UNDERSTANDING THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND FRAILTY

by

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Dalhousie University is located in Mi'kma'ki, the

ancestral and unceded territory of the Mi'kmaq.

We are all Treaty people.

Dedication Page

I am grateful for the opportunity to learn and grow during my dissertation process. I want to thank my mentors and colleagues for their patience and support. It has been a long ride, but one with many great experiences. Thank you for letting me learn from you.

To my dad, who instilled a hard work ethic, pushed me to try difficult things, and knew when I needed tough love. Thank you.

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Abstract

Frailty, characterized by decreased physiological reserve and increased vulnerability to stressors, is a significant concern among aging populations. Physical activity has been identified as crucial for mitigating frailty, yet gaps remain in understanding how different factors influence this relationship. This dissertation addresses these gaps by examining the associations between physical activity and frailty, considering factors such as age, sex, activity types, measurement tools, and the impact of other lifestyle behaviours. Three manuscripts investigate various aspects of this relationship.

Manuscript 1 shows that engaging in both or either of the recommended levels of moderate-to-vigorous physical activity (MVPA) and resistance training (RT) is associated with reduced frailty, with males showing the strongest associations, especially in older ages. Manuscript 2 investigates how frailty measurement tools influence the relationship between physical activity and frailty. This manuscript revealed a difference in association by frailty tool used, particularly with moderate-to-vigorous physical activity and resistance training analysis. Manuscript 3 expands on these findings by examining the influence of lifestyle behaviors on frailty. It shows that poor lifestyle behaviors are linked to increased frailty risk, regardless of physical activity levels. However, active individuals generally exhibit lower frailty levels than inactive individuals, suggesting physical activity's potential to mitigate the negative effects of poor lifestyle behaviors.

This dissertation contributes to understanding the complex relationship between physical activity and frailty. It emphasizes the importance of considering age, sex, frailty measurement tools, and lifestyle behaviors when designing interventions to prevent and reduce frailty in aging populations. Further research is recommended to explore sex and age differences in physical activity interventions and develop a framework for selecting appropriate frailty measurement tools in future studies.

List of Abbreviations Used

ACSM	American College of Sports Medicine
ADL	Activities of Daily Living
CFS	Clinical Frailty Scale
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CLSA	Canadian Longitudinal Study on Aging
EFS	Edmonton Frail Scale
FI	Frailty Index
FRAIL	Fatigue, Resistance, Ambulation, Illness, and Loss of weight Scale
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HR	Hazard Ratio
MEC	Mobile Examination Center
MVPA	Moderate-to-Vigorous Physical Activity
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
PASE	Physical Activity Scale of the Elderly
RT	Resistance Training
SHARE-FI	Survey of Health, Aging, and Retirement in Europe Frailty Instrument
SOF	Study of Osteoporotic Fractures

TFI	Tilburg Frailty Indicator
WHO	World Health Organization

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Chapter 1 Introduction

The risk of becoming frail has increased globally (1), which is concerning given its association with adverse health outcomes such as falls, hospitalizations, institutionalization, and premature mortality (2,3). Frailty is defined as a multifaceted condition that reduces one's physiological reserve, ultimately leading to increased vulnerability (4,5). Therefore, finding ways to mitigate frailty has become a priority among health professionals and researchers aiming to alleviate individual and healthcare burdens. Various methods have been explored for reducing frailty (6,7); one of the most promising is engaging in physical activity (8–10). A recent systematic review and meta-analysis of randomized control trials by Negm et al. (2019) concluded that physical activity is one of the most effective frailty interventions (8). The World Health Organization (WHO) recommends that individuals aged 65 years and older engage in at least 150 minutes of moderate-to-vigorous aerobic activity per week (i.e., running/biking) and at least two days of resistance training per week (i.e., weightlifting/push-ups) (11). While experts agree that adhering to these age-based guidelines can help reduce frailty (9,10), many people struggle to attain them, especially older adults (12,13).

The WHO guidelines leave uncertainties about whether engaging in one type of physical activity (e.g., moderate-to-vigorous aerobic activity) but not another (e.g., resistance training) can effectively mitigate frailty or if both are necessary to achieve meaningful benefits. For example, an individual might meet or exceed the 150 minutes of moderate-vigorous aerobic activity each week but not partake in resistance training. The complex relationship between frailty and physical activity is an evolving but still relatively new study area. Exploring how different types of physical activity are independently associated with frailty may be prudent in addressing gaps in the literature.

A wide variety of frailty assessment tools have been developed for use in physical activity research (10,14). Many of these are well-validated screening instruments (15–17). That, while reliable, possesses inherent characteristics that can influence variability in activity- and frailty-related effect sizes. For example, some frailty tools exclusively measure changes in physical frailty (e.g., performance on chair stands or grip strength). Participating in a physical activity intervention may significantly improve their physical frailty score, but this may not fully capture a holistic view of their health. Frailty is more complex than just physical capability (18,19). In other words, a more comprehensive frailty measure may present a different narrative than one solely focused on physical changes. Limited studies have demonstrated whether physical activity interventions yield differing outcomes depending on the frailty assessment tools used (20). More research is needed to determine whether frailty tool selection impacts our understanding of the relationship between frailty and physical activity.

Frailty levels and physical activity behaviours differ by sex and age (13,21–24). There is a growing emphasis on using sex-disaggregated statistics in health research (25) to gauge how health interventions affect males and females differently. The health profiles and behaviours of both males and females change over the lifespan (26). For example, while physical activity levels decline with age for both sexes, females tend to be less active than males at every stage of life (27–29). Furthermore, at any age, females are more likely to have higher frailty scores than males (23). Understanding how the relationship between physical activity and frailty is impacted by sex and age is crucial for refining interventions appropriately for these populations.

Despite the aforementioned gaps, engaging in physical activity to promote health and reduce frailty is well-supported. However, physical activity is just one of many lifestyle behaviours an individual can adopt to support healthy aging. Lifestyle behaviours encompass “everyday activities that result from an individual’s values, knowledge, and norms shaped by broader cultural and socioeconomic context (30)”. These include, but are not limited to, diet quality, smoking habits, and sedentary time. While many studies examine these lifestyle behaviours individually (31–33)**,** few explore how combinations of them may affect frailty. For instance, an individual may meet the recommended amount of moderate-to-vigorous physical activity each week, but what if they are also an avid smoker and binge drinker? Does the health benefit derived from physical activity protect this individual from the adverse effects of smoking and excessive alcohol consumption? As important as it is to be physically active, it is imperative to understand better how an individual's lifestyle behaviors interact and impact frailty. If unhealthy behaviours impede the positive effects of physical activity on frailty, it could significantly impact care plan strategies.

Therefore, this thesis aims to understand the dynamic relationship between frailty and physical activity by examining:

1) different types of physical activity,

2) various tools for assessing frailty,

3) how these relationships may differ by age and sex,

4) how other lifestyle behaviours impact this relationship.

Chapter 2 Literature Review

2.1 Aging

The proportion of adults aged 65 and over has increased globally and nationally, with projections indicating this trend continues long-term (34–37). By 2050, it is estimated that 1 in 6 people worldwide will be over 65, up from 1 in 11 in 2019 (34). In Canada, this demographic shift is particularly pronounced. In 2014, over 6 million Canadians were 65 or older, constituting approximately 15.6% of the population. By 2030, this number is expected to rise to over 9.5 million, comprising 23% of Canadians (Figure 2.1) (35). Average life expectancy is also increasing; on average, Canadian females live to 84.2 years of age and males to 80; by 2030, this is expected to rise to 86.2 and 82.9, respectively (35).

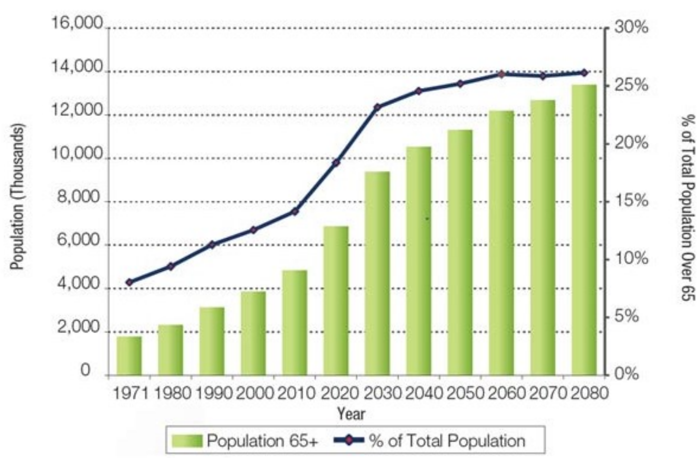

Figure 2.1 Total and proportion of population 65 and over by decade, 1971-2080

Source: Statistics Canada (1971-2010) and Office of Superintendent of Financial Institutions (2020-2080)

Understanding how this large proportion of Canadians age is crucial. While aging is a natural physiological process, individuals have some control over maintaining high levels of physical, psychological, and social functioning in old age without major diseases (38). Active aging is defined by the World Health Organization as "the process of optimizing opportunities for health, participation, and security in order to enhance quality of life as people age" (39). Strategies for active aging include being physically active, consuming fruits and vegetables, moderate alcohol consumption, not smoking, maintaining meaningful social connections, and engaging in activities that challenge cognition (40–42). However, age-related muscle mass and strength decline, exacerbated by chronic diseases and poor lifestyle behaviors, can lead to frailty (43). Understanding the benefits of healthy behaviors and the consequences of unhealthy ones is essential for reducing the impact of frailty at the individual level.

2.2 Frailty

2.2.1 Introduction to Frailty

To date, there is no consensus on an operational definition of frailty. Generally, frailty is considered to be age-related, occurs across multiple physiological systems, and leads to an increase in vulnerability (44). This document will define frailty using the World Health Organization (WHO) definition, which states that frailty is "a progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes" (36). This definition offers a holistic perspective while capturing the commonly agreed-upon aspects of frailty.

Frailty poses a significant public health concern as it can have adverse health effects with population-level consequences (46–48). Individuals with high levels of frailty have an elevated risk of hospitalization, early admission to long-term care, and mortality (50,51), leading to elevated healthcare costs (47). Identifying strategies to reduce or prevent the adverse effects of frailty is essential. However, differences in frailty conceptualizations and assessment tools hinder our understanding and management of frailty.

2.2.2 Frailty Conceptualization

There are currently two distinct approaches to conceptualizing frailty: the phenotypic and deficit accumulation models. The phenotypic model of frailty, introduced by Fried and colleagues in 2001 (52), views frailty as a "geriatric syndrome" characterized by specific signs and symptoms such as exhaustion, unintentional weight loss, low activity, slow walking speed, and weak grip strength. If individuals present with three or more of these signs and symptoms, they are identified as frail. In the case of the frailty phenotype, the term "syndrome" refers to a condition resulting from multiple causative factors (53–55). Researchers believe this syndrome aligns with the concept of a phenotype, defined as "the observable characteristics, at the physical, morphologic, or biochemical level, of an individual, as determined by the genotype and environment (55)".

In contrast, the deficit accumulation model, proposed by Rockwood and colleagues in 2001 (56,57), views frailty as a "state" characterized by the accumulation of age-related deficits across multiple domains of health (58). These deficits are health problems that manifest at the subcellular level before affecting tissues, organs, and function (59–61). Unlike the phenotypic model, the deficit accumulation model does not specify individual health deficits. Rather, it focuses on age-related health deficits associated with adverse health outcomes that collectively cover a range of health systems (62). This method allows for diverse pathways through which an individual could become frail.

One of the main differences between these two models is how they consider disability and comorbidities. Here, disability is defined as an impairment in one's ability to perform activities of daily living (e.g., walking up and down stairs, getting in and out of bed), and comorbidity is defined as an individual having two or more diseases (57,60,63). The phenotypic model suggests that frailty, disability, and comorbidity are related but distinct. It argues that frailty can lead to disability independent of (sub)clinical diseases and that frailty can occur with or without comorbidity. Therefore, these health outcomes should be distinctly defined, measured, and treated. On the other hand, the deficit accumulation model captures a multidimensional view of frailty that aims to be broad and inclusive. It is primarily concerned with quantifying the overall number of "things wrong" in an individual's health rather than the specific problems, encompassing items that capture both disability and comorbidity.

Although these models view frailty differently, they share similar characteristics (64). For instance, both models agree that:

- Frailty is uncommon, meaning that most community-dwelling people are not frail,
- Frailty is age-related,
- Females tend to have higher frailty levels than males,

- Frailty arises when the accumulation of damage exceeds the capacity for repair,
- With increased frailty, there is an increased risk of mortality.

Another similarity between these two models is that they have been translated into frailty assessment tools. The Frailty Phenotype commonly captures the phenotypic and deficit accumulation models by the Frailty Index. The next section will describe these tools and other commonly used frailty instruments.

2.2.3 Frailty Tools

There is no standard measurement tool for frailty. Many tools are available to assess frailty, though each has limitations that the user needs to consider. Reasons why a user may select a specific tool may be wanting to capture a multidimensional view of frailty, setting (i.e., community or clinical), the need for specialized equipment, the duration of the assessment, and the need for specialized training (65,66). Furthermore, frailty prevalence can differ by the tools employed and the thresholds defined to identify frailty (67–69). This section will introduce common frailty tools and discuss their limitations.

2.2.3.1 Frailty Phenotype

The Frailty Phenotype reflects the phenotypic model of frailty (52). It consists of the following five items:

- Muscle strength (determined by grip strength dynamometer)
- Weight loss (more than 10 pounds of unintended weight loss in the previous year)

- Walking speed (assessed by performance on a 15-meter walk test)
- Low levels of physical activity (measured by the Minnesota Leisure Time Activities questionnaire)
- Exhaustion (measured by questions about energy levels from a depression survey).

Individuals are deemed *frail* if they meet three of the five criteria and *pre-frail* if they meet one or two. It is fast to administer (<10 minutes) and is the most widely used frailty tool (70). Its popularity allows for the pooling and comparison of results across studies.

The frailty phenotype has been thoroughly tested for predictive, concurrent, internal construct, and convergent validity (70–72). For example, having a high score on the frailty phenotype is predictive of mortality, fractures, falls, impairment in ADL and IADLs, hospitalization, and emergency department visits (70,73–75). Measures that have been tested to demonstrate concurrent validity include ADL and IADLs, use of specific health and community services, depression scores, Short Physical Performance Battery (SPPB), Mini-Mental State Examination (MMSE), comorbidity, and health-related quality of life (76–78). Latent class analysis has been used to illustrate how higher levels of the frailty phenotype can affect mortality, demonstrating internal construct validity (74). Lastly, the frailty phenotype moderately correlates with the frailty index, demonstrating convergent validity (79). However, there is limited evidence regarding the reliability of this tool; one study has used intra-class correlation (ICC) coefficients to assess the reliability of both the frailty phenotype and the frailty index (70). It was reported that the frailty phenotype had an ICC of 0.65-0.77, which was less reliable than the frailty index (ICC= 0.85-0.84).

However, the Frailty Phenotype is limited in that it only captures physical aspects of frailty. There is consensus that frailty is more complex than a single health dimension and influences multiple health systems. Additionally, the phenotype includes a handgrip strength test, which requires specialized equipment (e.g., hand dynamometer) and training. It also requires adequate space to conduct the walking speed component of the assessment. These factors can be barriers for users who may not have access to the required equipment or personnel, though other options are available. The Frailty Phenotype has been adapted many times, with one systematic review identifying 262 unique variations (80). While these modified versions allow users to administer the tool within their setting or training level limits, the large number of variations makes drawing comparisons across studies difficult.

2.2.3.2 Frailty Index

The Frailty Index (FI) is a frailty tool that includes a variety of health deficits, such as symptoms, signs, diseases, disabilities, and laboratory abnormalities. Demographic, economic, social, environmental and health behaviour variables are usually excluded (81). It is recommended that the FI include 30 or more health deficits (58). Unlike many other frailty tools, these deficits can be interchangeable as long as they are age-related, associated with adverse health outcomes, and cover a range of health systems (62). Using these deficits, users can calculate an individual's FI score. An FI score is a ratio of the number of deficits an individual has to the total number of deficits measured. For example, a person with 10 out of 40 assessed deficits has an FI score of 10/40 = 0.25. Converting the score into a ratio allows for a continuous score ranging from 0-1, where higher scores represent worse frailty.

The advantages of using the FI are that it captures a multidimensional view of frailty and does not require specialized equipment. Its continuous score captures frailty as a spectrum rather than categorizing it into groups like other frailty tools. Furthermore, the frailty index is highly predictive of adverse outcomes such as mortality, hospitalization, and institutionalization (57,82–84) and has also demonstrated construct validation with age (83). Lastly, it has excellent inter-item consistency (Spearman and Pearson correlation coefficients = 0.31-0.52 (85); Intra-class correlation coefficient 0.85-0.84 (79). However, the most prevalent disadvantage of the FI is the time needed to collect the relevant data. Doing so can take 20-30 minutes in person; if done electronically using routinely collected data, however, calculating an FI can take seconds (86). Even so, while the FI's validity is widely tested, more research is needed to assess its reliability.

2.2.3.3 Tilburg Frailty Indicator

The Tilburg Frailty Indicator (TFI) is a multidimensional, self-report frailty tool developed by Gobbens et al. (2010) (87). It consists of 15 items that cover physiological factors (e.g., weight loss, difficulty walking, balance), psychological factors (e.g., memory, anxiety), and sociological factors (e.g., social relations, support). If an individual presents with at least 5 of the 15 items, the individual is considered frail (87). The TFI has been tested for predictive, concurrent, construct, internal, and test-retest validity. For instance, the TFI consistently predicts disability and healthcare utilization (88). Also, one study has reported excellent test-retest reliability with a Pearson correlation coefficient of 0.79 (88). An advantage of the TFI is that it is multidimensional and requires no specialized equipment or assessor training. However, it is lengthy to administer (~14 minutes), much more than other frailty tools. However, since the TFI is self-reported, it allows for at-home completion, cutting down in-setting administration time.

2.2.3.4 Survey of Health, Aging, and Retirement in Europe Frailty Instrument

The Survey of Health, Aging, and Retirement in Europe Frailty Instrument (SHARE-FI) approximates the Frailty Phenotype within the Survey of Health, Aging, and Retirement in Europe (SHARE) database ((89). The SHARE-FI collects the same five signs and symptoms as the Frailty Phenotype (i.e., exhaustion, weight loss, weakness, slowness, and low activity) using a modified collection method:

- Exhaustion is identified using the question, "In the last month, have you had too little energy to do the things you wanted to do?"
- Weight loss is identified using the questions "What's your appetite like?" and "Have you been eating more or less than normal?"
- Weakness is assessed by handgrip strength using a dynamometer.
- Slowness is identified by the question "Because of a health problem, do you have difficulty [expected to last more than 3 months] walking 100 metres?" and "... climbing one flight of stairs without resting?"
- Low activity is identified by the question, "How often do you engage in activities that require a low or moderate level of energy, such as gardening, cleaning the car, or doing a walk?"

The advantages of the SHARE-FI are that it is quick (< 5 minutes), requires no assessor training, and predicts adverse events (90,91). Furthermore, an online calculator for the SHARE-FI provides frailty scores tailored to males or females, acknowledging the well-established sex differences in frailty (94). The SHARE-FI's Cronbach's alpha reliability coefficients range from 0.73-0.83 (95). The main shortcomings of using the SHARE-FI are that it does not capture a multidimensional view of frailty and requires specialized equipment (e.g., a hand dynamometer).

2.2.3.5 Fatigue, Resistance, Ambulation, Illness, and Loss of Weight Scale

The self-reported Fatigue, Resistance, Ambulation, Illness, and Loss of weight (FRAIL) scale is made up of five components: Fatigue (feelings of being tired), Resistance (difficulty going up steps), Ambulation (walking difficulty), Illness (number of chronic conditions), and Loss of weight (weight loss of 5% or more in the past 12 months) (96). An individual is identified as frail if three or more components are present. The FRAIL scale is widely adopted because it is quick and cost-effective. It can also be obtained from a Comprehensive Geriatric Assessment (CGA), used by healthcare practitioners to assess the status of frail and older people to optimize their care (97). The FRAIL scale is predictive of mortality and the ability to perform ADLs/ IADLs (98). A 2020 study investigated the diagnostic test accuracy of the FRAIL scale against the Frailty Phenotype; it was acceptable for specificity (86.8%) and Youden index (0.50) but not sensitivity (63.6%) (98). However, the FRAIL scale largely assesses physical aspects of frailty, limiting its generalizability to other health domains.

2.2.3.6 The Study of Osteoporotic Fractures Index

The Study of Osteoporotic Fractures (SOF) Index reflects the phenotypic frailty model. It includes three components: involuntary weight loss (≥5% in the last year), inability to complete five chair stands, and reduced energy level (99). An individual is considered frail if two or more components are present. This tool is quick to administer

(< 5 minutes) and predictive of adverse outcomes like mortality, fractures, falls, disability, overnight hospitalization, and emergency department visits in community-dwelling older adults (100). It has good concurrent validity with variables such as the ability to perform ADL and IADLs, chronic medical conditions, Short Physical Performance Battery (SPPB), The Mini-Mental State Examination (MMSE), and quality of life (77,100). However, assessor training is needed for safety (chair-stand test), and the SOF is not multidimensional. Finally, although it is quick to administer, capturing only three components oversimplifies the complex nature of frailty.

2.2.3.7 Clinical Frailty Scale

The Clinical Frailty Scale (CFS) is a widely used and highly regarded frailty tool (101). Scored on a scale of one (very fit) to nine (terminally ill), each point corresponds to a visual and written description describing that level of frailty (57). A score of four or more identifies an individual as frail. The advantages of the CFS are that it is quick to administer (< 5 minutes), can be derived from medical charts or a CGA, requires no specialized equipment, and predicts adverse outcomes, including mortality and hospitalization (102,103). The CFS has good construct validity and inter-rater reliability (Kappa coefficient ≥0.7) (104). Construct validity has been explored using MMSE, history of falls, delirium, cognitive impairment, and the frailty index (57,104). A context-dependent limitation, however, is that the CFS requires clinical judgment. If specialized personnel are unavailable, other tools may be more suitable. However, increased international use has led to the development of the CFS classification tree for less experienced users (105).

2.2.3.8 Edmonton Frail Scale

The Edmonton Frail Scale (EFS) is a multidimensional frailty tool that includes nine components (106):

- cognition (clock drawing task)
- general health status (hospital admissions, self-rated health)
- functional independence (needs assistance with activities of daily living?)
- social support (reliable social support available?)
- medication use (> four regular medications, forgetting medications)
- nutrition (recent weight loss?)
- mood (often sad or depressed?)
- continence (urinary continence present?)
- functional performance (performance on the timed up-and-go task)

Frailty is categorized as non-frail (0-5), vulnerable (6-7), mildly frail (8-9), moderately frail (10-11), and severely frail (12-17) (106). The EFS does not require specialized equipment and is associated with independence, drug consumption, mood, mental status, function, and nutrition (107). This tool predicts adverse outcomes such as mortality, institutionalization, and postoperative operations (108). The EFS reported good concurrent and constructive validity, internal (Crohnbach's coefficient = 0.62), and inter-rater reliability (Kappa coefficient = 0.77) (109). Lastly, the EFS can be extracted from a CGA, making it easier to calculate in clinical settings. The main drawback of this tool is that assessor training is needed, although the assessor does not need clinical expertise. This makes it a feasible option for many people to administer this tool.

2.3 Physical Activity and Frailty

Different methods can reduce or prevent frailty, with physical activity being one of the leading interventions. This section aims to define physical activity, describe how it is measured, and evaluate its association with health and frailty.

2.3.1 Defining Physical Activity

Physical activity is defined as "any bodily movement produced by skeletal muscles that requires energy expenditure (110)." In other words, physical activity is any movement an individual does, including chores, transportation (i.e., biking, walking), or as a part of an occupation. Exercise is a subset of physical activity, defined as "any physical activity that is planned or structured with the objective of increasing or maintaining physical fitness (110)." Therefore, exercise can include many types of physical activities, such as engaging in a regular gym routine or playing on a sports team. Regular physical activity helps prevent and manage conditions such as cardiovascular disease, type 2 diabetes, obesity, several types of cancer, osteoporosis, low mood, and poor quality of life (111,112). However, the intensity of an individual's physical activity can depend on how they can prevent or manage these adverse health conditions.

The intensity of physical activity is a continuum from sedentary to vigorous (refer to Figure 2.2). Sedentary behaviour is defined as "any waking behaviour characterized by an energy expenditure ≤ 1.5 METs while in a sitting or reclining posture (113)." Each intensity in the continuum is associated with different health outcomes. For example, high levels of sedentary activity are associated with increased risks of metabolic syndrome, high waist circumference, obesity, and all-cause mortality (114,115). Alternatively, vigorous-intensity physical activity is associated with positive health outcomes such as preventing and managing heart disease, stroke, diabetes, and several types of cancer (116–118). There is a dose-response between the increasing intensity of physical activity and health benefits – with the best results observed at the highest intensity levels (118–120).

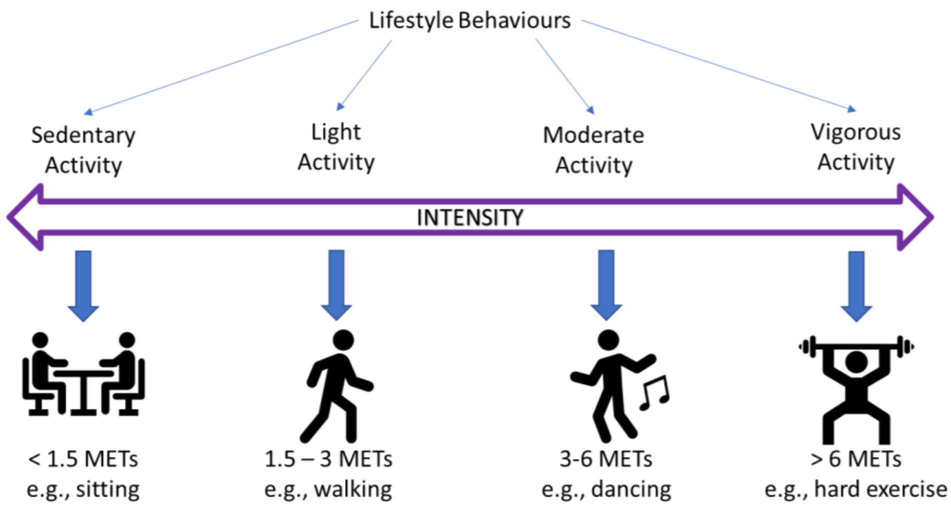

Figure 2.2 Physical activity continuum; MET – Metabolic equivalent of tasks

2.3.2 Measuring Physical Activity and Sedentary Behaviour

Physical activity and sedentary time can be measured using different methods like frailty. Subjective methods, mainly self-report activity questionnaires, are the most common in physical activity research (121). Common physical activity questionnaires in the older adult population include the Physical Activity Scale of the Elderly Questionnaire (PASE) (122), the International Physical Activity Questionnaire (IPAQ) (123), and the Minnesota Leisure Physical Activity Instrument (MLPAI) (124). The key advantages of subjective methods are that they are cost-effective and easy to administer (125,126). Key disadvantages are their lower validity and reliability compared to objective measurements. For instance, Cleland et al. (2018) validated the IPAQ in older adults in the United Kingdom compared to accelerometry (Actigraph GT3X+) (127).

They found that most older adults over-report their physical activity levels [IPAQ, median = 1291.0 minutes per week, Interquartile Range (IQR) = 917.3, 1642.8; Accelerometer, median = 965 minutes per week, IQR = 340, 1785.0]. This finding supports the reduced confidence in subjective measures of physical activity. Researchers suggest that to mitigate this discrepancy, questionnaires should list more activities that older adults are likely to engage in, improving recall (127,128).

Objective methods, such as accelerometers, have consequently gained popularity. Accelerometers measure an individual's acceleration in real time and detect up to three planes of movement (anteroposterior, mediolateral, and vertical) (129,130). The data collected from these devices can be translated into measures of interest such as energy expenditure and physical activity patterns (i.e., light activity) (131,132). Key accelerometers used in physical activity research are the activPAL and the ActiGraph (133,134). The abovementioned advantage of objective measures is that they are more accurate and reliable than subjective measures (135,136). For instance, when compared to doubly labeled water (a gold standard measure for total energy expenditure) in large epidemiological studies, the ActiGraph was more accurate than traditional questionnaires (e.g., AARP Physical Activity and Sedentary Behaviour Questionnaire and 24-hour Physical Activity Recall)(137). Other noteworthy advantages include these devices monitor activity on a minute-by-minute basis, which allows for detailed tracking, and they can store large amounts of data, providing researchers with extensive information for analysis (138).

A key disadvantage of the objective measures of activity is their inability to capture specific activities or changes in posture (136,139,140). Accelerometers are limited in that they typically cannot differentiate between lying, sitting, or standing and cannot capture energy expenditure during seated activities (i.e., biking, rowing); thereby, they capture stationary time rather than sedentary time. Stationary time refers to any waking behaviour done while lying, reclining, sitting, or standing, with no ambulation, irrespective of energy expenditure (141). Another disadvantage of accelerometers is that they capture activities that primarily use the upper body or resistance training activities (142) – subjective measures are needed to capture these activities. Furthermore, accelerometers cannot differentiate between sitting and standing positions (130,143). Standing is considered a light-intensity activity, which could be misclassified as sedentary time if only using accelerometers (144). One study has compared an accelerometer (Actigraph) to a device that can detect posture (ActiPAL) and found that Actigraph reported 9.5 hours/day of non-movement time, and the ActiPAL reported 10.2 hours/day of sitting time (140). Other reported disadvantages of this tool are that it is more expensive than subjective measures and requires specialized software and individual programming (143,145,146). Although these tools provide valuable information, it is important to understand these limitations when reporting study findings.

2.3.3 Physical Activity Guidelines

Everyone is encouraged to be active, although specific age-based recommendations exist. This next section will introduce some of the most relevant physical activity guidelines for older adults and describe their development. It will then discuss how these guidelines could be better suited for those with higher levels of frailty.

2.3.3.1 The World Health Organization Physical Activity Guidelines

In collaboration with global experts, the World Health Organization (WHO) developed global physical activity guidelines (147). Experts based these guidelines on scientific evidence on physical activity and health. An expert panel reviewed this evidence and revised physical activity recommendations until they reached a consensus. The WHO recommends adults aged 65 and above obtain at least 150–300 minutes of moderate-intensity aerobic physical activity, or at least 75–150 minutes of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity throughout the week. For additional health benefits – and to minimize the detriment of sedentary time –individuals can also:

- engage in moderate (or greater) intensity muscle-strengthening activities that involve all major muscle groups two or more days a week.
- increase moderate-intensity aerobic physical activity to more than 300 minutes, do more than 150 minutes of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity throughout the week.
- limit the amount of time spent being sedentary by replacing sedentary time with physical activity of any intensity (including light intensity).
- aim to do more than the recommended moderate- to vigorous-intensity physical activity levels.

2.3.3.2 Canadian Physical Activity Guidelines

The most recent version of the Canadian Physical Activity Guidelines was released in 2020 by the Canadian Society of Exercise Physiology (CSEP) (111,118,148). CSEP included an extensive process to formulate the current guidelines. Its Consensus Panel represented national organizations, including content experts, methodologists, stakeholders, and end-users. The process to inform these guidelines included *de novo* systematic reviews, each using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to ensure they included the best available evidence.

The main characteristic differentiating the new guidelines from older versions is the shift from a single movement behaviour guideline to a 24-hour movement guideline (149). This shift supports the growing evidence that the mixture of movement behaviours (i.e., sleep, sedentary time, and moderate-to-vigorous physical activity) influences various health outcomes. So, these behaviours should be considered in the physical activity guidelines. Table 2.3 describes the CSEP physical activity guidelines for Canadians aged 65 and older.

Table 2.1 The Canadian Society of Exercise Physiology's physical activity guidelines

Components of the Guidelines	
Physical Activity	Moderate to vigorous aerobic physical activities such that there is an accumulation of at least 150 minutes per week
	Muscle-strengthening activities using major muscle groups at least twice a week
	Physical activities that challenge balance
	Several hours of light physical activities, including standing
Sedentary Behaviour	No more than 3 hours of recreational screen time
	Breaking up long periods of sitting as often as possible
Sleep	Regularly getting 7 to 8 hours of good-quality sleep, with consistent bed and wake-up times
Considerations	Replacing sedentary behaviour with additional physical activity and trading light physical activity for more moderate to vigorous physical activity – while preserving sufficient sleep – can provide greater health benefits.
	Progressing towards any of these targets will result in some health benefits

2.3.3.3 American Physical Activity Guidelines

The current version of the American Physical Activity Guidelines was released in 2018 by the American College of Sports Medicine (ACSM). ACSM appointed an external scientific advisory committee that conducted systematic reviews of the literature on physical activity and health for older adults. Members from ACSM then compiled the committee’s work into the physical activity guidelines, which state:

- Adults and older adults should move more and sit less throughout the day. Some physical activity is better than none. Adults and older adults who sit less and do moderate-to-vigorous physical activity gain some health benefits.
- For substantial health benefits, adults and older adults should do at least 150 minutes (2 hours and 30 minutes) to 300 minutes (5 hours) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Preferably, aerobic activity should be spread throughout the week.
- Additional health benefits are gained by engaging in physical activity beyond the equivalent of 300 minutes (5 hours) of moderate-intensity physical activity per week.
- Adults and older adults should also do muscle-strengthening activities of moderate or greater intensity that involve all major muscle groups 2 or more days a week, as these activities provide additional health benefits.
- As part of their weekly physical activity, older adults should do multicomponent physical activity that includes balance training, as well as aerobic and muscle-strengthening activities.
- Older adults should engage in the level of physical activity relative to their level of fitness.
- Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely.

