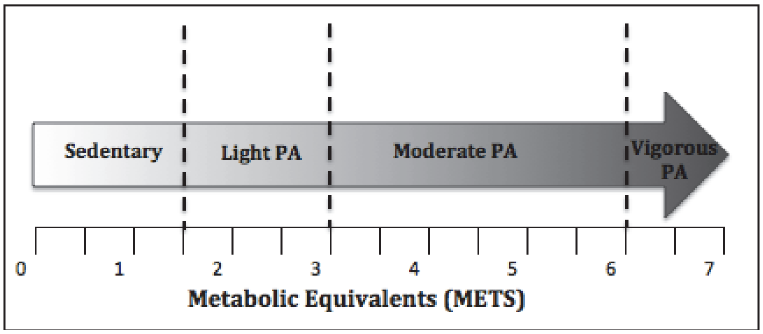

Figure 2.1. The energy expenditure continuum. *Adapted from Sedentary Behaviour Research Network, 2012* [147].

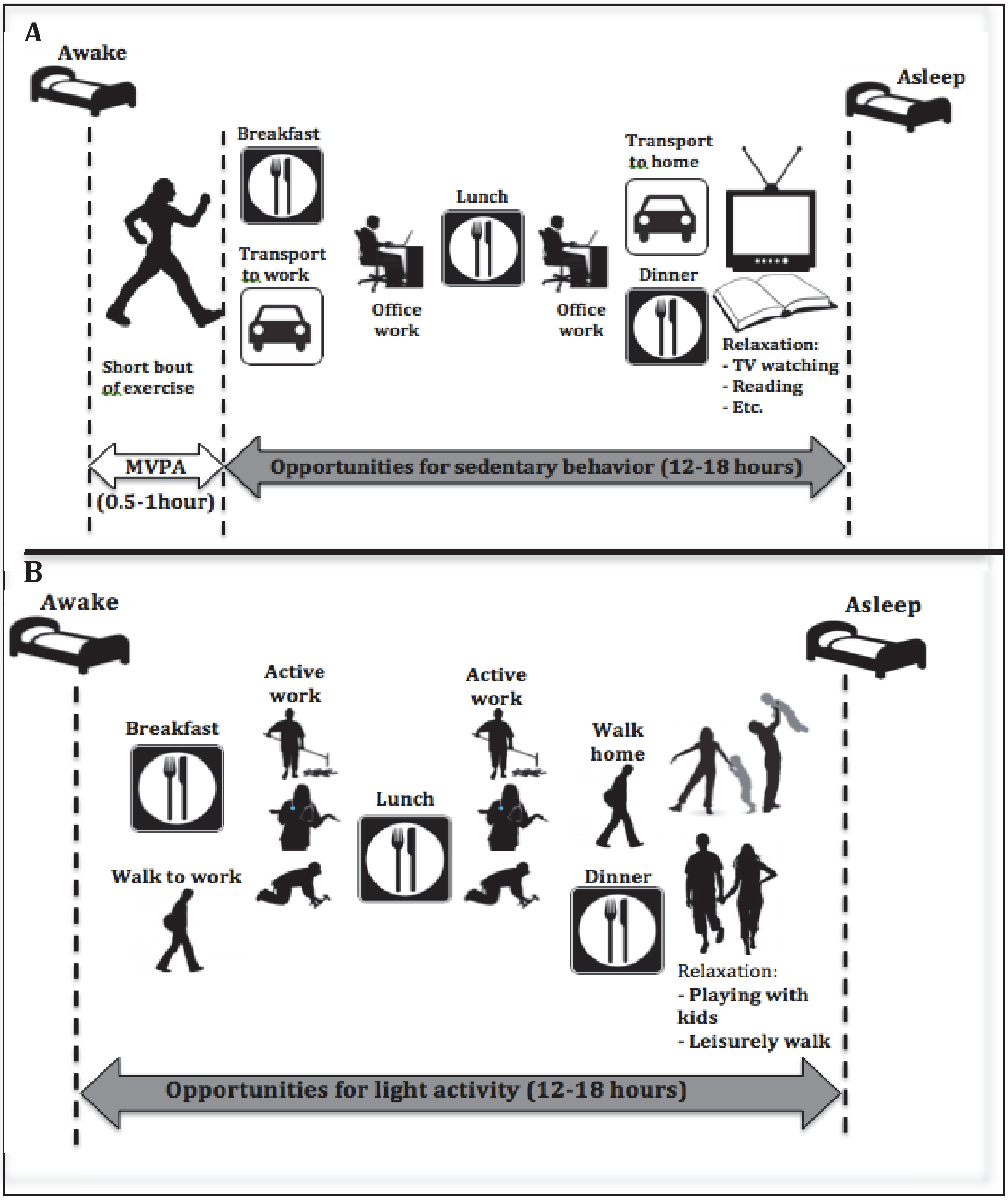

Figure 2.2 A. Daily pattern of sedentary behaviour opportunities and their distribution over the day**. B.** Daily pattern of light activity opportunities and their distribution over the day. *Adapted from Dunstan et al.* [204].

Chapter 3. Objectives

Given both the imminent aging of the population anticipated in the next 25 years and the increasing levels of sedentary behavior as a result of the technological age, this study aimed to identify the association between sedentary behavior, moderate-vigorous physical activity and frailty, which is associated with poor aging. The main purpose of this thesis was to examine if sedentary behaviour is associated with frailty, independent of moderate-vigorous activity. Data from the 2003-2004 and 2005-2006 National Health and Nutrition Examination Survey (NHANES) study was used. The objectives were as follows:

1) Examine whether the frailty index and frailty phenotype demonstrate common characteristics of frailty scales: distribution, mean score, sex differences in frailty scores, limit (99th percentile), relationship of frailty with age, prevalence of frailty (Chapter 4).
2) Examine the association between each definition of frailty and adverse health outcomes including disability, self-reported health, and healthcare utilization (Chapter 4).
3) Examine how sedentary behaviour and moderate-vigorous activity are each experienced during the day across different levels of frailty (Chapter 5).
4) Estimate and compare the extent to which high levels of sedentary behaviour and low levels of moderate-vigorous activity are associated with increased frailty and other domains of health including self-reported health, disability and healthcare utilization (Chapter 5).

Chapter 4

Frailty in NHANES: comparing the frailty index and phenotype

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4.1 Introduction

Chronological age - the number of years since birth- differs from biological age - the active rate at which the body is aging [205]. Biological age may be better at describing quality of life, life expectancy and current level of health [89]. The measurement of frailty represents a comprehensive assessment of biological age and thus is a useful estimate of an individual's health status [104,115]. Frailty signifies an increased vulnerability to adverse health outcomes, reflecting an age-associated decline in multiple physiological systems [6,8,87,88]. The two most commonly used approaches to frailty differ, viewing frailty either as a syndrome (frailty phenotype approach) [87] or as a state (frailty index approach) [6,89].

While the frailty phenotype and frailty index have been compared [110,111,113,123,143,206,207], their similarities and differences are still not fully understood. Examining frailty on different scales allows us to better understand frailty and how we can operationalize its measurement. Fried et al. [87] identify frailty as the presence of three or more of the five criteria: unintentional weight loss, low energy, slow gait, reduced grip strength and reduced physical activity. The frailty index [9]operationalizes frailty as the fraction of deficits present in an individual [116]. Multiple studies have examined frailty in the National Health and Nutrition Examination Survey (NHANES), a large-scale series of cross-sectional surveys that have been used to extensively describe the health of the U.S population. The majority of these studies have followed an adapted version of the phenotype proposed by Wilhelm-Leen et al. [195-200] (see Figure 4.1A). This definition can no longer be used, as components of the phenotype were not measured in cohorts after 2002. Although a frailty index is feasible, it has not yet been employed in the NHANES dataset.

This study compares two alternative measures of frailty using the NHANES data: a modified 4-item version of the frailty phenotype and a frailty index. The main objectives are to:

1) Examine whether the frailty index and frailty phenotype demonstrate common frailty characteristics in terms of distribution, mean score, sex

differences in frailty scores, limit (99th percentile), relationship of frailty with age, prevalence of frailty.

2) Examine the association between each definition of frailty and adverse health outcomes including disability, self-reported health, and healthcare utilization.

4.2 Methods

This study used data from the 2003-2004 and 2005-2006 cohorts of the United States National Health and Nutrition Examination Survey (NHANES). NHANES is a cross-sectional series of studies that examine the prevalence of major diseases and helps identify risk factors for adverse health outcomes. For more details about NHANES, refer to the NHANES website [(208)]. NHANES participants were selected using a complex algorithm and sample weights were provided to ensure that the sample properly represented the U.S population. There were 10 122 and 10 348 participants in the 2003-2004 and 2005-2006 cohorts respectively. The cohorts were amalgamated and only those 50 and older was included in this analysis for a total of 4 874 participants. Frailty was not directly measured, however frailty level could still be identified through the data available using the frailty index and phenotype approach. Due to missing frailty data, 778 participants were excluded for a final sample size of 4 096 (see below). The NHANES survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention. All patients provided written informed consent. Data was accessed through a public access data file available on the NHANES website [(208)].

4.2.1 Construction of the frailty index

Frailty indexes are used to operationalize frailty by counting the number of deficits an individual has [(116)]. This is based on the deficit accumulation approach; i.e., the more health deficits or problems an individual has, the frailer they will be [(104)]. The frailty index is calculated as a ratio of deficits present out of the total number of possible deficits, giving a continuous score from total fitness [0] to total frailty [1]. The frailty index focuses more on the number of items rather than the nature of the item, thus the items included in an index are not standard. We constructed a frailty index following the guidelines outlined by Searle et al. [116]. First, all NHANES variables were screened to establish whether conceptually, they were age and health-related; 136 variables remained. Successively, all remaining variables were screened to examine their association with age, saturation point, prevalence and the level of missing data. Variables were rejected if they did not increase in prevalence with age, if they were uncommon (present in less than 1% of the study population), overly common (deficit was present in 80% or more of individuals by age 80) or were too often missing (missing in more than 5%). The remaining deficits were screened to confirm that they encompassed a broad range of systems, as per standard criteria [116]. After these selection criteria were applied, 46 variables remained (see Table 4.1A). A table outlining each variable in detail, coding and frequencies can be found in Appendix 4A.

All variables that were to be included in the frailty index were recoded. The absence of a deficit was given a score of 0 and the presence of the deficit was given a score of 1. For variables for which there was an intermediate response, such as 'sometimes', a score of 0.5 was assigned. Ordinal variables were recoded to give a score on a scale between 0 and 1. An example of this is "How often do you experience difficulty with X? Never, Rarely, Occasionally, Often, All the time". This was converted to a score out of 1, by recoding each self-rating to represent a deficit ("Never = 0", "Rarely = 0.25", "Occasionally = 0.5", "Often = 0.75" and "All the time = 1"). Continuous variables were coded based on various cut-off points proposed in the literature. Once all of the variables were recoded on a 1-point scale, the frailty index was calculated using the following equation:

$$FI = \sum d_i / D_T \qquad (1)$$

where FI is the frailty index score on a 1 point scale; where $\sum d_i$ is the sum of the deficits present in the subject; where D_T is the total number of deficits possible in the dataset. If, for example, an individual had 23 out of a possible 46 deficits, they would have a frailty score of 23/46 = 0.5. Any individual who was missing 20% or more of the variables were excluded from the study (n=664). The high number of excluded cases, which is atypical of frailty indexes, is due to the inclusion of lab values in the frailty index; 426 individuals (out of the 664) did not have any lab tests done. The frailty index is a continuous score, however in order to compare it with the phenotype, it was also categorized based on proposed cut-off scores [209]. A FI score of FI ≤ 0.10 was considered 'non-frail', a score of 0.10 < FI ≤ 0.21 was 'vulnerable', a score of 0.21 < FI ≤ 0.45 was 'frail,' and FI > 0.45 was 'most frail' [209].

4.2.2 Construction of the frailty phenotype

Modified frailty phenotype criteria [195-201] (see Table 4.1B) have been used to examine frailty in NHANES. From 2003-2004 on, gait speed-one of the 5 criteria- was no longer captured in adults aged 50+ and thus no studies have used the phenotype since. Some studies have effectively used a four-item frailty phenotype in other datasets [202]. This study identified frailty using a modified phenotype including four of the proposed Wilhelm-Leen et al. [201] criteria:

- exhaustion, defined by "some difficulty", "much difficulty", or "unable to do" when asked how much difficulty they have "walking from one room to the other on the same level".
- low physical activity, defined as "less active" when asked "Compared with most (men/women) your age, would you say that you are more active, less active, or about the same?"
- weakness, defined by "some difficulty, "much difficulty", or "unable to do" when asked how much difficulty they have "lifting or carrying something as heavy as 10 pounds [like a sack of potatoes or rice]".
- low body weight, defined by BMI ≤ 18.5 kg/m^2.

Frail individuals were those with 3 or 4 of the items, pre-frail individuals were those with 1 or 2 of the items and robust individuals were those with no items present. If an individual had missing data for any of the 4 items, they were excluded from the study (n=234). Although the phenotype is typically a categorical variable, the proportion of items present out of the number of items in the phenotype was also calculated in order to compare its distribution with the frailty index.

4.2.3 Measurement of disability, healthcare utilization, and self-reported health

Activities of daily living (ADL) disability, self-reported health, and healthcare utilization were used in this study as dichotomous variables. ADL disability was present if there was any difficulty with at least one of the 4 ADLs measured in NHANES: using a fork or knife, dressing, getting out of bed, and walking between rooms on the same floor [210]. Instrumental activities of daily living (IADL) disability was present if there was any difficulty with at least one of the 3 IADLs measured in NHANES: managing money; doing household chores; and preparing meals [210]. Self-reported health was scored as high if the subject answered 'Excellent', 'Very good' or 'Good' to "Would you say your general health was" and low if the subject answered 'Poor' or 'Fair'. Healthcare utilization was scored as high if the subject answered 4+ and low if the subject answered 0-3 to "how many times in the last 12 months [they had] seen a doctor or other healthcare professional about their health at a doctor's office, clinic, hospital emergency room, at home or some other place".

4.2.4 Sample weights

Sample weights allow an unbiased estimate of the frailty of the population. NHANES provided sample weights for the 2003-2004 and 2005-2006 cohorts. However, the two-year weights for 2003-2004 and 2005-2006 are not directly comparable, as different population bases were used each year. Data from all participants in both groups were amalgamated to produce a sample size of 4 096. New sample weights were rescaled such that the sum of the weights matched the survey population at the midpoint of 2003-2006. In order to do that, the following formula was used MEC4YR = 1/2 * WTMEC2YR; where MEC4YR is the new four year sample weight of each individual and WTMEC2YR is the original sample weights of this individual provided by NHANES [208].

4.2.5 Statistical analysis

Statistical analyses were conducted with SPSS 20. An alpha level of 0.05 was used to determine statistical significance. The distribution of frailty in both the index and phenotype as well as the cumulative distribution of the frailty index with regards to phenotype category were examined and compared with one-way ANOVAs. One-way ANOVAs were used to compare mean scores by frailty measure and by sex and the 99th percentile was calculated for both frailty measures. The curve estimation procedure was used to assess the relative fit of linear, quadratic, cubic and exponential regression models of age and frailty score for both measures; the best fitting function was selected according to the R^2 value. The proportion of people classified at each frailty category was calculated for both definitions and the agreement in the classification between the two definitions was examined using Kappa coefficients. Since there are four frailty index categories and three phenotype categories, we combined the categories into two (non-frail, frail) and three levels (non-frail, vulnerable, frail). To create two levels of frailty, the non-frail and pre-frail categories of the phenotype were grouped; for the FI, we grouped the non-frail with the vulnerable and the frail with the most frail. To compare the agreement of the original three level phenotype with the FI, we grouped those in the frail and most frail categories of the FI together.