- When older adults cannot do 150 minutes of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow.

Although the previously mentioned guidelines are well-informed and scientifically supported, many older adults do not reach these recommendations (150). In Canada, only 13% of males and 11% of females aged 60 and older reach the physical activity recommendations (151,152). Even fewer frail older adults reach them (151,153). A handful of studies have reported the proportion of individuals meeting the physical activity guidelines across frailty levels (154–156). For example, Kehler and Theou (2019) reported a dose-response relationship between higher amounts of moderate-to-vigorous aerobic physical activity and lower frailty levels, with 38% of non-frail individuals – but only 3% of very frail individuals – meeting the recommendations (155).

Researchers have questioned whether physical activity guidelines should differ for the frail population (117,157,158). Merchant et al. (2021) described how physical activity could be prescribed based on what program best suits an individual's baseline functional status, thereby acknowledging that those who are very frail may need to start at a different activity level than those who are robust (157). However, more research is needed to understand if frail individuals should start with physical activity levels different from those of their healthier counterparts.

The next section describes what is currently understood about the impact of physical activity on frailty. Then, it discusses potential physical activity combinations that may benefit frail older adults that global and national guidelines do not represent.

2.3.4 Physical Activity and Frailty

Experts recommend physical activity to reduce frailty (159–161), emphasizing moderate-to-vigorous aerobic physical activities (MVPA) and resistance training (RT). Various activities, such as Tai Chi and walking programs, in different settings, like home or gym, have shown benefits across populations (162).

2.3.4.1 Moderate-to-Vigorous Aerobic Physical Activity (MVPA), Light Activity, and Resistance Training (RT)

Aerobic activity, including walking, biking, or dancing, engages large muscle groups rhythmically and continuously (163). While the precise mechanisms are not fully understood, research generally indicates that meeting recommended aerobic activity levels helps mitigate frailty (159,164–166). For example, a randomized control trial by Meng et al. (2020) examined the effects of a dance intervention on pre-frailty and frailty, measured by the Frailty Phenotype, in 66 nursing home older adults (167). The intervention was 40 minutes in duration, 3 times per week, for 12 weeks. Researchers found that frailty decreased over time in the dance group compared to the control group, with a mean difference between groups of 0.69 at 6 weeks and 1.06 at 12 weeks (p = 0.002).

Light-intensity physical activities, like standing or casual walking, benefit frailty, although to a lesser extent than moderate-to-vigorous activities. For instance, Powell et al. (2011) found that health benefits occur with any increase above the very lowest physical activity levels (168), supporting that light-intensity physical activity is favorable compared to no activity. However, moderate-to-vigorous physical activity provides the greatest health benefits; individuals would have to engage in 4-5× more light-intensity physical activity to elicit the same frailty reductions as moderate-to-vigorous physical activity (168). However, MVPA yields the most benefits, suggesting that frail individuals should aim for this intensity when possible. If not feasible, starting with light activity is encouraged to increase intensity gradually (169,170).

Resistance training, involving external or bodyweight resistance, strengthens muscles progressively, combating muscle-wasting and improving functional abilities (171). However, less studied than aerobic training, resistance training benefits frailty prevention and reversal. For example, a recent meta-analysis supports that engaging in resistance training is beneficial for preventing and reversing frailty (161). The reason why resistance training may be helpful for frail older adults is that by becoming stronger, individuals can maintain their abilities to perform activities of daily living (ADLs) (e.g., walking up and down stairs, getting in and out of chairs) and alleviate adverse effects of muscle-wasting and sarcopenia (161,172). Despite many frail individuals not meeting aerobic or resistance training targets, engaging in lower-intensity activities still offers benefits (170,173).

2.3.5 Engaging in Moderate-to-Vigorous Aerobic Activity or Resistance Training

Given that most frail older adults do not meet the current physical activity guidelines, this raises the question: *Can participating in any physical activity—but not meeting the guidelines—mitigate frailty?* This section will describe aerobic or resistance training studies and examine whether these activities impact frailty.

2.3.5.1 Moderate-to-Vigorous Aerobic Activities and Frailty

For some frail individuals, aerobic activities such as walking, biking, or jogging may be their preferred type of exercise. Some research has explored whether aerobic-only activities reduce frailty. For example, Huang et al. (2020) examined 415 older adults, where 104 were randomized into an aerobic training-only arm of an exercise program (174). This program was 60 minutes long, two days per week for 26 weeks, and included stepping, walking, and rest components. The researchers used heart-rate monitors to gradually increase the intensity of the program (target heart rate zone, week 1-2: 40% of heart rate reserve (HRR); week 3-8: 50% HRR; week 9-12: 60% HRR; week 13-26: 70% HRR). Using a 95-item FI, the aerobic training group significantly improved their frailty score compared to the control group (Estimated effect = 0.020; 95% CI = -0.039, -0.001; Cohen's d = -0.275). Although the effect size is modest, this estimated effect is considered a clinically meaningful reduction in the FI (175). Other studies have supported the work of Huang and colleagues by demonstrating that engaging in only aerobic exercise can mitigate frailty. Meng et al. (2020) compared a mild-to-moderate intensity square dancing class to a normal activities control group (167). The square-dancing class was 12 weeks long, and met thrice weekly for 40-minute sessions. At post-intervention, frailty (measured by Frailty Phenotype) decreased in the square-dancing group compared to the control group (square dancing: mean change = -1.06; 95% CI = -1.38, -0.75; control group: mean change = 0.25; 95% CI = 0.03, 0.47; $p < 0.001$). While the evidence indicates that aerobic-only activities can mitigate frailty, future work should explore whether the benefits are comparable to meeting the recommended physical activity guidelines.

2.3.5.2 Resistance Training Activities and Frailty

The lack of available evidence and conflicting research findings make it unclear whether resistance training alone can reduce frailty. One study by Huang and colleagues aimed to clarify the impact of various exercise programs (174). They included a resistance training-only intervention group who completed resistance band exercises (e.g., bicep curls, chest press, side rises, seated rowing, leg press, hip abduction, and side bend) and body weight exercises (e.g., shrugs, keep-ups, trunk curls, squats, kneeling kickbacks, toe raises, and calf raises). Each exercise was performed for two sets of 10 repetitions. Post-intervention showed no significant difference in frailty score (95-item FI) in the resistance training-only group compared to the control group (estimated intervention effect versus control = -0.014; 95% CI = -0.036, 0.009). Ng et al. (2015) had 246 community-dwelling older adults participate in a 24-week resistance training or an education control group (176). The resistance training group met twice weekly for 90 minutes, exercising in groups of 8 to 10 and continuously adjusting the intensity of their training to 60-80% of their one-repetition maximum. Converse to the previous study, at post-intervention, frailty reduction (by the Frailty Phenotype) was greater than in the control group (OR= 4.05; 95% CI= 1.50, 10.8). Other studies have examined the relationship between resistance training and frailty and generally found that resistance training interventions appear feasible and safe and may improve frailty status, functional task performance, and muscle strength (177–180). Overall, there is insufficient evidence to understand this relationship fully. Inconsistent findings may be due to study differences in program design or the frailty tools used.

2.3.6 Using Frailty Tools in Physical Activity Research

This section will identify considerations for frailty tools used in physical activity research. While many tools are available for examining frailty in physical activity studies, this dissertation will focus on four main tools: The Frailty Index, the Frailty Phenotype, the SOF Index, and the FRAIL Scale. The justification for these tools will be explained in forthcoming sections.

2.3.6.1 The Phenotypic Model of Frailty in Physical Activity Research

Tools that follow the phenotypic model of frailty, such as the Frailty Phenotype and the SHARE-FI, are prevalent in the physical activity and frailty literature. Although these are well-supported screening tools, they may be less suitable for physical activity research because they already include items about an individual's level of physical activity (Table 2.4), resulting in common method variance. Common method variance occurs when variations in responses are caused by the instrument itself rather than the real predispositions of the respondents that the instrument attempts to uncover (181). Common method variance can cause systematic measurement errors that can inflate or deflate the observed relationships between constructs, generating Type 1 and Type II errors (182,183).

The Frailty Phenotype is susceptible to common method variance when used to examine the relationship between frailty and physical activity. In the Frailty Phenotype, low activity is based on the short version of the Minnesota Leisure Time Activity Questionnaire (52), which asks about individual activities, such as active transportation, chores, and exercise. The exercise questions, in particular, ask if individuals participate in 'exercise at home,' 'exercise in a club/fitness center,' 'muscle-strengthening exercises,' and 'jogging or walking' (124).

The SHARE-FI captures low physical activity by asking individuals, "How often do you engage in activities that require a low or moderate energy level, such as gardening, cleaning the car, or walking?" While this question is less affected by common method variance than the questions included in the Frailty Phenotype as it does not specifically ask about exercise, it could impact results as it does ask about moderate-level activities. Since this is a single item and self-reported, it largely depends on the individual's interpretation of a moderate-level activity.

Therefore, both the Frailty Phenotype and the SHARE-FI could overestimate the effects of physical activity interventions. For example, inactive people can change their frailty status by simply participating in a physical activity intervention, even if this intervention does not impact their health. Therefore, frailty tools that evaluate physical activity—especially those with small items—can elicit biased findings due to common method variance (183,184).

Table 2.2 Items included in the Frailty Phenotype and the SHARE-FI

Criteria	Frailty Phenotype		SHARE-FI
	Female	**Males**	
Weight Loss	Weight loss greater than 10lbs (4.5 kg) or 5% of weight in the last year		"What has your appetite been like?" or "Have you been eating more or less than usual?"
Exhaustion	"How often in the last week did you feel this way? a) I felt like everything I did was an effort or b) I could not get going."		"In the past month, have you had too little energy to do the things you wanted to do?
Weakness	Max Grip strength BMI ≤ 23: ≤ 17.0 kg BMI 24-26: ≤17.3kg BMI 27-29: ≤ 18.0 kg BMI > 30: ≤ 21 g	Max Grip strength BMI ≤ 24: ≤ 29 kg BMI 25-26: ≤ 30 kg BMI 27-28: ≤ 30 kg BMI > 29: ≤ 32 kg	Max handgrip strength
Slowness	Height: ≤ 159 cm: ≥ 7 sec Height: > 159cm: ≥ 6 sec	Height: ≤ 173 cm: 7 sec Height: > 173 cm: 6 sec	"Because of a health problem, do you have difficulty [expected to last more than 3 months] walking 100 metres?" or "… climbing one flight of stairs without resting?"
Low Activity	Based on the Minnesota Leisure Time Activity Physical activity per week: <270 kcal/week	Based on the Minnesota Leisure Time Activity Physical activity per week: <383 kcal/week	"How often do you engage in activities that require a low or moderate level of energy, such as gardening, cleaning the car, or doing a walk?"
BMI – Body Mass Index; FI – Frailty Index; kg – kilograms; sec – seconds			

Modifying frailty tools is a common practice (80); however, how these tools are modified could influence the magnitude of frailty-related effects observed. For example, Nagai et al. (2018) examined the effect of a physical activity intervention using feedback as an adjunct to resistance strength in frail older adults (185). Participants completed a resistance training program twice per week for 24 weeks, including warm-up and stretching before training. The program consisted of leg presses, knee extensions, leg abduction, and seated rowing, with load and number of repetitions recorded using Weltonic Series equipment. These values were individually determined based on each participant's one-repetition maximum (1RM), with exercise intensity progressively increased from 50% to 80% of their 1RM. Individuals were identified as frail if they met three of the five included criteria (i.e., slowness, weakness, exhaustion, low activity, weight loss) of a modified Frailty Phenotype. Low physical activity was assessed with the question, "Do you engage in physical exercise to improve your health?" If individuals answered "no," they were classified as having low physical activity. This intervention was intended to improve health outcomes, yet individuals could change their score on this criterion by simply being in the intervention group without tangible health results.

2.3.6.2 Frailty Tools with Items Unaffected by Physical Activity

Many tools include variables individuals cannot change through physical activity, such as "Do you live alone?". Including too many extraneous items could obscure the relationship between physical activity and frailty and complicate the interpretation of results. While not commonly used in physical activity research, the Strawbridge Questionnaire is a good example of this issue (186). The Strawbridge Questionnaire consists of four domains: physical, nutrition, cognitive, and sensory. It is well documented that physical activity can improve physical health (e.g., improve balance) (187), cognition (188–190), and nutritional health via weight loss or energy intake (191,192). Nevertheless, physical activity cannot improve sensory impairment. The scoring of each domain contributes to the overall frailty score, meaning that individuals with visual or auditory impairments will not exhibit changes in these criteria on the frailty tool regardless of the benefits derived from the physical activity intervention. Similar variables are often used in other frailty tools, like the Tilburg Frailty Indicator (TFI) and the Kaigo-Yobo Checklist (KYC). These include poor vision (TFI, KYC), poor hearing (TFI), chewing difficulty (KYC), and living alone (TFI). Although these variables are important in capturing frailty, they are not well-suited for physical activity intervention studies as they are unaffected by physical activity. Individuals who report unchangeable variables may be classified as pre-frail or frail and may never be classified as non-frail, regardless of the impact of the intervention.

2.3.6.3 Using Only Part of a Frailty Tool

It is poor practice to assess only one domain of a multi-domain frailty tool, such as using only a physical function criterion to identify frailty. Physical function is defined as "basic actions and complex activities; activities considered essential for maintaining independence, and those considered discretionary that are not required for independent living but may have an impact on quality of life" (193). In sum, individuals can perform their day-to-day activities. Although physical function and frailty are related (194,195), they are not synonymous. Espinoza et al. (2019) implemented a Geriatric Walking Clinic for older adults and assessed its impact on frailty (196). Frailty was measured using two Frailty Phenotypic criteria: weakness (handgrip strength) and slowness (10-foot walk test). Six weeks post-intervention, the researchers found a significant increase in gait speed but no difference in grip strength. They concluded that "frailty decreased by the gait speed criteria of the Frailty Phenotype." This conclusion is misleading in a few ways. First, using only a single component of a frailty tool does not equate to the tool's identification of frailty. Second, while gait speed captures aspects of physical function, this study demonstrates that a walking intervention can improve certain components of an individual's physical function. However, attributing improvements in gait speed to an overall improvement in frailty oversimplifies the concept of frailty, which is much more complex.

2.3.6.4 Different Frailty Tools Can Result in Discrepant Findings

How a tool categorizes frailty can impact frailty scoring, potentially leading to discrepant findings across different physical activity interventions (67–69). For example, Rezola-Pardo et al. (2019) conducted a 3-month physical activity intervention that included strength, aerobic, and balance components two times per week (197). Comparing the Frailty Phenotype, the SOF index, and the TFI three months after the intervention, only the Frailty Phenotype showed a significant reduction in frailty from baseline (p <0.05, Cohen's d = 0.37); the SOF index and TFI showed no change (SOF: p > 0.05, Cohen's d=0.23; TFI: p >0.05, Cohen's d=0.09). Since physical activity has been recognized as one of the most effective interventions for preventing or mitigating frailty, we must investigate why these discrepancies occur and assess whether commonly used frailty tools can pose limitations to physical activity research.

2.3.6.5 Tool Selections for Dissertation

Due to the abundance of available assessment tools, this dissertation focuses on four specific tools to illustrate the relationship between frailty tool selection, frailty status, and engagement in physical activity. These are the Frailty Index, the Frailty Phenotype, the SOF Index, and the FRAIL Scale. These were selected because they are commonly used in physical activity literature and are valid and reliable. Furthermore, they are easy to modify for secondary research using available databases.

While many health databases are available for researchers, many lack measures of frailty. The available data, however, can be used to develop modified versions of frailty tools. Modifications are common practice (80), and health databases capture information using various frailty tools, such as information on several chronic conditions, mental well-being, and physical activity. However, some tools are better suited for adaptation than others. For instance, the Edmonton Frailty Scale includes a clock-drawing task for cognition, which is not commonly included in health databases and is difficult to adapt (109). Tools commonly used in database-driven research are short, have yes/no answers, and include items commonly found in health databases. The Frailty Phenotype, the SOF Index, and the FRAIL Scale are better candidates for modification. The Frailty Index is also conducive to modification, as while it aims to include many items, these items are non-specific and can, therefore, be adapted based on the information available in an individual database.

While additional frailty tools have been modified or developed for database research, they are not commonly used in physical activity literature nor discussed in the present work. The Frailty Phenotype is important to include in this dissertation because it is widely employed in physical activity studies *while* also incorporating a measure of physical activity within its frailty assessment. Furthermore, it assesses physical frailty rather than providing a comprehensive view. Understanding how tools that capture only physical frailty differ from those encompassing a broader range of health-related factors is essential for this research. The SOF Index is included because while it measures physical frailty, it uses only three items. This allows for examining how such a simplistic tool impacts the association between physical activity and frailty. The FRAIL scale is noteworthy because it assesses physical frailty and includes chronic conditions. By considering the number of chronic conditions an individual has, we can better understand how multiple comorbidities may impact the relationship between frailty and physical activity. Finally, including the Frailty Index provides a multi-dimensional view of frailty beyond physical frailty alone. The Frailty Index can include items not impacted by physical activity, addressing a limitation previously discussed in the frailty and physical activity literature. Including the Frailty Index offers further insight into this limitation.

2.4 Age and Sex Differences in Frailty and Physical Activity

The above tools were also selected because they have been shown to capture sex and age differences (94,198–204). It is well-understood that health outcomes and lifestyle differ by age and sex (205,206), though the research supporting this is relatively recent. For many years, young males comprised the majority of clinical trials, disregarding the unique biological and societal differences by age and sex (207–209). Excluding females and older adults in these trials could lead to them being given treatments that were only tested in another sex or age category. Today, researchers are encouraged to examine whether research findings differ by sex and age to inform individualized treatments better. The next sections will cover why it is important to consider sex and age differences in frailty and physical activity research.

2.4.1 Age Differences in Frailty

Chronological age is positively associated with frailty (52,56,57,210). For instance, across several frailty index measures, people accumulate deficits at about 3% per year (56,57). While it is paramount to consider age in frailty research, this is not always done appropriately. These next sections highlight two age considerations in frailty research.

When people think of someone frail, they often imagine someone in their later stages of life. This is unsurprising, as most aging research and frailty screening start assessments at age 65 (52,211,212). There is evidence, however, that frailty can occur in young and middle-aged adults (213–216). Rockwood and colleagues analyzed the prevalence of frailty in those 15-102 years of age (215) and found that deficits accumulated exponentially with age across the lifespan (prevalence of frailty; younger than 30 years: 2.0%, 95% CI = 1.7%-2.4%; older than 65 years: 22.4%, 95% CI = 19.0%-25.8%; older than 85 years: 43.7%, 95% CI = 37.1%-50.8%). Frailty can even occur in children with chronic diseases (217–219). Studies in children are limited using frailty tools constructed for adults aged 65 or older rather than younger populations. With research demonstrating that frailty can occur in younger people, it is important to use tools appropriate for use in younger adults, such as the Frailty Index, and to develop tools for younger ages.

The second consideration is that many studies group all older adults aged 65 and older together. Suggesting that someone in their late 60s has a similar health profile as someone in their late 80s is not reasonable; frailty increases exponentially with age. A systematic review including 61,500 individuals aged 65 and older reported that frailty prevalence increases significantly after the age of 65 (65-69 years: 4%; 70-74 years: 7%; 75-79 years: 9%; 80-84 years: 16%; >85 years 26%), with the highest rates observed in studies that used the frailty index (210). Studies that equate these ages neglect how frailty is experienced by the oldest old and cloud our understanding of how different interventions may benefit older age groups.

2.4.2 Age Differences in Physical Activity

Physical activity fluctuates throughout the lifespan (220,221). Changes in physical activity have been linked to life transitions and events (222). Life transitions could include childhood to puberty, school to work, marriage, having children, and retirement. Life events may include the occurrence of a disease, job changes, or the death of a loved one. Many children may play sports, but as they transition into adolescence, they may drop out of sports and other exercises due to a lack of support, peer pressure, negative experiences in school, or identity conflicts (222,223). Dropping out at a young age is concerning as physical activity in youth can predict how active an individual is in adulthood (224,225) – active children are more likely to be active adults. Yet, physical activity levels decrease with age (222,226). This begs the question: Are those inactive in adulthood also unlikely to be active in old age?

In frailty studies, considering age differences in physical activity is important. There is variability in physical activity after the age of 65. Some studies observed that exercise and physical activity increase after retirement (221). With more time for hobbies, many older adults take up recreational sports and activities for health reasons or to become more social. Van der Zee et al. (2019) aimed to track the voluntary exercise behaviours of 43,889 individuals from the Netherlands Twin Register dataset (226). Baseline age included those 8-80 years of age, and the tracking duration ranged from 2-22 years follow-up. The findings showed that physical activity is stable until age 64. After age 64, non-competitive sports participation declines, dropping total regular exercise participation. By age 64, 77% of people report not engaging in the recommended amount of physical activity, whereas at age 82, this proportion increases to 100%. This decline in physical activity after the age of 65 is supported by other studies (220,221,227).

2.4.3 Sex Differences in Frailty

Females tend to have higher frailty levels than males (94,228). A meta-analysis from 2019 estimating the global incidence of frailty and pre-frailty among community-dwelling adults aged 60 and older (229) found that frailty and pre-frailty rates were significantly higher in females than males (frailty: 44.8 [95% CI = 36.7, 61.3] versus 24.3 [95% CI = 19.6, 30.1] cases per 1000 person-years; pre-frailty: 173.2 [95% CI = 87.9, 341.2] versus 129.0 [95% CI = 73.8, 225.0] cases per 1000 person-years). Similarly, females (frailty index 0.20) had higher frailty levels than males (frailty index 0.17; $p < 0.001$) in the National Health and Nutrition Examination Survey (the dataset that will be used in this dissertation) (67).

While a sex difference exists, its mechanisms are unclear. It appears to be a complex relationship driven by many interacting factors. A narrative review by Gordon and Hubbard suggests that sex differences in frailty are due to biological, behavioural, and social factors (228). An example of a biological sex difference is the occurrence of common chronic conditions in males and females (230,231). Males tend to acquire more lethal conditions (i.e., heart disease and cancer), whereas females acquire more disabling conditions (i.e., arthritis, cataracts, and depression). Another example is that females have greater physiological reserve (i.e., the potential capacity of a cell, tissue, or organ system to function beyond its basal level in response to changes in physiological demands) than males, so they acquire more deficits in multiple organ systems (232). This greater physiological reserve could help explain why females can survive longer with higher levels of frailty.

Behaviour and societal factors also contribute to the frailty differences in males and females. For example, males are more likely to engage in high-risk behaviours such as smoking or alcohol consumption (233). Excessive smoking and alcohol consumption are known to have negative health consequences, and there is evidence that they are associated with a higher prevalence of frailty (234–236). Furthermore, females are more likely to access health care than males. This could lead to earlier preventative health care and frailty intervention (237). Social norms may also play a role. For instance, high income and education levels are protective against frailty (232,238). Although equity for males and females is growing in some countries, there still exists a gap in how males and females are treated or have access to education, the labor market, and health resources (i.e., physician and home care use, hospital services, outpatient surgery, and preventative services).

2.4.4 Sex Differences in Physical Activity

Older males tend to be more active than older females. In a study examining objective and self-reported measures, older males were more physically active than older females (239). Throughout their lifespan, males and females engage in physical activity and exercise differently (240–242). Females are consistently identified as 6-10% less active than males across age groups, regardless of measurement instrument, protocol, or definition (243–245). This holds true in older people; habitual physical activity is 10-30% greater in older males than in older females (239).

Though males are more physically active than females, the reasons for this discrepancy are still being explored. It appears that males and females are active or inactive for different reasons and that these reasons change with age. At younger ages, boys play to demonstrate physical prowess and social status (245,246), generally more boisterous and involved in activities that demonstrate speed, strength, endurance, and aggression (247). Girls, however, are motivated to be active by friendships, body image, and self-expression, resulting in less intense activities that focus more on taking turns, orderly sequences, and solitary activities (248,249). Boys engaging in skills-based activities could better prepare them for sport in later years, which may explain why girls drop out of sport more than boys (250,251). Differences in motivation for activities also occur in young adulthood. Males report exercising for social and competitive reasons, whereas females are more likely to exercise for appearance (e.g. weight loss) (241). Exercising for appearance is associated with decreased quality of life and increased likelihood of disordered eating, lower body self-esteem, and higher body dissatisfaction (241,252,253). In comparison, exercising for health and fitness, as more often reported by males, is associated with higher quality of life (241). The motivation behind why males and females exercise could explain, in part, why females are less active than males.

Females are more likely to have a negative relationship with exercise and physical activity, impacting the sustainability of this habit.

2.5 Lifestyle Behaviours

Lifestyle behaviours are everyday activities that result from an individual's values, knowledge, and norms influenced by broader cultural and socioeconomic contexts (254). Some examples include sedentary behaviour, sleep quality, diet quality, smoking, and alcohol consumption. This chapter will review what is currently known about how these specific lifestyle behaviours impact frailty or the relationship between physical activity and frailty.

2.5.1 Sedentary and Stationary Behaviour

The Sedentary Behaviour Research Network defines sedentary behaviour as "any waking behaviour characterized by an energy expenditure ≤ 1.5 METs while in a sitting or reclining posture" and stationary time as "any waking behavior done while lying, reclining, sitting, or standing, with no ambulation, irrespective of energy expenditure" (113,141). Experts generally agree that high sedentary time harms physical function and frailty (115,255). This dissertation will use stationary time when referring to accelerometer measurements that cannot differentiate between lying, sitting, or standing. The term sedentary time is used otherwise, though it is understood that a study or question may interpret stationary time as sedentary.

The relationship between sedentary behaviour and frailty is not clearly understood. Current knowledge is primarily derived from observational studies, which are less robust than experimental ones. Notwithstanding, a systematic review of observational studies concluded that high sedentary time is positively associated with frailty (255). Physical activity may not alleviate the negative impact of sedentary time on frailty (169,255,256). This is reflected in the latest version of Canadian Physical Activity Guidelines, which, along with reaching physical activity recommendations, states that older adults should limit sedentary time to 8 hours or less – including no more than 3 hours of recreational screen time – and break up long periods of sitting as often as possible (118). Furthermore, studies have also reported a deleterious association between prolonged sedentary behaviour and frailty (22,255). A commentary from Kehler and Theou (2019) states that prolonged sedentary bout accumulation (>30 minutes) may be more detrimental to frailty risk than non-bouted accumulation (155). Therefore, although more research is needed, the existing literature supports that high levels of sedentary time are associated with increased frailty.

Physical and sedentary activities are on the energy expenditure continuum (see Figure 2). It is generally agreed upon that reducing sedentary time and increasing physical activity is the best way to reduce and prevent frailty (147,155,257). Less is known, however, about how high levels of sedentary time while reaching physical activity guidelines impact frailty. Mañas et al. (2019) suggested that 27 minutes a day of MVPA is needed to eliminate the increased risk of frailty measured by the Frailty Trait Scale (captures energy balance and nutrition, activity, the nervous system, vascular system, strength, endurance, and gait speed) associated with sedentary behaviour (258). Another study examined the association between frailty and the combination of physical activity and sedentary behaviour in older adults (257). The results showed that frailty prevalence increased when an individual engaged in low levels of physical activity and excessive sedentary time (<150 min/week of MVPA + ≥ 540 min/day of sitting time) when compared to being physically active and engaging in low sedentary time (≥ 150 min/week of MVPA + <540 min/day of sitting time). Furthermore, the frailty prevalence in people who were physically active and highly sedentary (≥ 150 min/week of MVPA + ≥ 540 minutes/day of sitting time) was not significantly different from those who were active and not highly sedentary (≥ 150 min/week of MVPA + <540 min/day of sitting time). This suggests that being highly sedentary may not diminish the benefits of physical activity in mitigating frailty.

2.5.2 Sleep Quality

While widely used, the term "sleep quality" does not have a consensus definition. Better sleep quality is commonly indicated by shorter sleep latencies, fewer awakenings, and sleeping the recommended amount of hours for one's age (259). Poor sleep quality can increase the risks of hypertension, dyslipidemia, cardiovascular disease, weight-related issues, metabolic syndrome, type II diabetes, and colorectal cancer (260,261).

Poor sleep quality has been linked with frailty. A 2020 meta-analysis by Pourmotabbed et al. examined the relationship between sleep and frailty risk (262). When compared to the reference category of 6-8 hours of sleep per night, both the high sleep category (> 8 hours) and the low sleep category (<6 hours) had higher frailty scores. This study also found that daytime drowsiness, sleep-disordered breathing, and prolonged sleep latency increase the risk of frailty. A 2019 systematic review identified consistent evidence for the relationship between perceived sleep quality and frailty, though these findings were largely based on cross-sectional data (263).

It is still unclear how sleep can impact the relationship between physical activity and frailty. Sleep is a mediating factor for engaging in physical activity, impacting frailty. In other words, poor sleep quality decreases the likelihood of engaging in physical activity, which worsens frailty. Conversely, better sleep increases the likelihood of physical activity, improving frailty (264). A longitudinal study found that those who sleep longer than the recommended duration for their age group had inadequate activity, low muscle strength, and slow walking speed, all contributing to frailty (265). What remains unknown is whether engaging in physical activity can mitigate frailty in individuals with poor sleep quality.

2.5.3 Diet Quality

Like 'sleep quality,' 'diet quality' is poorly defined. Diet quality usually involves categorizing foods into "healthy" and "unhealthy" components, when one should instead aim to consume *adequate* amounts of healthy foods and nutrients (e.g., fruits, vegetables, whole grains, fiber) and *moderate* (or very limited) amounts of "unhealthy" foods and nutrients (e.g., saturated fat, sugar, sodium) (266,267). Dietary choices can contribute to the risk of developing hypertension, hypercholesterolemia, obesity, and inflammation, subsequently increasing the risk of cardiovascular disease, diabetes, and cancer (266,268).

Optimal diet quality has been linked to preventing and reversing frailty. Many experts consider diet a risk factor for frailty (269,270); however, the evidence is mixed. Observational studies have shown that a higher-quality diet is associated with a lower prevalence of frailty (271,272). This is demonstrated by increased intake of fruits and vegetables, adherence to protein and energy intake recommendations, and adherence to the Mediterranean Diet (270,273–276). Furthermore, malnutrition is also associated with higher frailty (277,278). However, a 2021 meta-analysis of randomized control trials comparing a nutritional supplements group with a placebo group did not find a statistically significant difference in Frailty Phenotype status between those groups (n = 215 participants; OR = 2.30; 95% CI = 0.72, 7.01; GRADE = very low) (270).

While more research is needed to understand how diet quality is related to frailty, some research has explored how a healthy diet and physical activity impact frailty together. A systematic review by Brunilda et al. (2020) evaluated the role of physical activity and nutrition in frail older adults, identifying early interventions to slow frailty and disability (280). They reported moderate evidence that nutrition, protein supplementation, and physical activity interventions benefit pre-frail and frail older adults (281). Other studies have also found that physical activity is essential in frailty management and that diet has an additive effect (280,281).

2.5.4 Smoking

Smoking can increase the risks of cancer, heart disease, stroke, lung disease, diabetes, and chronic obstructive pulmonary disease (282). Tobacco use remains one of the leading causes of death in the United States, accounting for approximately 1 in 5 deaths per year (283). Unsurprisingly, smoking also has an adverse impact on frailty. A recent meta-analysis found that in current smokers, the risk of frailty is 63% higher than in non-smokers (284). However, there is limited information on how smoking may impact the relationship between physical activity and frailty.

Neiderstrasser et al. (2019) identified modifiable risk factors for the development and progression of frailty in older adults using data from the English Longitudinal Study on Aging (285). They found that the average 67-year-old who participates in mild physical activity (or is sedentary) and is a current or previous smoker has a 59% greater chance of becoming frail by the time they are 79 years old. In contrast, a person of the same age who engages in moderate-to-vigorous physical activity and has never smoked has a 22% chance of becoming frail. Although this finding is promising, more work is needed to understand if being a smoker negates the positive impact of physical activity on frailty.

2.5.5 Alcohol Consumption

Drinking alcohol has become a normal societal behaviour, though numerous health concerns are connected to high alcohol consumption (286), including more than 200 diseases and injuries (287,288). The amount of alcohol considered harmful varies globally and individually. The World Health Organization defines harmful drinking as the amount that causes detrimental health and social consequences for the drinker, the people around the drinker, and society at large (288).

The association between alcohol consumption and frailty is ambiguous. Some studies report that alcohol consumption is positively associated with increased frailty, while others report that alcohol consumption reduces frailty (236,289,290). Observational studies suggest a U- or J-shaped relationship between alcohol consumption and frailty (236,289). A U-shaped relationship implies that non-drinkers and excessive drinkers have an increased risk of frailty, while individuals who drink in moderation have a decreased risk. A J-shaped relationship implies a decreased risk of frailty for non-drinkers and moderate drinkers but an increased risk with excessive alcohol consumption. One meta-analysis found that alcohol consumption is associated with a lower risk of frailty (pooled odds for highest alcohol use categories compared to non-drinkers = 0.44; 95% CI = 0.19, 1.00; $p = 0.05$) (236). However, the authors state that social components might partly explain the protective effect of alcohol consumption on frailty. Another possibility is the idea of a "sick quitter," an individual who has quit drinking alcohol due to health reasons and is now classified as a non-drinker. This could make comparison groups misleading as some non-drinkers may have poorer health than healthier drinkers classified as "current drinkers."