To examine the overlap between frailty and disability, we calculated the proportion of frail individuals who also reported ADL and IADL disability. Logistic regressions examined the strength of the association between each measure of frailty, self-reported health and healthcare utilization. Due to possible co-linearity between the adverse health outcomes and each measure of frailty, self-reported health and healthcare utilization were removed from the index for their respective regression analyses. Using self-reported health and health care utilization as outcomes, four regression models were created for both definitions. We first examined the contribution of the two frailty measures independently and then added them both in the same model. The fourth model examined a sub-group of those who were categorized as robust by the frailty phenotype to determine if frailty index score was still associated with the adverse outcomes. Alcohol consumption, smoking status, race, income, education, marital status, gender and age were examined as potential covariates; only those that significantly contributed to the model were retained.

4.3 Results

A total of 4 096 participants (mean age 63.4±10.3; 53.5% women, 18.0 % ADL disability) were included in this analysis. The characteristics of the sample can be seen in Appendix 4B. Characteristics were comparable for those who were excluded due to missing frailty data (mean age 64.6 ±10.9, 52.3% women, 19.3% ADL disability). The distribution of scores on both frailty scales, measured as a proportion of deficits present out of total deficits possible, resemble a right skewed, Poisson distribution (Appendix 4C). The mean frailty index score increased across categories of the frailty index, from 0.14 in those who were 'robust' to 0.26 in those who were 'pre-frail' to 0.43 in those who were 'frail' ($p<0.001$)(see Figure 4.2). Females had higher levels of frailty than males in both the frailty index, 0.20 and 0.17 respectively, and the frailty phenotype, 0.13 and 0.09 respectively ($p<0.001$). The 99th percentile of frailty scores was 0.55 in the frailty index and 0.75 in the frailty phenotype. The relationship between age and frailty was best described using a non-linear, exponential model rather than a linear, logistic or quadratic model (see Figure 4.1). The mean frailty index score increased by 2.3% per year, in log scale, while the mean phenotype score increased by 1.1% per year, also on a log scale. The prevalence of frailty was 3.6% in the frailty phenotype and 34.4% in the frailty index. Appendix 4D demonstrates the proportion of individuals in each category of the frailty index and phenotype. Although all participants classified as frail in the phenotype were also classified as frail in the index, 30.8% and 13.6% of the sample were categorized as robust in the phenotype, despite being categorized as vulnerable and frail in the frailty index. The Kappa agreement between dichotomous frailty measures was 0.166, while the Kappa agreement examining three levels of frailty (robust, pre-frail, frail) was 0.116.

As the level of both the frailty phenotype and the frailty index increased, more individuals experienced limitations with at least one ADL or IADL. Among frail people, based on phenotype, 95% had IADL disability and 97.8% ADL disability; among frail people, based on FI, 85.6% had IADL disability and 56.6% ADL disability (see Figure 4.3). Both the frailty index and the phenotype were associated with self-reported health and healthcare utilization (Table 4.2, Models 1-3). In the combined model, the odds ratios associated with the frailty index were higher than that of the phenotype for both self-reported health and healthcare utilization (Table 4.2, Model 3). In a logistic regression examining only those categorized as robust in the phenotype, self-reported health and healthcare utilization were still significantly associated with frailty index (Table 4.2, Model 4). Similar results were found for all models when the frailty index score was considered as a continuous variable in the regressions ($p < 0.001$).

4.4 Discussion

This secondary analysis of NHANES showed that the properties of both the frailty index and frailty phenotype were consistent with previously accepted characteristics of other frailty measures [84,110] including the right skewed distribution of frailty, higher levels of frailty in women compared to men, an upper limit of deficit accumulation and an exponential increase with age. However the magnitude of these characteristics differed (e.g. prevalence was 34.4% for FI and 3.6% for phenotype). There was a high degree of overlap between frailty and disability, regardless of the definition of frailty used. Both measures were associated with self-reported health and healthcare utilization, although the frailty index had a stronger association with both measures and appeared to better discriminate at the lower to middle end of the frailty continuum.

The findings of this study must be interpreted with caution. The cross-sectional nature of the NHANES study is a limitation as no temporal order can be drawn; it is unknown if the predictions would have been the same in a longitudinal study. The variables included in Wilhelm-Leen et al.'s [201] phenotype were modified from the original criteria [87] in order to operationalize them for the NHANES dataset. Although this is common [123,199,201,202] the modifications deviated considerably from the original items. Gait speed, considered to be an important phenotype item [211], was excluded from the modified phenotype, however the 'exhaustion' item defined by difficulty when "walking from one room to the other on the same level" is highly related to mobility; thus some information on mobility was likely included in the phenotype used in this study.

Previous studies have demonstrated that the frailty phenotype and the frailty index have common characteristics with differing magnitudes and are both able to accurately predict adverse outcomes [113,123,212]. In a European population aged 50+, researchers reported a 2% higher increase with age in the phenotype than the frailty index [212], a 0.51 kappa agreement in the dichotomized frailty measures [110] and a 10% higher frailty prevalence with the frailty index compared to the phenotype [110]. A systematic review of community dwelling adults discovered that the prevalence of frailty varies significantly (from 4.0% to 59.1%), mainly due to different operationalization of frailty. In this study, the prevalence of frailty was 3.6% in the frailty phenotype and 34.4% in the frailty index. The frailty phenotype initially appeared to have underestimated levels of frailty in the population compared to other studies that reported phenotype prevalence estimates of 6.9% in a US population 65+ [87], 16.6% in a Canadian population aged 65+ [7], and 11% in a European population aged 50+ [110]. However, the prevalence was comparable to findings that used Wilheem-Leen et al.'s [201] modified criteria in previous waves of NHANES: 6.4% [199], 2.5% [195] and 2.8% [201]. These previous NHANES studies included individuals 65+; as such, it is likely the slightly different phenotype prevalence is due to both the younger study population as well as a change in the number of items included in the phenotype (using 4 instead of 5 items). Contrarily, the frailty index appears to have overestimated frailty when compared to other findings in Canadian populations aged 65+ including 24% [209], 22.7% [124] and finally 21.6% in a European population aged 50+ [110]. This is likely due to the inclusion of lab values in the current frailty index, where the prevalence scores for the deficits were much higher compared to the remaining variables (Appendix 4A).

While the definitions of frailty and disability remain distinct concepts, it is clear there is significant overlap between frailty and disability. In the current study ADL and IADL limitations were more common at the highest levels of frailty; 56.6% (index) and 97.8% (phenotype) of frail individuals had ADL disability, while 85.6% (index) and 95% (phenotype) of frail individuals had IADL disability. Theou et al. [7] found comparable proportions of ADL disability in frail Canadians over the age of 65 with 66.6 % disability in those classified as frail by a frailty index and 83.9% in those classified by the frailty phenotype. Wong et al. [213] found that 29.1% and 92.7% of phenotypic frail individuals had disabilities in ADLs and IADLs in a population aged 65+; while 28% of disabled women 65+ years old in the Women's Health and Aging were frail [214]. Overall, recent studies, including this one, have found that agreement between frailty and disability is much more common than previously suggested [(4)] and that frailty is not simply a pre-disability stage.

In addition, frailty index was shown to predict adverse outcomes even among people who were considered non-frail by phenotype [(110)]. A sub-analysis in individuals categorized as robust by the phenotype demonstrated that frailty level was significantly associated with self-reported health and healthcare utilization suggesting that the frailty index may be a more sensitive measure of frailty due to its ability to discriminate at the lower to middle end of the frailty continuum [(84,206)]. The sensitive, continuous nature of the frailty index helps identify individuals who are vulnerable and allows intervention before an individual reaches an absolute frail state. While the frailty index may provide a more sensitive measure, criticism has focused on the complexity and time involved in collecting the at least 30 items needed to create a frailty index. Using data that has already been collected such as electronic medical records or secondary data could overcome this criticism.

This study was the first to identify and compare two frailty measures that can be used in the NHANES population. It is also one of only a few studies to examine frailty in a population as young as 50+; frailty studies have typically focused on the older population above the age of 65. The deficit accumulation approach is based on a life course approach and suggests that frailty is not a state into which one enters but rather is a result of the accumulation of health deficits throughout life. Furthermore, most studies comparing the two measures have focused on mortality; this study compared the association between frailty and self-reported health and healthcare utilization.

The data from the current study demonstrates that both frailty scales have similar characteristics, differing in magnitude, and are both associated with adverse health outcomes. The frailty index and the frailty phenotype are both reliable measures of frailty as demonstrated by their strong concurrence with disability as well as their associations with self-reported health and healthcare utilization. The frailty index may still be a more sensitive measure of frailty due to it’s ability to discriminate lower levels of frailty better. The identification of the index and phenotype as valid measurements of frailty in

NHANES is important for studies examining frailty in future NHANES cohorts. Nevertheless, one definition of frailty may not simply be agreed upon as there are strengths and weaknesses associated with each. Other definitions of frailty should continue to be explored; past studies have suggested that there are as many as eight different frailty measures that have demonstrated comparable properties [110]. The ongoing research on the operational definitions of frailty can help identify and predict who is at increased risk of adverse outcomes.

Tables

Deficits included in Frailty Index:

1. Stroke
2. Thyroid condition
3. Cancer
4. Heart attack
5. Heart disease
6. Angina/angina pectoris
7. Osteoporosis
8. Ever had diabetes
9. Ever had arthritis
10. Heart rate at rest
11. Systolic blood pressure
12. Ever had high blood pressure
13. Cough regularly
14. Broken hip
15. Medications
16. Confusion or inability to remember things
17. Difficulty managing money
18. Difficulty standing up from armless chair
19. Difficulty getting in and out of bed
20. Difficulty standing for long periods of time
21. Difficulty stooping, crouching, kneeling
22. Difficulty grasping/holding small objects
23. Difficulty lifting or carrying
24. Difficulty preparing meals
25. Difficulty using fork and knife
26. Difficulty dressing yourself
27. Difficult attending social event
28. Difficulty pushing or pulling large objects
29. Difficulty seeing steps/curbs in dim light
30. General vision
31. Cataract operation
32. General hearing
33. Weak/failing kidneys
34. Leaked/ lost control of urine
35. Self-reported health
36. Health compared to 1 year ago
37. Frequency of healthcare use
38. Overnight hospital stays
39. Homocysteine (umol/L) levels
40. Folate, serum (nmol/L) levels
41. Glycohemoglobin (%) levels
42. Red blood cell count (million cells/uL)
43. Hemoglobin (g/dL) levels
44. Red cell distribution width (%)
45. Lymphocyte percent (%)
46. Segmented neutrophils percent (%)

Table 4.1A. 46 deficits included in Frailty Index

Phenotype Items	Original definition (Fried et al., 2001)	NHANES version (Wilhelm-Leen et al., 2010)	Present study version
Unintentional weight loss	weight loss of ≥10 pounds in prior year or, at of ≥5% of body weight in prior year	low body weight, defined by BMI ≤18.5 kg/m^2	low body weight, defined by BMI ≤p18.5 kg/m^2
Weakness	grip strength in lowest 20% of sample (after adjustment for gender and BMI)	self-reported difficulty with "lifting or carrying something as heavy as 10 pounds"	self-reported difficulty with "lifting or carrying something as heavy as 10 pounds"
Self-reported exhaustion	if the participant answered "much or most of the time" at least once to "how often in the last week did [they] 1) feel that everything [they] did was an effort or 2) fell that [they] could not get going."	self-reported difficulty with "walking from one room to the other on the same level".	self-reported difficulty with "walking from one room to the other on the same level".
Slow walking speed	measured time to walk 15 feet in slowest 20% of sample (after adjustment for gender and standing height)	measured time to walk 8 feet (after adjustment for gender)	******* not available***
Low physical activity	weekly kilocalories as measured by the Minnesota Leisure Time Activities Questionnaire in lowest 20% of sample	self-reported less active " when asked "compared with most (men/women) your age, would you say that you are more active, less active, or about the same?"	self-reported less active " when asked "compared with most (men/women) your age, would you say that you are more active, less active, or about the same?"

Table 4.1B. Items included in the original phenotype and the modified NHANES phenotypes

Table 4.2 Logistic regression examining the association of the two measures of frailty with self-reported health and healthcare utilization for the whole sample (models 1-3) and for those who were classified as robust by the phenotype (model 4).

	Category	**Self-reported health *** Odds ratio (95% Confidence Interval)	**Healthcare utilization**** Odds ratio (95% Confidence Interval)
Model 1: Phenotype	Robust (0items /4) n = 2852	1	1
	Pre-frail (1-2items /4) n = 1097	5.34 (4.45 – 6.42)	2.42 (2.00-2.94)
	Frail (3-4items /4) n = 146	39.82 (24.02 – 66.03)	6.54 (4.3-9.65)
Model 2: Index	Non-frail (FI <0.10) n =1151	1	1
	Vulnerable 0.10 < FI ≤ 0.21 n = 1551	5.98 (4.10 – 8.72)	4.31 (2.98-6.22)
	Frail 0.21 < FI ≤ 0.45 n = 1242	38.38 (26.11 – 56.41)	15.27 (10.61-21.99)
	Most-frail FI > 0.45 n = 152	247.87 (133.64 – 459.73)	54.04 (32.28-90.45)
Model 3: Phenotype& Index			
Phenotype	Robust	1	1
	Pre-frail	2.52 (2.04 – 3.09)	1.19 (0.97-1.45) **non-significant**
	Frail	7.51(4.34 – 13.00)	1.42 (0.95-2.14) **non-significant**
Index	Non-frail	1	1
	Vulnerable	5.27 (3.61 – 7.71)	4.23 (2.92-6.12)
	Frail	22.56 (15.16 – 33.57)	13.86 (9.43-20.37)
	Most-frail	75.20 (38.95 – 145.19)	43.05 (24.19-76.6)
Model 4:† (n=2745) Index	Non-frail n =1031	1	1
	Vulnerable n = 1261	4.59 (2.72 – 7.75)	3.94 (2.70-5.75)
	Frail n = 550	22.77 (12.83 – 40.43)	11.74 (7.79-17.71)
	Most-frail n = 10	317.61 (12.97 – 7779.79)	421.49 (0.0-5034.39) **non-significant**

* controlled for significant covariates (gender, age, income, race, education)

** controlled for significant covariates (gender, age, education)

†only individuals classified as robust by the phenotype were included in this sub analysis (n=2745)

Figures

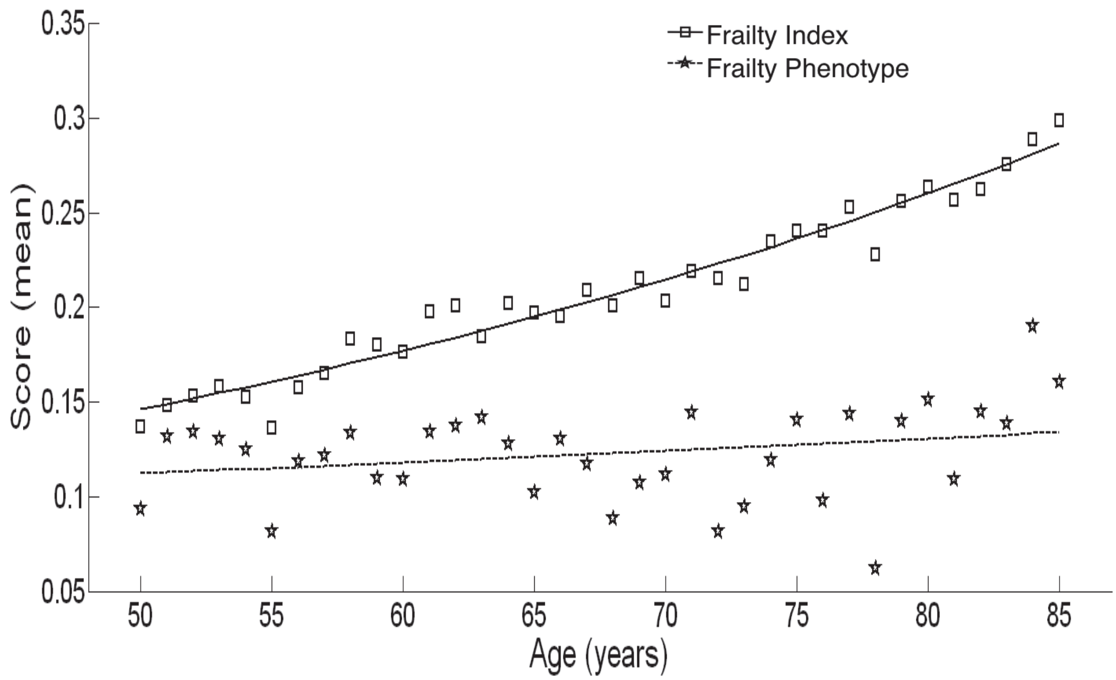


Figure 4.1 Relationship of frailty with age for frailty index and frailty phenotype

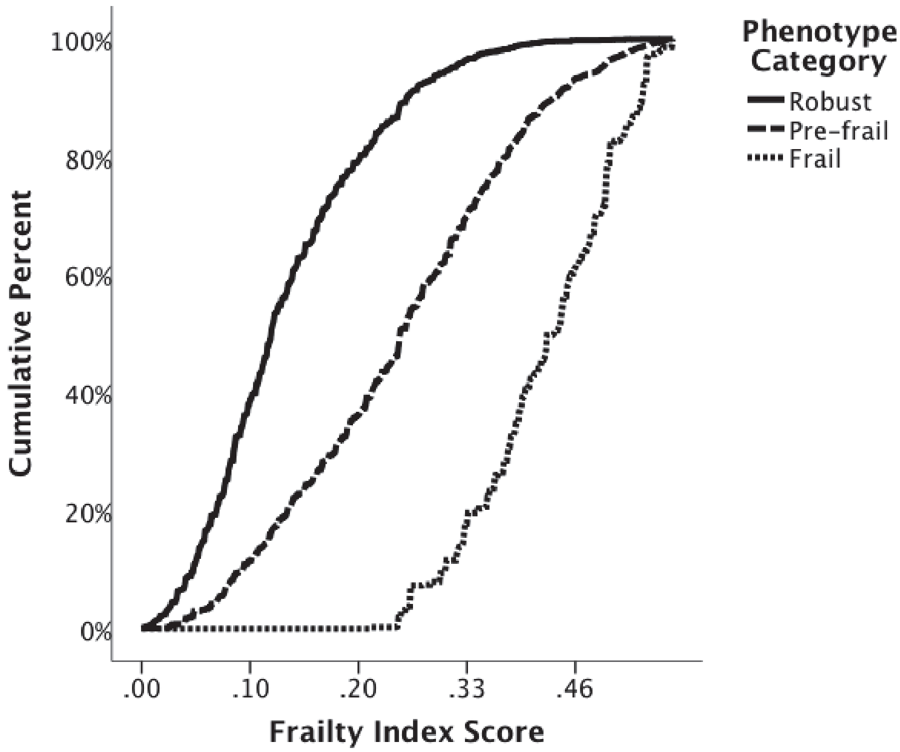


Figure 4.2. Cumulative distribution of frailty index score by frailty classification according to the phenotype (robust, pre-frail or frail)

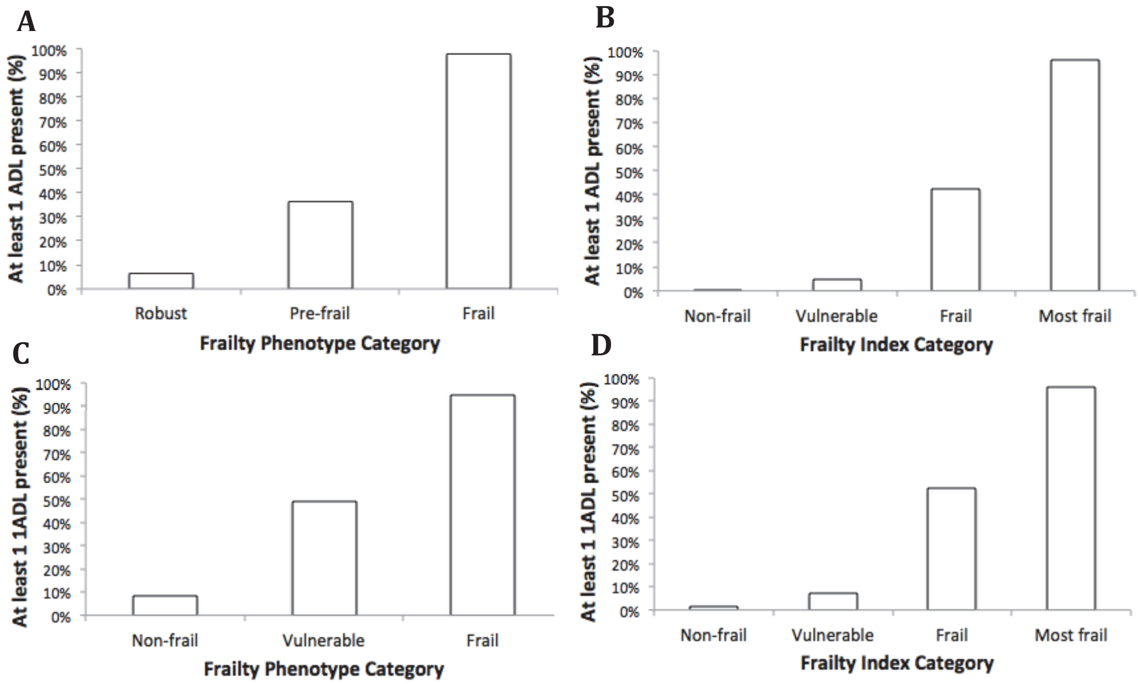
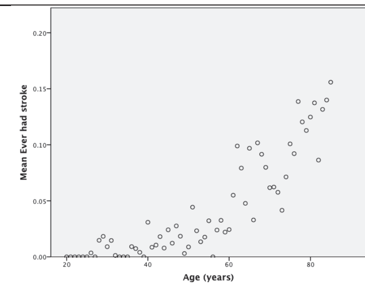
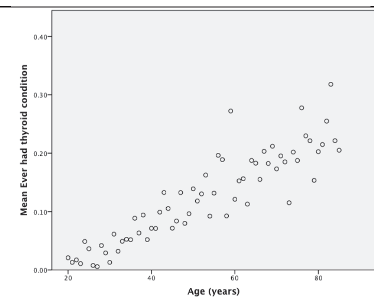
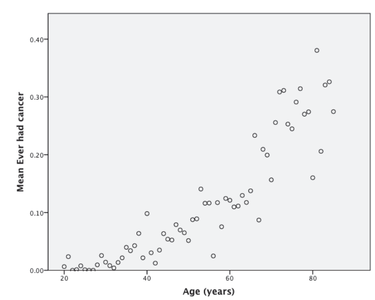
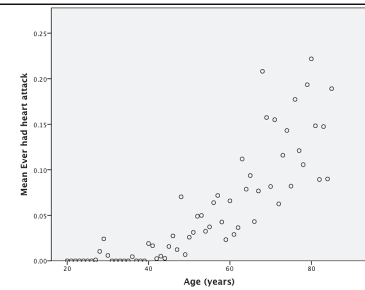
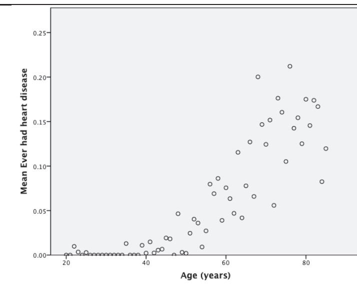
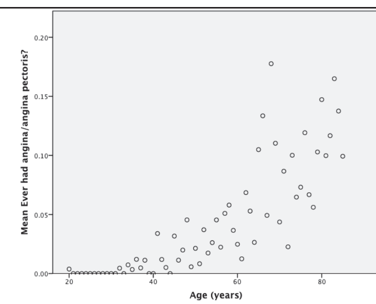


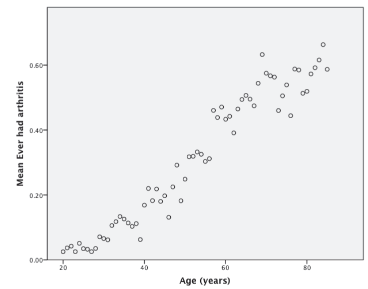
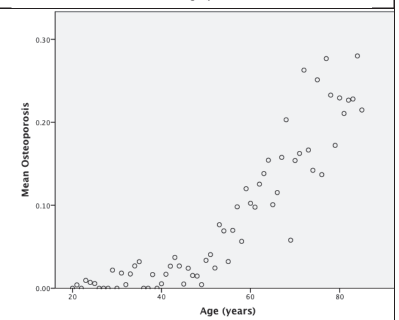
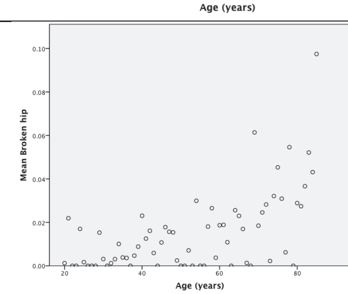
Figure 4.3. Proportion of participants who experience limitation with at least one **A.** ADL at each frailty phenotype category**. B**. ADL at each frailty index category. **C**. IADL at each frailty phenotype category. **D**. IADL at each frailty index category

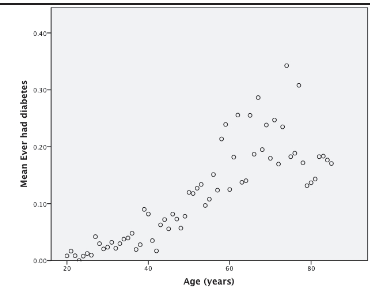
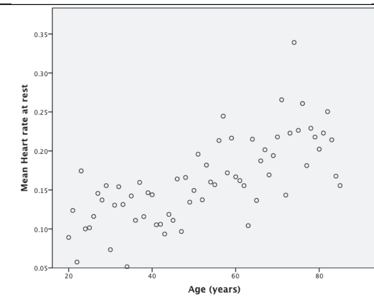
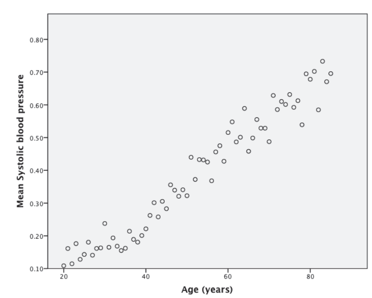
4.7 Appendix

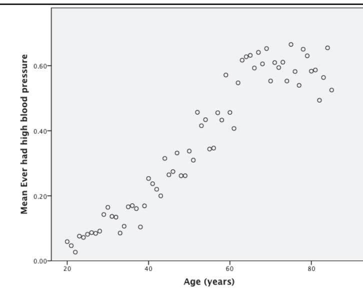
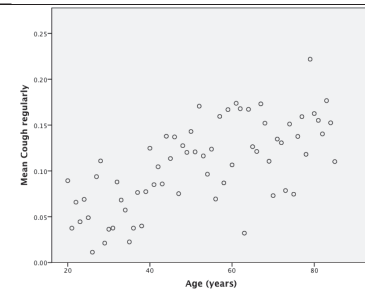
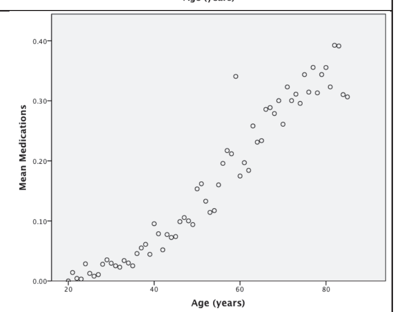
Appendix 4A. Frailty index: coding and frequency of the 46 included deficits

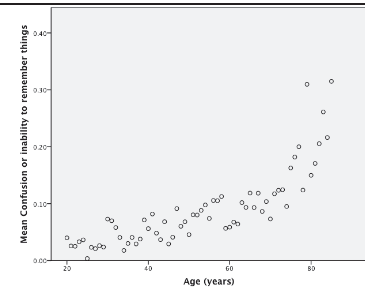
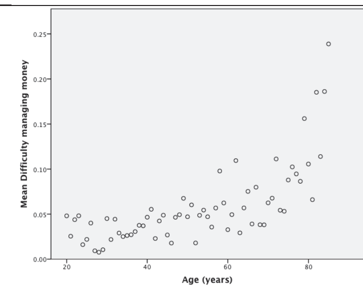
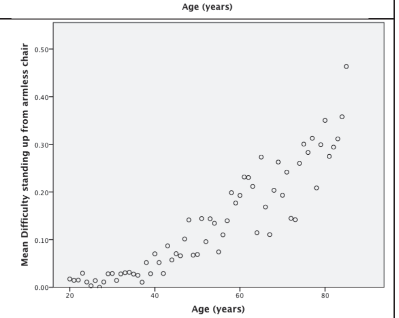
	Deficit	**Coding**	**Frequency** n (sample %, weighted sample %)	**Graph**
1	Ever had stroke	0: No 1: Yes	0 = 3802 (92.8, 94.4) 1 = 287 (7.0, 5.5) missing = 7 (0.2, 0.1)	
2	Ever had thyroid condition	0: No 1: Yes	0 = 3471 (84.7, 82.9) 1 = 614 (15.0, 16.8) missing = 11 (0.3, 0.3)	
3	Ever had cancer	0: No 1: Yes	0 = 3444 (84.1, 83.9) 1 = 646 (15.8, 16.0) missing = 6 (0.1, 0.2)	

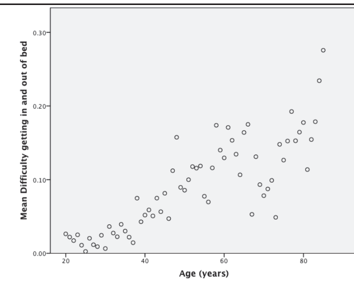
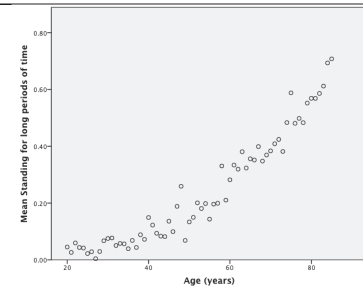
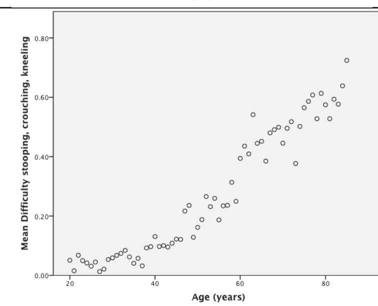
4	Ever had heart attack	0: No 1: Yes	0 = 3701 (90.4, 91.8) 1 = 383 (9.4, 7.9) missing = 12 (0.3, 0.3)	
5	Ever had heart disease	0: No 1: Yes	0 = 3696 (90.2, 91.4) 1 = 369 (9.0, 8.0) missing = 31 (0.8, 0.6)	
6	Ever had angina/angina pectoris?	0: No 1: Yes	0 = 3803 (92.8, 93.9) 1 = 274 (6.7, 5.7) missing = 19 (0.5, 0.4)	