Studies have explored the independent relationships between alcohol and physical activity and alcohol and frailty (236,291). Yet, none have explored how being a current drinker who engages in regular physical activity impacts frailty. No conclusions can be drawn from this study until more research is available.

Overall Thesis Rationale, Objectives, and Hypothesis

The following studies are presented to better understand the dynamic relationship between frailty and physical activity by examining different types of physical activity, different tools for frailty, how age and sex affect the relationship between physical activity and frailty, and how other lifestyle behaviours impact this relationship.

Manuscript 1: Reaching the recommended level of moderate-to-vigorous aerobic activity and resistance training is associated with decreased frailty and mortality. We aim to determine if reaching the recommended level of moderate-to-vigorous aerobic activity or resistance training alone could also show favorable associations. Additionally, we will investigate if these associations differ by age and sex. I test the hypothesis that engaging in only one type of activity (e.g., resistance training only) is associated with decreased frailty and mortality risks while engaging in both together will provide the strongest association. Furthermore, I hypothesize that this relationship is impacted by age and sex differences, such that being younger and male will have stronger associations.

Manuscript 2: Many frailty tools exist in the literature, each with its own conceptualization and criteria. We aim to explore whether associations between frailty, moderate-to-vigorous physical activity, and resistance training vary based on the common frailty tool used. Additionally, we will examine if these relationships differ by age and sex. I hypothesize that the relationship between frailty and activities will differ across frailty tools, more specifically that tools that capture physical frailty (e.g., the Frailty Phenotype and the SOF) will have a stronger association with physical activity and reduced stationary time. Secondly, we hypothesized that these relationships will differ by age and sex, such that being younger and male will have stronger associations between physical activity and reduced stationary time.

Manuscript 3: Physical activity is just one of many lifestyle behaviours that impact frailty. Knowing how other lifestyle behaviours influence the relationship between these two variables is important. We aim to examine how lifestyle behaviours may support or hinder the association between physical activity and frailty. Further, to examine if these associations differ by sex and age. I hypothesize that being active will have a protective effect on the relationship between poor lifestyle behaviours and frailty. Also, this association will be stronger in males and younger adults.

Chapter 3 - Manuscript 1: Are the Recommended Levels of Moderate-to-Vigorous Aerobic Activity and Resistance Training Inversely Associated with Frailty and Mortality?

Chapter 3 Abstract

Objective: To examine the association of meeting the Moderate-to-Vigorous Physical Activity (MVPA) or Resistance Training (RT) components of the physical activity (PA) guidelines with frailty and mortality and to determine if these associations vary by age and sex.

Study Design: Secondary analysis of 17,716 individuals [46±19 years (range: 20-85 years), 52.2% female] from the National Health and Nutrition Examination Survey (cycles 1999-2006).

Main Outcome Measures: Self-reported MVPA (≥150 mins/week) and RT (≥2 days/week) levels were used to divide participants into Combined (both met), MVPA Only, RT Only, or Inactive (neither met) groups. Frailty was measured with a 46-item Frailty Index (FI) and all-cause mortality was obtained using the National Death Index data.

Results: A total of 1,878 (10.6%) people were included in the Combined group, 3,741 (21.1%) in the MVPA Only group, 1,257 (7.1%) in the RT Only group, and 10,840 (61.2%) in the Inactive group. Older females needed to engage in MVPA to experience a beneficial effect on frailty, whereas males benefited from engaging in either or both types of activity regardless of age. Robust females (HR = 0.65, 95% CI = 0.46, 0.93) and frail males (HR = 0.72, 95% CI = 0.59, 0.88) in the Combined group had a lower risk of mortality compared to the Inactive group.

Conclusion: There is a decreased association with frailty and mortality when achieving MVPA or RT guidelines alone, though sex and age differences demonstrate that MVPA is especially critical as females age.

Chapter 3: Introduction

Frailty is a multifaceted condition characterized by reduced physiological reserve, increased vulnerability, and a heightened risk of adverse health outcomes, including all-cause mortality (52,56,292). Strategies to mitigate frailty are crucial for reducing both individual and healthcare burdens. One of the most promising interventions is engaging in physical activity (8). The World Health Organization recommends that adults participate in at least 150 minutes of moderate-to-vigorous aerobic physical activity (MVPA) and engage in resistance training (RT) at least two days per week to mitigate the risks of frailty and mortality (293). Unfortunately, many adults do not meet these recommendations (12,227).

Although adhering to these guidelines is considered best practice, some studies suggest that meeting only one component (e.g., >150 minutes/week of MVPA) may still provide benefits (174,294). It remains unclear whether achieving just one component of these guidelines can sufficiently mitigate frailty and mortality risk or if adherence to both components is necessary. Additionally, it is crucial to identify which populations benefit from different aspects of the guidelines, as physical activity behaviors, frailty levels, and mortality risk vary by sex and age (22,94,215,222). For instance, at any age, females are generally more likely to have higher frailty scores and be less active than males, yet they tend to live longer. Understanding how the relationships between physical activity, frailty, and mortality risk differ by sex and age is vital for tailoring interventions appropriately for these populations. The primary objective of this study was to examine the associations between adherence to MVPA and/or RT guidelines and frailty and all-cause mortality. The secondary aim was to determine if these associations vary by sex or age.

Chapter 3: Methods

Participants and Study Design

We conducted a secondary analysis of cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) (1999-2006 cycles), which includes a representative sample of community-dwelling individuals from the USA (295). The study included males and females aged 20 years and older with available data on frailty index (FI), mortality records, and self-reported physical activity (PA). The final sample comprised 17,716 participants, of whom 52.2% were female (N = 9,250) (See Appendix C – Figure 1). Study participants provided written informed consent. NHANES protocols have been approved by the Centers for Disease Control and Prevention Institutional Review Board.

Physical Activity Outcomes

Physical activity levels were assessed using a questionnaire. Participants were asked about the types of activities they regularly engaged in. For those who reported any physical activity, additional questions gathered details on the type, intensity, frequency, and duration of these activities. This information was used to calculate weekly MVPA levels. Participants were classified as meeting the recommended MVPA levels if they engaged in ≥150 minutes of MVPA per week (296).

Two questions in NHANES assessed levels of RT. The first question asked participants, "Over the past 30 days, did you do any activities specifically designed to strengthen your muscles, such as lifting weights, push-ups, or sit-ups?" If the participant responded "yes," they were then asked, "Over the past 30 days, how often did you do these activities?" The second questionnaire asked, "Over the past 30 days, what activities did you do?" This was followed by a list of activities, including muscle-strengthening exercises. If participants reported engaging in any of these activities, they were asked, "Over the past 30 days, how often did you do this activity?" If the two questionnaires provided different RT frequencies, the higher reported value was used. To estimate a weekly average, the 30-day RT data were divided by 4.3. Reaching the recommended RT levels was defined as engaging in RT for ≥2 days per week (296).

Participants were grouped into the following:

1) Combined: (≥150 minutes/week MVPA and ≥2 days/week RT)
2) MVPA Only: (≥150 minutes/week of MVPA and <2 days/week RT),
3) RT Only: (<150 minutes/week of MVPA and ≥2 days/week RT),
4) Inactive: (<150 minutes/week MVPA and <2 days/week RT)

Frailty and All-Cause Mortality Measures

Frailty levels were identified using a 46-item FI that was previously constructed and validated using NHANES data (297) (See Appendix C – Table 2). The FI operationalizes frailty by counting the number of deficits an individual has relative to the total number of deficits measured (59). For example, if someone has 10 out of a possible 46 deficits, their FI would be 0.22, with higher values indicating greater frailty. Participants were excluded if they were missing more than 20% of the FI variables (N = 2,569) (See Appendix C –

Figure 1). The proportion of participants within each of the following FI levels was determined: 1) FI ≤ 0.10, 2) 0.10 < FI ≤ 0.20, 3) 0.20 < FI ≤ 0.30, and 4) FI > 0.30. These cut-points were used for descriptive purposes and for simple slope associations. All-cause mortality data were obtained from the National Death Index mortality files linked to NHANES. Follow-up time extended from the time of the interview up to December 31, 2015 (Mean: 11.7 ± 3.6 years), with a total of 3,627 participants (20.5%) having died during this follow-up period.

Covariates

Sex was collected by NHANES personnel during the interview and was coded by personnel as either male or female. Frailty and physical activity levels differ by demographic factors, socioeconomic status, smoking habits, body mass index, and cohort (298–300). Therefore, the following covariates were included in the analysis: race (Mexican-American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race), education level (less than 9th grade, 9th-11th grade, high school graduate/General Educational Development, some college/associate degree, college graduate or above), marital status (married, widowed, divorced, separated, never married, living with partner), employment status (working at a job/business, looking for work, not working at a job/business), smoking status (every day, some days, never), body mass index (kg/m^2), and NHANES cycle.

Statistical Analysis

Statistical analyses were performed using RStudio 12.2.5001 (R Foundation for Statistical Computing, Vienna, Austria) (301). Means ± standard deviations and frequencies (percentages) were reported for continuous and categorical variables. Descriptive characteristics were tested for differences across the four physical activity groups using one-way analysis of variance (ANOVA) for continuous variables and Chi-square tests for categorical variables. Bonferroni post-hoc testing was conducted for significant between-group comparisons.

Covariate-adjusted multiple linear regression models were used to examine the associations between MVPA and/or RT and frailty. Cox proportional hazard models were employed to investigate the associations between MVPA and/or RT and mortality. The Schoenfeld residuals test assessed the proportional hazards assumption for all-cause mortality regressions, and no violations were found. All models were adjusted for age, race, education level, marital status, employment status, body mass index, smoking status, and NHANES cycle. Cox proportional hazards models were additionally adjusted for frailty. Interactions between age, sex, and physical activity with frailty and all-cause mortality were tested. Sensitivity analyses were performed to examine the relationship between all-cause mortality and physical activity, excluding frailty as a covariate, to understand how frailty influenced this relationship. Significant interactions were further analyzed by stratifying by sex and/or centering age around 30, 40, 50, 60, and 70 years to explore simple associations. An α of 0.05 was used to denote statistical significance. All analyses were weighted using sampling weights, and the complex survey design was accounted for using the R survey package (302).

Chapter 3: Results

General Characteristics

A total of 17,716 participants were included in the analysis, with 52.2% female, as shown in Table 3.1. The proportions of individuals in each activity category were as follows: 1,878 (10.6%) in the Combined group, 3,741 (21.1%) in the MVPA Only group, 1,257 (7.1%) in the RT Only group, and 10,840 (61.2%) in the Inactive group. All descriptive characteristics differed significantly across the four physical activity groups (all $p < 0.02$). For instance, compared to the Inactive group, participants in the MVPA Only, RT Only, and Combined groups were younger (mean ages: 49.0 ± 18.7, 47.9 ± 19.3, 43.4 ± 17.4 years; all $p < 0.001$) and more likely to be male (52.5%, 60.7%, and 53.7%, respectively; all $p < 0.006$). The proportion of participants in the lowest frailty category (FI < 0.10) was 47.7% in the Inactive group, 59.4% in the MVPA Only group, 61.1% in the RT Only group, and 73.1% in the Combined group, with all groups differing significantly ($p = 0.003$).

Differences in Frailty Index Score by Physical Activity Groups

Figure 3.1 illustrates the mean FI scores for each physical activity group stratified by sex. For females, being in the Combined or MVPA Only group was associated with a lower FI score compared to the Inactive group (Combined Group: 0.08 ± 0.08; MVPA Only: 0.10 ± 0.09; all $p < 0.001$). For males, all other activity groups also showed lower FI scores compared to the Inactive group (Combined: 0.08 ± 0.07; MVPA Only: 0.11 ± 0.09; RT Only: 0.10 ± 0.10; all $p < 0.001$).

Associations between Physical Activity Groups and Frailty

A sex-by-age interaction was observed when examining the association between physical activity groups and the FI; thus, we further explored simple associations by age groups (Figure 3.2). Across all ages, being a female in the Combined group (β = -0.15 to -0.25; all $p < 0.001$) and the MVPA Only group (β = -0.09 to -0.19; all $p < 0.001$) was associated with a lower FI score compared to the Inactive group. The RT Only group also showed a decreased association with frailty, but this was significant only for younger females (Age 30: β = -0.15, 95% CI = -0.27 to -0.03; Age 40: β = -0.11, 95% CI = -0.21 to 0.00). All other physical activity groups were associated with lower frailty scores in males across all ages compared to the Inactive group (See Appendix C – Table 3).

Rate of All-cause Mortality by Physical Activity Group, by Sex and Frailty

All-cause mortality rates increased with higher frailty levels for both sexes (see Figure 3.3). For Inactive females, mortality rates across frailty categories were 4.7%, 11.8%, 40.6%, and 60.7%. For Inactive males, the rates were 9.9%, 35.0%, 51.3%, and 71.5%. Few significant differences were observed for all-cause mortality rates across physical activity groups. In females, those in the lowest frailty category had a lower proportion of deaths in the Combined group compared to the Inactive group (Combined: 1.8% vs. Inactive: 4.7%; $p = 0.03$). In the highest frailty category, only females in the MVPA Only group had a lower proportion of deaths compared to the Inactive group (MVPA Only: 43.3% vs. Inactive: 60.7%; $p = 0.03$). For males in the lowest frailty category and the 0.2-0.3 category, those in the Combined group had a lower proportion of deaths compared to the Inactive group.

Association between Physical Activity Groups and All-cause Mortality

Significant sex-by-frailty interactions were observed when examining the association between physical activity groups and all-cause mortality. Females in the

Combined group, with a FI centered at 0.10, had a lower risk of all-cause mortality compared to the Inactive group, as shown in Figure 4 (HR = 0.65, 95% CI = 0.46 to 0.93). For males in the Combined group, lower odds of all-cause mortality were observed, but only when the FI was centered around 0.20 (HR = 0.72, 95% CI = 0.59 to 0.88) and 0.30 (HR = 0.67, 95% CI = 0.49 to 0.90) (see Appendix C – Table 4). In the sensitivity analysis, which excluded FI as a covariate (see Appendix C – Table 5), both sexes in the Combined and MVPA Only groups showed a negative association with all-cause mortality compared to the Inactive group [Females: OR (95% CI) – Combined: 0.52 (0.39 to 0.69); MVPA Only: 0.66 (0.54 to 0.81); Males: OR (95% CI) – Combined: 0.50 (0.39 to 0.63); MVPA Only: 0.81 (0.68 to 0.98)].

Table 3.1 Descriptive characteristics by physical activity groups

N (%) or Mean (SD)	Total Sample N = 17,716	Inactive Group N = 10,840	MVPA Only Group N = 3,741	RT Only Group N = 1,257	Combined Group N = 1,878
Age (years)	46.0 (19.0)	50.7 (19.1)	49.0 (18.7)[e]	47.9 (19.3)[e]	43.4 (17.4)[e]
Sex					
Female	9250 (52.2)	6,109 (56.4)[e]	1,777 (47.5)	494 (39.3)	870 (46.3)
Male	8466 (47.8)	4,731 (43.6)	1,964 (52.5)[e]	763 (60.7)[e]	1,008 (53.7)[e]
Race					
Mexican American	3927 (22.2)	2,802 (25.8)[e]	645 (17.2)[e]	244 (19.4)	236 (12.6)[e]
Non-Hispanic Black	3447 (19.5)	2,157 (19.9)	569 (15.2)[e]	314 (25.0)[e]	407 (21.7)
Non-Hispanic White	8961 (50.6)	5,009 (46.2)[e]	2,251 (60.2)[e]	605 (48.1)	1,096 (58.4)[e]
Other Hispanic	741 (4.2)	488 (4.5)	138 (3.7)	48 (3.8)	67 (3.6)
Other	640 (3.6)	384 (3.5)	138 (3.7)	46 (3.7)	72 (3.8)
Education					
Less than Grade 9	2610 (14.7)	2111 (19.5)[e]	317 (8.5)[e]	120 (9.5)[e]	62 (3.3)[e]
9-11th Grade	2902 (16.4)	2088 (19.3)[e]	469 (12.5)[e]	172 (13.7)	173 (9.2)[e]
High School Graduate	4193 (23.7)	2647 (24.4)	904 (24.2)	305 (24.3)	337 (17.9)[e]
Some College	4610 (26.0)	2532 (23.4)[e]	1,076 (28.8)[e]	382 (30.4)[e]	659 (35.1)[e]
College Graduate or Above	3330 (18.8)	1437 (13.3)[e]	970 (25.9)[e]	277 (22.0)[e]	646 (34.4)[e]
Missing	32 (0.2)	25 (0.2)	5 (0.1)	1 (0.08)	1 (0.1)

N (%) or Mean (SD)	Total Sample N = 17,716	Inactive Group N = 10,840	MVPA Only Group N = 3,741	RT Only Group N = 1,257	Combined Group N = 1,878
Marital Status					
Married	9696 (54.7)	5889 (54.3)	2,212 (59.1)[e]	632 (50.3)	963 (51.3)[e]
Divorced	1542 (8.7)	963 (8.9)	317 (8.5)	105 (8.4)	157 (8.4)
Never Married	2704 (15.3)	1,442 (13.3)[e]	551 (14.7)	241 (19.2)[e]	470 (25.0)[e]
Separated	545 (3.1)	361 (3.3)	89 (2.4)	49 (3.9)	46 (2.4)
Living with a Partner	1102 (6.2)	693 (6.4)	210 (5.6)	83 (6.6)	116 (6.2)
Widowed	1670 (9.4)	1,204 (11.1)[e]	274 (7.3)[e]	101 (8.0)	91 (4.8)[e]
Missing	457 (2.6)	288 (2.7)	88 (2.4)	46 (3.6)	35 (1.9)
Occupation Status					
Working at a job or business	9838 (55.5)	5,583 (51.5)[e]	2,200 (58.8)[e]	797 (63.4)[e]	1,258 (67.0)[e]
Looking for Work	313 (1.8)	151 (1.4)[e]	89 (2.4)[e]	25 (2.0)	48 (2.6)
Not working at a job or business	7561 (42.7)	5,103 (47.1)[e]	1,452 (38.8)[e]	434 (34.5)[e]	572 (30.5)[e]
Missing	4 (0.02)	3 (0.03)	0 (0)	1 (0.08)	0 (0)
Smoker Status					
Everyday	3192 (18.0)	2,173 (20.0)[e]	601 (16.1)[e]	193 (15.4)	225 (12.0)[e]
Some days	682 (3.8)	423 (3.9)	129 (3.4)	54 (4.3)	76 (4.0)
Never	13,842 (78.1)	8,244 (76.1)	3,011 (80.5)[e]	1,010 (80.4)	1,577 (84.0)[e]
Body Mass Index (kg/m^2)	27.7 (6.0)	28.9 (6.6) [bcd]	28.1 (6.0) [ad]	27.7 (5.9) [ad]	27.1 (5.4) [abc]
Frailty Index (0-1)	0.13 (0.11)	0.11 (0.11)[bcd]	0.11 (0.09) [ad]	0.14 (0.12) [ad]	0.08 (0.08) [abc]

N (%) or Mean (SD)	Total Sample N = 17,716	Inactive Group N = 10,840	MVPA Only Group N = 3,741	RT Only Group N = 1,257	Combined Group N = 1,878
Frailty Index Categories					
≤ 0.10	9549 (54.0)	5168 (47.7)[e]	2221 (59.4)[e]	768 (61.1)[e]	1372 (73.1)[e]
(0.10, 0.20]	4554 (25.7)	2924 (27.0)[e]	994 (26.6)	275 (21.9)[e]	361 (19.2)[e]
(0.20, 0.30]	2149 (12.1)	1544 (14.2)[e]	387 (10.3)[e]	120 (9.5)	98 (5.2)[e]
> 0.30	1484 (8.4)	1204 (11.1)[e]	139 (3.7)[e]	94 (7.5)	47 (2.5)[e]

SD = Standard Deviation; MVPA = Moderate-to-Vigorous Physical Activity; RT = Resistance Training. Inactive Group: < 150 minutes/week MVPA and <2 days/week RT; Combined: ≥150 minutes/week MVPA and ≥2 days/week RT.

[a] different vs Inactive group;
[b] different vs MVPA Only group;
[c] different vs RT Only group;
[d] different vs Combined group;
[e] different from all other activity groups.

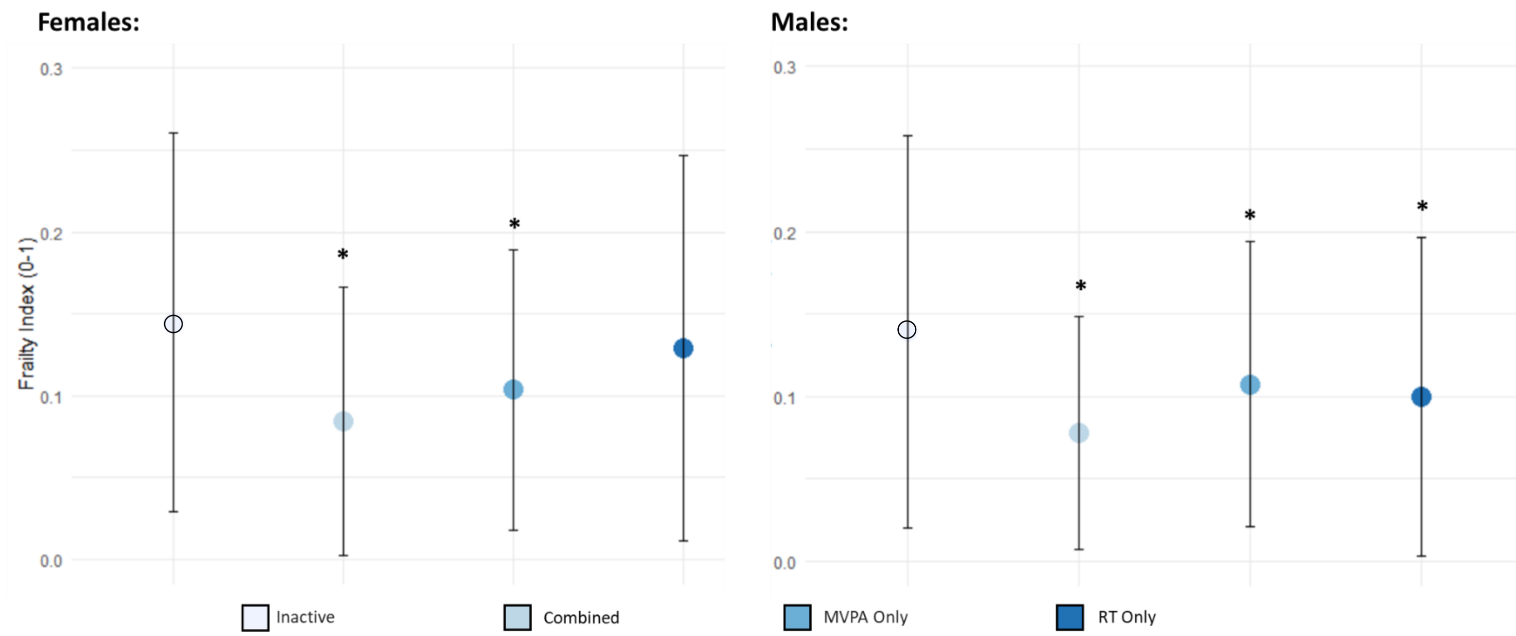

Figure 3.1 Means and standard deviations of frailty index scores across physical activity groups. * = $p < 0.05$ versus the inactive group. MVPA = Moderate-to-vigorous physical activity; RT = Resistance training.

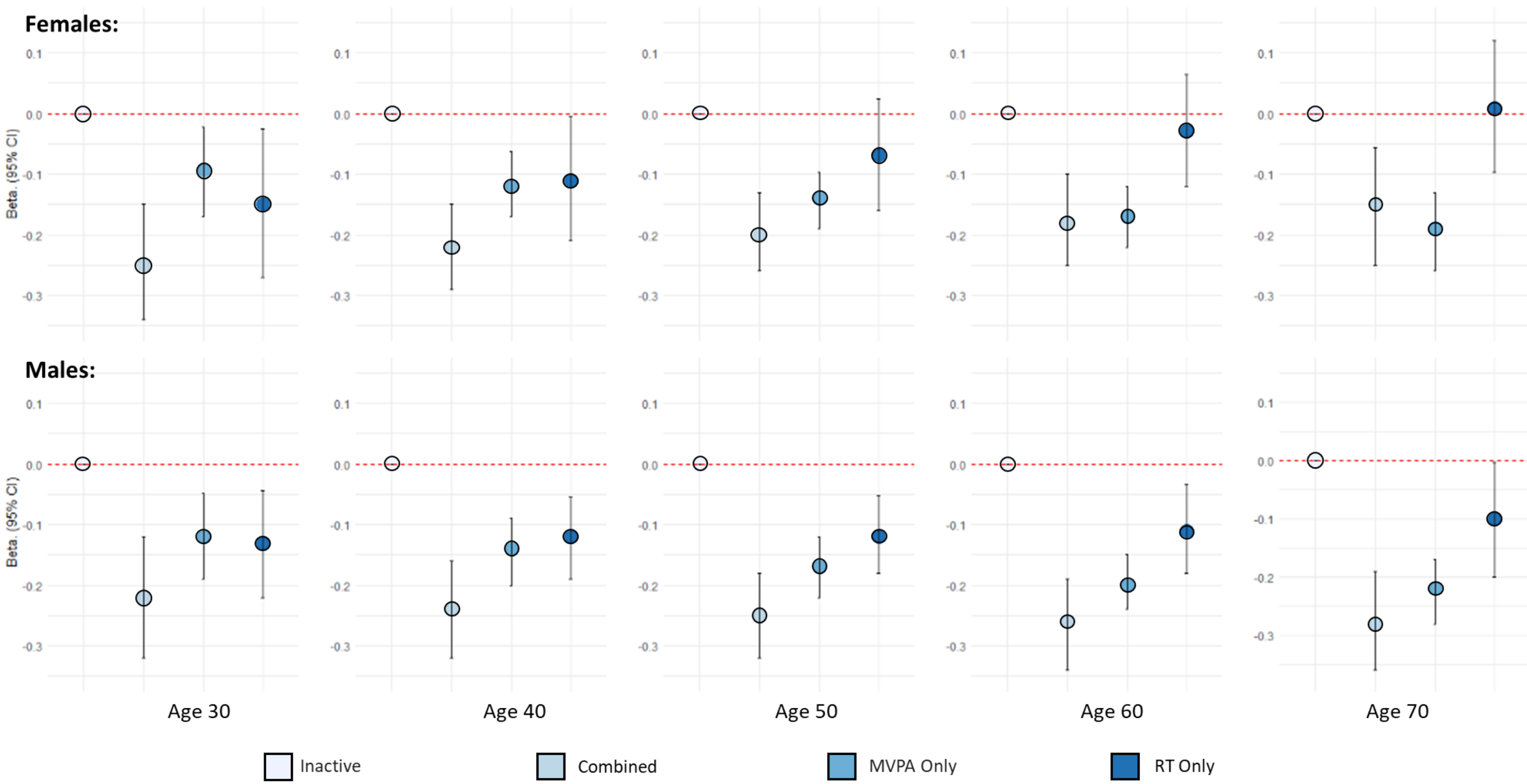

Figure 3.2 Simple associations between physical activity groups and frailty, separated between females and males.
MVPA = Moderate-to-vigorous physical activity; RT =Resistance training; CI = Confidence interval. If the CI lines cross the dotted red line (inactive/reference group) then the activity group is not significant (for regression values, See Appendix C - Table 3). Linear regression models adjusted for race, education, marital status, occupation status, smoking status, body mass index, and NHANES cycle. Age was centered around 30, 40, 50, 60, and 70 years to obtain the simple association.

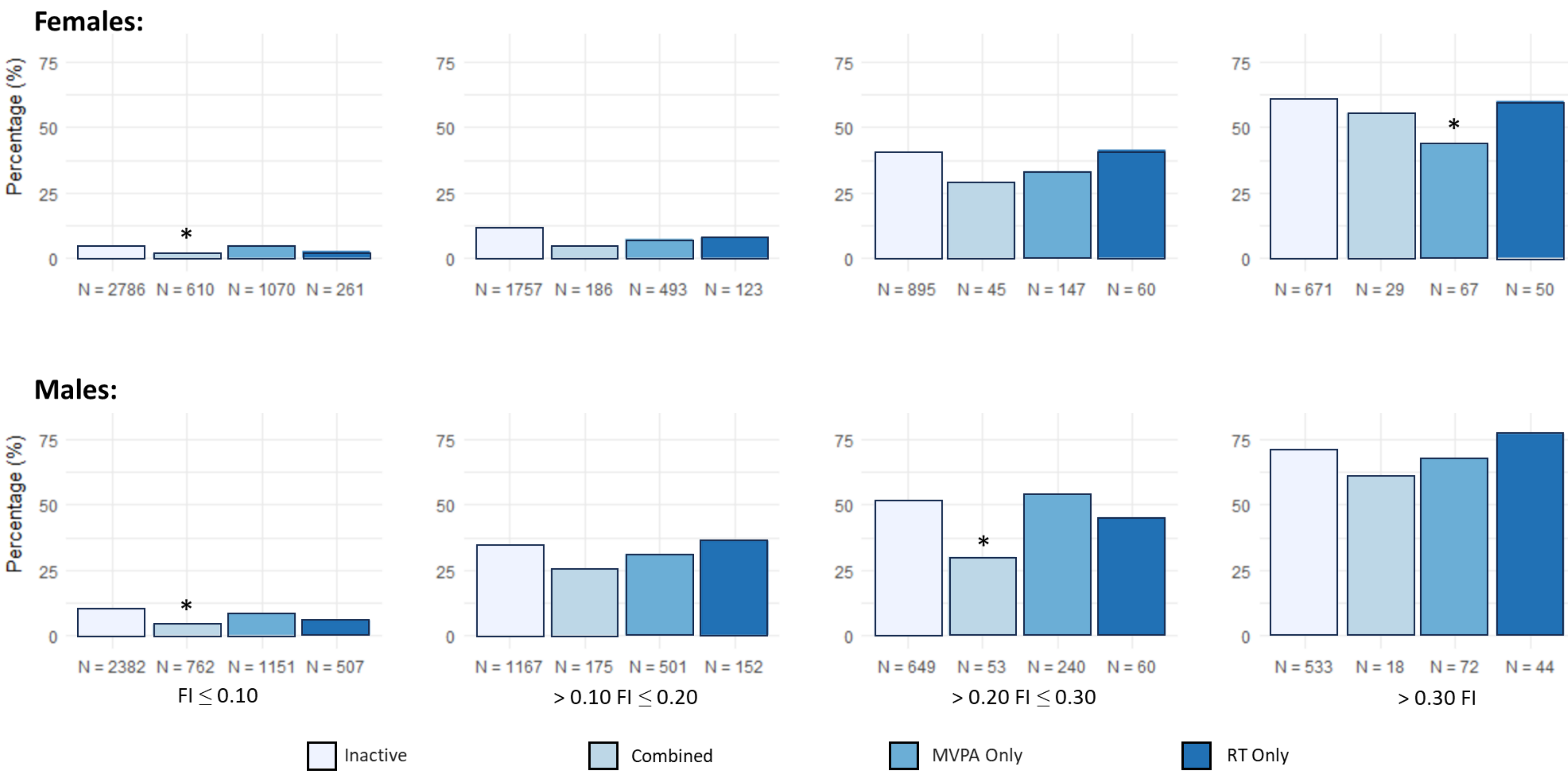

Figure 3.3 Mortality rate of each physical activity group for females and males, stratified by frailty. * = $p < 0.05$ versus the inactive group. FI = Frailty index; MVPA = Moderate-to-vigorous physical activity; RT = Resistance training.