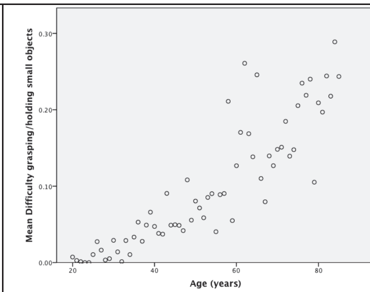
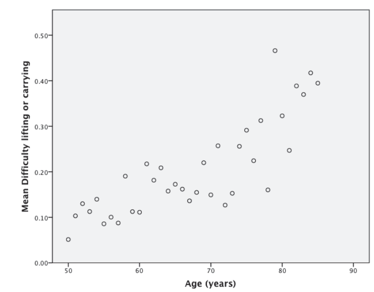
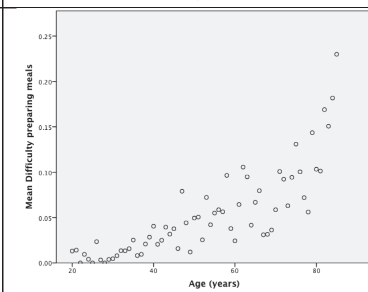
7	Ever had arthritis	0: No 1: Yes	0 = 2235 (54.6, 55.9) 1 = 1848 (45.1, 43.7) missing = 13 (0.3, 0.4)	
8	Ever had osteoporosis	0: No 1: Yes	0 = 3611 (88.2, 88.1) 1 = 474 (11.6, 11.7) missing = 11 (0.3, 0.2)	
9	Ever had a broken hip	0: No 1: Yes	0 = 4001 (97.7, 98.2) 1 = 93 (2.3, 1.8) missing = 2 (0.0, 0.0)	

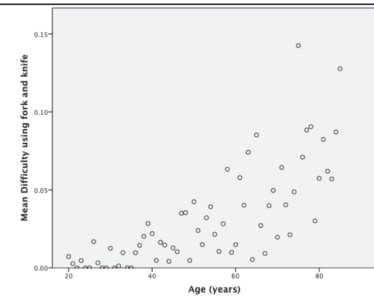
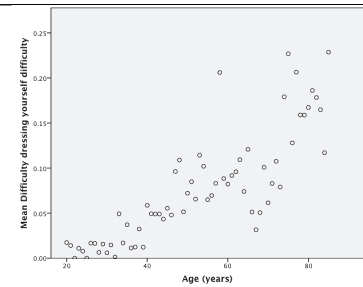
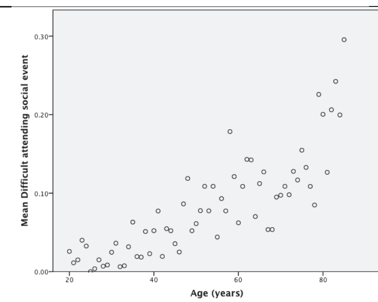
10	Ever had diabetes	0: No 1: Yes or Borderline	0 = 4001 (97.7, 83.1) 1 = 847 (20.7, 16.8) missing = 3 (0.1, 0.0)	
11	Heart rate at rest	0: 60-99 1: < 60 or 100+	0 = 3200 (78.1, 79.1) 1 = 767 (18.7,18.0) missing = 129 (3.1, 2.9)	
12	Systolic blood pressure	0: <120 0.5: 120-139 1: 140+	0 = 1007 (24.6, 28.8) 0.5 = 1515 (36.9, 37.8) 1= 1374 (33.5, 29.0) Missing = 202 (4.9, 4.5)	

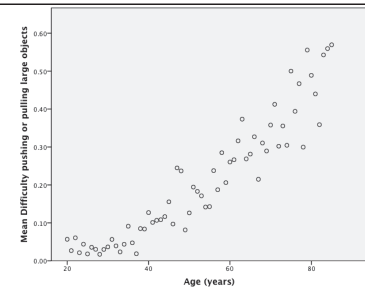
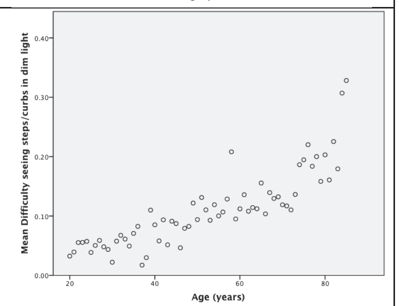
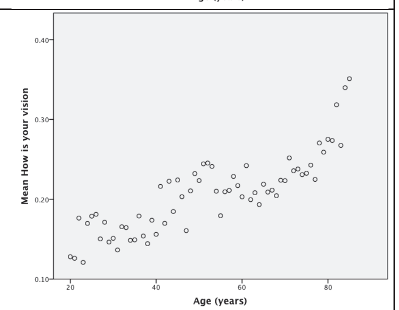
13	Ever had high blood pressure	0: No 1: Yes	0 = 1897 (46.3, 50.0) 1 = 2177 (53.1,49.6) missing = 22 (0.5, 0.4)	
14	Cough regularly	0: No 1: Yes	0 = 3616 (88.3, 87.3) 1 = 474 (11.6,12.6) missing = 6 (0.1, 0.1)	
15	Medications	0: 0-3 0.5: 4-7 1: 8+	0 = 2525 (61.6, 63.8) 0.5 = 1153 (28.1, 26.3) 1= 410 (10.0, 9.7) Missing = 8 (0.2, 0.2)	

16	Confusion or inability to remember things	0: No 1: Yes	0 = 3550 (86.7, 89.4) 1 = 544 (13.3, 10.5) missing = 2 (0.0, 0.0)	
17	Difficulty managing money	0: No difficulty 1: Some or much difficulty, unable to do	0 = 3567 (87.1, 89.4) 1 = 326 (8.0, 6.1) missing = 203 (5.0, 4.5)	
18	Difficulty standing up from armless chair	0: No difficulty 1: Some or much difficulty, unable to do	0 = 3197 (78.1, 81.8) 1 = 897 (21.9, 18.1) missing = 2 (0.0, 0,0)	

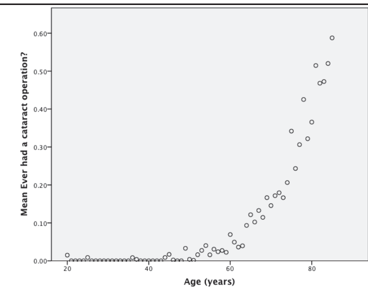
19	Difficulty getting in and out of bed	0: No difficulty 1: Some or much difficulty, unable to do	0 = 3482 (85.0, 88.1) 1 = 611 (14.9, 11.8) missing = 3 (0.1, 0.1)	
20	Standing for long periods of time	0: No difficulty 1: Some or much difficulty, unable to do	0 = 2507 (61.2, 67.1) 1 = 1501 (36.6, 31.0) missing = 88 (2.1, 1.9)	
21	Difficulty stooping, crouching, kneeling	0: No difficulty 1: Some or much difficulty, unable to do	0 = 2306 (56.3, 62.1) 1 = 1743 (42.6, 37.0) missing = 47 (1.1, 0.8)	

22	Difficulty grasping/holding small objects	0: No difficulty 1: Some or much difficulty, unable to do	0 = 3477 (84.9, 86.9) 1 = 617 (15.1, 13.1) missing = 2 (0.0, 0.0)	
23	Difficulty lifting or carrying	0: No difficulty 1: Some or much difficulty, unable to do	0 = 3213 (78.4, 83.4) 1 = 883 (21.6, 16.6) missing = 0 (0.0, 0.0)	
24	Difficulty preparing meals	0: No difficulty 1: Some or much difficulty, unable to do	0 = 3578 (87.4, 90.7) 1 = 334 (8.2, 6.3) missing = 184 (4.5, 3.0)	

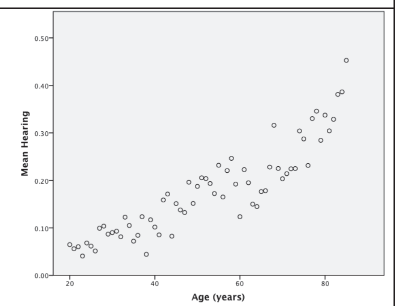
25	Difficulty using fork and knife	0: No difficulty 1: Some or much difficulty, unable to do	0 = 3890 (95.0, 90.1) 1 = 206 (5.0, 9. 8) missing = 0 (0.0, 0.1)	
26	Difficulty dressing yourself difficulty	0: No difficulty 1: Some or much difficulty, unable to do	0 = 3596 (87.8, 1 = 498 (12.2, missing = 2 (0.0,	
27	Difficult attending social events	0: No difficulty 1: Some or much difficulty, unable to do	0 = 3425 (83.6, 87.4) 1 = 539 (13.2, 10.2) missing = 132 (3.2, 2.4)	

28	Difficulty pushing or pulling large objects	0: No difficulty 1: Some or much difficulty, unable to do	0 = 2728 (66.6, 70.9) 1 =1249 (30.5, 26.8) missing = 119 (2.9,2.3)	
29	Difficulty seeing steps/curbs in dim light	0: No difficulty 0.5: Little or moderate difficulty 1: Extreme difficulty or unable to do	0 = 2938 (71.7, 75.1) 0.5 = 876 (21.4, 20.1) 1 = 176 (4.3, 3.2) missing = 106 (2.6, 1.6)	
30	self-rated vision	0: Excellent 0.25: Good 0.5: Fair 0.75 Poor 1: Very poor	0 = 1103 (26.9, 31.2) 0.25 = 1989 (48.6, 50.5) 0.5 = 750 (18.3, 14.4) 0.75 = 166 (4.1, 2.6) 1 = 58 (1.4, 1.0) missing= 30 (0.7, 0.4)	

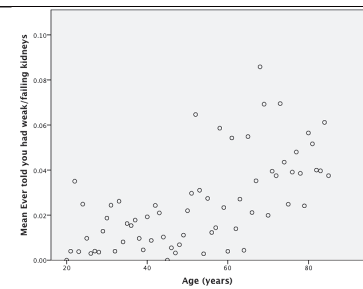
31	Ever had a cataract operation?	0: No 0.5: One eye 1: Both eyes	0 = 3321 (81.1, 85.2) 0.5 = 222 (5.4, 4.0) 1 = 553 (13.5, 10.7) missing = 0 (0.0, 0.0)

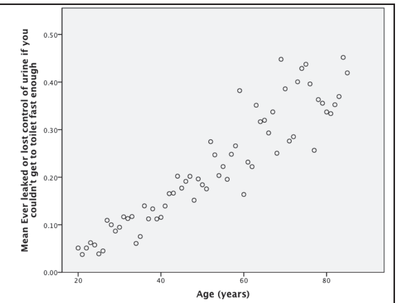
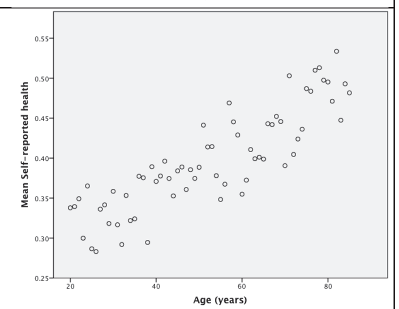
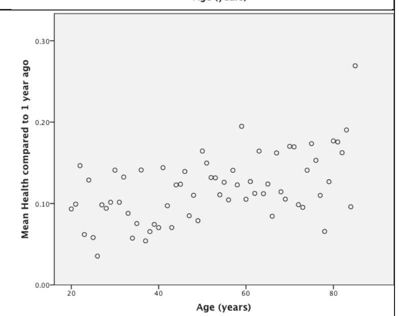


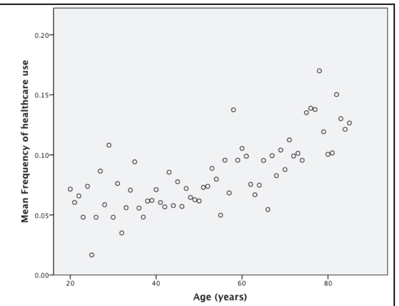
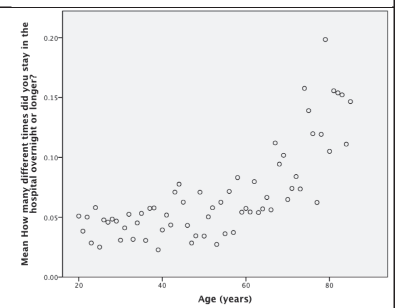
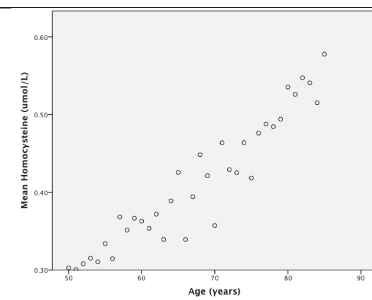
32	Hearing	0: Good or excellent 0.5: Little or moderate trouble 1: Lot of trouble or deaf	0 = 2512 (61.3, 62.4) 0.5 = 1237 (30.2, 30.1) 1 = 341 (8.3, 7.3) missing = 6 (0.1, 0.3)

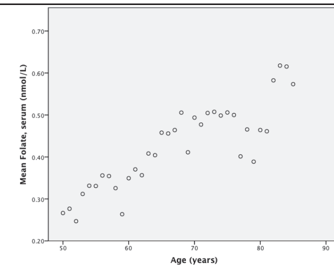
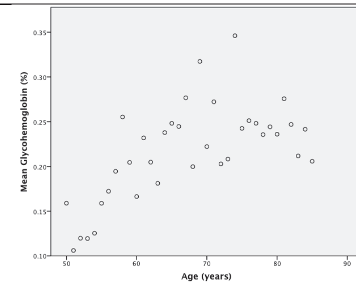
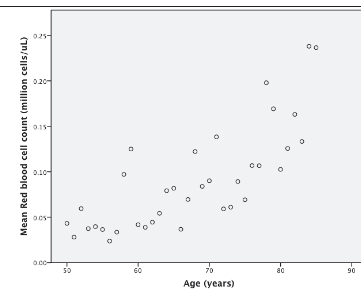


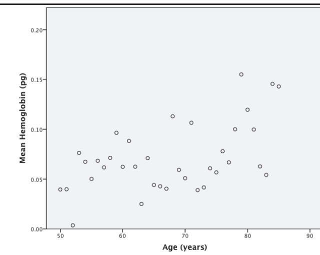
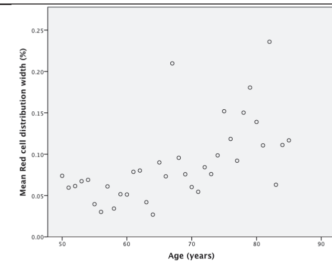
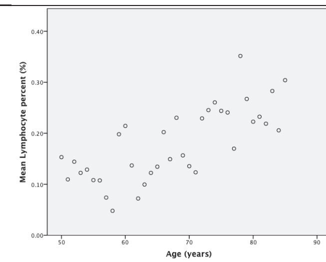
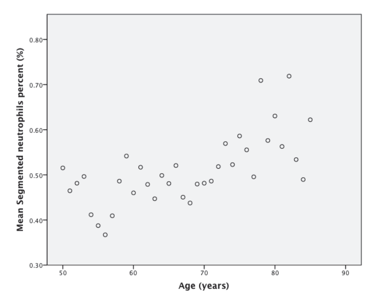
33	Ever told you had weak/failing kidneys	0: No 1: Yes	0 = 3925 (95.8, 96.8) 1 = 162 (4.0, 3.1) missing = 9 (0.2, 0.1)



34	Ever leaked or lost control of urine if you couldn’t get to the toilet fast enough?	0: No 1: Yes	0 = 2725 (66.5, 68.4) 1 = 1205 (29.4, 27.2) missing = 166 (4.1, 4.3)	
35	Self-reported health	0: Excellent 0.25: Very good 0.5: Good 0.75 Fair 1: Poor	0 = 535 (13.1, 16.0) 0.25 = 982 (24.0, 28.4) 0.5 = 1370 (33.4, 32.7) 0.75 = 919 (22.4, 17.0) 1 = 290 (7.1, 5.8) missing= 0 (0.0, 0.0)	
36	Health compared to 1 year ago	0: Better or same 1: Worse	0 = 3502 (85.5, 86.3) 1 = 593 (14.5, 13.7) missing = 1 (0.0, 0.0)	

37	Frequency of healthcare use	0: 0-3 0.5: 4-9 1: 10+	0 = 3283 (80.2, 81.9) 0.5 = 808 (19.7, 18.0) 1 = 5 (0.1, 0.1) missing = 0 (0.0, 0.0)	
38	How many different times did you stay in the hospital overnight or longer?	0= 0 1-2 = 0.5 3+ = 1	0 = 3426 (83.9, 86.6) 0.5 = 580 (14.2, 12.0) 1 = 75 (1.8, 1.3) missing = 5 (0.1, 0.1)	
39	Homocysteine (umol/L)	0: <8 0.5: 8-15 1: > 15	0 = 1079 (26.3, 30.4) 0.5 = 2506 (61.2, 59.7) 1 = 388 (9.5, 7.3) missing = 123 (3.0, 2.7)	

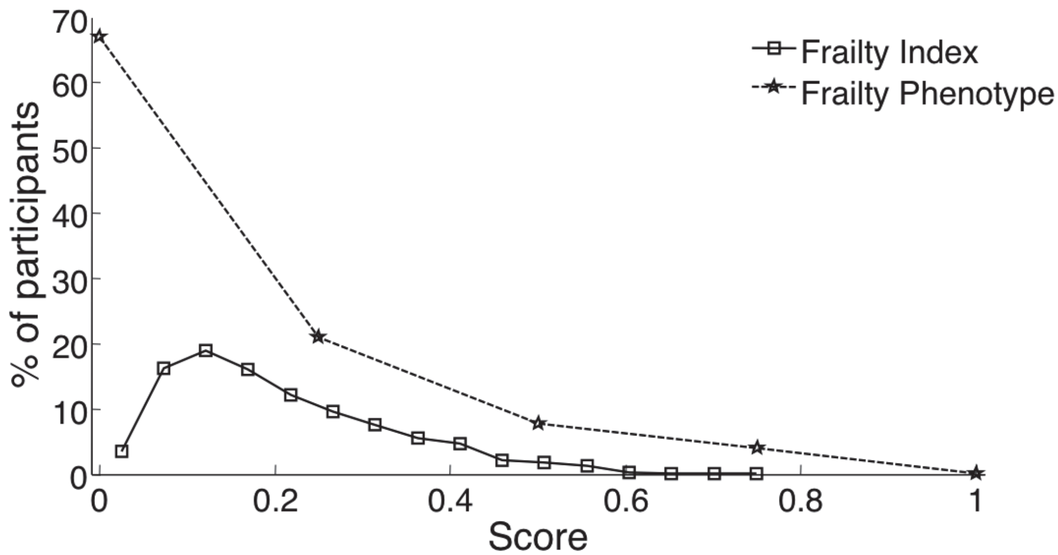
40	Folate, serum (nmol/L)	0: 4.5-29.5 nmol/L 0.5: 29.6-45.3 1: <4.5 or >45.3	0 = 1862 (45.5, 42.8) 0.5 = 1204 (29.4, 31.6) 1 = 881 (21.5, 22.6) missing = 149 (3.6, 3.0)	
41	Glycohemoglobin (%)	0: < 5.7 0.5: 5.7-6.4 1: > 6.4	0 = 2339 (57.1, 60.6) 0.5 = 810 (19.8, 16.4) 1 =563 (13.7, 9.5) missing = 384 (9.4, 13.6)	
42	Red blood cell count (million cells/uL)	0: 3.93-5.69 M/uL 1: <3.93or >5.69	0 = 3642 (88.9, 90.7) 1 = 350 (8.5, 7.2) missing = 104 (2.5, 2.1)	

43	Hemoglobin (g/dL)	0: 12.1-17.2 g/dL 1: <12.1 or >17.2	0 = 3428 (83.7, 81.1) 1 = 290 (7.1, 5.5) missing = 378 (9.2, 13.5)	
44	Red cell distribution width (%)	0: 11.5-14.5 1: <11.5 or <14.5	0 = 3619 (88.4, 90.3) 1 = 373 (9.1, 7.6) missing = 104 (2.5, 2.1)	
45	Lymphocyte percent (%)	0: 20-45 1: <20 or >45	0 = 3245 (79.2, 82.2) 1 = 731 (17.8, 15.5) missing = 120 (2.9, 2.3)	
46	Segmented neutrophils percent (%)	0: 40-60 1: <40 or >60	0 = 1989 (48.6, 49.9) 1 = 1987 (48.5, 47.8) missing = 120 (2.9, 2.3)	

Appendix 4B. Characteristics of sample (weighted)

	All n= 4096	**Female** (n= 2190)		**Male** (n= 1906)	
		50-64 y.o n= 1236	**65-85 y.o n= 955**	**50-64 y.o n = 1153**	**65-85 y.o n= 753**
Race/Ethnicity (%)					
Non-Hispanic white	80.2%	76.6%	83.6%	78.7%	84.0%
Non-Hispanic black	9.2%	10.6%	8.2%	9.6%	7.3%
Mexican-American	3.9%	4.3%	2.9%	4.7%	3.4%
Other	6.7%	8.5%	5.4%	6.9%	5.3%
Body mass index ($kg/m^2 \pm SD$)	28.8 (6.2)	29.5 (7.5)	28.1 (5.9)	29.0 (5.5)	28.1 (5.0)
Education (%)					
Less than high school	20.0%	14.4%	28.2%	14.8%	26.8%
High school	27.4%	26.0%	34.7%	23.9%	25.6%
Some college/AA degree	28.7%	33.4%	22.7%	32.9%	22.3%
College graduate or more	23.9%	26.2%	14.4%	28.4%	25.3%
Marital Status					
Married	67.9%	65.9%	46.1%	81.7%	77.6%
Widowed	14.9%	7.8%	42.1%	1.9%	11.7%
Divorced/separated	13.2%	20.8%	8.5%	12.1%	8.4%
Never married	4.0%	5.5%	3.2%	4.2%	2.3%
Income					
Less than $25 000	26.6%	19.4%	45.1%	17.5%	29.7%
$25 000 to $75 000	48.5%	49.0%	46.2%	45.8%	54.8%
More than $75 000	24.8%	31.6%	8.8%	36.7%	15.4%
Smoked at least 100 cigarettes in lifetime (%)	54.4%	46.4%	41.1%	64.0%	69.6%
At least 12 drinks in a year (%)	67.7%	63.6%	47.3%	82.7%	77.1%

Appendix 4C. Distribution of frailty index score and frailty phenotype score (out of 1).



Appendix 4D. Proportion of participants in each category of the frailty index and frailty phenotype

		Frailty Index				
		Non-frail	Vulnerable	Frail	Most-frail	**Total**
Phenotype Category	Robust	**25.2%**	30.8%	13.5%	0.1%	69.6% (n= 2851)
	Pre-frail	2.9%	**7.1%**	15.0%	1.8%	26.8% (n= 1098)
	Frail	0.0%	0.0%	**2.2%**	**1.4%**	3.6% (n= 147)
	TOTAL:	28.1% (n= 1032)	37.9% (n= 1552)	30.7% (n= 1257)	3.3% (n= 135)	100% (n=4 096)

Chapter 5

Sedentary behaviour, moderate-vigorous physical activity and frailty in NHANES 2003-2004, 2005-2006

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5.1 Introduction

The benefits of physical activity have been linked with increased physical resiliency [14], and decreased disability [5,17], chronic disease [18,19] and frailty [21,22,24]. Despite the known benefits, the arrival of the technological age has resulted in a decrease in the physical activity level of the population [144] due to an increasing number of sedentary, desk jobs [27] and passive entertainment such as TVs, computers or video games [68]. Older adults have much lower levels of physical activity compared to younger adults; Matthews et al. [28] reported that levels of sedentary behaviour steadily increased with age from 7.25hrs/day in 30-40 year olds to 9.28 in those 70+. While it has been reported that frail older adults, those at an increased vulnerability to adverse health outcomes [7,87,104], tend to be more inactive than non-frail individuals of the same age [215], this evidence is limited and usually focuses on the overall levels of physical activity. An examination of whether patterns of physical activity (such as intensity, day of the week and time of day) differ amongst individuals with varying levels of frailty may provide an understanding of where we need to target interventions.

Research on low levels of physical activity and adverse health outcomes has focused mainly on moderate-vigorous intensity activity (MVPA) [14,15,19,24,57,60,138-141,159,216]; whereas research on the association between sedentary behaviour and adverse health outcomes is limited. Studies that exist show that sedentary behaviours such as TV viewing, work, sitting, and driving are linked to poor health outcomes including cardiovascular problems, metabolism, depression and obesity [23,25,43,45]. This association, albeit attenuated, remains even in those who meet the recommended level of moderate-vigorous physical activity [44].

Frailty is used extensively as a risk stratification tool [217,218] and has been linked with overall levels of physical inactivity [215,219]. However, these studies have not examined the direct and independent impacts of MVPA and sedentary behaviour on frailty. The purpose of this study was to examine the associations between sedentary behaviour, MVPA and frailty. The primary objectives were:

1) To examine how sedentary behaviour and moderate-vigorous physical activity are each experienced during the day across different levels of frailty.
2) To estimate and compare the extent to which high levels of sedentary behaviour and low levels of moderate-vigorous physical activity are associated with increased frailty and other domains of health including self-reported health, disability and healthcare utilization.

5.2 Methods

5.2.1 Sample

This is a secondary analysis of the 2003-2004 and 2005-2006 cohorts of the United States National Health and Nutrition Examination Survey (NHANES). NHANES is a cross-sectional study administered by the Centers for Disease Control and Prevention (CDC) and is considered to be an important large-scale study on identifying prevalence of major diseases and their associated risk factors [208]. For more details about NHANES, refer to the NHANES website [208]. NHANES participants were selected using a complex algorithm and sample weights were provided to ensure that the sample properly represented the U.S population. The 2003-2004 cohort had 10122 participants and the 2005-2006 cohort had 10348. The combined cohorts included 4 874 individuals over the age of 50. We excluded individuals with missing accelerometer or frailty data (see below) for a final sample size of 3146. The NHANES survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention. All patients provided written informed consent. Data was accessed through a public access data file available on the NHANES website [208].

5.2.2 Variables

Physical activity (sedentary behaviour and moderate-vigorous physical activity)

Sedentary behaviour and moderate-vigorous physical activity (MVPA) were measured using ActiGraph AM-7164s, physical activity monitors. Pregnant women, those taking insulin and those who were unable to walk were not given an accelerometer and therefore were excluded from the study. Participants were instructed to wear the monitor on an elastic waist belt on the right hip, underneath the clothing during waking hours for 7 days. The monitors were not waterproof and thus participants were instructed to remove them during any bathing or swimming activities. The accelerometers do not display the data and thus respondents were blind to the data collected while wearing the monitor.

The monitors detect and record the intensity of a movement and store this data according to one-minute time intervals known as epochs. There were 10 080 consecutive minute-by-minute data points for each individual that were categorized in one minute epochs according to: day of the week, hour of the day, minute of the hour, intensity value, step count and sequential observation number in minutes. The intensity of the activity was measured using counts per minute – an arbitrary unit. NHANES provided summary statistics for the daily average of each individual that stated steps per day, wear time and time in light, moderate, vigorous and sedentary behaviour, The NHANES cut-points for each level of physical activity are: sedentary behaviour (0-100 counts/min), light (101-2020 counts/min), moderate (2021-5999 counts/min) and vigorous (6000+ counts/min) [208]. Since the levels of vigorous physical activity were very low, moderate and vigorous physical activity were combined. We also identified those participants who followed the physical activity guidelines suggestion of engaging in at least 2 1/2 hours of moderate to vigorous physical activity (MVPA) each week in bouts of 10 minutes or more [42,159] or 10 000 steps/day [220]. All data that was marked as non- reliable or not in calibration (based on a preliminary review of the raw data by NHANES researchers) was excluded. Only individuals with a minimum of 4 valid days were included in the analysis; a valid day was defined as minimum of 10 hours of wear time. 1421 individuals were excluded from the analysis due to missing physical activity data including not being given an accelerometer, accelerometer not in calibration, unreliable data or too few valid days. Step count was only available for 1475 individuals in the 2005-2006 dataset. The patterns of physical activity (SB and MVPA) examined at each level of frailty were: overall daily activity, activity differences across days of the week, activity differences across times of the day, and proportion who followed PA guidelines.

Frailty

Frailty indexes are used to operationalize frailty by counting the number of deficits an individual has [(116)]. This is based on the deficit accumulation approach; i.e., the more health deficits or problems an individual has, the frailer they will be [(104)]. The frailty index is calculated as a ratio of deficits present out of the total number of possible deficits, giving a continuous score from total fitness [0] to total frailty [1]. The frailty index focuses more on the number of items rather than the nature of the item, thus the items included in an index are not standard. We constructed a frailty index following the guidelines outlined by Searle et al. [(116)]. First, all NHANES variables were screened to establish whether conceptually, they were age and health-related; 136 variables remained. Successively, all remaining variables were screened to examine their association with age, saturation point, prevalence and the level of missing data. Variables were rejected if they did not increase in prevalence with age, if they were uncommon (present in less than 1% of the study population), overly common (deficit was present in 80% or more of individuals by age 80) or were too often missing (missing in more than 5%). The remaining deficits were screened to confirm that they encompassed a broad range of systems, as per standard criteria [(116)]. After these selection criteria were applied, 46 variables remained. See Appendix 4B for a table outlining each variable in detail including coding, frequencies and preval3ences.

All variables that were to be included in the frailty index were recoded. The absence of a deficit was given a score of 0 and the presence of the deficit was given a score of 1. For variables for which there was an intermediate response, such as 'sometimes', a score of 0.5 was assigned. Ordinal variables were recoded to give a score on a scale between 0 and 1. An example of this is “How often do you experience difficulty with X? Never, Rarely, Occasionally, Often, All the time”. This was converted to a score out of 1, by recoding each self-rating to represent a deficit ("Never = 0", "Rarely = 0.25", "Occasionally = 0.5", "Often = 0.75" and "All the time = 1"). Continuous variables were coded based on various cut-off points proposed in the literature. Once all of the variables were recoded on a 1-point scale, the frailty index was calculated using the following equation:

$$FI = \sum d_i / D_T \qquad (1)$$

where FI is the frailty index score on a 1 point scale; where $\sum d_i$ is the sum of the deficits present in the subject; where D_T is the total number of deficits possible in the dataset. If, for example, an individual had 23 out of a possible 46 deficits, they would have a frailty score of 23/46 = 0.5. Any individual who was missing 20% or more of the variables were excluded from the study. Among those with valid physical activity data, a frailty index score could not be calculated for 307 individuals. The high number of excluded cases, which is atypical of frailty indexes, is due to the inclusion of lab values in the frailty index. The frailty index is meant to be used as a continuous score however in order to examine how physical activity differs among levels of frailty, it was also categorized based on proposed cut-off scores [209]. A FI score of $I \leq 0.10$ was considered ‘non-frail’, a score of $0.10 < FI \leq 0.21$ was ‘vulnerable’, a score of $0.21 < FI \leq 0.45$ was ‘frail,’ and $FI > 0.45$ was ‘most frail’ [209].