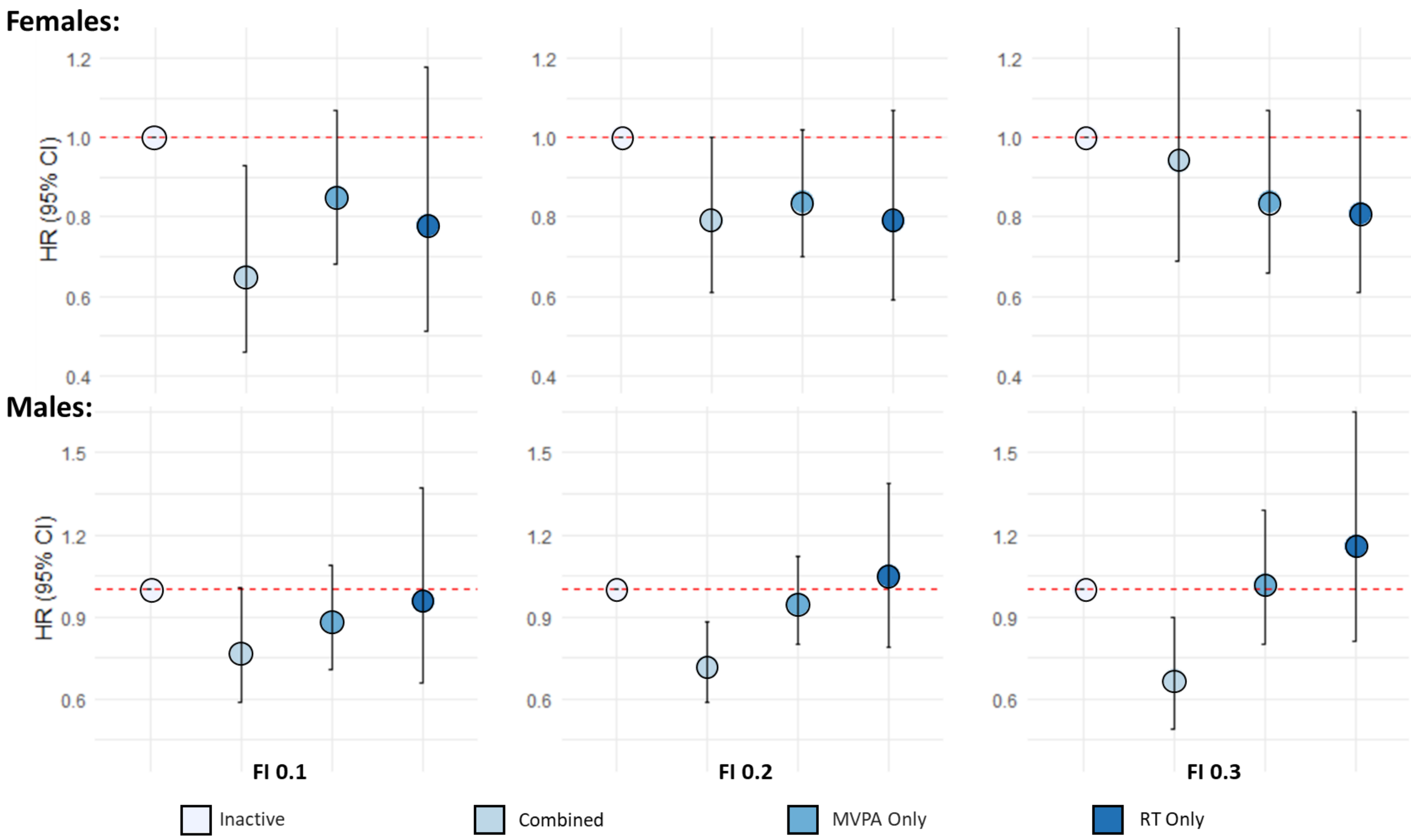

Figure 3.4 Associations between physical activity groups and mortality for females and males. MVPA = Moderate-to-vigorous physical activity; RT = Resistance training; FI = Frailty index; HR = Hazard ratio; CI = Confidence interval. If the CI lines cross the dotted red line (inactive/reference group), then the activity group is not significant (for regression values, see Appendix C- Table 5). Cox regression models adjusted for age, race, education, marital status, occupation status, smoking status, body mass index, and NHANES cycle. Frailty was centered around 0.1, 0.2, and 0.3 scores to obtain the simple associations.

Chapter 3: Discussion

This study demonstrated that engaging in either component of the physical activity recommendations was associated with decreased frailty compared to those who did not meet either recommendation, except for older females who participated in resistance training only. Notably, the magnitude of differences in FI between active and inactive individuals was greater than 0.03, a clinically significant difference (175). This suggests that achieving either component of the activity guidelines can lead to meaningful improvements in frailty outcomes. Additionally, the relationship between physical activity and frailty varied by age and sex, with males showing the strongest associations, especially in older ages. Further older females needed to engage in moderate-to-vigorous physical activity (MVPA) to observe a beneficial effect on frailty. Meanwhile, males benefited from engaging in either or both types of activity regardless of age. The study found minimal direct relationships between physical activity groups and mortality. However, the sensitivity analysis revealed that frailty may mediate this relationship. In both sexes, participation in the Combined or MVPA Only groups was associated with a protective effect on all-cause mortality, emphasizing the importance of achieving the recommended level of MVPA. Notably, the Combined group was particularly effective in reducing the risk of all-cause mortality for males with higher FI levels and for females with lower FI levels.

The mechanisms underlying frailty are not fully understood (44), making it challenging to determine how MVPA or RT uniquely mitigates frailty. Nonetheless, experts have proposed mechanisms by which these activities reduce and prevent frailty

(165). MVPA and RT both influence cardiovascular and neuromuscular adaptations, but they do so in different ways. MVPA primarily impacts cardiovascular adaptations, while RT more directly affects neuromuscular adaptations (303,304). These physiological changes are directly related to frailty. For instance, MVPA has been shown to increase muscle oxidative capacity (305), which enhances fatigue resistance and muscle endurance. In contrast, RT is known to increase muscle strength and mass (306), thereby improving functional outcomes. Each component of the physical activity guidelines addresses specific health deficits that contribute to frailty, which may explain why engaging in either type of activity is associated with lower levels of frailty.

Our findings are consistent with studies indicating that aerobic training alone can be effective in mitigating frailty (174). Furthermore, the strength of the association between frailty and the MVPA-only group strengthens as males and females age (Females, Age 30: $\beta = -0.094$; Age 70: $\beta = -0.19$; Males, Age 30: $\beta = -0.12$; Age 70 = -0.22). However, there is conflicting evidence regarding the impact of RT alone on frailty (178,306). Our study found that RT is associated with lower frailty compared to inactivity, though this effect is primarily observed in males across ages and younger females. In males, the strength of association remains similar across age groups.

A potential explanation for this sex difference could be that males experience a greater magnitude of adaptation in response to RT compared to females. For example, a systematic review and meta-analysis by Jones et al. (2021) found that females gained more relative lower-body strength ($g = -0.21$, 95% CI: -0.33 to -0.10) compared to males. In contrast, males achieved greater gains in absolute upper-body strength ($g = 0.48$, 95%

CI: 0.09 to 0.88), absolute lower-body strength (g = 0.33, 95% CI: 0.19 to 0.47), and absolute muscle size (g = 0.45, 95% CI: 0.23 to 0.66) (307). Another explanation for the sex differences is that females not only engage in less resistance training than males, but they also engage in lower-intensity resistance training (308,309). A study by van Uffelen et al. (2017), reported that females (aged 60-67) are less likely than males to prefer vigorous exercise activities (OR= 0.33, 95% CI= 0.24-0.47), or activities that require skill and practice (OR= 0.40, 95% CI=0.30-0.86) (310). Future studies should not only focus on the impact of the frequency of resistance training on the frailty levels of males and females but also on the impact of the duration, type, and intensity of resistance training.

Physical activity groups showed few associations with the risk of all-cause mortality across different ages and sexes when controlling for frailty levels. This finding contrasts with a substantial body of evidence highlighting the importance of physical activity in reducing mortality risk (294). However, in the sensitivity analysis, which excluded frailty from the model, both sexes showed a protective effect against all-cause mortality when engaged in the Combined or MVPA Only groups. Few studies have explored the relationship between physical activity, frailty, and mortality. Bisset et al. (2021) investigated the impact of aerobic exercise on frailty and mortality in older male and female mice, matched for baseline frailty and randomized into exercise (running wheel) and inactive (no wheel) groups (311). Their study found that while exercise did not affect mortality, it reduced the development of frailty. They concluded that exercised mice experienced healthier aging compared to inactive controls. This study contributes to the 'dying healthier' literature (312), suggesting that individuals who engage in regular exercise may maintain better physical and mental health in their later years compared to those who remain inactive.

The strength of this study lies in its analysis of different physical activity recommendations within a representative sample of non-institutionalized U.S. adults. Additionally, the study utilized a FI that has been validated within the NHANES dataset (295). However, the cross-sectional nature of NHANES limits the ability to infer causation from the findings in relation to the association of physical activity with frailty. Furthermore, there are notable differences between the analytic sample and the excluded sample (Appendix C – Table 1), which suggests that the results might have varied if those with missing data had been included. Another limitation is the reliance on self-reported physical activity, which may be less reliable than objectively measured physical activity (311). Future research should explore how these findings might differ with more robust and validated measures of physical activity

Chapter 3: Conclusion

The main takeaway from this study is that meeting either the MVPA or RT guidelines alone is associated with a decreased level of frailty. While achieving both guidelines may be considered best practice, adults who meet just one of them still experience benefits, reinforcing the notion that “something is better than nothing.” Additionally, the impact of physical activity on frailty and mortality differed by sex and age. Specifically, older females needed to engage in MVPA to have a lower risk of frailty, whereas RT alone was not significantly associated with lower frailty in this group. Although there was little association between physical activity groups and all-cause mortality when accounting for age, sex, and frailty level, the sensitivity analysis revealed that MVPA is crucial for reducing mortality risk in both sexes due to its impact on frailty.

Chapter 3 Linking Manuscripts 1 and 2

Manuscript 1, titled "Are the Recommended Levels of Moderate-to-Vigorous Aerobic Activity and Resistance Training Inversely Associated with Frailty and Mortality?", examined the association between achieving the recommended amount of MVPA and/or RT with frailty and mortality while also considering age and sex differences. Although this manuscript explored the differences in recommended physical activity "types", it maintained consistency in frailty tools across regression models (i.e., the frailty index). However, many frailty tools have a wide range of characteristics and conceptualizations.

Aligned with this manuscript's aim of understanding the relationship between physical activity and frailty, manuscript 2 aimed to address the following questions:

1. Does the association between physical activity or sedentary time and frailty vary based on the frailty tool used?
2. Do these associations differ across sex and age?

Chapter 4 - Manuscript 2: Does the Association between Physical Activity and Frailty vary across Frailty Tools?

Chapter 4: Abstract

Background: Increasing physical activity and decreasing sedentary time have been shown to mitigate frailty. However, more work is needed to identify tools that are appropriate for physical activity and frailty research.

Objective: To investigate if the associations between physical activity or stationary time (ST) and frailty vary based on the frailty tool used. Also, to examine if these associations differ across sex and age groups.

Design: Cross-sectional study.

Setting: We conducted a secondary analysis of the National Health and Nutrition Examination Survey (NHANES) cycles 2003-2006, a US nationally representative study.

Participants: Adults ≥60 years old

Measures: Moderate-to-Vigorous Physical Activity (MVPA), Light Activity (LA), and ST were measured by hip-worn accelerometry, and Resistance Training (RT) was self-reported. The frailty tools included the Frailty Index, and modified versions of the Study of Osteoporotic Fractures Index (SOF), Frailty Phenotype (FP), and FRAIL Scale. Linear regressions were used and interaction terms between age, sex, and frailty were tested.

Results: A total of 1985 participants (71.1±7.8 years, 954 females, 48%) were included. Participants engaged in 77±98 min/week of MVPA, 4.7±1.6 hrs/day of LA, 9.5±0.9 hrs/day of ST, and 0.9±2.4 days/week of RT. MVPA was negatively associated with all frailty tools (β range: -5.27, -0.24). However, associations differed by frailty tool, sex, and age. Both LA (negatively) and ST (positively) were associated with all frailty tools, except when ST was examined in frail males using the FP. Only the FP and SOF had positive associations with RT.

Conclusion: Associations between PA, ST, and frailty differed by frailty tool, sex, and age. Further, being a younger male who engages in MVPA and RT was protective against frailty. Future research is needed to examine the association of different frailty tools with physical activity and ST.

Chapter 4: Background

The proportion of those 65 years and older is growing worldwide, and aging is associated with a heightened risk of frailty (229). Frailty is defined as a multifaceted condition that reduces physiologic reserve and leads to a state of increased vulnerability (52,56). Frailty is directly linked with the higher likelihood of experiencing adverse health outcomes that negatively impact the individual, their loved ones, and our healthcare system (313). Therefore, treating and understanding frailty has become a priority for healthcare professionals and researchers.

One of the greatest challenges in frailty research is the lack of a standardized measurement tool (314). Azzopardi et al. (2016) identified 79 original or adapted frailty instruments that were linked to the international classification of physical functioning, disability, and health (315). In addition to having so many tools, there is a large variation in the characteristics of these tools, with the most common tools capturing physical frailty or a multi-dimensional view of frailty (315). Physical frailty captures physical functioning, whereas a multi-dimensional approach to frailty includes physical aspects of frailty, as well as other important health domains such as cognition and social well-being (316). These differences in conceptualization may impact frailty treatment and research findings interpretation.

Physical activity is one of the leading interventions to reduce and prevent frailty (317). However, it is unclear if frailty tool selection impacts the relationship between activity and frailty. Some commonly used frailty tools in the physical activity literature include the Frailty Phenotype, the Frailty Index (FI), the Study of Osteoporotic Fractures Index (SOF), and the Fatigue, Resistance, Aerobic, Illness, and Loss of weight Scale

(FRAIL). Although these tools are well-validated, there could be issues when using them in physical activity research (318). An example of an issue can be gleaned from one of the characteristics of the Frailty Phenotype. This tool includes the criterion ‘low physical activity’, which is captured by the Minnesota Leisure Time Activity Questionnaires (52). Having this question within the frailty tool in physical activity research makes results susceptible to common method variance. Common method variance can cause systematic measurement errors that can inflate or deflate the observed relationships between constructs, generating Type 1 and Type II errors (183). Thus, having a physical activity measure in a frailty tool would inflate the relationship when examining physical activity and frailty. A concern with multi-dimensional frailty tools is that some items may diminish the impact physical activity has on frailty. This is true for the FI if it includes too many items that physical activity cannot change (i.e., do you have poor vision), which may undermine the impact of physical activity on frailty.

An example from the literature that examines how different frailty tools could impact physical activity findings can be found in the study by Arrireta et al. (2019) (318). This study examined the effect of a multicomponent exercise program on frailty using the Frailty Phenotype, the SOF, and the Tilburg Frailty Indicator. Older males and females were randomized into a 6-month individualized and progressive multicomponent exercise group or routine activities (Control group). The intervention consisted of two 1-hour supervised group training sessions per week. After 6-months, the proportion of participants who were considered frail had decreased as assessed by the Frailty Phenotype (Baseline: 61%, Endpoint: 53.7%) and the Tilburg Frailty Indicator (Baseline: 58.1%, Endpoint: 41.9%) but not the SOF (Baseline: 16.7%, Endpoint: 11.9%). This study highlights that different tools may provide different outcomes and lead to divergent conclusions regarding the impact of physical activity on frailty.

Study findings could also vary based on other aspects independent of the selected frailty tool. For instance, the relationship between physical activity and frailty could also be influenced by activity type (e.g., aerobic activity, resistance training, stationary activity) (156,164,179), age (e.g., 60 years old vs. 80 years old) (319), and by sex (e.g., male or female) (94). It is important to know how frailty tool results differ based on the type of activity, as many novel activity interventions are being explored to mitigate frailty (320). The primary objective of this study was to test if associations between frailty, moderate-to-vigorous physical activity, light, stationary, and resistance training activities vary based on the Frailty Phenotype, the FI, the SOF, and the FRAIL. Our secondary aim was to examine if these associations differed based on sex or age. We hypothesized that the relationship between frailty and activities would differ across frailty tools. Specifically, tools that capture physical frailty (e.g., the Frailty Phenotype and the SOF) will have a stronger association with physical activity and reduced stationary time. Secondly, we hypothesized that these relationships would differ by age and sex, such that being younger and male will have stronger associations with increased physical activity, reduced stationary time and frailty.

Chapter 4: Methods

Participants and Study Design

We conducted a secondary analysis of the National Health and Nutrition Examination Survey (NHANES) cycles 2003-2006. NHANES includes a representative sample of residents of the United States of America. Cycles 2003-2006 were included in this analysis as they are the only cycles with accelerometer data available. Trained personnel collected demographic and other questionnaire data during in-home visits; sex was coded by NHANES personnel as either male or female. Medical personnel conducted the examination component, including medical, dental, and physiological measurements. All participants in NHANES provided consent to participate. For this analysis, we included males and females aged 60 and older with complete data for all frailty tools, accelerometers, and self-reported resistance training (See Appendix D; Figure 1 & Table 1). The age cut point of 60 years was chosen as some frailty tools are only validated for this population (52).

Frailty Tools

Four main tools have been selected for this study: the FI, the Frailty Phenotype, the SOF Index, and the FRAIL Scale. These tools were selected as they are commonly used (317), valid, and reliable (61,98). Furthermore, the variables needed for these frailty tools were available in the NHANES dataset.

- <u>46-item FI:</u> The Frailty Index was developed by Rockwood and colleagues and operationalizes frailty by counting deficits (56,57); the more health deficits an individual has, the more frail they are. The FI, calculated as a ratio of deficits present out of the total number of possible deficits, provides a continuous score from total fitness (0) to total frailty (1). However, the ratio typically does not exceed 0.7, as individuals at this level of frailty tend to die (321). Here, we used a 46-item FI, developed and validated in a previous study using NHANES data

(67), which includes deficits related to disability, comorbidity, symptoms, and abnormal laboratory values (See Appendix D—Table 2).

- The Frailty Phenotype: This tool was developed by Fried and colleagues (52). It identifies frailty as the presence of ≥3 of the following 5 criteria: unintentional weight loss, low energy, slow gait, reduced grip strength, and reduced physical activity. This study used a modified 4-item Frailty Phenotype (See Appendix – Table 3). This modified Frailty Phenotype has been developed and published elsewhere using NHANES data (67) and includes:
    - Exhaustion: Defined as experiencing "some difficulty," "much difficulty," or being "unable to do" when asked about the difficulty of "walking from one room to the other on the same level."
    - Low physical activity: Defined as being "less active" compared to most individuals of the same age, as assessed by the question, "Compared with most (men/women) your age, are you more active, less active, or about the same?"
    - Weakness: Defined as experiencing "some difficulty," "much difficulty," or being "unable to do" when asked about the difficulty of "lifting or carrying something as heavy as 10 pounds [like a sack of potatoes or rice]?"
    - Low body weight: Defined as having a body mass index (BMI) ≤18.5 kg/m^2.

Frail individuals had 3 or 4 of the items, pre-frail individuals had 1 or 2 of the items, and robust individuals had 0 items.

- The SOF Index: This short 3-item tool was designed to measure pre-frailty and frailty (99). The SOF identifies frailty by having ≥2 of the following 3 components.
    - Exhaustion: Defined as “some difficulty,” “much difficulty,” or “unable to do” when asked how much difficulty participants have “walking from one room to the other on the same level.”
    - Chair stands difficulty: Defined as “some difficulty,” “much difficulty,” or “unable to do” when asked how much difficulty participants have “when standing from an armless straight chair?”
    - Unintentional weight loss: Defined as the participant having a 5% decrease between their self-reported weight 1 year ago and current self-reported weight.

  The SOF identifies frailty as having ≥2 items, whereas pre-frail is identified as having 1 item, and robust as having 0 items. This study has modified these items as reported below (Appendix D – Table 4):

- The FRAIL Scale: This tool was developed by the Internal Association of Nutrition and Aging Task Force (96) and consists of 5 components: Fatigue, Resistance, Ambulation, Illness, and Loss of Weight. The modified FRAIL included the following items (See Appendix D – Table 5):

- Fatigue: defined by “some difficulty,” “much difficulty,” or “unable to do” when asked how much “difficulty participants have walked from one room to the other on the same level.”
- Resistance: defined by “some difficulty,” “much difficulty,” or “unable to do” when asked how much difficulty participants have “walking up ten steps without resting.”
- Ambulation: defined by “some difficulty,” “much difficulty,” or “unable to do” when asked how much difficulty participants have “walking a quarter-mile [that is about 2 or 3 blocks]?”
- Illness: defined by the answer “yes” to ≥5 conditions: Asthma, Angina, Arthritis, Cancer, Chronic Bronchitis, Heart Attack, Liver Disease, Stroke, or Thyroid Problems.
- Unintentional weight loss: defined as the participant having a 5% decrease between their self-reported weight 1 year ago and current self-reported weight.

The FRAIL scores range from 0 to 5 and identify frailty as those who obtain 3-5 items, pre-frail as 1-2 items, and robust as those who have 0 items.

Physical Activity, Stationary Activity, and Resistance Training

Aerobic activity was measured by accelerometry in the 2003/2004 and 2005/2006 cycles of the NHANES using the ActiGraph AM-7164. Participants were instructed to wear the monitor on their hip during waking hours for 7 days and remove it during any bathing or swimming activities. Minute-by-minute physical activity was collected, accounting for stationary time, light, moderate, and vigorous intensity levels. The intensity threshold for moderate-to-vigorous physical activity (MVPA) was defined as ≥2020 counts-per-minute, whereas stationary activity was defined as <100 counts-per-minute (322). Light intensity was defined as any activity between (i.e., <2020 & >100 counts-per-minute). These cut-off values have been used previously in NHANES (156,322), and the total accumulation of the counts-per-minute was used. Individuals were excluded if data was unreliable or had too few valid days (at least 4 days of 10 or more hours/day of wear time). Data flagged as "data reliability is questionable" by NHANES personnel were treated as missing.

Resistance training (RT) levels were measured using two questions in NHANES. The first question asked participants, "Over the past 30 days, did you do any activities specifically designed to strengthen your muscles, such as lifting weights, push-ups, or sit-ups?" If the participant indicated 'yes,' a follow-up question asked, "Over the past 30 days, how often did you do these activities?" The second questionnaire asked, "Over the past 30 days, what activities did you do?" It was followed by a list of possible activities that an individual may engage in, including muscle-strengthening activities such as push-ups, sit-ups, and weightlifting. If an individual engaged in one of these activities, they were further asked, "Over the past 30 days, how often did you do this activity?" If both questionnaires had different values for RT, the higher reported value was used for this study. Resistance training data were divided by 4.3 to account for how often individuals engaged in RT activities over a week.

The activity variables used were:

1) MVPA (hours/day),

2) RT (days/week),

3) Stationary Time (hours/day), and

4) Light Activity (hours/day).

Covariates

Frailty and physical activity levels differ by demographic factors, socioeconomic status, cohort, and accelerometer wear time (298,299). Therefore, the following covariates were included in the analyses: race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race – Including Multi-Racial), level of education (<9th grade, 9-11th grade, high school graduate/General Educational Development or equivalent, some college or an associate degree, college graduate or above), marital status (married, widowed, divorced, separated, never married, living with a partner), NHANES cycle, and accelerometer wear time.

Statistical Analysis

Statistical analyses were performed using R and R Studio 12.2.5001 (R Foundation for Statistical Computing, Vienna, Austria) (301,323). Mean ± standard deviation or frequency (percent) was used to report on the continuous and categorical variables in Table 1, respectively. For descriptive purposes, the FI was categorized into <0.10, (0.10, 0.20), (0.20, 0.30), and >0.30 (321). After testing for relevant assumptions, multi-variate linear regressions were used to examine the association between each frailty tool and each continuous activity variable, with the frailty tool as the independent variable and physical activity as the dependent variable. Interactions between age, sex, and frailty on physical activity were tested. When the interactions were significant, the analysis was stratified by sex and/or centered by age around 65, 70, 75, and 80 years old, and the simple associations were examined. All models were adjusted for age, sex, race, education, marital status, and accelerometer wear time. $\alpha = 0.05$ was used to determine statistical significance.

Chapter 4 Results

A total of 1,985 participants were included (71.1± 7.8 years, 48.1% female) who engaged in 77 ± 98 min/week of MVPA, 0.9 ± 2.4 days/week of RT, 4.7 ± 1.6 hrs/day of Light Activity, and 9.5 hrs/day of Stationary Time (Table 4.1).

Time spent in physical activity and stationary time by frailty tools are shown in Figure 4.1. Regardless of the frailty tool, people at every other level engaged in less activity than the most robust group ($p = 0.03$). For instance, there were inverse relationships between the time spent in MVPA and frailty as measured by the FI (FI:< 0.10 = 1.3 ± 1.6 hrs/week; ≥ 0.10 FI <0.20 = 0.8 ± 1.9 hrs/week; ≥ 0.20 FI <0.30 = 0.5 ± 0.5 hrs/week; ≥ 0.30 = 0.4 ± 0.7hrs/week; $p < 0.01$). In contrast, positive relationships were observed between stationary time and frailty across all tools ($p > 0.01$). Two of the frailty tools (SOF and FRAIL) did not show any differences in RT between frailty levels (SOF; Robust: 0.9 ± 2.5 days/week, Pre-frail: 0.9 ± 2.2 days/week, Frail: 0.6 ± 2.1 days/week); (FRAIL; Robust: 1.0 ± 1.7 days/week, Pre-frail: 0.70 ± 1.9 days/week, Frail: 0.5 ± 2.4 days/week); all $p = 0.08$]. Neither the Frailty Phenotype nor FRAIL observed differences in MVPA [Frailty Phenotype, Pre-frail = 0.7 ± 1.4hrs/week, Frail = 0.5 ± 0.9 hrs/week; FRAIL, Pre-frail = 0.8± 1.4 hrs/week, Frail = 0.2 ± 0.6hrs/week) or RT (Frailty

Phenotype, Pre-frail = 0.7 ± 2.0 days/week, Frail = 0.3 ± 1.7 days/week) between Pre-Frail and Frail groups. In addition, the FRAIL did not assess differences in Light Activity between these groups (Pre-frail = 4.4 ± 1.7 hrs/day, Frail = 3.9 ± 1.7 hrs/day; p = 0.44). For more information, see Appendix D – Table 6.

When examining the fully adjusted regression models between frailty with physical activity and stationary time, we observed that age and/or sex must be considered for all outcomes due to statistically significant interactions. Table 4.2 summarizes the associations between the frailty tools and the activity measures. However, see Appendix D – Tables 7-10 for detailed regression outputs.

There were disagreements across tools when examining the association between MVPA and frailty. The FI and the FRAIL demonstrated inverse relationships between MVPA and frailty [(FI, β range: -3.45, -1.57; FRAIL Scale, β range: -1.43, -0.41); p < 0.05]. Although the Frailty Phenotype and SOF also observed the same inverse associations, it was only dependent on specific frailty levels, sex, and/or age group [e.g., Frailty Phenotype (Robust as reference category), (Females, Pre-frail: β = - 0.29, 95% CI = -0.64, 0.06; Frail: β = -0.55, 95% CI = -0.96, -0.13), (Males, Pre-frail: β = -0.85, 95% CI = -1.16, -0.53; Frail: β = -0.11, 95% CI = -1.78, 1.56; see Appendix – Table 7 for more details.)].

For the RT analysis, we only needed to consider age differences when using the SOF, where females had an inverse relationship with frailty at specific ages (Frail Females, Age 65: β = -0.67, 95% CI = -1.17, -0.17; Age 70: β = -0.35, 95% CI = -0.67, -0.17). There was no association between RT and the SOF in males, and the interaction with age was not statistically significant (p = 0.53).

More agreement across tools was noted when examining the association of frailty with stationary and light activity time. For stationary time, all tools reported an increased association with frailty, excluding males considered frail by the Frailty Phenotype (β = 0.57, 95% CI = -0.01, 1.14). As light activity time increased, there was a negative association with frailty across all tools ($p < 0.05$). For stationary and light activity models, only the Frailty Phenotype statistically interacted with sex, and there were no statistically significant interactions with age.

Table 4.1 Descriptive characteristics

Variable	Mean ± SD or N (%) N = 1,985
Age (years)	71.1 ± 7.8
Sex	
Females	954 (48.1)
Males	1031 (51.9)
Race	
Non-Hispanic White	1217 (61.3)
Non-Hispanic Black	311 (15.7)
Mexican American	364 (18.3)
Other Hispanic	32 (1.6)
Other Race	61 (3.1)
Education	
Less than 9th grade	403 (20.3)
9-11th grade	290 (14.6)
Highschool Graduate	503 (25.3)
Some College	437 (22.0)
College Graduate	349 (17.6)
Missing	3 (0.2)
Marital Status	
Living with a partner	36 (1.8)
Married	1224 (61.7)
Never Married	52 (2.6)
Divorced	207 (10.4)
Separated	35 (1.8)
Widowed	431 (21.7)
Moderate-to-Vigorous Physical Activity (min/week)	77 ± 98
Resistance Training (days/week)	0.9 ± 2.4
Stationary Time (hrs/day)	9.5 ± 0.9
Light Physical Activity (hrs/day)	4.7 ± 1.6
≥ 150 min/week Moderate-to-Vigorous Physical Activity + ≥2 days/week Resistance Training	
Yes	82 (4.3)
No	1903 (95.9)
≥ 150 min/week Moderate-to-Vigorous Physical Activity	
Yes	298 (15.0)
No	1687 (85.0)
≥2 days/week Resistance Training	
Yes	325 (16.4)
No	1660 (83.6)

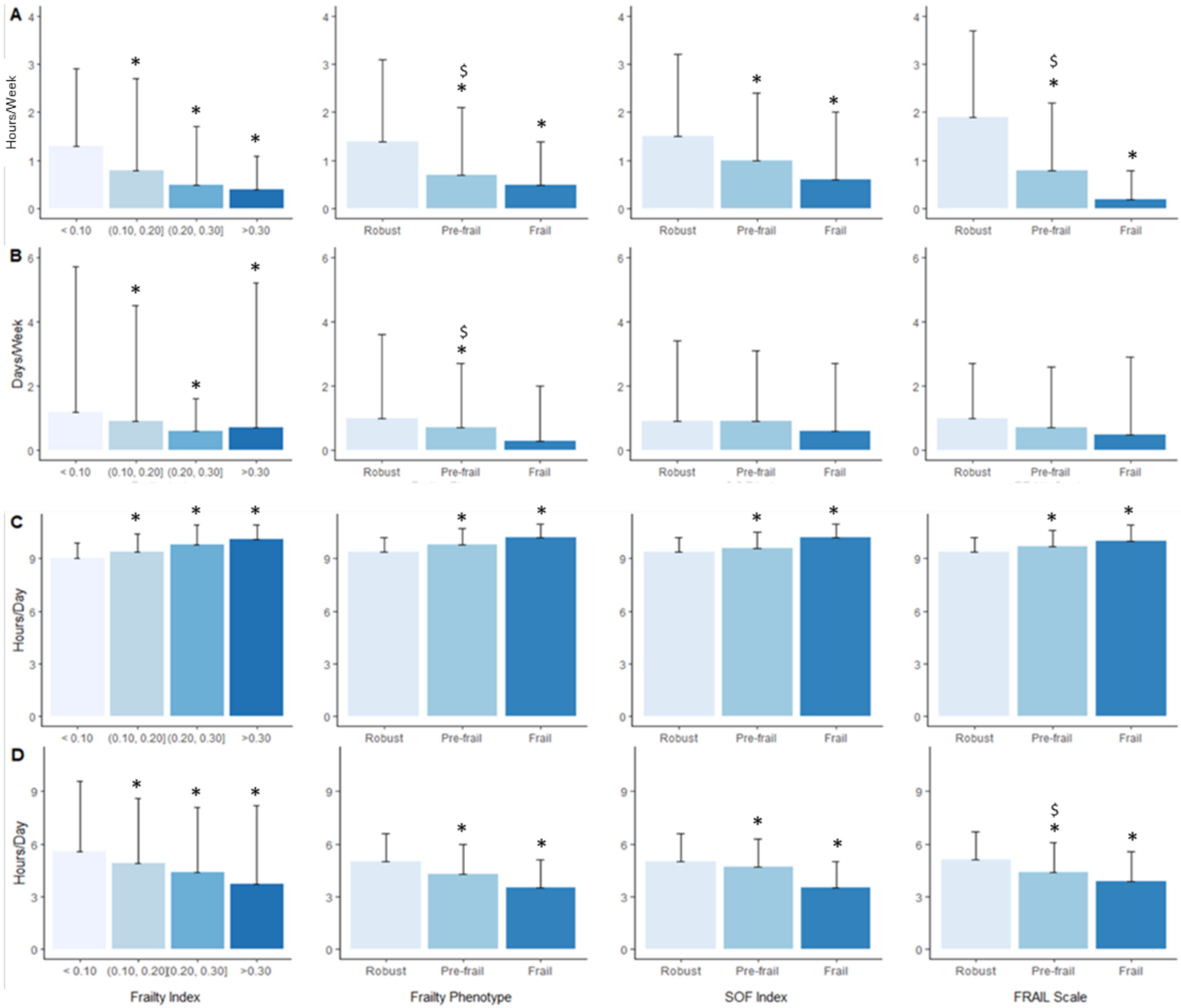

Figure 4.1 Levels of physical activity and stationary time by frailty tools; A: Moderate-to-vigorous physical activity; B: Resistance training; C: Stationary time; D: Light activity. * - significantly different than robust category; $ - not significantly different than most frail group (see appendix D – table 6 for more details)

Table 4.2 Summary of the associations between frailty tools (independent variable) and physical activity measures (dependent variable)

Frailty Index (Continuous; Range [0-1])		Frailty Phenotype (Robust as Reference)		SOF Index (Robust as Reference)		FRAIL Scale (Robust as Reference)
Moderate-to-Vigorous Aerobic Activity (hrs/week)						
Females Age 65: ↓ Age 70: ↓ Age 75: ↓ Age 80: ↓	**Males:** Age 65: ↓ Age 70: ↓ Age 75: ↓ Age 80: ×	**Females** Prefrail: × Frail: ↓	**Males** Prefrail: ↓ Frail: ×	**Females** <u>Age 65:</u> Prefrail: × Frail: ↓ <u>Age 70:</u> Prefrail: × Frail: ↓ <u>Age 75:</u> Prefrail: ↓ Frail: ↓ <u>Age 80:</u> Prefrail: ↓ Frail: ×	**Males** <u>Age 65:</u> Prefrail: ↓ Frail: × <u>Age 70:</u> Prefrail: ↓ Frail: × <u>Age 75:</u> Prefrail: ↓ Frail: ↓ <u>Age 80:</u> Prefrail: × Frail: ×	<u>Age 65:</u> Prefrail: ↓ Frail: ↓ <u>Age 70:</u> Prefrail: ↓ Frail: ↓ <u>Age 75:</u> Prefrail: ↓ Frail: ↓ <u>Age 80:</u> Prefrail: × Frail: ↓
Resistance Training (days/week)						
×		Prefrail: × Frail: ↓		**Females:** <u>Age 65:</u> Prefrail: × Frail: ↓ <u>Age 70:</u> Prefrail: × Frail: ↓ <u>Age 75:</u> Prefrail: × Frail: × <u>Age 80:</u> Prefrail: × Frail: ×	**Males:** Prefrail: × Frail: ×	Prefrail: × Frail: ×
Stationary Time (hrs/day)						
↑		**Females** Prefrail: ↑ Frail: ↑	**Males** Prefrail: ↑ Frail: ×	Prefrail: ↑ Frail: ↑		Prefrail: ↑ Frail: ↑
Light Activity (hrs/week)						
↓		**Females** Prefrail: ↓ Frail: ↓	**Males** Prefrail: ↓ Frail: ↓	Prefrail: ↓ Frail: ↓		Prefrail: ↓ Frail: ↓

X – non-significant. SOF – Study of Osteoporotic Fractures; FRAIL – Fatigue, Resistance, Ambulation, Illness, and Loss of Weight; Models adjusted for race, education level, marital status, and accelerometer wear time, and centered for age to analyze simple slope comparisons. See Appendix D – Table 7-10 for more details.