Other adverse health outcomes

The association between sedentary behaviour, MVPA and adverse health outcomes was also examined for activities of daily living (ADL) disability, self-reported health, and healthcare utilization. All of these measures were scored as dichotomous. ADL disability was identified if there was difficulty with at least one of the 4 ADLs measured in NHANES: using a fork or knife, dressing, getting out of bed, and walking between rooms on the same floor. Self-reported health was scored as high if the subject answered ‘Excellent’, ‘Very good’ or ‘Good’ to “Would you say your general health was” and low if the subject answered ‘Poor’ or ‘Fair’. Healthcare utilization was scored as high if the subject answered 4+ and low if the subject answered 0-3 to "how many times in the last 12 months [they had] seen a doctor or other healthcare professional about their health at a doctor's office, clinic, hospital emergency room, at home or some other place".

Covariates

The covariates, included in our analysis, that have previously been shown to be associated with frailty and physical activity were: sex, age, smoking status, alcohol consumption, BMI, race, education, income, marital status, accelerometer wear time. Race, education level, income bracket and marital status were collected as categorical information. Individuals were asked if they had smoked over 100 cigarettes in their lifetime and if they had at least 12 alcoholic drinks a year. BMI was calculated from a measured height and weight and valid wear time was calculated from the accelerometer data.

5.2.3 Sample weights

Sample weights allow an unbiased estimate of the frailty of the population. NHANES provided sample weights for the 2003-2004 and 2005-2006 cohorts. However, the two-year weights for 2003-2004 and 2005-2006 are not directly comparable, as different population bases were used each year. Data from all participants in both groups were amalgamated to produce a sample size of 3 146. New sample weights were rescaled such that the sum of the weights matched the survey population at the midpoint of 2003-2006. In order to do that, the following formula was used MEC4YR = 1/2 * WTMEC2YR; where MEC4YR is the new four year sample weight of each individual and WTMEC2YR is the original sample weights of this individual provided by NHANES [208].

5.2.4 Statistical Analysis

All statistical analyses were conducted using IBM SPSS 20and SAS 9.23 and were weighted to ensure that the sample was representative of the U.S population. An alpha level of 0.05 was used to determine statistical significance.

Physical activity patterns

Descriptive statistics were used to describe the daily sedentary behaviour and MVPA patterns of participants across different levels of frailty. Total daily time spent in different levels of physical activity intensity was compared between frailty levels using one-way ANOVAs and Tukey's post hoc test. Two-way ANOVAs were used to examine if sedentary behavior and MVPA were accumulated differently across frailty category by day of the week or by time of the day. Morning was considered from 6am to 12pm, afternoon was from 12pm to 6pm and evening was from 6pm to 12am. A transformation regression was also used to create spline regression lines to compare intensities by frailty group at different times of the day; knots (the points where the segments connect) were used for every 20 points. By visual inspection, twenty was determined to be the optimal number of knots to adequately demonstrate a smooth pattern of physical activity over the course of the day. The percentage of individuals who met the recommended 2.5hrs/week of MVPA and who walked 10 000 steps/day were compared across frailty groups using the Kruskal-Wallis test.

Associations between frailty, sedentary behaviour and MVPA

Weighted multiple linear regression models were used to examine if sedentary behaviour and MVPA were associated with frailty. Associations were examined in separate models of sedentary behaviour and of MVPA as well as in a combined model. We used logistic regression models to examine if sedentary behaviour and MVPA were associated with self-reported health, health care utilization and ADL disability. For both the linear and logistic regression, manual backwards regression was used to remove covariates based on least significance. Two covariates- sex and age- were included in every model regardless of their significance; all other covariates were only included if they added significance to the model.

5.3 Results

A total of 3146 participants (mean age 63.3±10.1; 53.7% women; 17.0% ADL disability) were included in this analysis (see Appendix 5A for the characteristics of the sample). Those who were excluded due to missing physical activity or frailty data (mean age 65.9 ±12.0, 54.3% women, 19.8% ADL disability) were slightly older with slightly higher levels of ADL disability. An average of 6.24±0.94 valid days of accelerometer data was available for each person; those who were non-frail or vulnerable were more likely to have more valid of accelerometer data than those who were frail or most frail ($p<0.001$) (see Appendix 5B).

Physical activity patterns

On average across all levels of frailty, individuals had 8.59 hrs/day of sedentary behaviour, 5.40 hrs/day of light activity and 15.3 min/day of MVPA. Average daily levels of vigorous, moderate as well as light activity were highest in those who were non-frail, followed by those who were vulnerable, then frail and finally those who were most frail ($p<0.001$, see Figure 5.1). The opposite pattern was seen with sedentary behavior, where the highest levels were seen in those who were most frail and the lowest in those who were non-frail ($p<0.001$) (see Figure 5.1).

For all frailty groups, there were no differences between weekdays (Monday-Friday) in levels of sedentary behaviour and MVPA. However, sedentary behavior was significantly higher on Sunday compared to all other days for the non-frail, vulnerable and frail groups ($p<0.001$) but not for the most frail group ($p=0.93$) (see Figure 5.2A). In the non-frail and vulnerable groups, levels of MVPA were significantly lower on Sunday than every other day of the week ($p<0.05$) except Saturday ($p=0.34$); levels of MVPA were significantly lower on Saturday compared with Monday ($p<0.05$) as well. There was no difference in MVPA level between days in either the frail ($p=0.20$) or the most frail groups ($p=0.98$) (see Figure 5.2B).

Daily physical activity intensity was similar across all levels of frailty; the most inactive times were before 9:00am and after 6:00pm and the most active time was between 11:00am and 3:00pm.. Nevertheless physical activity intensity was highest at all times of day in the non-frail group, and lowest in the most frail group ($p<0.001$) (See Appendix 5C). All groups were significantly more sedentary in the evening ($p<0.001$) and less sedentary in afternoon ($p<0.001$) (see Figure 5.3A). In the non-frail and vulnerable, levels of MVPA were significantly lower in the evening ($p<0.001$) with no difference between morning and afternoon ($p=0.94$). In those who were frail, levels of MVPA were significantly lower in the evening compared to the afternoon only ($p<0.01$); while the most frail had no difference in levels of MVPA by time of day ($p=0.25$) (See Figure 5.3B).

Only 7.1% of the population met the recommended 2.5 hours of MVPA per week and 33.2% achieved the 10000 steps per day guidelines. Guidelines were least followed in the most frail (1.4 % 2.5hrs of MVPA/week, 6.2% 10000 steps/day) and frail groups (3.5% 2.5hrs of MVPA/week, 11.1% 10000 steps/day) and most followed in the non-frail (8.6% 2.5hrs of MVPA/week, 54.5% 10000 steps/day) and vulnerable groups (9.0% 2.5 of MVPA/week, 35.7% 10000 steps/day). See Appendix 5D.

Associations between frailty, sedentary behaviour and MVPA

Both sedentary behaviour and MVPA were significantly associated with frailty index score (see Table 5.1, Model 1 and 2). Lowering sedentary behaviour by one hour daily decreases frailty index score by 0.019, while adding 1 hour daily of MVPA decreases FI score by 0.084. These associations remained when both measures were included in the model (see Table 5.1, Model 3). The standardized beta coefficients allow the relative comparison of the explained variance between predictor variables; sedentary behaviour explained higher proportion of variance of frailty than MVPA. In the logistic regression, each additional hour per day of sedentary behaviour was associated with a higher odds ratio for ADL disability, low self-reported health and high healthcare use (see Table 2, Models 1-3). Each additional hour day of MVPA was also associated with a lower odds ratio for ADL disability, low self-reported health and high healthcare use, however MVPA was no longer significantly associated with healthcare use when levels of sedentary behaviour was included in the model ($p=0.36$) (See Table 2, Models 1-3). Full tables of all models with details on covariates can be found in Appendix 5E, 5F, 5G and 5H.

5.4 Discussion

This study examined the associations between frailty and patterns of physical activity in a US population above the age of 50. Participants overall spent a significant amount of time in sedentary behaviors (8.6hrs/day) and a limited proportion (7.1%) met the recommended level of weekly MVPA. Levels of physical activity differed significantly by frailty group. Those who were more frail were more likely to have higher levels of sedentary behaviour and lower levels of MVPA; consequently, they were less likely to meet both the recommendation of 2.5hrs of weekly moderate-vigorous physical activity and the targeted 10 000 steps per day. Among non-frail individuals, levels of sedentary behaviour were generally higher on Sundays, and lower in the afternoons. These patterns were not seen in those who were frail, suggesting that frail individuals remain sedentary and inactive regardless of the time of day or day of the week. The impact of one additional hour of MVPA appears to be higher than one fewer hour of sedentary behaviour; even so sedentary behaviour appeared to better explain the variance associated with frailty. High sedentary behaviour and low MVPA were also associated with higher likelihood of poor self-reported health and high ADL disability and sedentary behaviour was associated with higher healthcare utilization.

The cross-sectional nature of the NHANES study is a very important limitation as a temporal relationship cannot be inferred; it is unknown if the associations would have been the same in a longitudinal study. While the accelerometers are recognized as a preferred method to measure physical activity, their inability to capture physical activity that is not step based likely resulted in the underestimation of stationary bike, elliptical activity and weight lifting activities. Furthermore, the accelerometers were not waterproof and had to be removed for bathing, swimming or other water-activities and were also only worn during waking hours. Frail individuals had fewer valid days of accelerometer data, thus their physical activity levels may not be as accurate as individuals who wore the accelerometer all week long. Finally, wear time is a limitation when comparing an individual with 20 hours of wear time and an individual with just 10 hours of wear time. In order to minimize this limitation, most physical activity patterns were presented in percent of total wear time and this wear time was included as a covariate in the regression models.

Physical activity patterns

The lower levels of physical activity in frail individuals is consistent with previous evidence that physically inactive individuals have higher levels of functional disability [221], and other adverse health outcomes such as frailty [24]. Individuals who have high levels of sedentary behaviour are more likely to become frail [24,143] just as individuals who are frail are more likely to engage in high levels of sedentary behaviour [42] or be more inactive than non-frail individuals of the same age [215].

Levels of sedentary behaviour were highest on Sunday in all groups except for the most frail group. Similarly, levels of MVPA were lowest on Sunday in those who were non-frail, while frail individuals were consistently inactive on every day of the week. Most studies are in agreement with our findings that weekends are associated with lower physical activity in both the younger and the older population [222-225]; even so a limited number of studies have found that there is no difference in physical activity by weekday [226]. Sunday is frequently regarded as a day of rest, whether due to religious significance [227] or a 'deserved' day of rest at the end of a week [228,229]. The inability to sustain high levels of activity throughout the full week is thought to be due to a variety of potential reasons: loss of motivation [230,231], lack of adequate time [232], lack of self-efficacy [233], etc. However, the majority of theses studies have examined children and adolescents, with very few focusing on the older adult population [234,235].

Across all frailty groups, levels of sedentary behaviour were lowest in the afternoon and highest in the evening. This is consistent with previous studies, which have found higher levels of sedentary behaviour between 6pm and 12am [236,237] on both weekdays and weekend days [238]. Sedentary behaviours are often accumulated in the evening where levels of MVPA are low as it is common for individuals to watch television, use the computer, read a book or sit at the end of the day [45,239]. However, the frail remained inactive regardless of the time of day. Once again, those who are frail fail to demonstrate the typical pattern of the rest of the population. Future studies should further explore the differences in patterns of physical among older adults. Identification of these physical activity patterns can help suggest periods where interventions may be most appropriate to increase physical activity and decrease sedentary behaviour in these individuals. Although the benefits of MVPA have been the primary focus with respect to physical activity to date, the risk of leading a sedentary lifestyle also warrants significant consideration.

Associations between frailty, sedentary behaviour and MVPA

Peterson et al. [24] and Hubbard et al. [143] reported an association between high self-reported physical activity and decreased frailty incidence. Both studies examined frailty after a 5year follow-up in an older population; Peterson et al. [24] measured frailty as the presence of functional limitations and Hubbard et al. [143] used a frailty index. The current study findings were also consistent with findings from a small sample (n=50) study by Theou et al. [240] in which sedentary behaviour, measured by accelerometers, was significantly associated with frailty, measured by a frailty index. Despite the persuasive evidence that sedentary behaviors are associated with adverse health outcomes, no study had previously examined if these behaviors were independent of MVPA. This study was able to identify the distinct effects of sedentary behaviour and MVPA on frailty. For example, in order to decrease the frailty score of an individual by 0.05, all other covariates held constant, the individual can increase their MVPA by approximately 1 hour (1*[β=0.045]) or decrease their sedentary behaviour by just under 3 hours (3*[β=0.016]. An even smaller decrease in sedentary behaviour by just 1.5 hours daily or a 30min daily increase in MVPA would still decrease frailty index score by 0.023. While these estimates apply to the whole sample, it is likely the benefits and risks are not uniformly distributed across levels of the frailty. Future research could examine how the impact of physical activity levels differs between a frail and a non-frail person.

ADL disability, self-reported health and healthcare utilization were associated with low MVPA and high sedentary behaviour. Other studies have confirmed associations between time spent in MVPA and disability [241] as well as between sedentary behaviour and disability [49,242]. The positive association between levels of

MVPA and self-reported health in the present study was comparable to a study of MVPA and self-reported health in a Norwegian population, aged 65+, which found that those who were more active were more likely to report their health as ‘good’ or ‘very good’ [50]. Another accelerometer study of a community-dwelling population, aged 65+ in the UK found that overall daily step count was associated with self-reported health, as measured by a complex health survey form. While MVPA and sedentary behaviour were both associated with healthcare utilization; MVPA was no longer significant when sedentary behaviour was included as a covariate. Previous studies in older populations have demonstrated associations between increased physical activity and decreased overnight hospitalization [51], decreased emergency care visits [243] and decreased physician visits [244].

5.5 Conclusion

This study was the first to distinguish the physical activity patterns of varying levels of frailty, demonstrating that there are some difference in the way physical activity is accumulated. For example, healthier individuals tended to have a “rest day” on Sunday, while the frailest group fails to demonstrate this pattern; for them, ‘every day is a Sunday.’ The study also established a positive relationship between sedentary behaviour and frailty, independent of MVPA using robust measures of frailty and physical activity; the frailty index, a reliable predictor of adverse health outcomes [8,84] and the accelerometer, a reliable mechanism to measure daily physical activity without the risk of reporting bias [160]. Future research should examine the causal association between physical activity and frailty using a longitudinal study. The government, healthcare professionals and society in general should also consider the benefits of any level of physical activity, specifically the reduction of sedentary behaviors. Decreasing sedentary behavior has the potential to be an easy, cost effective, feasible lifestyle change that could encourage healthy aging and decrease frailty.

Tables

Table 5.1 Adjusted linear regression examining the associations between frailty and sedentary behaviour and moderate-vigorous physical activity (MVPA).

		Univariate Pearson correlation	Unstandardized β coefficient (SE)	Standardized β coefficient	p-value
***Model 1**	*Sedentary behaviour (hrs)*	0.23	0.019 (0.001)	0.3	p<0.001
****Model 2**	*MVPA (hrs)*	-0.33	-0.084 (0.007)	-0.22	p<0.001
***Model 3**	*Sedentary behaviour (hrs)*		0.016 (0.002)	0.25	p<0.001
	MVPA (hrs)		-0.045 (0.009)	-0.12	p<0.001

* controlled for significant covariates (age, gender, wear time, race, marital status)
** controlled for significant covariates (age, gender, wear time, race)

Table 5.2. Adjusted logistic regression examining the associations between other adverse health outcomes and sedentary behaviour and moderate-vigorous physical activity (MVPA).

		Outcome: Self-reported health *		Outcome: Healthcare use **		Outcome: ADL disability***	
		Univariate Pearson correlation	Odds ratio (95% CI)	Univariate Pearson correlation	Odds ratio (95% CI)	Univariate Pearson correlation	Odds ratio (95% CI)
Model 1	*Sedentary behaviour (hrs)*	0.036	1.34 (1.24-1.45)	0.09	1.30 (1.20-1.41)	0.14	1.43 (1.32-1.56)
Model 2	*MVPA (hrs)*	-0.136	0.11 (0.06-0.20)	-0.85	0.42 (0.25-0.73)	-0.19	0.06 (0.03-0.14)
Model 3	*Sedentary behaviour (hrs)*		1.16 (1.05-1.27)		1.28 (1.16-1.33)		1.31 (1.19-1.43)
	MVPA (hrs)		0.24 (0.12-0.50)		0.77 ✝ (0.44-1.34)		0.15 (0.07-0.33)

✝ non-significant addition to model
* controlled for significant covariates (Model 1: age, gender, wear time, race; Model 2-3: age, gender, wear time, race, education)
** controlled for significant covariates (Model 1-3: age, gender, wear time)
*** controlled for significant covariates (Model 1-3: age, gender, wear time, race)

Figures

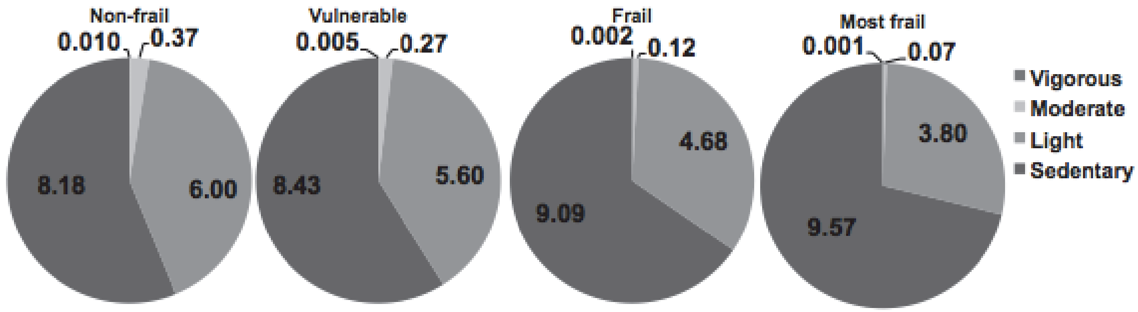


Figure 5.1. Total daily time (hours) spent in sedentary behaviour, light, moderate and vigorous activity by frailty group.

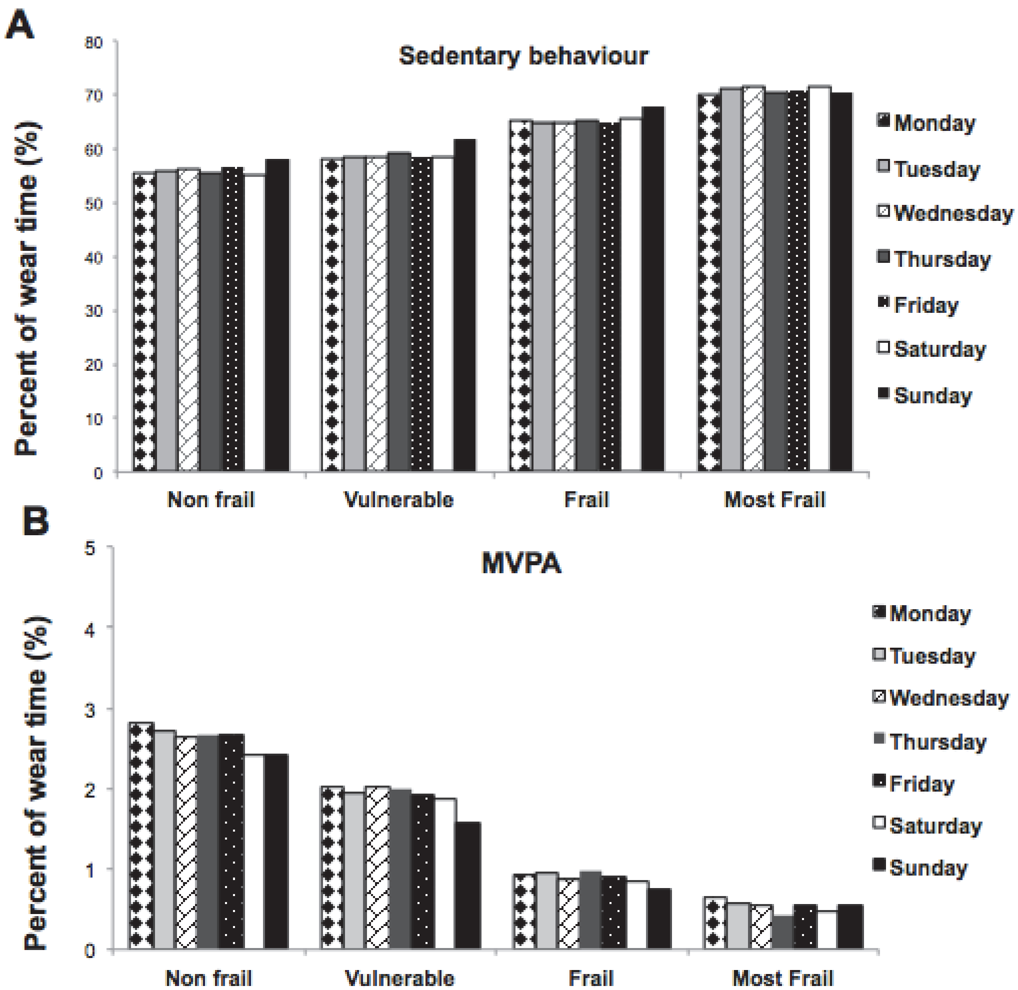


Figure 5.2. Percent of wear time, by day of the week and frailty group, spent in A. Sedentary behaviour and **B**. moderate-vigorous physical activity (MVPA). *Note the difference in scale between figure A and B.*

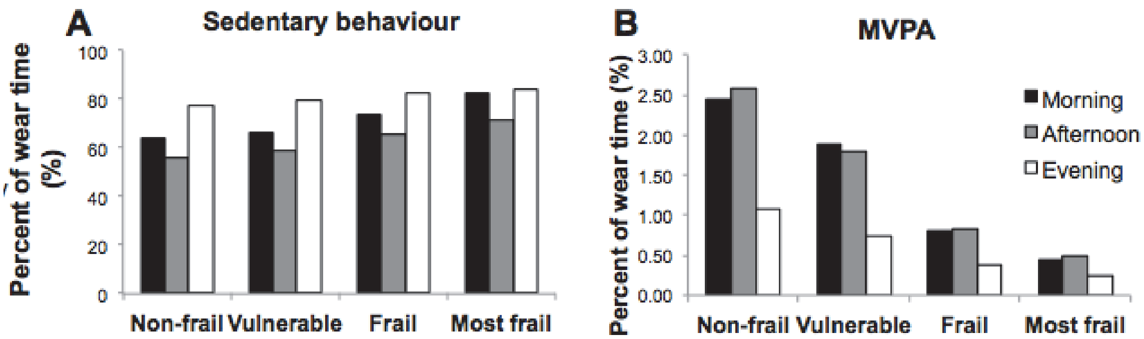


Figure 5.3. Percent of wear time, by time of the day and frailty group, spent in A. Sedentary behaviour and B. moderate-vigorous physical activity (MVPA).

Appendix

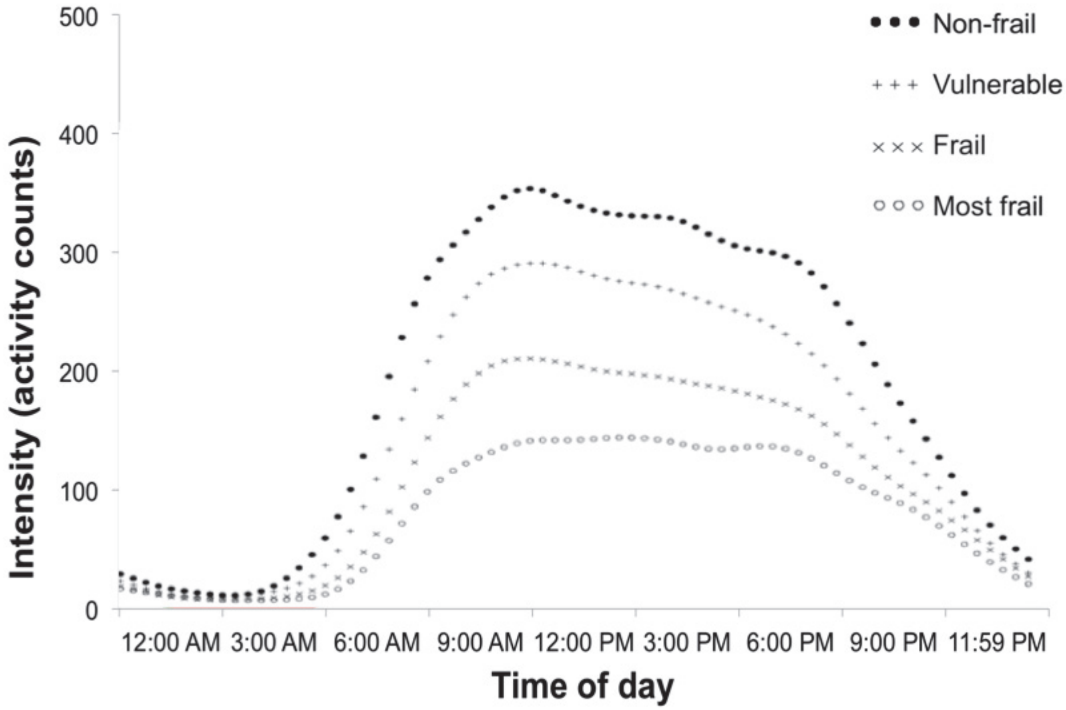
Appendix 5A. Characteristics of the sample (weighted)

	All n = 3146	Non-frail n = 713	Vulnerable n = 1225	Frail n = 1086	Most frail n = 122
Age (years ± SD)	63 ± 10	58 ± 7	63 ± 10	68 ± 10	70 ± 11
Sex (% female)	53.7	46.4	55.3	56.5	74.3
Race/Ethnicity (%)					
Non-Hispanic white	81.4	81.5%	81.7%	80.9%	80.0%
Non-Hispanic black	8.2	7.0%	7.7%	9.7%	11.9%
Mexican-American	6.3	7.2%	7.0%	4.7%	2.2%
Other	4.2	4.3%	3.6%	4.6%	6.0%
Body mass index (kg/m^2 ± SD)	25.2 ± 7.3	25.6 ± 7.7	25.2 ± 7.3	25.1 ± 7.4	25.5 ± 7.3
Education (%)					
Less than high school	18.9	11.1%	17.7%	25.9%	42.5%
High school	26.9	23.4%	27.0%	30.6%	25.9%
Some college/AA degree	29.5	32.5%	28.9%	28.1%	22.0%
College graduate or more	24.6	33.0%	26.5%	15.4%	9.6%
Marital Status					
Married	68.6	76.5%	70.5%	60.4%	47.6%
Widowed	13.6	5.9%	12.0%	21.7%	31.8%
Divorced/separated	13.9	14.2%	13.4%	14.1%	15.7%
Never married	3.8	3.4%	4.0%	3.9%	4.9%
Income					
Less than $25 000	36.8%	36.2%	36.5%	37.3%	42.1%
$25 000 to $75 000	43.8%	43.1%	44.0%	44.8%	37.2%
More than $75 000	19.4%	20.7%	19.5%	17.9%	20.7%
Smoked 100+ cigarettes ever (%)	49.4	46.8%	50.4%	50.0%	54.3%
Drank 12+ drinks in last year (%)	66.4	67.7%	66.7%	65.3%	60.8%

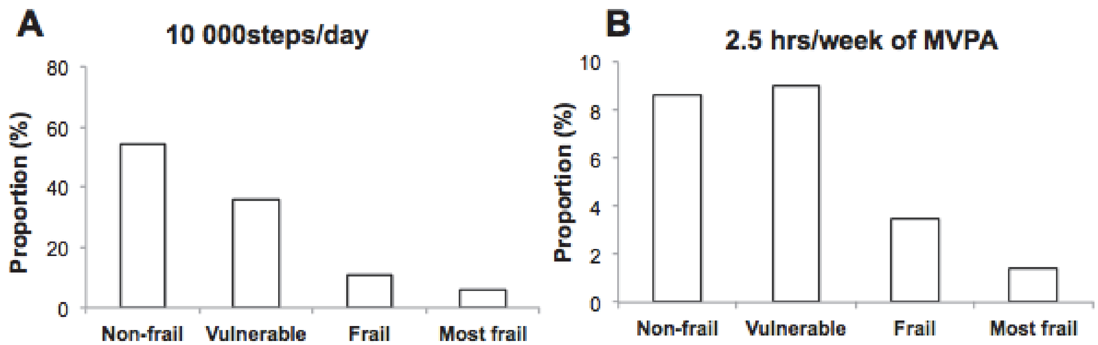
Appendix 5B. Proportion of participants having 4-7 days of valid accelerometer data by frailty group

	Number of valid days of accelerometer wear			
	4	**5**	**6**	**7**
Whole sample	7.1%	13.8%	27.1%	52.0%
Frailty group				
Non-frail	6.5%	14.1%	25.0%	54.4%
Vulnerable	6.0%	11.8%	29.9%	52.3%
Frail	8.7%	15.0%	25.5%	50.8%
Most frail	11.8%	23.9%	26.0%	38.2%

Appendix 5C. Level of physical activity intensity across the day by frailty group, using a spline regression



Appendix 5D. Proportion of participants who A. walked 10 000 steps per day or B. met the guidelines for weekly moderate-vigorous physical activity (MVPA).



Appendix 5E. Adjusted linear regression examining the associations between frailty and sedentary behaviour and moderate-vigorous physical activity (MVPA).

		Outcome: Frailty		
		Unstandardized β coefficient (SE)	**Standardized β coefficient**	**p-value**
Model 1	*Sedentary behaviour (hrs)*	0.019 (0.001)	0.3	p<0.001
	Age (yrs)	0.003 (0.000)	0.29	p<0.001
	Gender	0.022 (0.004)	0.1	p<0.001
	Wear time (hrs)	-0.022 (0.002)	-0.31	p<0.001
	Race	0.007 (0.003)	0.05	p<0.05
	Marital status	0.009 (0.004)	0.04	p<0.05
Model 2	*MVPA (hrs)*	0.019 (0.001)	-0.3	p<0.001
	Age (yrs)	-0.006 (0.001)	0.09	p<0.001
	Gender	0.004 (0.0001)	0.32	p<0.001
	Wear time (hrs)	-0.084 (0.007)	-0.22	p<0.001
	Race	0.008 (0.004)	0.02	p<0.05
Model 3	*Sedentary behaviour (hrs)*	0.016 (0.002)	0.25	p<0.001
	MVPA (hrs)	-0.045 (0.009)	-0.12	p<0.001
	Age (yrs)	0.003 (0.001)	0.27	p<0.001
	Gender	0.017 (0.003)	0.07	p<0.001
	Wear time (hrs)	-0.019 (0.002)	-0.26	p<0.001
	Race	0.006 (0.003)	0.04	p<0.05
	Marital status	0.009 (0.004)	0.04	p<0.05

Appendix 5F. Adjusted logistic regression examining the associations between self-reported health and sedentary behaviour and moderate-vigorous physical activity (MVPA).