Chapter 4: Discussion

This study demonstrated that the association between physical activity and/or stationary time with frailty differs by frailty tool, sex, and age. Our hypothesis was rejected, as there was no clear difference between tools that captured physical frailty and a multi-dimensional view of frailty. All the tools demonstrated varying associations between frailty and physical activity (See Table 4.2). This was especially true when examining MVPA or RT activities, as there were large discrepancies in the relationships by frailty tools (Appendix D – Table 7 & 8). These discrepancies are concerning as many frailty prevention initiatives include MVPA and RT activities as best practices (317). However, this study demonstrated that our understanding of the relationship between physical activity and frailty may depend on frailty tool selection. This study cannot uncover which tool is "best" due to the lack of a gold standard comparison representing the true relationship between physical activity and frailty. The ability to fully understand the relationship between activity and frailty could depend on the frailty tool being used.

Sex and/or age differences were observed for every tool. For instance, there were differences in association based on age when using the FRAIL in MVPA analysis, with the strongest associations between MVPA and frailty at younger ages (Frail, Age 65: β= -1.43, 95% CI = -1.67, -1.20; Age 70: β = -1.12, 95% CI = -1.28, -0.96; Age 75: β = -0.80, 95% CI =-0.94, -0.67; Age 80: β = -0.49, 95% CI = -0.67, -0.31). However, age or sex differences were not observed for the FRAIL in the present study's RT, Light, or Stationary analysis (Table 4.2). The opposite was true for the Frailty Phenotype, which did not need to consider age differences; though, sex differences existed for MVPA, Light, and Stationary activities, but not RT. There was no interpretable pattern across tools and activities to understand where and when sex and/or age needed to be considered. However, testing for these interactions for all activity or stationary analysis seems important to see if the population sample needs to consider these important differences. This study supports the well-established evidence that physical activity, stationary time, and frailty differ by age and sex (56,220) and contributes to the literature regarding how age and sex differences need to be considered across frailty tools.

When analyzing the MVPA and RT associations with frailty, there are inconsistent patterns across tools. This supports the notion that depending on the tool used, one may see varying results in activity/stationary analysis in frailty research. Interestingly, this study reports more consistent findings across frailty tools for light and stationary activities. Across all tools, more time spent in light activity was associated with decreased frailty levels. Further, more stationary time was related to worse frailty across tools, except for frail males assessed by the Frailty Phenotype (β = 0.57, 95% CI = -0.01, 1.14). In summary, the tools agree more when examining the association between light activity and stationary time with frailty (See Appendix D– Table 9 & 10).

The relationship between RT and frailty was only evident for specific tools (i.e., Frail individuals by the Frailty Phenotype and Frail Females aged 65 and 70 by the SOF). This could be because they are based on physical frailty rather than a multi-dimensional view of frailty. Physical frailty assesses a single dimension of health: the physical ability to complete tasks. For example, the Frailty Phenotype is based on unintentional weight loss, muscle weakness, slow walking speed, low physical activity, and exhaustion. A multi-dimensional view of frailty includes items that capture co-morbidity, disability, psychological components, and physical ability (e.g., the FI). Compared to MVPA, RT is more effective at improving muscle mass and strength in older adults (324). Talar et al. (2021) conducted a systematic review and meta-analysis to gather evidence of randomized control trials examining the effects of resistance training programs (≥ 8 weeks) on strength, physical function, and body composition of adults (65 +) who were diagnosed with pre-frailty or frailty (180). Their study found that resistance training was a highly effective strategy for improving muscular strength, physical function, and body composition parameters in older adults with pre-frailty and frailty. It was particularly effective in improving physical function, reinforcing strength training interventions to delay and attenuate the negative effects of physical frailty.

Compared to the other frailty tools, the SOF had the smallest significant associations with MVPA and RT, with noted age and sex differences. These findings align with the work of Trombetti et al. (2018), who used the SOF in a secondary analysis of one of the largest physical activity-focused randomized controlled trials in older adults (325). They included 1,635 community-dwelling older adults (70-89 years) with functional limitations. The intervention was a 24-month structured, moderate-intensity physical activity program incorporating aerobic, resistance, and flexibility activities or a health education control group. They reported that the risk of frailty was not different between the physical activity and health education groups (adjusted prevalence difference = -0.21, 95% CI = -0.049, 0.007). In contrast, our study did find an inverse relationship between MVPA and frailty severity using the SOF. In summary, the SOF demonstrated the most inconsistent relationships compared to the other frailty tools, as demonstrated in Figure 4.1.

The strength of this study was the analysis of different frailty tools across activity and stationary time in a representative sample of non-institutionalized U.S. older adults. Further, this study used an FI and Frailty Phenotype validated within the NHANES dataset (297). Accelerometers are valuable in this study as this method of measuring physical activity is more reliable than self-reported measures (326). The cross-sectional nature of the NHANES is the most important limitation of this study, as causation cannot be inferred. Additionally, many cut-points in the literature are used to measure stationary, light, and MVPA activities. This study used commonly used cut-points that are available in the NHANES database (322), though it is recognized other cut-points are available (127). The Frailty Phenotype, the SOF, and the FRAIL were all modified based on available items in the NHANES database. However, modifying a frailty tool is common practice (80), the formal criterion of these tools could provide different results. Lastly, the accelerometers used could not distinguish between lying, sitting, and reclining versus standing positions. Therefore, we could not understand how frailty tool associations differ between sedentary and non-sedentary postures. It is unclear whether standing is associated with frailty.

Chapter 4: Conclusion

The key finding of this study is that associations between frailty and physical activity, as well as stationary time, vary depending on the frailty measurement tool used. Particularly, the relationship between MVPA and RT exhibits significant inconsistencies across different tools. Moreover, it is crucial to examine age and sex interactions in analyzing physical activity, stationary time, and frailty. This study highlights the unique nature of physical and stationary activity, with a general trend showing that as individuals age, the impact of activity on frailty diminishes while the impact of stationary time increases.

Linking Manuscript 3

Manuscripts 1 and 2 demonstrate that engaging in one type of physical activity is associated with a lower frailty index score and that associations between physical activity, sedentary time, and frailty differ depending on the tool used. However, physical activity is one of many lifestyle behaviors that can impact frailty. Therefore, it's important to understand how physical activity is associated with frailty, considering an individual's engagement in other "positive" or "negative" lifestyle behaviors. Therefore, Study 3 aims to answer the following questions:

1) How do lifestyle behaviors support or hinder the association between physical activity and frailty?
2) Do these associations differ by sex and age?

Chapter 5 – Manuscript 3: Can an Active Lifestyle Off-Set the Relationship that Poor Lifestyle Behaviours Have on Frailty?

Chapter 5: Abstract

Objective: To examine the association of lifestyle behaviours (LSB) with physical activity (PA) and frailty; also, to examine if associations differ by sex and age.

Methods: 24,828 individuals [49.6 ± 17.6 years (range: 20–85), 51.6 % female] from the National Health and Nutrition Examination Survey (cycles 2009–2018) were included. Individuals were divided into Active (≥150 min/week of moderate-to-vigorous physical activity (MVPA)) and Inactive (<150 min/week MVPA) based on self-report PA. Frailty was measured by a 46-item Frailty Index (FI). LSB consisted of sedentary time, sleep, diet quality, and alcohol and smoking habits. LSB was summed into a score [0-5]. Linear regression models were used with each LSB in isolated and the summed LSB with frailty.

Results: There were 7,495 (30.1 %) Active and 17,333 (69.8 %) Inactive individuals. The FI was lower in the Active participants (Active: 0.10 ± 0.08; Inactive: 0.15 ± 0.12; p < 0.01). A worse LSB score was associated with an increased FI in all behaviours but females who binge drink and smoke (p-all>0.14). For inactive individuals, all LSBs were associated with an increased FI except those who binge drink and male smokers (p = 0.08). There was a significant association between increased summed LSB and an increased FI (β range: Active, 0.024–0.037; Inactive, 0.028, 0.046. p-all< 0.001).

Conclusion: PA was associated with a lower FI, even among those with a poor LSB score. This association is dependent on age, with older individuals reporting a stronger association.

Chapter 5: Introduction

Finding ways to mitigate frailty has become essential among health professionals and researchers to lessen individual and healthcare burdens. Frailty is defined as a multifaceted condition that reduces one's physiologic reserve and increases vulnerability (52,56), related to adverse health outcomes such as falls, hospitalizations, institutionalization, and premature mortality (48,292). Fortunately, some interventions have been shown to be effective in mitigating frailty. One of the leading interventions is engaging in recommended levels of physical activity (161,281). For instance, a recent systematic review and meta-analysis of randomized controlled trials concluded that physical activity is one of the most effective frailty interventions (8). Despite being among the most effective interventions, other modifiable lifestyle factors may also contribute to a person's frailty level, but our understanding of the interactions between these behaviours is poorly understood.

Individuals engage in many lifestyle behaviours, defined as "activities that an individual does every day, whether consciously or unconsciously, that is shaped by an individual's values and knowledge, or by broader cultural or societal norms (327)." These behaviours may include time spent in sedentary activity, sleep quality, diet quality, smoking, and alcohol consumption, each of which has been linked to negatively impacting frailty (236,262,269,284,328). For instance, high amounts of sedentary time, poor sleep quality, and being a smoker are all positively associated with frailty (236,262,263,284,328,330). In contrast, for some behaviours, there are mixed findings as to whether engaging in high amounts of that behaviour has a negative relationship with frailty; such as poor diet quality and binge drinking (236,270,273,331). In observational studies, a higher diet quality (i.e., increased intake of fruits and vegetables, adherence to protein and energy intake recommendations, and adherence to a Mediterranean Diet) is associated with a lower frailty level (271,272). However, in a recent meta-analysis of randomized controlled trials (2021), researchers compared a nutritional supplements group with a placebo group and did not find a statistically significant difference in Frailty Phenotype status between those groups (n = 215 participants; OR= 2.30; 95 % CI= 0.72, 7.01; GRADE = very low)(270). As for drinking behaviours, the relationship between alcohol consumption and frailty is ambiguous, with some studies reporting moderate-to-heavy drinking is protective of increased frailty (236,331,332) and others showing it is linked to increased frailty (289,333). To date, there is some insight into the relationship between individual lifestyle behaviours and frailty (i.e., smoking's association with frailty), but how these behaviours in combination impact frailty are less understood.

Understanding how lifestyle behaviours relate, in combination, to frailty is not a new concept. Despite inconsistencies in methodology, studies generally show that more positive lifestyle behaviours are associated with lower frailty (334–336). For instance, one study included 11,539 individuals in a cross-sectional study aiming to evaluate the associations of four lifestyle factors (physical activity, diet quality, alcohol intake, and smoking) with an FI (336). A sum-score of these factors was used to measure lifestyle, with a range from 0 (lowest) to 8 (highest). This study concluded that a one-increment increase of the lifestyle score was associated with lower frailty. A more recent study from 2022 aimed to understand how the Mediterranean lifestyle (diet, customs, and traditions) was related to frailty incidence in older adults (335). This study included 1,880 older adults (≥60 years; 2.2 % frail by the Frailty Phenotype at baseline) and used a 27-item

MEDLIFE Index to understand adherence to the Mediterranean diet, Mediterranean dietary habits (practices around meals), physical activity, rest, social habits, and conviviality (i.e., friendliness). These 27-items were summed and sectioned into tertiles. At 3.3-year follow-up, there was 136 incident frailty cases. Compared to those in the lowest tertile (lowest adherence to the Mediterranean lifestyle), the third tertiles of the MEDLIFE Index was associated with lower frailty (OR = 0.38, 95 % CI = 0.21, 0.69) but not the second tertile (OR = 0.88, 95 % CI = 0.58, 1.134). With physical activity being the leading intervention in frailty reduction and prevention (161,281), it would be informative to understand if leading a physically active lifestyle may negate some of the negative impacts of other lifestyle behaviours on frailty.

There is limited available evidence to fully understand how other lifestyle behaviours impact the relationship between physical activity and frailty. Mañas et al. (2019) suggested that 27 min a day of MVPA is needed to eliminate the increased risk of frailty measured by the Frailty Trait Scale associated with sedentary behaviour (258). Additionally, having poor sleep quality decreases the likelihood of engaging in physical activity, and performing less physical activity negatively impacts frailty (264). Lastly, Neiderstrasser et al. (2019) identified that the average 67-year-old who participates in mild physical activity (or is sedentary) and is a current or previous smoker has a 59 % greater chance of becoming frail by the time they are 79 years old (285). In contrast, a person of the same age who engages in MVPA at least once per week and has never smoked has a 22 % chance of becoming frail. Less is known if diet quality and drinking consumption are associated with frailty given that an individual is physically active. Lastly, there is a gap in the current evidence in how lifestyle behaviours impact the relationship between physical activity and frailty differs by sex and age. This is an important consideration as frailty levels and physical activity behaviours differ by sex and age (22,94,215,222,227). For instance, it has been recognized that males and females accumulate different health-related deficits, and at different rates (206,233), whereby age-matched females tend to be frailer (94). It is important to know how the relationship between physical activity and frailty is impacted by sex and age so that interventions can be refined appropriately for these populations. Therefore, the objective of this study was to examine how lifestyle behaviours may strengthen or weaken the association between physical activity and frailty. Further, to examine if these associations differ by sex and age. Our hypothesis is that being active will have a strengthening effect on the relationship between poor lifestyle behaviours and frailty. Also, that this association will be stronger in males and younger adults.

Chapter 5 Methods

Participants

A secondary analysis was conducted using the 2009–2018 cycles of the NHANES database, which comprises a representative sample of community-dwelling citizens from the United States of America. Trained personnel collected demographic and other questionnaire data during in-home visits; sex was coded by NHANES personnel as either male or female. Medical personnel conducted the examination component, including medical, dental, and physiological measurements. We included males and females aged ≥ 20 years and older who had complete data for frailty, physical activity, and all other lifestyle behaviours (See Appendix E – Figure 1). Individuals with missing data were excluded from the analysis. The final sample included 24,828 participants

[Females, N = 12,816 (52 %)]. See Appendix E – Table 2 for the comparisons between the included and excluded samples.

Frailty Measure

Frailty levels were identified using a 46-item FI previously constructed and validated using NHANES data (67,155). The FI was selected for its comprehensive, multi-dimensional approach that captures frailty as a spectrum. The NHANES FI included comorbidities, activities of daily living, laboratory values, and cognition. The FI is based on the deficit accumulation approach and operationalizes frailty by counting the number of deficits an individual has as a ratio to the total number of deficits measured (59,62). For example, if someone has 10 out of a possible 46 deficits, their FI would be 0.22 (10÷46), with a higher value indicating a worse frailty level. Variables included in the FI must increase with age, be associated with poor outcomes, cover a range of physiological systems, and cannot be too rare (< 1%) or too common (> 80% by age 80) (62). Participants were excluded if they were missing >20 % of the FI variables (N = 2569) (See Appendix E – Table 2 for comparison to analytical sample).

Physical Activity

Physical activity levels were determined via a questionnaire, where participants were asked to report the activities in which they regularly engaged (i.e., basketball, gardening, running), as well as the intensity (i. e., vigorous, moderate), frequency (e.g., days per week) and duration of activity (e.g., time spent in activity). These details determine weekly MVPA levels, with the recommended level of MVPA defined as ≥150 min/week. This cut-off was chosen based on the physical activity recommendations from the World Health Organization and the American College of Sports Medicine (147,296). If an individual reported engaging in 150 min a week or more of MVPA they were considered sufficiently active; those who reached below 150 min/week were considered insufficiently active. For simplicity, this paper will refer to these groups as ‘Active’ and ‘Inactive’.

Other Lifestyle Behaviours

The NHANES database provides in-depth questionnaires that account for an individual’s lifestyle, such as their sleep, dietary, and alcohol consumption behaviours. In this study, we included the following lifestyle behaviours: sedentary time, diet quality, time spent sleeping, alcohol consumption, and smoking habits. These behaviours were selected based on their documented negative associations with frailty in the literature (176,339). Additionally, their consistent collection within NHANES enables a larger analytical sample – thereby maintaining statistical power in our analyses even with the dichotomization of physical activity level and sex. For instance, cognitive training is an important behaviour for frailty prevention (176); however, a variable to represent cognitive training is unavailable in the NHANES dataset. Refer to Appendix E– Table 1, for more information on lifestyle questions included in NHANES, possible responses to each question, and how each variable was coded for statistical analysis. Of note, diet was captured with a previously published Nutrition Index (NI) in the NHANES database (340,341). The NI is constructed following the deficit accumulation approach by combining 41 nutrition-related parameters that are related to higher frailty (341): counting the number of nutritional deficits of an individual and dividing by the total nutritional deficits considered, with a higher NI score indicating poorer diet quality. The

NI was selected for this study as outcomes vary based on diet-items studied; thereby, it may be useful to study deficits in aggregate (343). Each behaviour was summed into a total score that captured an individual's lifestyle behaviours (range: 0–5). The higher the lifestyle behaviour score the poorer lifestyle the individual has.

Covariates

We included the following covariates in our analysis: age, sex (Female, Male), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race – Including Multi-Racial), level of education [less than 9th grade, 9th-11th grade, high school graduate/General Educational Development or equivalent, some college or an associate degree, college graduate or above], marital status (married, widowed, divorced, separated, never married, living with a partner) and NHANES cycle. These variables were selected as covariates as individuals of varying socio-economic status differ in terms of frailty level and engagement in physical activity (298,299). NHANES cycle was included because individuals could vary by frailty and activity level by cycle; thereby, it is important to account for those differences.

Statistical Analysis

Statistical analyses were performed using RStudio 12.2.5001 (R Foundation for Statistical Computing, Vienna, Austria) (323). Means ± standard deviations and frequencies (percentages) were reported for the total sample, the Active sub-sample, and the Inactive sub-sample for continuous and categorical variables, respectively. We tested whether descriptive characteristics were different across the Active and Inactive groups via t-test for continuous variables and chi-square analyses for categorical variables.

Bonferroni post-hoc testing was conducted on significant between-group comparisons when variables had more than two categories.

Covariate-adjusted multiple linear regression models were used for each individual lifestyle behaviour and the Lifestyle behaviour score to examine its association with frailty. All models were adjusted for age, sex, race, education, marital status, and NHANES cycle. Interactions between age, sex, and lifestyle behaviours (individually and as a score) on frailty were examined. When the interactions were statistically significant, the analysis was stratified by sex and/or centered by age around 30, 40, 50, 60 and 70 years and simple associations were examined. To better understand the relationship between physical activity, lifestyle behaviours, and frailty, the R^2 change between linear regression models was examined to understand the amount of variance in frailty that lifestyle accounted for above the variance already accounted for by the covariates. Additionally, Pearson's correlation was used to understand the correlation between individual lifestyle behaviours, physical activity, and frailty. An $\alpha < 0.05$ was used to denote significance. All analyses were weighted using sampling weights, and the complex survey design was accounted for using the R survey package (302).

Chapter 5 Results

General Characteristics

A total sample of 24,828 participants were included in the analysis, with a similar number of males (48.4 %) and females (51.6 %), as presented in Table 5.1. The proportion of individuals in the Active group was 7,495 (30.1 %), and in the Inactive was 17,333 (69.8 %). Most of the descriptive characteristics between groups were significantly different between activity groups, excluding specific marital statuses. The FI was lower in the Active participants (0.10 ± 0.08) versus and the Inactive participants (0.15 ± 0.12; $p < 0.01$).

Differences in the Frailty Index of each Lifestyle Behaviour, by Activity Groups

Figure 5.1 shows the mean FI in each lifestyle behaviour, by activity groups. In the Active group, there was a significantly lower mean FI in those who do not engage in poor diet, smoking habits, binge drinking and poor sleep (p all ≤ 0.02). In the Inactive group, those who engaged in poor diet quality, binge drinking and poor sleep had significantly higher FI means than those who did not ($p < 0.01$); excluding those who engaged in high sedentary time. Inactive individuals who engaged in high sedentary time had a lower FI mean (Mean ± SD, High Sedentary: 0.14 ± 0.11; Low Sedentary: 0.16 ± 0.13; $p < 0.001$).

Correlation between Lifestyle Behaviours

Inspection of the Active group reveals a moderate positive correlation between two lifestyle behaviours (Binge Drinking and Smoking, $r = 0.20$) and no moderate positive correlations in the Inactive sample. However, both correlation matrices had six moderate negative associations, with the only difference being that Active individuals had a negative association between high sedentary time and poor sleep ($r = -0.36$), and inactive individuals had a negative association between poor sleep and binge drinking ($r = -0.31$). Appendix E - Tables 3 and 4 present the correlation matrices for the lifestyle behaviours of the Active and Inactive individuals.

Change in R^2 between Lifestyle Behaviours and Frailty

The coefficient of determination (R^2) was used to understand the goodness of fit when adding lifestyle behaviours to a regression model with frailty as the outcome, by activity groups (Appendix E - Tables 5 and 6). In the Active and Inactive individuals, covariates alone accounted for 37 % of the total variance in frailty. In the Active group, the lifestyle behaviours accounted for an additional 3 % of the variance above covariates alone ($p < 0.01$); whereas Inactive individual's lifestyle behaviours account for an additional 4 % ($p < 0.01$). Also, when models that included all covariates were compared to a model with all covariates plus one lifestyle behaviour (e.g., covariates + binge drinking), both Active and Inactive individuals change in R^2 was significant ($p < 0.01$). Though significant, the R^2 range for each group were similar ($R^2 = 0.00 – 0.02$).

Associations between Individual Lifestyle Behaviours and Frailty, by Activity Groups

There was a sex-by-age-by-lifestyle behaviour interaction in some regression models when examining the association between individual lifestyle behaviours and frailty, by activity group (See Appendix E – Table 7 and 8). Therefore, where appropriate, we sub-grouped by sex and/or examined simple slopes by age (i.e., age centered at 30, 40, 50, 60, 70; Table 5.2). In the Active group, engaging in poor lifestyle behaviours was associated with increased frailty in all behaviours except binge drinking in females ($\beta = - 0.0054$, 95 % CI =− 0.015, 0.0039) and smoking in both sexes (β= 0.0056, 95 % CI = − 0.00070, 0.012). Being an older, active male who binge drinks was found to be protective of increased frailty (Age 50–70: β range= − 0.019 to − 0.041). In the Inactive group, all behaviours were associated with increased FI except binge drinking ($\beta = - 0.00056$, 95 % CI = − 0.0076, 0.0065) and smoking in males (β=0.0072, 95 % CI = − 0.00074, 0.015).

Proportion of Individuals in each level of the Lifestyle Behaviour Score, by Activity Groups

Figure 5.2 visually demonstrates the amount of people in the Active and Inactive groups that score between 0 and 5 poor lifestyle behaviours, with higher scores representing worse behaviours. In both the Active and Inactive groups, the most amount of people engaged in one negative behaviour (Active: 39.6% vs. Inactive: 37.7 %). Furthermore, there was no significant difference in the number of individuals who engaged in one negative behaviour between activity groups ($p = 0.15$). At every other score, there was a significant difference in the proportion of individuals in each lifestyle behaviour score with more active people engaging in zero poor behaviours and more inactive people engaging in 2 or more poor behaviours (p all < 0.01). Lastly, in both groups, after a score of 1 the proportion of people engaging in additional negative lifestyle behaviours decreased (Lifestyle Behaviour Score 2–5; Active, 24.1 %, 8.0 %, 1.4 %, 0.2 %; Inactive, 29.2 %, 11.2 %, 2.6 %, 0.3 %).

Association between Lifestyle Behaviour Score and the Frailty Index, by Activity Groups

There was an age-by-lifestyle behaviour interaction when examining the association between Lifestyle Behaviour Score and the FI in both activity groups; therefore, we examined the simple associations by age (i.e., age centered at 30, 40, 50, 60, and 70; Figure 5.3). Across all ages and activity groups, there was a significant association between increased Lifestyle Behaviours Score and increase in the FI (β range: Active, 0.024–0.037; Inactive, 0.028–0.046. p-all <0.01). Furthermore, as age increases so did the association between the Lifestyle Behaviour Score and the FI (Active, Age 30:

$\beta = 0.024$, 95 % CI = 0.018, 0.03; Age 70: $\beta = 0.037$, 95 % CI = 0.029, 0.045; Inactive, Age 30: $\beta = 0.028$, 95% CI = 0.023, 0.033; Age 70, $\beta = 0.046$, 95 % CI = 0.040, 0.052). The main difference is that the slope of each line is statistically different from each other; in other words, at every age, the Active group had a lower frailty score than the Inactive group ($p < 0.001$).

Table 5.1 General characteristics by activity groups

Mean ± SD or N (%)	Total Sample N = 24, 828	≥150 mins/week of MVPA N = 7,495	<150 mins/week of MVPA N= 17,333
Age (Years)	49.6 ± 17.6	45.5 ± 17.4	51.4 ± 17.4*
Sex, Female	12,816 (51.6)	3,385 (45.2)	9,431 (54.4)*
Race			
Non-Hispanic White	10,722 (43.2)	3,460 (46.2)	7,262 (41.9) *
Non-Hispanic Black	4,719 (19.0)	1,334 (17.8)	3,385 (19.5)*
Non-Hispanic Asian	2,683 (10.8)	943 (12.6)	1,740 (10.0)*
Mexican American	4,102 (16.5)	1,031 (13.8)	3,071 (17.7)*
Other	2,602 (10.5)	727 (9.7)	1,875 (10.8)
Education			
Less than 9th Grade	2,548 (10.3)	383 (5.2)	2,165 (12.5)*
9-11th Grade	3,407 (13.7)	610 (8.2)	2,797 (16.2)*
High School	5,670 (22.8)	1,421 (19.0)	4,249 (24.6)*
Some College	7,434 (29.9)	2,415 (32.3)	5,019 (29.0)*
College	5,737 (23.1)	2,657 (35.5)	3,080 (17.8)*
NA	32 (0.1)	9 (0.1)	23 (0.1)
Marital Status			
Married	12,830 (52.7)	3,836 (51.1)	9,004 (52.0)
Divorced	2,739 (11.0)	763 (10.2)	1,976 (11.4)
Separated	827 (3.3)	199 (2.7)	628 (3.6)*
Living with Partner	2,111 (8.5)	632 (8. 4)	1,479 (8.5)
Never married	4,400 (17.7)	1,740 (23.2)	2,660 (15.4)*
Widow	1,907 (7.7)	330 (4.4)	1,577 (9.1)*
NA	14 (0.06)	5 (0.08)	9 (0.05)
Drinking, Binge Drinking#	2,904 (11.7)	947 (12.6)	1,957 (11.3)*
Smoking, Former/Current Smoker	4,966 (20.0)	1,206 (16.1)	3,760 (21.7)*
Sleep$, Less or more than recommendation	14,173 (57.1)	4,590 (61.2)	9,583 (55.3)
Sedentary Time, ≥ 8 hours/day	7,996 (67.8)	2,317 (30.9)	5,679 (32.8)*
Poor Diet Quality, Lowest Quartile of the Nutrition Index	6,890 (27.8)	1,517 (20.2)	5,373 (31.0)*
Continuous Nutrition Index (0-1)	0.35 ± 0.16	0.31 ± 0.15	0.37 ± 0.16*
Frailty Index (0-1)	0.13 ± 0.11	0.10 ± 0.08	0.15 ± 0.12*

#Binge Drinking Definition: Males = 5 + alcoholic drinks on the same occasion on at least one day in the past month; Females = 4 + alcoholic drinks on the same occasion on at least one day in the past month. $Poor Sleep: Age 18-64 = <7 or >9 hours; Age 65+ = <7 or >8 hours.
* Statistically different between the absolute number of each group. One-way analysis of variance testing for continuous variables and Chi-square analyses for categorical variables. Bonferroni post-hoc testing was conducted on significant between-group comparisons.

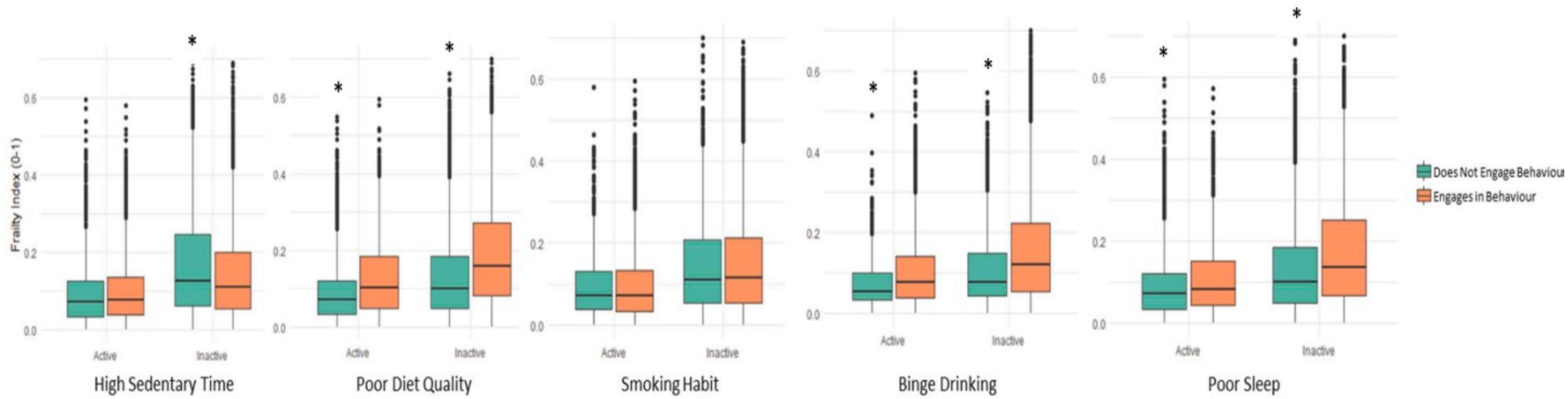

Figure 5.2 Mean (standard deviation) of the frailty index for each behaviour, by activity group. * = p <0.05, comparison between engaging and not engaging in a behaviour, by activity group. The standard deviation stops at zero as the FI cannot be a negative number.

Table 5.3 Description of associations between individual lifestyle behaviours and the frailty index, by activity group

High Sedentary Time		Diet Quality		Sleep Quality		Drinking Habit		Smoking Habit	
Active	**Inactive**	**Active**	**Inactive**	**Active**	**Inactive**	**Active**	**Inactive**	**Active**	**Inactive**
↑	Age 30: ↑ Age 40: ↑ Age 50: ↑ Age 60: ↑ Age 70: ↑	Age 30: ↑ Age 40: ↑ Age 50: ↑ Age 60: ↑ Age 70: ↑	Age 30: ↑ Age 40: ↑ Age 50: ↑ Age 60: ↑ Age 70: ↑	Age 30: ↑ Age 40: ↑ Age 50: ↑ Age 60: ↑ Age 70: ↑	Age 30: ↑ Age 40: ↑ Age 50: ↑ Age 60: ↑ Age 70: ↑	**Females:** ✕ **Males:** Age 30: ✕ Age 40: ✕ Age 50: ↓ Age 60: ↓ Age 70: ↓	✕	✕	**Females:** Age 30: ↑ Age 40: ↑ Age 50: ↑ Age 60: ↑ Age 70: ↑ **Males:** ✕
✕ = non-significant. ↑ = significant increase in the FI association. ↓ = significant decrease in the FI association. The size of the arrow represents that strength of association. For visualization purposes, the size of the arrow represents that strength of association. Linear regression model adjusted for race, education, marital status, all other lifestyle behaviour, when appropriate, simple sloped on age or sub-grouped for sex. Sedentary Time Definition = ≥ 8 hours/day of sedentary time; Poor Sleep: Age 18-64 = <7 or >9 hours; Age 65+ = <7 or >8 hours; Binge Drinking Definition: Males = 5 + alcoholic drinks on the same occasion on at least one day in the past month; Females = 4 + alcoholic drinks on the same occasion on at least one day in the past month. See Appendix E – Table 7 and 8 for more details.									

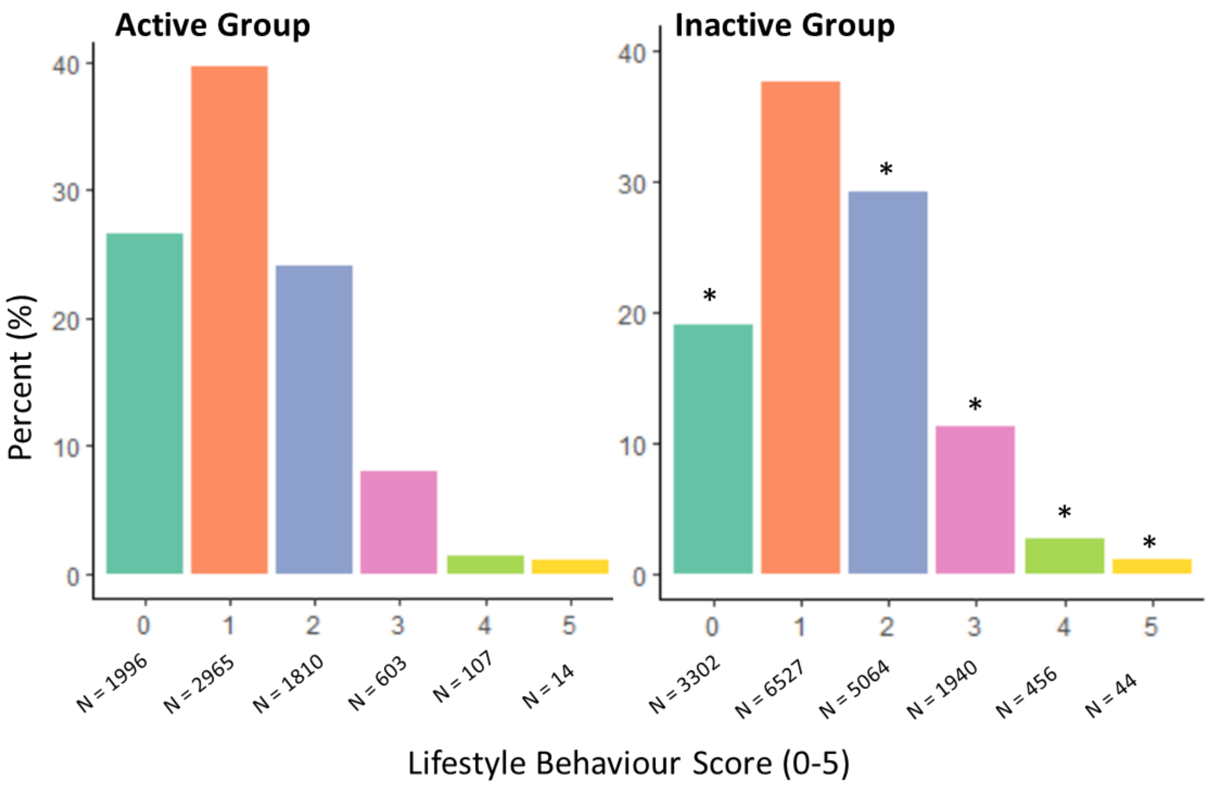

Table 5.4 Frequency of lifestyle behaviour score. Higher score is higher amount of negative lifestyle behaviours. * = significant difference (p <0.05) compared to the active group. See appendix E – table 9 for more detail.

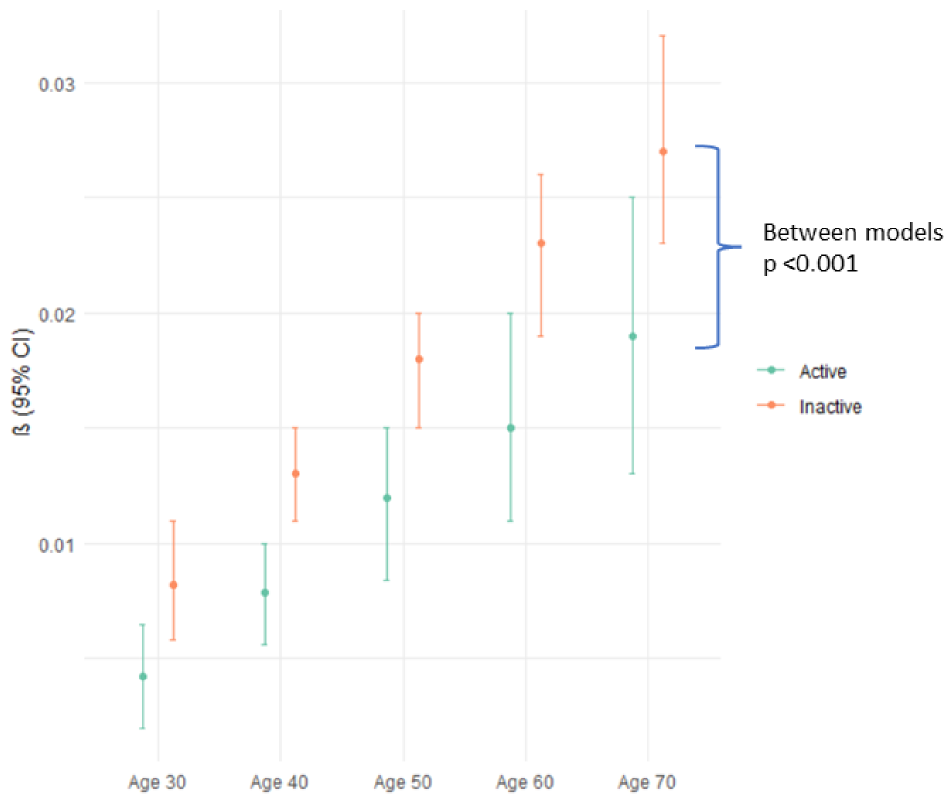

Table 5.5 Age-adjusted simple association between lifestyle behaviour score and the frailty index, by activity group. Linear regression testing interaction between activity group and lifestyle behaviour score on frailty was used for significant testing between slopes. See appendix E– table 10

Chapter 5 Discussion

This study demonstrated that engaging in poor lifestyle behaviours is negatively associated with frailty in active and inactive individuals, both in isolation and when combined in a score. When examined in isolation there is a complexity in how these lifestyle behaviours are associated with frailty, especially given that the majority of analysis differed by age and sex. Younger adults who engaged in poor lifestyle behaviours had a lower FI score compared to their older counterparts. Furthermore, in some cases, males experienced more protective effects compared to females from some behaviours, such as, in drinking and smoking habits. Among individual lifestyle behaviours, high sedentary time, poor diet quality, and poor sleep quality were all associated with increased frailty in both active and inactive individuals. Whereas being a smoker was only associated with increased frailty in inactive females and not associated with frailty in inactive males and active individuals. Binge drinking was not associated with frailty in inactive individuals and active females; however, it was protective in older, active males. These findings are important as they demonstrate the need for individualized lifestyle interventions that consider age-and-sex differences. In contrast, the Lifestyle Behaviour Score has a simple message. At every age, as an individual's Lifestyle Behaviour Score increased, so did their FI in both inactive and active individuals; however, the strength of the association was higher in inactive individuals at every age group. In other words, active individuals had a significantly lower FI score than inactive individuals – no matter the age or how many behaviours they engaged in. These results suggest that being active may have a protective effect on poor lifestyle behaviours when compared to being inactive. A holistic lifestyle approach to mitigating frailty would be needed given that other lifestyle behaviours are impeding the benefits of physical activity.

How lifestyle behaviours impact frailty is not fully understood (45,314); therefore, it is difficult to fully understand why some behaviours are individually associated with frailty and others are not. Compared to the literature, our work supports the notion that having poor diet quality and poor sleep quality is associated with increased frailty (255,262,269), and that this association is relevant for both active and inactive individuals. Being highly sedentary was also associated with higher frailty scores in both activity groups; however, in Figure 5.1 there is a significant difference in FI score in those who engaged in high sedentary time resulting in lower frailty scores. This may be due to the need to consider age and sex differences to better understand frailty's relationship with high sedentary time. The association between binge drinking and smoking with frailty differs from what we expected; though, it is not entirely surprising. For instance, this study found that binge drinking was not associated with frailty for inactive individuals or active females, but has a protective association with older, active males (Age 50: $\beta = -0.019$, 95 % CI = − 0.033, − 0.0056; Age 60: $\beta = -0.030$, 95 % CI = − 0.049, − 0.10; Age 70: $\beta = -0.041$, 95 % CI = − 0.066, − 0.015). Our study isn't the first to report that alcohol consumption is associated with lower frailty or is not associated with frailty (236,332,336,344–346). For instance, one longitudinal study reported that moderate drinkers had a 31 % decreased risk of frailty over 3 years when compared to non-drinkers, and that there was no association between heavy drinkers and frailty (332). Some researchers believe these contradicting results may be because of the way alcohol consumption is captured. Instead of asking for a count of alcoholic beverages, one study asked about alcoholic consumption patterns, such as drinking with meals or having a Mediterranean drinking pattern (i.e., moderate alcohol intake, with wine preference [≥80 % of alcohol proceeds from wine], and drinking only with meals) (332). Researchers found that drinking with meals or having a Mediterranean drinking pattern was associated with decreased frailty by the Frailty Phenotype. Whereas another study captured alcohol consumption through the questions "are your family and/or friends concerned about your alcohol consumption?" and "are you concerned about your alcohol consumption?". This study found that concerns from family and friends about alcohol consumption were positively associated with frailty outcome in those 60–69, and concerns with one's own alcohol consumption was associated with frailty in those 70–79 (347). The first study may have captured individuals who drink socially and casually, whereas the second study is likely to identify individuals with excessive alcohol consumption and alcoholism. These findings demonstrate the importance of understanding an individual's relationship with consuming alcohol rather than simply counting drinks consumed.

This study contradicts what has been previously published about the relationship between smoking and frailty (235,284). This study reports there is little association between smoking and frailty; with only inactive females reporting an increased association between the FI and being a current smoker. Other studies have also shown no association between these two variables; for instance, Yet et al. (2015) aimed to identify factors (demographic characteristics, lifestyle factors, and health indicators) associated with frailty, measured by the Tilburg Frailty Indicator, in community-dwelling older adults from five European countries (344). This study reported that current smoking was not significantly associated with frailty (Odds Ratio = 1.37, 95 % CI = 0.93, 2.01; p = 0.11). One of the reasons smoking could have contradictory findings might be from dichotomizing the smoking variable into 'current smoker' and 'non-smoker'; though this is common practice (235,284), it does not consider the amount of smoking or former smokers. In fact, one study reports that there is a dose-response between smoking and frailty, with heavy smokers with the highest degree of frailty and never smokers with the lowest (348). Another reason that could explain the low association between smoking and frailty in this study is that estimates on self-report, particularly of socially undesirable behaviours, are subject to report bias (349,350). Though this could be true for all the behaviours included in this study, none of the other behaviours are enforced by prohibiting in public places, workplaces, and health warnings on packages quite like tobacco use – such as smoking, this could lead to an increased tendency to underreport. Further, how this question is worded and delivered could impact findings. For instance, adolescents and adults have been shown to see 'ever smoked' or 'lifetime smoking' differently (351). Adolescents are more likely to see 'ever' or 'lifetime' smoking as having ever taking a puff from a cigarette, whereas adults are more likely to interpret this as having smoked 100 or more cigarettes in one's lifetime. Though there are no adolescents in this study, this example demonstrates how different responses may occur for the same wording of a survey question. Lastly, in the current study, NHANES collects questionnaire information through in-person interviews. This is important as there is support to show that social desirability affects the estimate of undesirable behaviours with in-person reports (351). Online self-reporting allows individuals to be more honest in their reporting as it takes their identity away from the undesirable behaviour (351–353).

Our study supports other literature that demonstrates that a lifestyle behaviour score is associated with frailty (335,336,354). In our study, we found that an increase in poor lifestyle behaviours is associated with an increase in the FI; further, that this association differs by age. However, what is novel about our study is that we sub-grouped the analysis into those who met the MVPA guideline and those who did not. Further, we examined correlation matrix to understand if individuals who are physically active tend to engage in other positive lifestyle behaviours (See Appendix E– Table 3 and 4); for example, we wanted to know if someone who is active also tends to eat healthy, sleep well, and abstain from smoking. However, the results show that just because an individual engages in physical activity does not mean that they engage in all other "positive" lifestyle behaviours. For example, in active individuals, smokers also tended to binge drink ($r = 0.20$), but smokers also reported being less sedentary ($r = -0.34$). Additionally, when examining the changes in R^2 between lifestyle behaviours and frailty in both activity groups, we are able to demonstrate that these lifestyle behaviours account for the variance explaining frailty above and beyond the variance accounted by the covariates alone (Active Group: $\Delta R^2 = 0.03$; $p < 0.01$; Inactive Group: $\Delta R^2 = 0.03$; $p < 0.01$. See Appendix E– Table 5 and 6). Though statistically significant, this difference may not be meaningfully significant, more research is needed to understand this relationship. Furthermore, these tables show that there is overlap between lifestyle behaviours meaning they form together to explain an "unhealthy" lifestyle. Also, we demonstrate that the accumulation of negative behaviours is detrimental in both active and inactive individuals; however, the magnitude in which this increase occurs is significantly different ($p < 0.001$). In other words, at every age, the inactive group had a larger FI estimate than the active group. Younger adults appear to be better protected against frailty than other adults who report a higher lifestyle behaviour score. In summary, physical activity appears to mitigate the association of increased frailty, even when an individual engages in other poor lifestyle behaviours.

Combining the LSB into a continuous score is not novel in the frailty literature (336,354–356). For example, a study by Sotos-Prieto et al (2022) aimed to assess the association between a lifestyle-based Healthy Heart Score (HHS), which estimates a 20-year risk of cardiovascular disease, and the risk of frailty in older female nurses (355). The HHS was based on a 20-year cardiovascular disease-risk prediction model using the previously- derived gender-specific coefficients of a set of modifiable behavioural factors including current smoking, high body mass index, low physical activity, lack of moderate alcohol intake, and unhealthy diet. Frailty incidence was assessed by the FRAIL Scale. Compared to the lowest quantile of the HHS, there was an increased hazard ratio of frailty across quantiles (HR range: 1.67-5.92; p-trend > 0.001). Though, unlike the present study, this paper did not include the protective association demonstrated by being an active individual compared to an inactive individual. Further, our study demonstrates that the lifestyle behaviour score differs by age, reporting larger frailty associations with increases in the negative Lifestyle Behavior Score. With physical activity being a leading intervention for frailty reduction, it's important to understand how other lifestyle behaviours, age, and sex may mitigate this relationship.

The strength of this study was the analysis of lifestyle behaviours by activity groups in a representative sample of non-institutionalized U.S older adults. Further, this study used an FI that has been validated within the NHANES database (339)The cross-sectional nature of the NHANES database is the most important limitation of this study, as causation cannot be inferred. However, the associations (or lack thereof) we observed between frailty and lifestyle behaviours could guide the scope of future controlled trials and underscore the importance of physical activity even at older ages.

Additionally, the dichotomization of lifestyle behaviours limits our understanding of the association between behaviours and frailty. Simplifying the spectrum of responses among continuous variables could lead to oversimplifications of observed associations with frailty where more nuanced effects may be present. Such categorizations, however, are common practice and can provide broad guidance where causal effects cannot be inferred. Wherever possible, these groupings were driven by the leading national or international guidelines. In this work, dichotomization also helps address the potential for noise introduced by biases during self-reporting. Future research exploring such relationships should investigate dose-response effects more precisely, particularly in the case of behaviours where the association with frailty observed diverged unexpectedly from prior literature. Furthermore, potential biases such as recall bias and social desirability bias may have influenced self-reported lifestyle behaviors and, consequently, the findings of the study. However, that NHANES collects such self-reported variables allows for a large and rich database spanning a variety of topics, which is not easily achievable in small-scale research. Further research striving to comprehend these behaviours on a continuous scale and incorporating relevant objective measures is prudent. Lastly, though we compared the differences between the analytical sample and those with missing values, those who were excluded may have impacted the results.

Chapter 5: Conclusion

The takeaway message of this study is that being physically active has a protective effect on the association between poor lifestyle and frailty, though, both inactive and active individual's frailty associations increase with increased poor behaviours. Further, this association is dependent on age, with younger individuals having lower frailty estimates than older individuals.

Chapter 6 Discussion

In the final chapter of my thesis, I will summarize each of the study findings, consider their limitations, discuss the potential implications of the results, and identify areas of future inquiry. Further, I will connect each manuscript to my overall thesis objective of understanding the dynamic relationship between physical activity and frailty. Figure 6.1 demonstrates how I will discuss each manuscript and connect them to the overall objective. In brief, I wanted to understand the physical activity and frailty relationship by:

1) Modifying physical activity to see how frailty changes (manuscript 1),
2) Modifying frailty to see how physical activity changes (manuscript 2),
3) Seeing how modifying lifestyle behaviours impact the relationship between physical activity and frailty (manuscript 3), and
4) Understanding how sex and/or age impact physical activity and frailty throughout all objectives (manuscripts 1, 2, & 3).

Lastly, as each study has its discussion section, this chapter aims to synthesize the findings and interpret how they relate to the overall body of evidence.

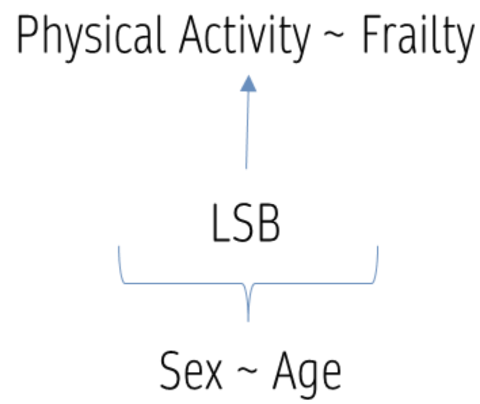

Table 6.1 Visual diagram of how this dissertation aims to understand the relationship between physical activity and frailty through (1) modifying physical activity to see how frailty changes, (2) modifying frailty to see how physical activity changes, (3) seeing how modifying lifestyle behaviours impacts the relationship between physical activity and frailty, and (4) understanding how sex and/or age impact physical activity and frailty throughout all objectives. LSB = Lifestyle behaviors; ~ = Relationship.

6.1 Summary of Findings

Across all manuscripts, physical activity remains strongly linked to frailty; however, this dissertation demonstrates potential connections between these variables. The studies show that the relationship between physical activity and frailty depends on the type of activity engaged in, the type of tool to measure frailty, the other lifestyle behaviours one engages in, and the sex and age of the individual.

Manuscript 1 found that engaging in either component of the physical activity recommendations was associated with decreased frailty compared to those who engage in neither component of the physical activity recommendations; however, these associations differed by age and sex, with males showing the strongest associations, especially in older ages. Older females needed to engage in moderate-to-vigorous physical activity (MVPA) to observe a beneficial effect on frailty. Meanwhile, males benefited from engaging in either or both types of activity regardless of age. In both males and females, engaging in the recommended amount of MVPA and RT or only MVPA significantly reduced the mortality risk.

Manuscript 2 found that the associations between MVPA, RT, and frailty differed by frailty tool selection; however, little difference was found in the light activity and stationary time associations with frailty. Also, we found that sex and age differences were observed for every frailty tool, though not in a consistent pattern.

Lastly, manuscript 3 demonstrated that engaging in poor lifestyle behaviours is negatively associated with frailty for both active and inactive individuals, both when examined as individual lifestyle behaviours or as a combined score. This study showed that as an individual accumulates poor lifestyle behaviours at every age, their frailty index score increases in both active and inactive individuals. However, the strength of the association differs by activity group, with active individuals reporting a significantly lower frailty index score than inactive individuals, no matter the age or how many poor lifestyle behaviours they engage in.

6.2 Strengths and Limitations

Physical activity and frailty have been examined extensively over time; however, gaps in the literature limit our understanding of the relationship between these variables. This dissertation addresses some of these gaps and adds to the evidence. For example, there is limited knowledge of the unique relationship of RT with frailty; many studies focus on MVPA or the combined effects of MVPA and RT (281,317). This study provides insight into the association between RT and frailty. Furthermore, it uses the FI as the measure of frailty – this tool is a less commonly used tool in RT and frailty studies

(357,358). The FI is beneficial because it provides a comprehensive health assessment and yields a continuous score, ranging from fit to frail, making it more responsive to change than other tools (62,359).

Another strength of this dissertation is that all associations were tested for significant interactions with sex and age. Males tend to be less frail and more physically active than females; thus, it is important to understand how physical activity and frailty associations differ by sex. Furthermore, this dissertation examined frailty in individuals aged 20 years and older in manuscripts 1 & 3 and 65 and older in manuscript 2. Most studies aiming to understand frailty include only individuals aged 65, especially those not using the frailty index. Since frailty can develop earlier than 65, including younger and middle-aged adults in frailty research is important. Future studies should explore how the association between physical activity and frailty may differ by frailty tool in middle-aged and younger individuals.

Another strength of this dissertation is that it uses the NHANES database, a large nationally representative sample of the United States. This database enables the utilization of numerous covariates to adjust data and minimize potential confounding. The extensive health data in NHANES also enables the development of an FI, which incorporates self-reported variables, physical measurements, and laboratory values. Additionally, utilizing the FI adds further value to this dissertation. The FI is a valid and reliable tool that has gained international recognition (56,84).

One of the limitations of my dissertation is the lack of consensus among health professionals and researchers on the definition, conceptualization, and measurement of frailty (87,314,360). As demonstrated by using the FI across manuscripts, I primarily focus on the deficit accumulation conceptualization, except for manuscript 2, which aims to understand frailty across various frailty tools. Consequently, the findings largely aim to understand the relationship between physical activity and frailty as measured by the FI.

Secondly, a main limitation of my dissertation is that each manuscript is limited by the cross-sectional design and dated nature of this US NHANES dataset. The cross-sectional design does not allow me to make firm statements about specific mechanisms in the relationship between physical activity and frailty. However, I can demonstrate relationships and interpret results with associative inferences. Further, some of the cycles included in this dissertation were collected 20+ years ago. Though dated, it does not mean the results are not valuable. Previous research has demonstrated that participation in physical activity has remained stable over the past decade (361,362); this suggests that the associations observed between frailty and physical activity in this dissertation could still apply to present-day individuals. Even so, future studies should use more recent Canadian data, such as the Canadian Longitudinal Study on Aging, to examine the association of physical activity with frailty.

The benefit of using NHANES in my dissertation is that it is an inexpensive and timely method due to its accessibility. NHANES is a free-to-use dataset; this is beneficial as it allows individuals to explore research questions and allows for insight into potential future research studies. For instance, manuscript 2 demonstrates that physical activity and frailty associations differ by frailty tool selection; moreover, this difference is most prominent when examining resistance training associations. This finding informed a new hypothesis that resistance training may influence physical frailty tools more through improving physical function components in its criteria rather than overall frailty. Future research can build on this hypothesis with more intensive research designs.

The collection methods used within NHANES also have limitations. As per the NHANES protocol, sex was captured by personnel labeling individuals as 'female' or 'male' rather than asking them to report their sex and/or gender. This does not allow researchers to understand true sex or gender differences; rather, we are exploring the perceived sex/gender of the interviewed individual. Secondly, including other lifestyle behaviors across the cycles of NHANES would have added depth to the analysis in manuscript 3. For instance, it would have been interesting to know how activities that improve cognition (i.e., reading) were associated with frailty.

Another limitation is that the resistance training questions included in NHANES only focused on the frequency of the activities and not on the type or intensity. More detailed information on resistance training could have provided better context for the sex differences reported in manuscript 1 and could better inform what resistance training programs are needed to mitigate frailty (e.g., muscle endurance or strength). For example, females engage in resistance training at a lower intensity and therefore, may not engage at an intensity that impacts their frailty level (309). In addition, NHANES did not include the resistance training questionnaire across all cycles which did not allow us to examine resistance training in manuscript 3. Lastly, in manuscript 2 we used accelerometer data which may have resulted in including resistance training activities within the MVPA allocation. Using logbooks where individuals timestamp their activities could have allowed us to separate these two distinct activities, but this may not be feasible in a large population study such as NHANES.

This dissertation focused on the association between adhering to the physical activity guidelines (≥150 mins/week of MVPA and/or ≥ 2 days/week of resistance training) and frailty. This does not allow us to examine whether being insufficiently active (e.g., 100 mins/week of MVPA) or well-exceeding the guidelines (e.g., 300 mins/week of MVPA) is associated with lower frailty levels. Future studies should examine the association between physical activity and frailty across the physical activity continuum.

Another limitation of the NHANES database is the potential for recall, selection, and social desirability bias. Participants with higher levels of frailty are more likely to have cognitive impairment than their robust counterparts (363) and may have a harder time accurately recalling information when completing questionnaires about their health status or their physical activity levels. Selection bias arises because participants in the NHANES study may differ demographically from those who do not participate. NHANES attempts to mitigate this bias in several ways. For example, it oversamples certain groups, such as African Americans, Mexican Americans, individuals of lower socioeconomic status, and those over the age of 60 (364,365). Additionally, NHANES provides weighted samples to ensure external validity, ensuring that study results are generalizable and reflect the U.S. population. Furthermore, NHANES offers incentives for participation, such as free physical examinations and monetary reimbursement for any expenses incurred. These incentives help recruit participants by addressing barriers such as travel expenses. Social desirability bias refers to the tendency to underreport socially undesirable behaviours (i.e., smoking) and overreport more desirable behaviours (i.e., physical activity) which could have affected the reporting of the lifestyle behaviours included in this dissertation (366–368), including physical activity (368,369).

6.3 Implications and Future Research

This dissertation's findings offer insights into potential research avenues to enhance our understanding of the complex relationship between physical activity and frailty. In this section, I will summarize the key findings from my dissertation and suggest future research directions based on these findings.

6.3.1 Key Findings

The primary aim of my dissertation is to enhance our understanding of the relationship between physical activity and frailty, culminating in recommendations for preventing or reversing frailty based on the findings. Table 6.1 summarizes these recommendations. A comprehensive approach, including multiple lifestyle behaviors, appears necessary to reduce frailty. An example of such an approach is the 24-hour movement guidelines for Canadians (118,370), which encompasses exercise, physical activity, sedentary time, and sleep for older adults (65+). Table 6.1 includes guidelines for diet, while smoking and alcohol consumption were excluded due to contradictory findings. For example, in this dissertation, binge drinking seems beneficial for active older males - possibly due to increased socialization among active drinkers (289,371), as discussed further in Manuscript 3. Incorporating various lifestyle behaviors into comprehensive guidelines would acknowledge their contributions to an individual's frailty level and the cumulative negative effects on frailty outcomes. Lastly, the table presents outcomes by sex where relevant. While the 24-hour movement guidelines offer recommendations by age category, understanding how sex influences these health outcomes could provide better guidance for both males and females. Though, it should be noted that results are based on associations, and more work is needed to fully understand these relationships.

Table 6.2 Recommendations for reducing and/or preventing frailty, with age and sex considerations.

Recommendations for reversing frailty:	
Engaging in the full physical activity guidelines is best practice; however, benefits are also seen when engaging in MVPA only. * Increase hours/week of light activity time. Decrease hours/day of sedentary time. * Obtain a healthy diet. * Sleep the recommended hours per night for your age group (7-9 hours/night for those 18-65 years old and 7-8 hours/night for those 65 and older) * Aim to limit the number of unhealthy behaviours (e.g., high sedentary time or poor sleep) you engage in *	
Female Specific:	Male Specific:
Younger women (< 40 years old) may mitigate frailty by engaging in only RT	At any age, men can engage in only RT to prevent and/or reduce frailty
* = strength of association increases with age; [$] = association shown only in active individuals; [&] = association only shown in inactive individuals.	

The table above suggests that males of all ages may mitigate frailty by engaging only in resistance training (RT). This novel finding is explained in both manuscripts 1 and 2. Both manuscripts reported that increasing time spent in moderate-to-vigorous physical activity (MVPA) and light activity, as well as reducing sedentary time, was associated with lower frailty, as measured by the FI, for both sexes and across age groups. However, the key difference lies in the association with resistance training. At first glance, you would see that these manuscripts contradict one another. In manuscript 1, we found that resistance training was negatively associated with the FI only in younger females (age 40) and males across all ages. This suggests that males may mitigate frailty by engaging in resistance training alone, while females only see this benefit at younger ages.

However, in manuscript 2, we examined resistance training to understand its association with frailty using several frailty tools. When comparing the FI from Manuscript 2 to that of Manuscript 1, we see that resistance training is not associated with the FI regardless of age or sex differences. A key difference in Manuscript 2 is that the sample includes individuals aged 60 and older, as some of the frailty tools were tested and developed specifically for older adult populations (Visualization found in Figure 1). Therefore, manuscript 2 demonstrates no difference between males and females in resistance training associations in older age, which aligns with the results found in Manuscript 1.

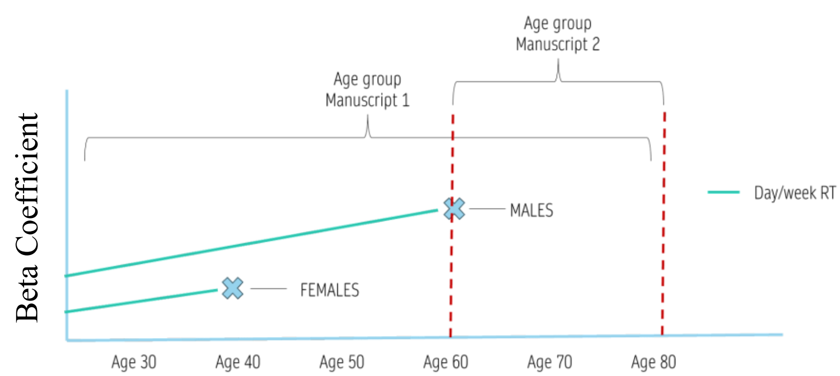

Table 6.3 Visual representation of resistance training and frailty associations in manuscripts 1 and 2 by age and sex. Age groups included in manuscript 1 include ages 30-80, and manuscript 2 includes ages 60-80. Findings for both manuscripts demonstrate that after age 60, males show no association between resistance training and frailty and females show no association between resistance training and frailty after age 40. RT - Resistance training; X = No association

Another key finding from this dissertation is that frailty may be a mediating factor in the relationship between physical activity and mortality. Manuscript 1 revealed that frailty may modify the relationship between physical activity and mortality. This is a novel and significant finding, as there is limited evidence in the literature exploring the association between physical activity and mortality while considering the impact of frailty (311). These findings suggest that individuals who exercise may maintain better physical and mental health in their later years compared to those who are inactive. This contributes to a growing body of evidence on the concepts of 'dying healthier' and increasing 'healthspan' (312,372–374). These concepts aim to extend an individual's healthy years without chronic and debilitating disease (375).

Living long and in good health is a common goal for many individuals, yet it is not always achieved. Some suggested reasons why some individuals age in good health while others do not include differences in demographics (376), education (377,378), stress and mental health (379,380), and lifestyle behaviours (377,381,382). While some of these factors cannot be influenced, such as demographics, others can be modified. Based on the findings from Manuscript 1, physical activity emerges as a modifiable factor that can contribute to increasing healthspan and aiding individuals to age healthier.

Lastly, understanding how the recommendations for physical activity can reduce and prevent frailty is critical, as physical activity is a lead intervention for mitigating frailty. However, I find the selection of frailty tools most concerning in physical activity and frailty research. This is critical as my dissertation found that tool selection could impact the relationship between physical activity and frailty, potentially leading to biased findings being disseminated. Although the findings from my dissertation cannot provide insights into which frailty tool is the best for physical activity and frailty analysis, I believe it opens the door for conversation around this topic, such as excluding tools that capture physical activity as a criterion. In Manuscript 2, it was reported that there was no difference in MVPA and frailty results when using either a multidimensional tool or a physical frailty tool—however, a significant difference was found in the RT analysis.

In sum, this dissertation aligns with the large body of evidence on the importance of physical activity for reducing and preventing frailty while also providing insights into *how* and *for whom* these interactions are most pronounced. Although these findings are exploratory, they indicate the need for further research. Future research could support more detailed recommendations for individuals aiming to mitigate frailty. The following section will outline future research directions to build on my dissertation's findings.

6.3.2 Future Research Directions

Based on my dissertation's key findings, I have formulated ideas for how future research could expand upon them. This section will briefly outline the next steps for investigating sex and age differences, lifestyle behaviours, and frailty tool selection in physical activity research.

6.3.2.1 Sex and Age Differences in Physical Activity and Frailty Literature

In my key findings, I suggest that comprehensive physical activity guidelines, such as the 24-hour movement guidelines, could benefit from including sex differences in their recommendations. While my findings support that adhering to the full physical activity guidelines (150 min/week of MVPA + 2 days/week of RT) benefits both males and females, there is room for personal preference and adaptability within these guidelines. For example, males and females could choose to focus on the MVPA component of the guidelines, as it appears to lead to potential decreases in frailty levels at any age. However, other recommendations may vary depending on age and sex. My findings suggest that males may experience a decrease in frailty levels by engaging in the recommended amount of either MVPA or RT alone. In contrast, females may need to focus on the MVPA component of the guidelines to observe a decreased association with the FI. It is well-established that frailty status and physical activity behaviours differ by sex and age, as discussed in my literature review. However, I propose that future research explore these differences through intervention studies to understand their implications better.

To better understand the sex and age differences in the relationship between physical activity types and frailty, I propose a study design similar to Huang et al. (2020) (174). In this study, participants (aged 65-85; 47% female) were randomized into aerobic training (AT), resistance training (RT), combined training (AT + RT), or a control group (CG) for 26 weeks. A 95-item FI was used to measure frailty. This study found that, compared to those in the CG, the AT group improved total FI by 0.020 (CI – 0.039 to -0.001, effect size -0.275); however, no significant differences were found in the RT and the AT+RT groups in the study end. Based on my dissertation findings, I hypothesize that significant RT findings could be observed at younger ages and/or specifically in males. Additionally, stratifying by sex might provide better insight into whether females need MVPA to mitigate frailty outcomes. A study like this would add depth to the literature by understanding if programming more specifically for sex and age differences is needed.