		Outcome: Self-reported health Odds ratio (95% CI)
Model 1	*Sedentary behaviour (hrs)*	1.34 (1.24-1.45)
	Age (yrs)	1.00 (0.99-1.01) *
	Gender (female)	1.05 (0.84-1.31) *
	Wear time (hrs)	0.70 (0.64-0.76)
	Race	
	Non-hispanic white	1
	Non-hispanic black	2.56 (1.79-3.67)
	Hispanic	3.83 (2.57-6.71)
	Other	1.46 (0.85-2.50) *
Model 2	*MVPA (hrs)*	0.11 (0.06-0.20)
	Age (yrs)	1.00 (0.99-1.01) *
	Gender (female)	0.82 (0.65-1.03)
	Wear time (hrs)	0.89 (0.83 -0.95)
	Race	
	Non-hispanic white	1
	Non-hispanic black	2.29 (1.6-3.28)
	Hispanic	3.51 (2.35-5.23)
	Other	1.42 (0.83-2.43) *
Model 3	*Sedentary behaviour (hrs)*	1.16 (1.05-1.27)
	MVPA (hrs)	0.24 (0.12-0.50)
	Age (yrs)	0.99 (0.98-1.0) *
	Gender (female)	0.97 (0.75-1.26) *
	Wear time (hrs)	0.78 (0.71-0.87)
	Race	
	Non-hispanic white	1
	Non-hispanic black	2.18(1.56-3.05)
	Hispanic	3.46 (2.52-4.76)
	Other	1.48 (0.74-2.98)*
	Education	
	< High school vs Completed high school	1.41 (1.00-1.98)
	< High school vs Some college	1.12 (0.8-1.57)*
	< High school vs College degree or more	1.23 (0.85-1.78)*

* non-significant addition to model

Appendix 5G. Adjusted logistic regression examining the associations between healthcare utilization and sedentary behaviour and moderate-vigorous physical activity (MVPA)

		Outcome: Healthcare utilization
		Odds ratio (95% CI)
Model 1	*Sedentary behaviour (hrs)*	1.30 (1.20-1.41)
	Age (yrs)	1.00 (0.99-1.02) *
	Gender (female)	1.01 (0.80-1.27) *
	Wear time (hrs)	0.76 (0.69-0.83)
Model 2	*MVPA (hrs)*	0.42 (0.25-0.73)
	Age (yrs)	1.01 (1.00-1.02)
	Gender (female)	0.89 (0.70-1.12) *
	Wear time (hours)	0.91 (0.85-0.98)
Model 3	*Sedentary behaviour (hrs)*	1.28 (1.16-1.33)
	MVPA (hrs)	0.77 (0.44-1.34) *
	Age (yrs)	1.00 (0.99-1.02) *
	Gender (female)	0.98(0.77-1.25)*
	Wear time (hours)	0.77 (0.70-0.85)

* non-significant addition to model

Appendix 5H. Linear regression examining the associations between ADL disability and sedentary behaviour and moderate-vigorous physical activity (MVPA).

		Outcome: ADL disability
		Odds ratio (95% CI)
Model 1	*Sedentary behaviour (hrs)*	1.43 (1.32-1.56)
	Age (yrs)	1.01 (1.00-1.02) *
	Gender (female)	1.07 (0.84-1.36) *
	Wear time (hours)	0.72 (0.65-0.79)
	Race	
	Non-hispanic white	1
	Non-hispanic black	1.94 (1.31-2.87)
	Hispanic	1.34 (0.81-2.23) *
	Other	1.14 (0.62-2.07) *
Model 2	*MVPA (hrs)*	0.06 (0.03-0.14)
	Age (yrs)	1.01 (1.00-1.02)
	Gender (female)	0.81 (0.64-1.04) *
	Wear time (hours)	0.96 (0.89 – 1.03) *
	Race	
	Non-hispanic white	1
	Non-hispanic black	1.71 (1.16-2.51)
	Hispanic	1.20 (0.73-1.99) *
	Other	1.09 (0.60-1.98)*
Model 3	*Sedentary behaviour (hrs)*	1.31 (1.19-1.43)
	MVPA (hrs)	0.15 (0.07-0.33)
	Age (yrs)	1.00(0.99-1.02) *
	Gender (female)	0.91 (0.71-1.17) *
	Wear time (hours)	0.78 (0.71-0.87)
	Race	
	Non-hispanic white	1
	Non-hispanic black	1.81(1.22-2.68)
	Hispanic	1.36 (0.81-2.26) *
	Other	1.12 (0.61-2.04)*

* non-significant addition to model

Chapter 6. Conclusion

The accompaniment of high levels of sedentary behaviour with a rapidly aging population has given rise to concern about the effect of physical activity- or lack of- on the health of older adults. This thesis examined the relationship between sedentary behaviour, MVPA and frailty. The main objectives were to: (1) examine whether the frailty index and frailty phenotype demonstrate common characteristics of frailty scales(Chapter 4); (2) examine the association between each definition of frailty and adverse health outcomes (Chapter 4); (3) examine how sedentary behaviour and moderate-vigorous activity are each experienced during the day across different levels of frailty (Chapter 5); (4) estimate and compare the extent to which high levels of sedentary behaviour and low levels of moderate-vigorous activity are associated with increased frailty and other domains of health (Chapter 5).

Construction of a frailty index and a frailty phenotype in NHANES (chapter 4) revealed that despite differing magnitudes, both measures demonstrated previously established characteristics of frailty including a right skewed distribution of frailty, higher levels of frailty in women compared to men, an upper limit of deficit accumulation and an exponential increase with age. Both the frailty index and phenotype were associated with disability, self-reported health and healthcare utilization, with a particular high overlap between frailty and disability. Despite the effectiveness of both definitions of frailty, the frailty index demonstrated stronger associations with self-reported health and healthcare utilization as well as the ability to discriminate levels of frailty better at the lower to middle end of the frailty continuum.

Chapter 5 demonstrated that the overall population is highly sedentary, averaging approximately 8.5 hours of sedentary behaviour daily with only a small proportion (approximately 7%) meeting the recommended weekly levels of MVPA. Sedentary behaviour was highest in the most frail individuals while MVPA was highest in non-frail individuals. Although overall physical activity levels were low in the whole sample, there were some differences in physical activity patterns between frailty groups. Non-frail individuals demonstrated higher levels of sedentary behaviour in the evenings and on Sundays as compared to the rest of the week. Frail individuals did not demonstrate these patterns, instead remaining sedentary regardless of time of day and day of the week.

Chapter 5 also demonstrated that individuals who are highly sedentary or highly inactive (low levels of MVPA) were at increased risk of being frail. Sedentary behaviour and MVPA had independent effects on frailty; regardless of the amount of MVPA an individual does, sedentary behaviour can still increase the risk of being frail. Although overall sedentary behaviour was able to better explain the variance associated with frailty, the impact of one additional hour of MVPA was stronger than one fewer hour of sedentary behaviour. Decreasing sedentary behaviour by 3 hours daily or increasing MVPA by 1 hour daily would decrease the frailty index score by approximately 0.045. An even smaller decrease in sedentary behaviour by just 1.5 hours daily or a 30min daily increase in MVPA would still decrease frailty index score by 0.023. While these are estimates for the overall population, it is likely that the benefits and risks are not uniformly distributed across levels of the frailty. Individuals who were highly sedentary or highly inactive were also more likely to have poor self-reported health, high ADL disability and higher healthcare usage.

6.1 Strengths

In previous studies that examined physical activity and frailty, sedentary behaviour and MVPA have not been examined independently. Even so, from previous studies that examined other adverse health outcomes we know that sedentary behaviour has often been confounded by moderate-vigorous activity and vice versa. This is, to the best of our knowledge, the first study that examined the independent effects of sedentary behaviour and MVPA on frailty. NHANES is a high quality dataset; furthermore, complex statistical processes were used to ensure that the sample was representative of the country's population and thus generalizable. Many studies that examined frailty and its precursors have focused on the older population, aged 65 and over. As frailty is a construct that begins earlier than 65, this study included both the middle aged and older aged population to examine the associations at a broader age range as well.

Another major strength of this thesis is the measurement of frailty and physical activity, using valid and reliable tools. This thesis compared the two most commonly used approaches to frailty (chapter 4), discovering that although both were reliable, the frailty index had some advantages over the frailty phenotype. The frailty index is considered to be a more robust and sensitive measure of frailty than other frailty indicators. Due to this and the findings of chapter 4, we used the frailty index in chapter 5 to examine the relationship of physical activity and frailty. Accelerometers are reliable devices to measure physical activity during daily life. Many studies have used self-report, TV watching, reading, etc. as a proxy measure of sedentary behaviour, but these measures are not as accurate especially in older adults. The use of accelerometers eliminates the risk of reporting bias, which has often associated with self-reported data.

6.2 Limitations

It must be acknowledged that the cross-sectional design of the NHANES dataset restricts any indication of a temporal relationship between sedentary behaviour, MVPA and frailty. However, *temporality* is only one component of the Bradford Hill criteria of causation, a commonly used method of assessing causation [245]. We must also consider strength of association, consistency, specificity, dose-response relationship, biological plausibility, coherence, experiment and analogy. *Strong, statistically significant associations* were found between sedentary behaviour, MVPA and frailty. The results were *consistent* with a large majority of studies that have examined the relationship between sedentary behaviour and adverse health outcomes [24,49,50,143,246] as well as MVPA and adverse outcomes [24,143,241]. *Specificity,* the idea that one exposure causes one outcome, is not immediately apparent in the domain of physical activity and adverse health outcomes. However, the decreased risk of adverse health outcomes in those who are physical activity offers support to some extent of specificity. A *dose-response* relationship was identified, as levels of sedentary behaviour got increasingly higher as levels of frailty increased. Furthermore, this association demonstrated both *biological plausibility and coherence* with existing theory and knowledge*;* there is strong evidence suggesting that physical inactivity is bad for an individual's health [24,42,47,50,120,140,173,234]. Although the effect of physical activity on health is better observed over a longer period of time, some *experimental* trials have demonstrated that physical activity interventions have a positive effect on health [247-249]. Finally, we consider the analogy of smoking and lung cancer in reference to sedentary behaviour and frailty. Just as smoking can cause an increased risk of lung cancer, sedentary behaviour can also result in a higher risk of becoming frail.

There is a possibility of selection bias in the NHANES study; those who consented to participate in the study are likely systematically different from those who chose not to participate. NHANES oversampled certain groups of individuals including: African Americans, Mexican Americans, low income individuals and individuals over the age of 60. However, NHANES ensured that external validity, the extent to which results of a study are generalizable to the population, was maintained by using weighted samples to ensure that the sample was representative of the U.S population. In addition, there were many incentives associated with participating in the study; notably, participants were offered free physical examinations and received monetary reimbursement to cover any potential expenses. Only ambulatory, non-pregnant individuals were given an accelerometer, thus the sample included in the analysis of chapter 5 does not adequately represent individuals with severe mobility issues.

The final limitation is one of the afore mentioned strengths- the accelerometer. While accelerometers are able to capture physical movement accurately, they may not have captured all of the physical movement of an individual. The accelerometers were not waterproof so had to be removed for bathing, swimming or other water-activities and were also only worn during waking hours. Additionally, the accelerometers record ambulatory, uniaxial movement well, but may underestimate stationary bike, elliptical activity and weight lifting activities. There has been diversity in the use of accelerometers across studies including different models, different locations on the body including hip [142,189] and wrist [189] as well as the use of different algorithms to quantify movement. Different cut off points have often used in different studies making conclusions from some studies controversial and comparison between studies quite difficult [250]. Cut-offs for physical activity intensity categories have yet to be determined, especially for frail people; proposed cut-off points from NHANES was used in the analyses of this thesis for consistency. Despite these limitations, accelerometers are known to be the most reliable and frequently used measure of daily sedentary behaviours compared to subjective alternatives [28,37-41,47].

6.3 Implications for future research

As described in the thesis, there is currently a research gap on sedentary behaviour and frailty, specifically when considering MVPA as well. Future research should continue to examine associations between sedentary behaviour, MVPA and frailty so that the results can be replicated in different settings using different methods to confirm the findings. Although findings are often generalized between the U.S and Canada, studies could consider replicating the methodology used in this thesis in a Canadian population using the Canadian Health Measures Survey (CHMS), another large scale series of studies that have used accelerometers to quantify physical activity. Due to the cross-sectional nature of NHANES, we are unable to infer a temporal relationship between high levels of sedentary behaviour, low levels of MVPA and frailty. A longitudinal study is crucial in confirming the consequences of high sedentary behaviour and low MVPA. These studies could aid in determining the duration of sedentary behaviour that causes adverse health outcomes in order to help create a public health guideline.

Future studies should also further explore the differences in patterns of physical activity among middle aged and older adults. Identification of these physical activity patterns can help suggest periods where interventions may be most appropriate to increase physical activity and decrease sedentary behaviour in these individuals. This thesis did not examine how the bout duration or frequency of certain types physical activity affected frailty. There has been limited evidence with regards to bout duration and frequency and their consequences [251]; this research area requires further examination. Although accelerometers provide an objective, thorough measure of physical activity, they fail to capture the type of sedentary behaviour/physical activity. Using a daily log as well as an accelerometer could provide information on the type of sedentary behaviour an individual engages in; this would allow for consideration in interventions that target popular forms of sedentary behaviour.

6.4 Implications for policy makers

Although the benefits of exercise (mostly MVPA) have been the primary focus of the physical activity movement, the risk of leading a sedentary lifestyle also warrants significant consideration. This thesis demonstrated that sedentary behaviour, independent of MVPA, had a negative association with adverse health outcomes, including frailty, ADL disability, self-reported health and health care utilization. Governments, healthcare professionals and society in general should not only emphasize the benefits of exercise, but should also consider the reduction of sedentary behaviors. Future policy interventions targeting physical activity should consider sedentary behaviour and MVPA as two distinct concepts. Specifically, the Canadian Physical Activity Guidelines recommend a minimum of 2.5hrs/week of MVPA (42,159); a public health guideline on sedentary behaviour should also be created. This is of particular importance in the technological age as more and more individuals are beginning to spend the majority of their day and life in a sedentary state. While the increase in sedentary desk jobs is inevitable, modifications in workplaces and office spaces have the potential to help counter the difficulty of sedentary behaviour. Elderly patients are often prescribed bed rest and minimal movement in order to ensure that they are safe and not overexerted; a significant finding could cause a simple change in the policy surrounding care of the elderly. Finally, the identification of specific patterns of physical activity in the frail can identify specific areas where interventions may be needed. In summary, decreasing sedentary behaviour has the potential to be an easy, cost effective, feasible lifestyle change that would encourage healthy aging, and decrease frailty, disability, chronic disease and healthcare utilization.

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Appendix A. Signed copyright request form

27 July 2014

Reviews in Clinical Gerontology
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I am preparing my Master of Science thesis for submission to the Faculty of Graduate Studies at Dalhousie University, Halifax, Nova Scotia, Canada. I am seeking your permission to include a manuscript version of the following paper(s) as a chapter in the thesis:

Frailty in Relation to Sedentary Behaviours and Moderate-Vigorous Intensity Physical Activity
Joanna Blodgett, Olga Theou, Susan Kirkland, Pantelis Andreou, Kenneth Rockwood
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