6.3.2.2 Lifestyle Medicine and Relationship with Lifestyle Behaviours

Another area of interest stemming from my work on manuscript 3 is better understanding an individual’s relationship with lifestyle behaviors and the added complexity of compounding poor behaviors. Although my findings demonstrated that physical activity could mitigate some of the negative consequences of poor lifestyle choices, they also showed that, whether active or not, the accumulation of poor lifestyle behaviors is positively associated with frailty.

In manuscript 3, we combined lifestyle behaviours in a summed score from 0-5 as it is a commonly used methodology in the lifestyle research (383). To do this, we dichotomized the five included lifestyle behaviours using suggested cut-points from national and international guidelines, which may have resulted in valuable information being lost. For example, if alcohol consumption had been analyzed continuously in manuscript 3, we may have found that frailty increases as the number of drinks increases, which could have explained some of the contradictory findings. Future studies should create multiple lifestyle behaviour groups to account for different intensities of a behaviour (i.e., quartiles). Future studies should also explore whether the association between these lifestyle behaviours and frailty differs by the frailty tool used.

Lifestyle behaviors should be considered holistically when aiming to mitigate frailty, supporting the growing research on lifestyle medicine (384,385). Rippe (1999) first defined lifestyle medicine as “the discipline of studying how daily habits and practices impact both the prevention and treatment of disease, often in conjunction with pharmaceutical or surgical therapy, to provide an important adjunct to overall health (386).” This approach aims to shift modern medicine from an “end-stage” approach to a “preventative” approach through lifestyle changes. Evidence demonstrates the effectiveness of a preventative approach, or lifestyle medicine, on an individual’s health and well-being (384,387). For instance, Conti et al. (2024) conducted a randomized controlled trial with residents in a long-term care facility (388). These residents were randomized into a three-month intervention, including bi-weekly physical exercise, a healthy diet, and weekly psychological well-being sessions, while the control group received routine care. At the study's end, the intervention group showed significant improvement in the total scores of all scales compared to the control group (Control Group vs. Intervention Group; Mean (SD). Barthel Index Score: 30.04 (29.54) vs. 44.96 (26.72), $p = 0.02$; Katz ADL Score: 1.85 (2.17) vs. 3.52 (1.93), $p = 0.01$; Tinetti Score: 9.26 (8.65) vs. 16.04 (8.17), $p = 0.01$), indicating the effectiveness of the intervention in improving functionality in older people living in long-term care settings.

Additionally, a meta-analysis of randomized controlled trials aimed to understand the treatment effect of multi-component lifestyle medicine interventions on depressive symptoms (389). The study found that these interventions reduced depressive symptoms significantly relative to care as usual ($p > 0.001$, $d = 0.20$) and waitlist and/or no intervention ($p > 0.01$, $d = 0.22$). This study also conducted a moderation analysis that examined the effect of multi-component lifestyle medicine interventions compared with 'care as usual' groups. This analysis found that multi-component lifestyle medicine intervention included two (standardized mean difference = -0.17, 95% CI: -0.30, -0.05, $p > 0.01$, $k = 16$) and three (standardized mean difference = -0.27, 95% CI: -0.43, -0.12, $p > 0.01$, $k = 14$) lifestyle factors had a small but significant effect on depressive symptoms. However, behavior change is not easy (390,391), so it's important to understand an individual's relationships with lifestyle behaviours. While studies in the frailty literature evaluate multi-component lifestyle interventions and their impact on frailty (392–394), similar to the methods used in the mentioned medicine studies, I believe individuals are aware of the importance of engaging in healthy behaviors. Therefore, it's not primarily an education gap regarding what is “better” for them. Instead, there might be something in the relationship individuals have with these behaviors that could act as a barrier to engaging in healthier behaviors.

This dissertation used population data to understand cross-sectional associations between physical activity and frailty, limiting my findings' generalizability at the individual level. However, my research findings, the frailty and physical activity/lifestyle literature that I have reviewed, and my experience working in the continuing care sector, allowed me to form opinions about how we can manage frailty at the individual level. As stated throughout this dissertation, I believe in measuring frailty holistically and that frailty is vastly complex and unique. We need to understand individuals' underlying relationship with lifestyle behaviours to facilitate change, improve their health, and mitigate frailty.

In manuscript 3, when summarizing result findings, one study found that an individual’s relationship with drinking (i.e., “Are your family and/or friends concerned about your alcohol consumption?” and “Are you concerned about your alcohol consumption?”) may be more meaningful than a simple count of alcohol consumed per week (347). This suggests a dependency on alcohol that represents alcoholism rather than casual drinking behavior. There is evidence to support that this dependency is also prevalent in smoking and diet habits (i.e., an addictive nature to these habits) (395–397). My findings point to the importance of behaviour change to mitigate frailty, and behaviour change alone is a prominent area of study (398,399). However, it is important to note that these behaviours (i.e., smoking, diet, and alcohol consumption) are related to creating dopamine spikes (400–402), addiction (395,397,403), coping with negative emotions (404,405), and reducing stress (406,407). Further, some individuals even report negative relationships between exercise/physical activity with body image and disordered eating behaviours (406,407). Therefore, understanding individuals' deeper relationship with these behaviors may need to be addressed before or during the behavior change process.

Therefore, my suggestion for future next steps for frailty and lifestyle behaviour research is the inclusion of behavioural therapy (i.e., cognitive behaviour therapy (CBT)) as a part of a multidomain lifestyle intervention. The inclusion of behavioural therapy as a part of a multidomain lifestyle intervention is not a new concept in the health literature; in fact, the inclusion of professional therapy can be found in many obesity studies (408,409). For example, a systematic review and meta-analysis from 2023 aimed to examine the contribution of cognitive behavioural therapy to the implementation of lifestyle changes in patients with obesity and type 2 diabetes (409). The meta-analysis found a medium, significant effect size of cognitive behavioural therapy for weight loss and weight maintenance, and a low, non-significant effect for reducing glycated hemoglobin (HbA1c) levels. This study concluded that CBT intervention effectively implemented lifestyle change, especially for weight loss and maintenance. This could be a key missing component in frailty interventions. The underlying assumptions of behavioural and CBT treatments are that behaviours are learned, unlearned, modified, and replaced by other behaviours through different strategies, some of which include goal setting, problem-solving, stimulus control, and self-monitoring (410,411). I believe behavioural therapy could get to the underlying causes of why an individual engages and/or chooses not to engage in specific behaviours and work with individuals to support behaviour change.

In conclusion, while physical activity is well-supported in the literature as a key element in mitigating frailty, it's important to recognize that it is just one of many lifestyle behaviors that affect health and well-being. Moreover, many of these behaviors may have addictive components, making behavior change challenging for individuals. Lifestyle coaches and professionals could be valuable in unpacking the underlying relationships with these negative behaviors. Therefore, a multidisciplinary approach, including behavioral therapy, may be necessary to address lifestyle factors and reduce frailty effectively.

6.3.2.2 Next steps in Frailty Tool selection and Physical Activity Research

In the next few paragraphs, I will suggest future research directions based on findings from manuscript 2, which aimed to understand how the relationship between physical activity and frailty differs by frailty tool selection. First, I will discuss how some frailty tools are poorly-suited for physical activity studies based on multicollinearity. Then, I will describe my hypothesis that some frailty tools may be more strongly influenced by RT research.

The research study from Tolley et al. (2021) highlights how frailty tools may introduce bias into physical activity and frailty research results (412). The study examined the associations between objectively measured physical activity and frailty in community-dwelling older adults aged 60 and above, aiming to assess if these associations varied depending on the definition of frailty used (i.e., multidimensional vs. physical definitions of frailty). 54 associations between physical activity and frailty were analyzed, with 39 using a physical frailty tool and 15 using a multidimensional tool. Researchers found no difference between the associations of physical activity and the different definitions of frailty. However, it's crucial to consider some key points from the study. Table 6.2 shows that all tools used to represent 'physical frailty' were variants of the frailty phenotype (11 original tools and 3 modified versions). On the other hand, ‘multidimensional frailty’ was assessed using four different tools: the FI, the FRAIL scale, the Brief Frailty Instrument for Tanzania (B-FIT), and the Frailty Trait Scale. Notably, out of the 18 tools included in the meta-analysis, 14 were biased as they incorporated a physical activity measure in their criteria. For example, the Frailty Trait Scale, included in four papers analyzing the multidimensional definition of frailty, incorporates the full Physical Activity Scale for the Elderly questionnaire (413). Only four papers in the meta-analysis utilized tools without a measure of physical activity in their criteria. This meta-analysis underscores the importance of understanding frailty tool selection and the criteria of each tool, as this could potentially skew research findings.

Table 6.4 Description of frailty tools included in Tolley et al. (2021) (412)

	Physical Frailty		**Multidimensional Frailty**			
Tools name (number of associations tested)	Frailty Phenotype (11)	Modified Frailty Phenotype (3)	Frailty Index (3)	FRAIL Scale (1)	Brief Frailty Instrument for Tanzania (B-FIT) (1)	Frailty Trait Scale (4)
Physical Activity Criterion	Minnesota Physical Activity Questionnaire	Hours of physical exercise; Days/week engaged in vigorous physical activity	No physical activity measure	No physical activity measure	No physical activity measure	Physical Activity Scale for the Elderly Questionnaire
Table modified from Tolley et al. (2021) (412)						

Another issue concerning physical activity and frailty tools is the resemblance some tools bear to physical function and/or performance assessments. This similarity could explain the differences observed in the association between frailty and resistance training by frailty tools in Manuscript 2. One possible explanation for this disparity is that resistance training is more strongly linked to measures of physical function than aerobic activities, potentially influencing physical frailty tools more than multidimensional ones.

A meta-analysis by Macdonald et al. (2020) supports this idea, aiming to evaluate the effectiveness of primary care interventions for physical frailty in community-dwelling adults aged 60 and above. The study found that physical frailty may be improved through exercise, particularly through resistance training (317). However, the authors noted that frailty is a complex construct comprising multiple interacting dimensions of capacity, resilience, and incapacity. They highlighted that some interventions may show little effect on frailty tools because physical performance measures do not solely determine frailty. For example, while endurance training focused on walking may improve gait speed, it may not necessarily enhance handgrip strength. The authors concluded that changes in specific measures cannot be interpreted as improvements in overall frailty without considering the individual's underlying risk factors associated with frailty.

The resemblance between physical function and some frailty tools is highlighted in a study by Racey et al. (2021). This meta-analysis and systematic review aimed to identify effective physical activity interventions in improving outcomes related to frailty, including frailty (281). A total of 26 studies were included, and the study concluded that significant effects were found between the physical activity interventions and frailty [standard mean difference: -1.29, 95% confidence interval: -2.22 to -0.36; risk ratio: 0.58, 95% confidence interval: 0.36 to 0.93]. However, a closer examination of the tools used reveals an overlap between frailty tools, physical function tools, and tools that include physical activity as a criterion. Of the 25 included studies, five primarily used mostly physical function tests in their criterion (i.e., chair stand and gait speed), nine included a physical activity criterion, four used full physical function batteries (such as the Barthel Index), and nine other tools did not fall into one of these categories. Thereby, 36% of the tools were physical function tests or batteries. If resistance training influences physical function, tools that use physical function measures, physical function batteries, or are frailty tools with a majority of criteria capturing physical function could show a significant change in an individual's physical function post-intervention rather than a change in frailty itself.

Frailty is a complex condition that researchers and health professionals do not fully understand its underlying mechanisms. To compound that complexity, researchers and health professionals can choose from many frailty tools, each with its own conceptualization and criterion. My future research suggestion would not necessarily be identifying a gold standard tool for frailty, but at least a framework for understanding what tool may not be well-suited for specific interventions and/or analysis. This dissertation has highlighted the problematic practice of using tools that include physical activity criteria in physical activity research. However, one of the most commonly used tools in physical activity research is the Frailty Phenotype (281,317,412), which includes a physical activity questionnaire in its criterion. A future research suggestion would be to develop a framework that includes many frailty tools and identifies which tools could highly bias physical activity research.

In summary, researchers need to be aware of the criteria included in frailty tools, or any outcome tool, for items that may bias findings. This dissertation has outlined some problematic items in commonly used frailty tools that could influence physical activity studies. The first issue is having physical activity questions or questionnaires included in a frailty tool and using it in a physical activity study, which causes multicollinearity in research findings. The second issue is that some frailty tools use a single, a few, or a whole battery of physical function measures. This may be a problem as the study results may capture changes in physical function rather than frailty – especially if the physical activity program includes a resistance training component.

6.4 Conclusion

The evidence produced in this thesis supports the large body of evidence that physical activity mitigates frailty. Further, it identifies how physical activity type, frailty tool selection, other lifestyle behaviours, and age and sex differences may impact that relationship. As physical activity is a leading intervention for preventing and/or reducing frailty, it is important to understand how it impacts frailty and for whom. This dissertation considers future frailty research and interventions that may be useful from a public health and epidemiological perspective.

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Appendix A Copy Right Approvals

Study 1: In accordance with The Journal of the American Medical Directors Association and Elsevier journals, authors may use and share their works for scholarly purposes, such as in a thesis or dissertation.

Study 2: Following The Journal of Frailty and Aging and Springer Nature, authors can reuse the published work in a thesis written by the author.

Study 3: In line with Archives of Gerontology and Geriatrics and Elsevier journals, theses and dissertations that contain embedded published journal articles as part of the formal submission can be posted publicly by the awarding institution on Science Direct with DOI links back to the formal publications.

Appendix B: Supplemental Tables and Figures from Manuscript 1

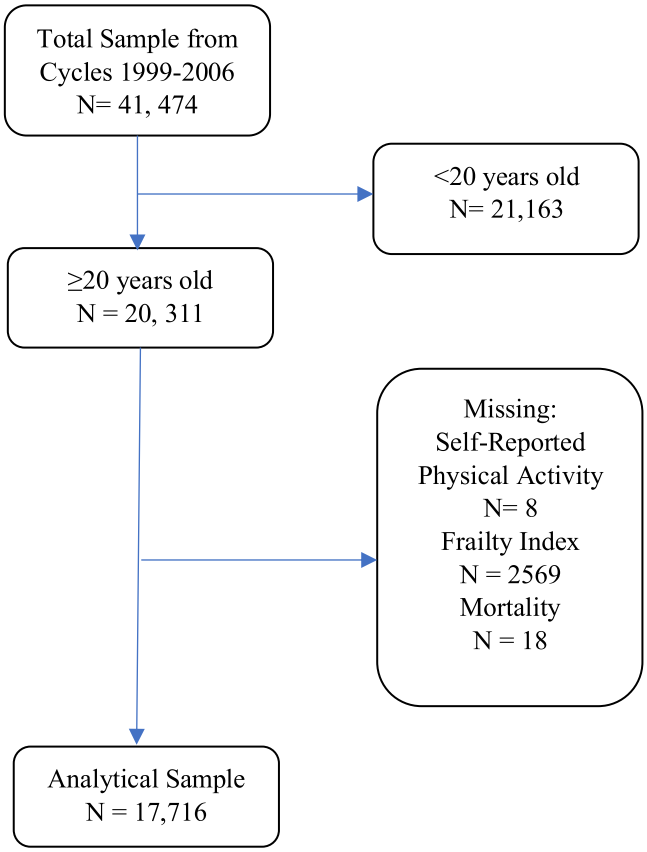

Figure 1: Flowchart of the NHANES participants included in the analysis.

Table 1: Comparison of Analytic Sample and Sample with missing Frailty Index (FI)

N (%) or Mean (SD)	Total Sample N = 17,716	Removed for Missing FI * N = 2595
Age (years)	46.0 (19.0)	53.7 ± 21.6
Sex		
Female	9250 (52.2)	1451 (55.9)
Male	8466 (47.8)	1144 (44.1)
Race		
Mexican American	3927 (22.2)	456 (17.6)
Non-Hispanic Black	3447 (19.5)	592 (22.8)
Non-Hispanic White	8961 (50.6)	1295 (49.9)
Other Hispanic	741 (4.2)	112 (4.3)
Other	640 (3.6)	140 (5.4)
Education		
Less than Grade 9	2610 (14.7)	474 (18.3)
9-11th Grade	2902 (16.4)	458 (17.6)
High School Graduate	4193 (23.7)	619 (23.9)
Some College	4610 (26.0)	573 (22.1)
College Graduate or Above	3330 (18.8)	435 (16.8)
Missing	32 (0.2)	36 (1.8)
Marital Status		
Married	9696 (54.7)	1168 (45.0)
Divorced	1542 (8.7)	231 (8.9)
Never Married	2704 (15.3)	436 (16.8)
Separated	545 (3.1)	85 (3.3)
Living with a Partner	1102 (6.2)	103 (4.0)
Widowed	1670 (9.4)	466 (18.0)
Missing	457 (2.6)	106 (4.1)
Occupation Status		
Working at job or business	9838 (55.5)	1193 (46.0)
Looking for Work	313 (1.8)	32 (1.2)
Not working at a job or business	7561 (42.7)	1352 (52.1)
Missing	4 (0.02)	18 (0.7)

N (%) or Mean (SD)	Total Sample N = 17,716	Removed for Missing FI * N = 2595
Smoker Status		
Everyday	3192 (18.0)	426 (16.4)
Some days	682 (3.8)	90 (3.5)
Never	13,842 (78.1)	2078 (80.1)
Missing	0 (0)	1 (0.04)
Body Mass Index (kg/m^2)	27.7 (6.0)	24.8 (11.1)
* Each variable significantly different than the analytical sample		

Table 2: NHANES 46-item frailty index

- Stroke	- Difficulty using fork and knife	- Heart rate at rest	- Homocysteine (µmol/L)
- Thyroid condition	- Difficulty dressing yourself	- Systolic blood pressure	- Folate, serum (nmol/L)
- Cancer	- Difficulty getting in/out of bed	- Cough regularly	- Medications
- Heart attack	- Difficulty standing up from armless chair	- Leaked/lost control or urine	- Self-reported health
- Heart disease	- Difficulty managing money	- General vision	- Health compared to 1 year ago
- Ever had high blood pressure	- Difficulty preparing meals	- Difficulty seeing steps/curbs in dim lights	- Frequency of healthcare used
- Angina\angina pectoris	- Difficulty standing for long periods of time	- General hearing	- Overnight hospital stays
- Osteoporosis	- Difficulty stooping, crouching, kneeling	- Glycohemoglobin (%)	
- Diabetes	- Difficulty grasping/holding small objects	- Red blood cell count (million cells/µL)	
- Arthritis	- Difficulty push or pulling large objects	- Hemoglobin (g/dL)	
- Ever had Broken hip	- Difficulty attending social event	- Red cell distribution width (%)	
- Cataract operation	- Difficulty lifting or carrying	- Lymphocyte percent (%)	
- Weak/failing kidneys	- Confusing or inability to remember things	- Segmented neutrophils percent (%)	

Table 3: Interactions between the physical activity groups and age with frailty as the outcome

	Females β (p-value)	Males β (p-value)
< 150 min/week MVPA & < 2 days/week RT *Age	Reference	Reference
≥ 150 min/week MVPA & ≥ 2 days/week RT *Age	0.0023 (0.19)	-0.0012 (0.41)
≥ 150 min/week MVPA & < 2 days/week RT *Age	**-0.0025 (0.043)**	**-0.0025 (0.025)**
< 150 min/week MVPA & ≥ 2 days/week RT *Age	**0.0039 (0.027)**	0.00069 (0.68)

Bold $p < 0.05$; MVPA = Moderate-to-Vigorous Physical Activity; RT = Resistance Training; CI = Confidence Interval.
Linear regression adjusted for age, race, education, marital status, occupation status, smoking status, body mass index, and NHANES cycle

Table 4: Associations between physical activity groups with frailty

		Age 30 β (95% CI)	Age 40 β (95% CI)	Age 50 β (95% CI)	Age 60 β (95% CI)	Age 70 β (95% CI)
Minutes of MVPA/Week	Days of RT/Week	Females				
<150	< 2	Reference	Reference	Reference	Reference	Reference
≥ 150	<2	**-0.094 (-0.17, -0.022)**	**-0.12 (-0.17, -0.063)**	**-0.14 (-0.19, -0.096)**	**-0.17 (-0.22, -0.12)**	**-0.19 (-0.26, -0.13)**
<150	≥ 2	**-0.15 (-0.27, -0.025)**	**-0.11 (-0.21, -0.0045)**	-0.068 (-0.16, 0.024)	-0.029 (-0.12, 0.065)	0.0095 (-0.097, 0.12)
≥ 150	≥ 2	**-0.25 (-0.34, -0.15)**	**-0.22 (-0.29, -0.15)**	**-0.20 (-0.26, -0.13)**	**-0.18 (-0.25, -0.10)**	**-0.15 (-0.25, -0.057)**
Minutes of MVPA/Week	Days of RT/Week	Males				
<150	< 2	Reference	Reference	Reference	Reference	Reference
≥ 150	<2	**-0.12 (-0.19, -0.048)**	**-0.14 (-0.20, -0.089)**	**-0.17 (-0.22, -0.12)**	**-0.20 (-0.24, -0.15)**	**-0.22 (-0.28, -0.17)**
<150	≥ 2	**-0.13 (-0.22, -0.044)**	**-0.12 (-0.19, -0.055)**	**-0.12 (-0.18, -0.051)**	**-0.11 (-0.18, -0.033)**	**-0.10 (-0.20, -0.0034)**
≥ 150	≥ 2	**-0.22 (-0.32, -0.12)**	**-0.24 (-0.32, -0.16)**	**-0.25 (-0.32, -0.18)**	**-0.26 (-0.34, -0.19)**	**-0.28 (-0.36, -0.19)**

Bold $p < 0.05$; MVPA = Moderate-to-Vigorous Physical Activity; RT = Resistance Training; CI = Confidence Intervals. Linear regression models adjusted for race, education, marital status, occupation status, smoking status, body mass index, and NHANES cycle. To obtain the simple associations, age was centered around 30, 40, 50, 60, and 70.

Table 5: Interactions between the physical activity groups, age, and frailty with mortality as the outcome

	Females β (p-value)	Males β (p-value)
<150 mins/week MVPA & <2 days/week RT *Frailty	Reference	Reference
≥150 mins/week MVPA & ≥ 2 days/week RT *Frailty	**25.61 (<0.01)**	5.91 (0.098)
≥150 mins/week MVPA & < 2 days/week RT *Frailty	3.11 (0.090)	**4.83 (0.029)**
<150 mins/week MVPA & ≥ 2 days/week RT *Frailty	2.11 (0.33)	**17.11 (0.0044)**
<150 mins/week MVPA & <2 days/week RT *Age	Reference	Reference
≥150 mins/week MVPA & ≥ 2 days/week RT *Age	0.99 (0.49)	1.01 (0.32)
≥150 mins/week MVPA & <2 days/week RT *Age	1.00 (0.49)	1.00 (0.72)
<150 mins/week MVPA & ≥ 2 days/week RT *Age	1.01 (0.33)	1.00 (0.69)
Bold p <0.05; MVPA = Moderate-to-Vigorous Physical Activity; RT = Resistance Training; CI = Confidence Interval. Logistic regression adjusted for age, race, education, marital status, occupation status, smoking status, body mass index, and NHANES cycle		

Table 6: Association between physical activity groups with mortality

		FI 0.10 HR (95% CI)	FI 0.20 HR (95% CI)	FI 0.30 HR (95% CI)
Minutes of MVPA/Week	Days of RT/Week	Females		
<150	< 2	Reference	Reference	Reference
≥ 150	<2	0.85 (0.68, 1.07)	0.84 (0.70, 1.02)	0.84 (0.66, 1.07)
<150	≥ 2	0.78 (0.51, 1.18)	0.79 (0.59, 1.07)	0.81 (0.61, 1.07)
≥ 150	≥ 2	**0.65** **(0.46, 0.93)**	0.79 (0.61, 1.00)	0.94 (0.69, 1.28)
Minutes of MVPA/Week	Days of RT/Week	Males		
<150	< 2	Reference	Reference	Reference
≥ 150	<2	0.88 (0.71, 1.09)	0.95 (0.80, 1.12)	1.02 (0.80, 1.29)
<150	≥ 2	0.96 (0.66, 1.37)	1.05 (0.79, 1.39)	1.16 (0.81, 1.65)
≥ 150	≥ 2	0.77 (0.59, 1.01)	**0.72** **(0.59, 0.88)**	**0.67** **(0.49, 0.90)**

Bold p <0.05; FI = Frailty Index; HR =Hazard Ratio; CI = Confidence Interval; MVPA = Moderate-to-Vigorous Physical Activity; RT = Resistance Training.
Cox regression models adjusted for age, race, education, marital status, occupation status, smoking status, body mass index, and NHANES cycle. Frailty Index was centered around 0.10, 0.20, and 0.30 scores to obtain simple associations.

Table 7: Interactions between the physical activity groups, age, and frailty with all-cause mortality as the outcome

	Females β (p-value)	Males β (p-value)
<150 mins/week MVPA & <2 days/week RT *Age	Reference	Reference
≥150 mins/week MVPA & ≥ 2 days/week RT *Age	1.00 (0.56)	1.00 (0.69)
≥150 mins/week MVPA & <2 days/week RT *Age	1.01 (0.25)	1.00 (0.80)
<150 mins/week MVPA & ≥ 2 days/week RT *Age	0.99 (0.57)	1.01 (0.36)

Bold p <0.05; MVPA = Moderate-to-Vigorous Physical Activity; RT = Resistance Training; CI = Confidence Interval.
Logistic regression adjusted for age, race, education, marital status, occupation status, smoking status, body mass index, and NHANES cycle

Table 8: Association between physical activity groups with mortality.

		Model 1 HR (95% CI)	Model 2 HR (95% CI)
Minutes of MVPA/Week	Days of RT/Week	Females	
<150	< 2	Reference	Reference
≥ 150	<2	**0.53 (0.44, 0.64)**	**0.66 (0.54, 0.81)**
<150	≥ 2	**0.72 (0.54, 0.96)**	0.86 (0.67, 1.11)
≥ 150	≥ 2	**0.32 (0.24, 0.43)**	**0.52 (0.39, 0.69)**
Minutes of MVPA/Week	Days of RT/Week	Males	
<150	< 2	Reference	Reference
≥ 150	<2	**0.71 (0.61, 0.82)**	**0.81 (0.68, 0.98)**
<150	≥ 2	**0.56 (0.43, 0.74)**	0.81 (0.60, 1.09)
≥ 150	≥ 2	**0.35 (0.28, 0.44)**	**0.50 (0.39, 0.63)**

Bold p <0.05; HR =Hazard Ratio; CI = Confidence Interval; MVPA = Moderate-to-Vigorous Physical Activity; RT = Resistance Training. Cox regression models adjusted for age, race, education, marital status, occupation status, smoking status, body mass index, and NHANES cycle.

Appendix C: Supplemental Tables and Figures from Manuscript 2

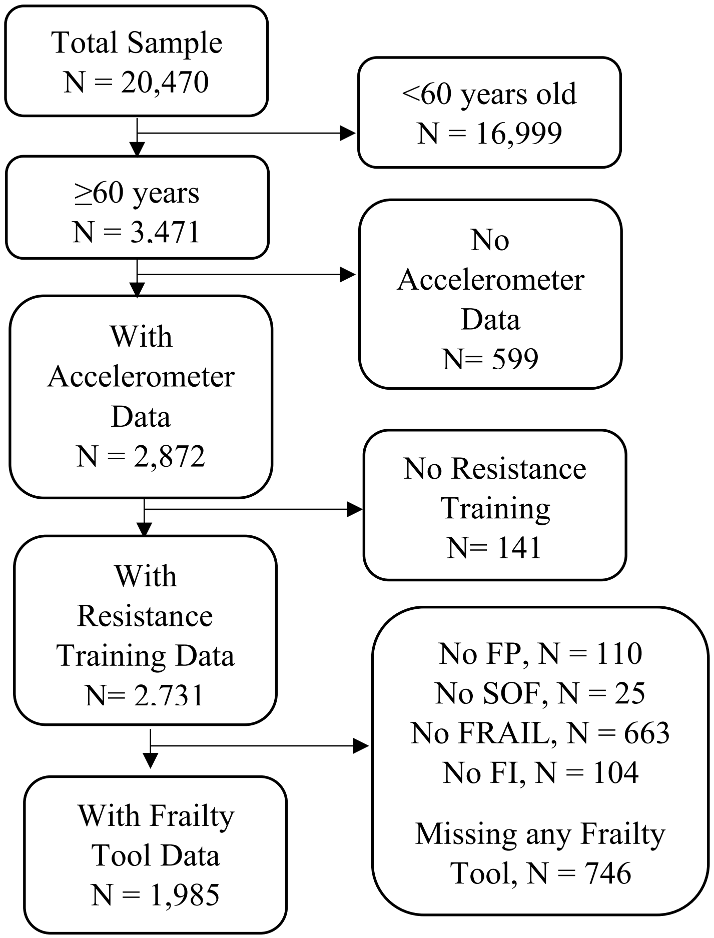

Figure 1: Flowchart of sample
PF – Frailty Phenotype; SOF – Study of Osteoporotic Fractures (SOF) Index; FRAIL - Fatigue, Resistance, Ambulation, Illness, and Loss of weight; FI – Frailty Index

Table 1. Comparison of general characteristics between analytical Sample and excluded sample

Variable	Mean ± SD or N (%) N = 1,985	Mean ± SD or N (%) * N = 1,486
Age (years)	71.1 ± 7.8	72.0 ± 8.0
Sex		
Females	954 (48.1)	756 (50.9)
Males	1031 (51.9)	730 (49.1)
Race		
Non-Hispanic White	1217 (61.3)	931 (62.7)
Non-Hispanic Black	311 (15.7)	202 (13.6)
Mexican American	364 (18.3)	307 (20.7)
Other Hispanic	32 (1.6)	12 (0.8)
Other Race	61 (3.1)	34 (2.3)
Education		
Less than 9th grade	403 (20.3)	404 (27.2)
9-11th grade	290 (14.6)	207 (13.9)
Highschool Graduate	503 (25.3)	346 (23.3)
Some College	437 (22.0)	309 (20.8)
College Graduate	349 (17.6)	213 (14.3)
Missing	3 (0.2)	7 (0.5)
Marital Status		
Living with a partner	36 (1.8)	22 (1.5)
Married	1224 (61.7)	919 (61.8)
Never Married	52 (2.6)	59 (4.0)
Divorced	207 (10.4)	143 (9.6)
Separated	35 (1.8)	27 (1.8)
Widowed	431 (21.7)	313 (21.1)
Missing	0 (0)	1 (0.1)
* Each variable is significantly different between samples ($p < 0.05$)		

Table 2: Variables included in the NHANES-FI

Comorbidities	***Sign/symptoms***
- Stroke	- Heart rate at rest
- Thyroid condition	- Systolic blood pressure
- Cancer	- Cough regularly
- Heart attack	- Leaked/lost control or urine
- Heart disease	- General vision
- Ever had high blood pressure	- Difficulty seeing steps/curbs in dim lights
- Angina\angina pectoris	- General hearing
- Osteoporosis	- Confusion or inability to remember things
- Diabetes	
- Arthritis	***Lab values***
- Ever had a broken hip	- Homocysteine (μmol/L)
- Weak/failing kidneys	- Folate, serum (nmol/L)
	- Glycohemoglobin (%)
Function	- Red blood cell count (million cells/μL)
- Difficulty using fork and knife	- Hemoglobin (g/dL)
- Difficulty dressing yourself	- Red cell distribution width (%)
- Difficulty getting in/out of bed	- Lymphocyte percent (%)
- Difficulty standing up from an armless chair	- Segmented neutrophils percent (%)
- Difficulty managing money	
- Difficulty preparing meals	***Other***
- Difficulty standing for long periods of time	- Medications
- Difficulty stooping, crouching, kneeling	- Self-reported current health
- Difficulty grasping/holding small objects	- Current health compared to 1 year ago
- Difficulty pushing or pulling large objects	- Frequency of healthcare used
- Difficulty attending social events	- Overnight hospital stays

Table 3: Variables included in the modified Frailty Phenotype

Original Variable	NHANES Variable	Responses in NHANES	Coding for analysis
Exhaustion: Self-reported Exhaustion	Difficulty walking from one room to the other on the same level.	- No difficulty - Some difficulty - Much difficulty - Unable to do - Do not do - Refused/DK - Missing	No difficulty – 0 Some/Much/Unable – 1
Low Activity: Lowest 20% of the population, based on time to walk 15 feet, adjusting for gender and standing height	Compared with most men/women your age, would you say that you are more active, less active, or about the same?	- More active, - Less active, - About the same, - Refused - DK - Missing	More Active/About the same – 0 Less active – 1
Weakness: Lowest 20% of handgrip strength by gender and body mass index	Lifting or carrying something as heavy as 10 pounds [like a sack of potatoes or rice]?	- No difficulty - Some difficulty - Much difficulty - Unable to do - Do not do - Refused/DK - Missing	No difficulty – 0 Some/Much/Unable – 1
Low body weight: >10 lbs lost unintentionally in the prior year	Body mass index $\leq$ 18.5 kg/m^2	Numerical Value	$\leq$ 18.5 kg/m^2 - 1 > 18.5 kg/m^2 - 0

Original Variable	NHANES Variable	Responses in NHANES	Coding for analysis
Slowest: Time to complete 8ft walk/20ft walk	N/A	N/A	N/A
Frail ≥ 3 score; Prefrail = 1-2 score; Robust = 0 score. NHANES – National Health and Nutrition Examination Survey; DK – Don't know; N/A – Not Available.			

Table 4: Variables included in the modified Study of Osteoporotic Fractures (SOF) Index

Original Variable	NHANES Variable	Responses in NHANES	Coding for analysis
Exhaustion: "Do you feel full of energy?"	Difficulty walking from one room to the other on the same level.	- No difficulty - Some difficulty - Much difficulty - Unable to do - Do not do - Refused/DK - Missing	No difficulty – 0 Some/Much/Unable – 1
Chair Stands: Inability to complete five chair stands	By yourself, and without any special equipment, how much difficulty do you have standing from an armless straight chair?	- No difficulty - Some difficulty - Much difficulty - Unable to do - Do not do - Refused/DK - Missing	No difficulty – 0 Some/Much/Unable – 1
Weight Loss: ≥ 5% over 2 years	If the participant had a 5% decrease between their self-reported weight one year ago and current self-reported weight, they were considered to have unintentional weight loss	Numerical Value	If the previous weight is over 5% more than the current weight = 1 If under 5% difference = 0
Frail ≥ 2 score; Prefrail = 1 score; Robust = 0 score. NHANES – National Health and Nutrition Examination Survey; DK – Don't know.			

Table 5: Variables included in the modified Fatigue, Resistance, Ambulation, Illness, and Loss of Weight (FRAIL) Scale

Original Variable	NHANES Variable	Responses in NHANES	Coding for analysis
Fatigue: "How much time during the previous four weeks did you feel tired?"	Difficulty walking from one room to the other on the same level.	- No difficulty - Some difficulty - Much difficulty - Unable to do - Do not do - Refused/DK - Missing	No difficulty – 0 Some/Much/Unable – 1
Resistance: "In the last four weeks by yourself and not using aids, do you have any difficulty walking up ten steps without resting?"	Difficulty walking up ten steps without resting?	- No difficulty - Some difficulty - Much difficulty - Unable to do - Do not do - Refused/DK - Missing	No difficulty – 0 Some/Much/Unable – 1
Ambulation: "In the last four weeks by yourself and not using aids, do you have any difficulty walking 300 meters or one block?"	Difficulty walking for a quarter-mile [that is about 2 or 3 blocks]?"	- No difficulty - Some difficulty - Much difficulty - Unable to do - Do not do - Refused/DK - Missing	No difficulty – 0 Some/Much/Unable – 1

Original Variable	NHANES Variable	Responses in NHANES	Coding for analysis
Illness: "Did your doctor ever tell you that you have… - Hypertension - Diabetes - Cancer - Chronic Lung Disease - Heart Attack - Angina - Asthma - Arthritis - Kidney Disease	Has a doctor ever told you that you have… - Asthma - Angina - Arthritis - Cancer - Chronic Bronchitis - Heart Attack - Liver Disease - Stroke - Thyroid Problems	- Yes - No - Don't know - Refused - Missing	If yes to five or more – 1 No/yes to less than 5 – 0
Loss of weight: "Have you lost more than 5 kg or 5% of your body weight in the past year?"	If a participant had a 5% decrease between their self-reported weight one year ago and current self-reported weight, they were considered to have unintentional weight loss	Numerical Value	If the previous weight is over 5% more than the current weight = 1 If under 5% difference = 0
Frail ≥ 3 score; Prefrail = 1-2 score; Robust = 0 score. NHANES – National Health and Nutrition Examination Survey; DK – Don't know.			

Table 6: Levels of physical activity and stationary time by frailty tools

Frailty Tools	N (%)	MVPA (hrs/week) Mean ± SD	Resistance Training (days/week) Mean ± SD	Stationary Time (hrs/day) Mean ± SD	Light Physical Activity (hrs/day) Mean ± SD
Frailty Index					
< 0.10	419 (21.1)	1.3± 1.6	1.2 ± 4.5	9.0 ± 0.9	5.6 ± 4.0
(0.10, 0.20]	768 (38.7)	0.8 ± 1.9	0.9 ± 3.6	9.4 ± 1.0	4.9 ± 3.7
(0.20, 0.30]	504 (25.4)	0.5± 0.5	0.6 ± 1.0	9.8 ± 1.1	4.4 ± 3.7
>0.30	294 (14.8)	0.4 ± 0.7	0.7 ± 4.5	10.1 ± 0.8	3.7 ± 4.5
Frailty Phenotype					
Robust	1413 (71.2)	1.4 ± 1.7	1.0 ± 2.6	9.4 ± 0.8	5.0 ± 1.6
Pre-frail	519 (26.1)	0.7 ± 1.4	0.7 ± 2.0	9.8 ± 0.9	4.3 ± 1.7
Frail	53 (2.7)	0.5 ± 0.9	0.3 ± 1.7	10.2 ± 0.8	3.5 ± 1.6
SOF Index					
Robust	1281 (64.5)	1.5 ± 1.7	0.9 ± 2.5	9.4 ± 0.8	5.0 ± 1.6
Pre-frail	518 (26.1)	1.0 ± 1.4	0.9 ± 2.2	9.6 ± 0.9	4.7 ± 1.6
Frail	186 (9.4)	0.6 ± 1.4	0.6 ± 2.1	10.2 ± 0.8	3.5 ± 1.5
FRAIL Scale					
Robust	1196 (60.3)	1.9 ± 1.8	1.0 ± 1.7	9.4 ± 0.8	5.1 ± 1.6
Pre-frail	726 (36.6)	0.8 ± 1.4	0.7 ± 1.9	9.7 ± 0.9	4.4 ± 1.7
Frail	63 (3.2)	0.2 ± 0.6	0.5 ± 2.4	10.0 ± 0.9	3.9 ± 1.7
SD – Standard Deviation; SOF – Study of Osteoporotic Fractures; FRAIL – Fatigue, Resistance, Ambulation, Illness, and Loss of Weight; MVPA – Moderate-to-Vigorous Physical Activity.					

Table 7: Association between frailty tools (independent variable) and moderate-to-vigorous physical activity hrs/week (dependent variable)

MVPA hrs/week	Model 1 β (95% CI)	Model 2 β (95% CI)
Frailty Index (range [0-1])		
Females	**-3.74 (-4.73, -2.74)**	
Age 65		**-3.45 (-5.60, -1.30)**
Age 70		**-2.82 (-4.17, -1.48)**
Age 75		**-2.20 (-2.98, -1.42)**
Age 80		**-1.57 (-2.59, -0.55)**
Males		
Age 65	**-5.78 (-8.55, -3.00)**	**-5.27 (-8.98, -1.55)**
Age 70		**-4.11 (-7.01, -1.22)**
Age 75		**-2.96 (-5.27, -0.65)**
Age 80		-1.81 (-3.97, 0.35)
Frailty Phenotype		
Females		
Robust	Reference	Reference
Pre-frail	**-0.39 (-0.76, -0.032)**	-0.29 (-0.64, 0.057)
Frail	**-0.76 (-1.17, -0.35)**	**-0.55 (-0.96, -0.13)**
Males		
Robust	Reference	Reference
Pre-frail	**-1.02 (-1.37, -0.67)**	**-0.85 (-1.16, -0.53)**
Frail	-0.35 (-2.01, 1.30)	-0.11 (-1.78, 1.56)

MVPA hrs/week	Model 1 β (95% CI)	Model 2 β (95% CI)
	SOF Index	
Females		
<u>Age 65</u>		
Robust	Reference	Reference
Prefrail	-0.22 (-0.53, 0.09)	-0.15 (-0.60, -0.31)
Frail	**-0.70 (-0.98, -0.42)**	**-0.72 (-1.19, -0.24)**
<u>Age 70</u>		
Robust		Reference
Prefrail		-0.19 (-0.51, 0.12)
Frail		**-0.56 (-0.91, -0.21)**
<u>Age 75</u>		
Robust		Reference
Prefrail		**-0.24 (-0.47, -0.007)**
Frail		**-0.40 (-0.68, -0.12)**
<u>Age 80</u>		
Robust		Reference
Prefrail		**-0.28 (-0.55, -0.02)**
Frail		-0.24 (-0.55 0.08)
Males		
<u>Age 65</u>		Reference
Robust	Reference	**-0.72 (-1.17, -0.27)**
Prefrail	**-0.67 (-0.93, -0.38)**	-0.84 (-1.93, 0.25)
Frail	-0.96 (-1.51, -0.40)	
<u>Age 70</u>		Reference
Robust		**-0.61 (-0.89, -0.33)**
Prefrail		-0.70 (-1.44, 0.04)
Frail		

MVPA hrs/week	Model 1 β (95% CI)	Model 2 β (95% CI)
<u>Age 75</u>		
Robust		Reference
Prefrail		**-0.50 (-0.73, -0.26)**
Frail		**-0.56 (-0.98, -0.14)**
<u>Age 80</u>		
Robust		Reference
Prefrail		-0.39 (-0.75, -0.02)
Frail		-0.41 (-0.70, -0.13)
FRAIL Scale		
<u>Age 65</u>		
Robust	Reference	Reference
Prefrail	**-0.70 (-0.88, -0.52)**	**-0.76 (-1.03, -0.50)**
Frail	**-1.36 (-1.50, -1.22)**	**-1.43 (-1.67, -1.20)**
<u>Age 70</u>		
Robust		Reference
Prefrail		**-0.59 (-0.77, -0.40)**
Frail		**-1.12 (1.28, -0.96)**
<u>Age 75</u>		
Robust		Reference
Prefrail		**-0.41 (-0.58, -0.23)**
Frail		**-0.80 (-0.94, -0.67)**
<u>Age 80</u>		
Robust		Reference
Prefrail		-0.23 (-0.48, 0.02)
Frail		**-0.49 (-0.67, -0.31)**

Bold $p<0.05$; MVPA = Moderate-to-Vigorous Physical Activity; SOF – Study of Osteoporotic Fracture; FRAIL – Fatigue, Resistance, Ambulation, Illness, and Loss of WeightModel 1: Unadjusted; Model 2: Adjusted for Age, Sex, Race, Education, Marital Status, and Wear time; The Frailty Index, the Frailty Phenotype, and the SOF Index analyses were stratified by Sex; the Frailty Index, the SOF Index, and the FRAIL Scale analyses were centered around ages 65, 70, 75, and 80 to obtain simple slope association.

Table 8: Association between frailty tools (independent variable) and resistance training days/week (dependent variable)

RT days/week	Model 1 β (95% CI)	Model 2 β (95% CI)
Frailty Index (range [0-1])	**-1.43 (-2.49, -0.37)**	-0.85 (-2.00, 0.31)
Frailty Phenotype		
Robust	Reference	Reference
Pre-frail	**-0.26 (-0.45, -0.06)**	-0.17 (-0.35. 0.015)
Frail	**-0.70 (-1.06, -0.34)**	**-0.61 (-1.01, -0.21)**
SOF Index		
Females		
Age 65	Reference	Reference
Robust	-0.063 (-0.42, 0.29)	0.06 (-0.51, 0.62)
Prefrail	**-0.39 (-0.72, -0.05)**	**-0.67 (-1.17, -0.17)**
Frail		
Age 70		Reference
Robust		0.02 (-0.35, 0.38)
Prefrail		**-0.35 (-0.67, -0.17)**
Frail		
Age 75		Reference
Robust		-0.02 (-0.34, 0.30)
Prefrail		-0.02 (-0.41, 0.37)
Frail		
Age 80		Reference
Robust		-0.06 (-0.53, 0.42)
Prefrail		0.31 (-0.31, 0.93)
Frail		
Males		
Robust	Reference	Reference
Prefrail	0.05 (-0.34, 0.43)	0.07(-0.35, 0.49)
Frail	-0.24 (-0.77, 0.28)	-0.16 (-0.69, 0.37)

RT days/week	Model 1 β (95% CI)	Model 2 β (95% CI)
FRAIL Scale		
Robust	Reference	Reference
Prefrail	**-0.25 (-0.47, -0.03)**	-0.17 (-0.38, 0.05)
Frail	**-0.52 (-0.91, -0.13)**	-0.26 (-0.70, 0.19)

Bold p<0.05; RT = Resistance Training; SOF = Study of Osteoporotic Fractures; FRAIL = Fatigue, Resistance, Ambulation, Illness, and Loss of Weight
Model 1: Unadjusted; Model 2: Adjusted for Age, Sex, Race, Education, Marital Status, and Wear time; The SOF Index analysis was stratified by Sex, and the analysis of Females for this tool was also centered on age at 65, 70, 75, and 80 to obtain the simple slope associations.

Table 9: Association between frailty tools (independent variable) and light physical activity hrs/week (dependent variable)

Light hrs/week	Model 1 β (95% CI)	Model 3 β (95% CI)
Frailty Index (range [0-1])	**-40.44 (-47.83, -33.05)**	**-37.23 (-45.10, -29.35)**
Frailty Phenotype		
Females		
Robust	Reference	Reference
Pre-frail	**-5.34 (-7.19, -3.49)**	**-4.86 (-6.62, -6.46)**
Frail	**-12.12 (-16.45, -7.79)**	**-11.13 (-15.79, -6.45)**
Males		
Robust	Reference	Reference
Pre-frail	**-5.46 (-7.94, -2.97)**	**-5.33 (-7.94, -2.72)**
Frail	**-8.11 (-15.77, -0.45)**	**-7.80 (-14.50, -1.11)**
SOF Index		
Robust	Reference	Reference
Pre-frail	**-2.11 (-3.58, -0.64)**	**-2.28 (-3.64, -0.91)**
Frail	**-10.37 (-12.06, -8.67)**	**-9.90 (-11.91, -7.90)**
FRAIL Scale		
Robust	Reference	Reference
Pre-frail	**-4.32 (-5.87, -2.76)**	**-4.27 (-5.88, -2.66)**
Frail	**-8.01 (-12.89, -3.12)**	**-7.25 (-12.61, -1.89)**

Bold $p<0.05$; SOF = Study of Osteoporotic Fractures; FRAIL = Fatigue, Resistance, Ambulation, Illness, and Loss of Weight
Model 1: Unadjusted; Model 2: Adjusted for Age, Sex, Race, Education, Marital Status, and Wear time. The Frailty Phenotype analysis was stratified by Sex.

Table 10: Association between frailty tools (independent variable) and stationary time (hrs/day) (dependent variable)

Stationary Time (hrs/day)	Model 1 β (95% CI)	Model 2 β (95% CI)
Frailty Index (range [0-1])	**3.23 (2.62, 3.83)**	**2.88 (2.24, 3.50)**
Frailty Phenotype		
Females		
Robust	Reference	Reference
Pre-frail	**0.41 (0.27, 0.55)**	**0.37 (0.23, 0.50)**
Frail	**0.92 (0.60, 1.24)**	**0.83 (0.50, 1.17)**
Males		
Robust	Reference	Reference
Pre-frail	**0.46 (0.28, 0.64)**	**0.44 (0.25, 0.63)**
Frail	0.60 (-0.05, 1.26)	0.57 (-0.01, 1.14)
SOF Index		
Robust	Reference	Reference
Pre-frail	**0.18 (0.07, 0.29)**	**0.19 (0.09, 0.29)**
Frail	**0.80 (0.67, 0.93)**	**0.75 (0.59, 0.90)**
FRAIL Scale		
Robust	Reference	Reference
Pre-frail	**0.36 (0.24, 0.47)**	**0.34 (0.23, 0.46)**
Frail	**0.67 (0.32, 1.02)**	**0.58 (0.20, 0.97)**
Bold $p<0.05$; SOF = Study of Osteoporotic Fractures; FRAIL = Fatigue, Resistance, Ambulation, Illness, and Loss of Weight Model 1: Unadjusted; Model 2: Adjusted for Age, Sex, Race, Education, Marital Status, and Wear time. The Frailty Phenotype analysis was stratified by Sex.		

Appendix D: Supplemental Tables and Figures from Manuscript 3

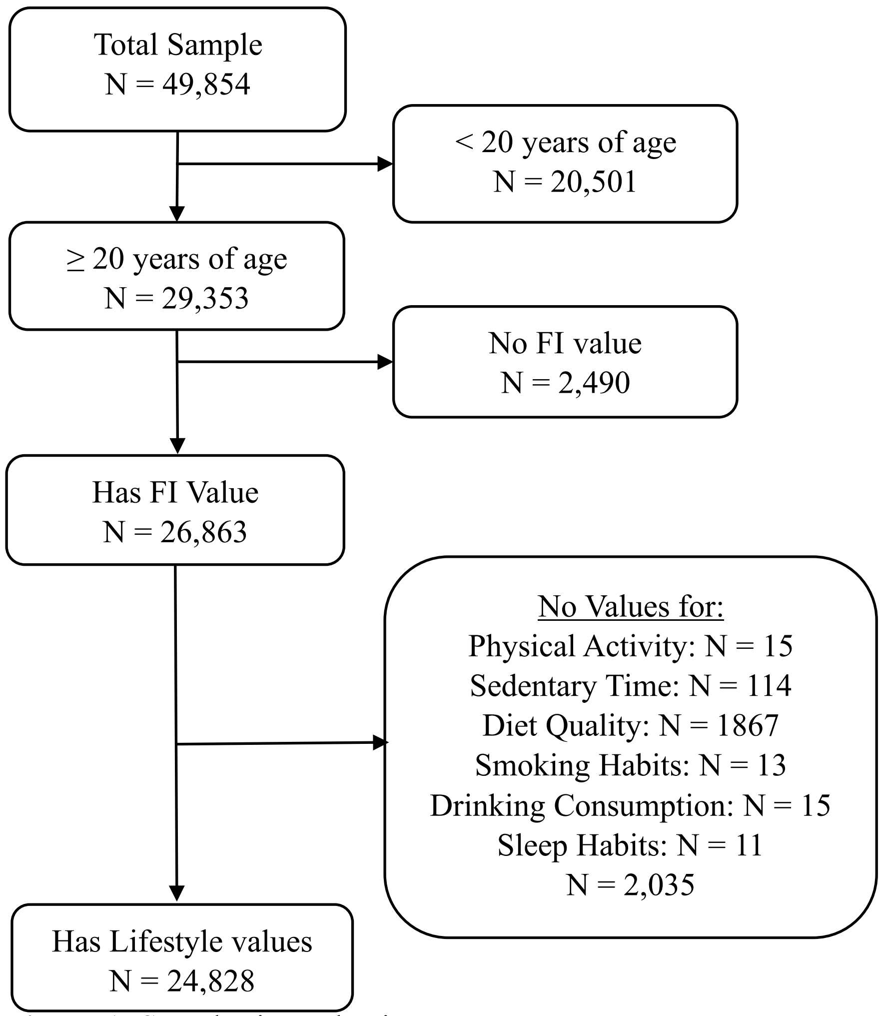

Figure 1: Sample size reduction

Table 1: Description of NHANES lifestyle behaviours

Lifestyle Behaviours	Classification/Responses in NHANES	Proposed Coding
Alcohol		
"In the past 12 months, how often did you drink any type of alcoholic beverage?" "In the 12 months, on those days that you drank alcoholic beverages, on average, how many drinks did you have?"	Binge Drinking: five or more alcoholic drinks for males and four or more alcoholic drinks for females on the same occasion on at least one day in the past month (1).	Males: 0 = Binge Drink (5+) 1 = Non-Binge Drink (<5) Females: 0 = Binge Drink (4+) 1 = Non-Binge Drink (<4)
Sleep Quality		
"How much sleep do you get a night (hours)?"	Per the Canadian 24-hour movement guidelines, if an individual is between 18-64, then 7-9 hours/night is recommended. If an individual is 65+, then 7-8 hours/night is recommended (2).	18-64 years old: 0 = <7 or >9 hours 1 = 7-9 hours 65 + years old: 0 = <7 or >8 hours 1 = 7-8 hours
Smoking Habits		
"Do you now smoke cigarettes?"	Responses include: Everyday, Some days, Not at all, Refused, Don't know	0= Every day, Some days 1 = Not at all
Sedentary Behaviour		
"How much time (outside of sleeping) do you usually spend sitting or reclining?"	As per the Canadian Movement Guidelines, those who answer being sedentary for eight hours or more will be considered highly sedentary (2)	0 = ≥ 8 hours 1 = < 8 hours
Diet Quality		
Previously developed Nutrition Index including 31 nutrition-related parameters.	The Nutrition Index score divides the number of nutritional deficits in an individual by the total number of deficits considered, yielding values between 0 and 1. The Nutrition Index was made into quartiles to make the variable categorical.	0 = Three Lowest Quartiles 1 = Highest Quartile

1. Alcohol, Tobacco, and Other Drugs [Internet]. [cited 2022 Jan 24]. Available from: https://www.samhsa.gov/find-help/atod. 2. Ross R, Tremblay M. Introduction to the Canadian 24-Hour Movement Guidelines for Adults aged 18–64 years and Adults aged 65 years or older: an integration of physical activity, sedentary behaviour, and sleep. Appl Physiol Nutr Metab [Internet]. 2020 Oct 15 [cited 2020 Oct 20]; Available from: https://cdnsciencepub.com/doi/abs/10.1139/apnm-2020-0843

Table 2: Comparison of analytic sample and sample with missing frailty index (FI)

Mean ± SD or N (%)	Removed for Missing FI N = 2,490
Age (Years)	50.5 ± 18.9 *
Sex, Female	1,283 (51.5)
Race	
Non-Hispanic White	834 (33.5) *
Non-Hispanic Black	743 (29.8) *
Non-Hispanic Asian	402 (16.1) *
Mexican American	268 (10.8) *
Other	243 (9.8)
Education	
Less than 9th Grade	260 (10.4)
9-11th Grade	375 (15.1)
High School	574 (23.1)
Some College	691 (27.8)
College	588 (23.6)
NA	2 (0.1)
Marital Status	
Married	1,075 (43.2) *
Divorced	292 (11.7)
Separated	86 (3.5)
Living with Partner	221 (8.9)
Never married	540 (21.7) *
Widow	270 (10.8) *
NA	6 (0.2)
Drinking, Binge Drinking#	125 (5.0) *
Smoking, Every day/Some day	413 (16.6) *
Sleep$, Less or more than recommendation	1,485 (59.6)
Sedentary Time, ≥ 8 hours/day	879 (35.3) *
Poor Diet Quality, Lowest Quartile of the Nutrition Index	329 (13.2) *
Continuous Nutrition Index (0-1)	0.36 ± 0.23

#Binge Drinking Definition: Males = 5 + alcoholic drinks on the same occasion on at least one day in the past month; Females = 4 + alcoholic drinks on the same occasion on at least one day in the past month. $Poor Sleep: Age 18-64 = <7 or >9 hours; Age 65+ = <7 or >8 hours.

* Statistically different between groups. One-way analysis of variance testing for continuous variables and Chi-square analyses for categorical variables. Bonferroni post-hoc testing was conducted on significant between-group comparisons.

Table 3: Pearson's correlations between lifestyle behaviours in active individuals

	Binge Drink	Smoking	High Sedentary	Poor Sleep	Poor Diet
Binge Drink	1				
Smoking	0.20	1			
High Sedentary	-0.35	-0.38	1		
Poor Sleep	-0.26	-0.16	-0.36	1	
Poor Diet	-0.38	-0.32	-0.30	-0.09	1
Green: moderate positive correlation (≥ 0.30); Yellow: no correlation< ±0.30; Red: moderate negative correlation (≥ - 0.30). All correlations are statistically significant (p < 0.05).					

Table 4: Pearson's correlations between lifestyle behaviours in inactive individuals

	Binge Drink	Smoking	High Sedentary	Poor Sleep	Poor Diet
Binge Drink	1				
Smoking	0.21	1			
High Sedentary	-0.36	-0.34	1		
Poor Sleep	-0.31	-0.25	-0.27	1	
Poor Diet	-0.41	-0.33	-0.33	-0.12	1
Green: moderate positive correlation (≥ 0.30); Yellow: no correlation< ±0.30; Red: moderate negative correlation (≥ - 0.30). All correlations are statistically significant (p < 0.05).					

Table 5: Comparison of R^2 change and significance between models for active individuals

Active	High Sedentary Time	Low Diet Quality	Poor Sleep Quality *	Binge Drinking *	Current Smoker
R^2 of each model					
Model 1	0.37				
Model 2	0.06				
Model 3	0.39				
Model 4	0.37	0.39	0.37	0.37	0.37
Model 5	0.39	0.37	0.39	0.39	0.39
Significance testing					
ANOVA M1 vs. M3	$\Delta R^2 = 0.03$; $p < 0.01$				
ANOVA M5 vs M4	$\Delta R^2 = 0.02$; $p < 0.01$	$\Delta R^2 = 0.0$; $p < 0.01$	$\Delta R^2 = 0.02$; $p < 0.01$	$\Delta R^2 = 0.02$; $p < 0.01$	$\Delta R^2 = 0.02$; $p < 0.01$
ANOVA M4 vs M1	$\Delta R^2 = 0.00$; $p < 0.01$	$\Delta R^2 = -0.02$; $p < 0.01$	$\Delta R^2 = 0.00$; $p < 0.01$	$\Delta R^2 = 0.0$; $p < 0.01$	$\Delta R^2 = 0.00$; $p < 0.01$

Bold p<0.05.
Model 1: all covariates;
Model 2: all lifestyle behaviours.
Model 3: all covariates + all lifestyle behaviours
Model 4: all covariates + a single lifestyle behaviour
Model 5: all covariates + all lifestyle behaviours but one.
* Binge Drinking Definition: Males = 5 + alcoholic drinks on the same occasion on at least one day in the past month; Females = 4 + alcoholic drinks on the same occasion on at least one day in the past month. * Poor Sleep: Age 18-64 = <7 or >9 hours; Age 65+ = <7 or >8 hours.

Table 6: Comparison of R^2 change and significance between models for inactive individuals

Inactive	High Sedentary Time	Low Diet Quality	Poor Sleep Quality *	Binge Drinking *	Current Smoker
R^2 of each model					
Model 1	0.37				
Model 2	0.081				
Model 3	0.40				
Model 4	0.38	0.38	0.37	0.37	0.37
Model 5	0.39	0.38	0.39	0.39	0.39
Significance testing					
ANOVA M1 vs. M2	$\Delta R^2 = 0.03$; p<0.01				
ANOVA M5 vs. M1	$\Delta R^2 = 0.02$; p<0.01	$\Delta R^2 = 0.01$; p<0.01	$\Delta R^2 = 0.00$; p<0.01	$\Delta R^2 = 0.00$; p <0.01	$\Delta R^2 = 0.00$; p<0.01
ANOVA M4 vs M1	$\Delta R^2 = 0.02$; p<0.01	$\Delta R^2 = 0.01$; p<0.01	$\Delta R^2 = 0.02$; p<0.01	$\Delta R^2 = 0.01$; p =0.6	$\Delta R^2 = 0.02$; p <0.01

Bold p<0.05;
Model 1: all covariates;
Model 2: all lifestyle behaviours.
Model 3: all covariate + all lifestyle behaviours
Model 4: No covariates + a single lifestyle behaviour,
Model 5: all covariates + a single lifestyle behaviour
Model 6: all covariates + all lifestyle behaviours but one.
* Binge Drinking Definition: Males = 5 + alcoholic drinks on the same occasion on at least one day in the past month; Females = 4 + alcoholic drinks on the same occasion on at least one day in the past month. * Poor Sleep: Age 18-64 = <7 or >9 hours; Age 65+ = <7 or >8 hours.

Table 7: Associations between individual lifestyle behaviours and frailty for those who engage in ≥150 mins/week of MVPA

	Age 30 β (95% CI)	Age 40 β (95% CI)	Age 50 β (95% CI)	Age 60 β (95% CI)	Age 70 β (95% CI)	R^2
Model 1						
High Sedentary Time	-0.0009 (-0.005, 0.003)					0.31
Poor Diet Quality	**0.021 (0.015, 0.028)**	**0.028 (0.022, 0.034)**	**0.035 (0.028, 0.042)**	**0.042 (0.033, 0.051)**	**0.049 (0.037, 0.060)**	0.34
Poor Sleeping	**0.014 (0.0083, 0.020)**	**0.019 (0.014, 0.023)**	**0.023 (0.018, 0.027)**	**0.027 (0.022, 0.033)**	**0.031 (0.024, 0.038)**	0.32
Binge Drinking	0.0028 (-0.0028, 0.0083)					0.31
Smoking Habit	**0.019 (0.013, 0.025)**					0.32
Model 2						
Sedentary Time ≥ 8 hours/day	**0.0070 (0.0024, 0.011)**					0.37
Diet Quality Poor Diet	**0.015 (0.0080, 0.021)**	**0.021 (0.015, 0.027)**	**0.027 (0.0.21, 0.034)**	**0.034 (0.025, 0.042)**	**0.040 (0.029, 0.051)**	0.39
Sleep Poor Sleep	**0.0071 (0.00082, 0.013)**	**0.011 (0.0063, 0.016)**	**0.015 (0.011, 0.020)**	**0.020 (0.014, 0.025)**	**0.024 (0.016, 0.031)**	0.38
Drinking Binge Drink	-0.0030 (-0.0094, 0.0034)					0.37
Smoking Habits Smoker	**0.0066 (0.00011, 0.013)**					0.37
Model 3						
Sedentary Time ≥ 8 hours/day	**0.00066 (0.0022, 0.011)**					0.39
Diet Quality Poor Diet	**0.013 (0.0058, 0.020)**	**0.020 (0.014, 0.025)**	**0.026 (0.019, 0.033)**	**0.032 (0.024, 0.041)**	**0.039 (0.027, 0.050)**	0.39
Sleep Poor Sleep	**0.0018 (0.0031, 0.006)**	**0.0074 (0.0028, 0.012)**	**0.013 (0.0071, 0.019)**	**0.018 (0.011, 0.026)**	**0.024 (0.014, 0.034)**	0.39
Drinking; Female Binge Drink	-0.0054 (-0.015, 0.0039)					0.40

	Age 30 β (95% CI)	Age 40 β (95% CI)	Age 50 β (95% CI)	Age 60 β (95% CI)	Age 70 β (95% CI)	R^2
Drinking; Males Binge Drink	0.0021 (-0.0045, 0.0088)	-0.0085 (-0.017, 0.000077)	**-0.019 (-0.033, -0.0056)**	**-0.030 (-0.049, -0.010)**	**-0.041 (-0.066, -0.015)**	0.40
Smoking Habits Smoker	0.0056 (-0.00070, 0.012)					0.40
Bold p<0.05; Model 1 adjusted for Age and Sex; Model 2 further adjusted for Race, Education, and Marital Status; Model 3 further adjusted for other lifestyle behaviours. * Binge Drinking Definition: Males = 5 + alcoholic drinks on the same occasion on at least one day in the past month; Females = 4 + alcoholic drinks on the same occasion on at least one day in the past month. * Poor Sleep: Age 18-64 = <7 or >9 hours; Age 65+ = <7 or >8 hours						

Table 8: Associations between individual lifestyle behaviours and frailty for those who engage in <150 mins/week of MVPA

	Age 30	Age 40	Age 50	Age 60	Age 70	R^2
Model 1						
Sedentary Time ≥ 8 hours/day	-0.0038 (-0.0091, 0.015)	**0.0051 (0.00022, 0.010)**	**0.014 (0.0088, 0.019)**	**0.023 (0.017, 0.029)**	**0.032 (0.025, 0.039)**	0.34
Diet Quality Poor Diet	**0.028 (0.021, 0.034)**	**0.033 (0.029, 0.038)**	**0.039 (0.034, 0.044)**	**0.045 (0.039, 0.052)**	**0.051 (0.043, 0.060)**	0.35
Sleep Poor Sleep	**0.014 (0.0083, 0.020)**	**0.019 (0.014, 0.023)**	**0.023 (0.018, 0.027)**	**0.027 (0.022, 0.033)**	**0.031 (0.024, 0.038)**	0.34
Drinking Binge Drink	**0.010 (0.0032, 0.018)**					0.33
Smoking Habits Smoker	**0.026 (0.019, 0.033)**					0.34
Model 2						
Sedentary Time ≥ 8 hours/day	**0.022 (0.017, 0.027); 0.38**					0.38
Diet Quality Poor Diet	**0.020 (0.014, 0.026)**	**0.025 (0.020, 0.030)**	**0.030 (0.025, 0.035)**	**0.033 (0.029, 0.042)**	**0.041 (0.032, 0.049)**	0.37
Sleep Poor Sleep	**0.0071 (0.00082, 0.013)**	**0.011 (0.0063, 0.016)**	**0.015 (0.011, 0.020)**	**0.020 (0.014, 0.025)**	**0.024 (0.016, 0.031)**	0.37
Drinking Binge Drink	0.0014 (-0.0053, 0.0081)					0.37
Smoking Habits Smoker	**0.013 (0.0067, 0.019)**					0.37
Model 3						
Sedentary Time ≥ 8 hours/day	**0.0063 (0.062, 0.090)**	**0.014 (0.010, 0.019)**	**0.022 (0.018, 0.027)**	**0.030 (0.025, 0.036)**	**0.039 (0.032, 0.046)**	0.40
Diet Quality Poor Diet	**0.019 (0.013, 0.025)**	**0.024 (0.019, 0.029)**	**0.029 (0.025, 0.034)**	**0.035 (0.028, 0.041)**	**0.040 (0.032, 0.048)**	0.40
Sleep Poor Sleep	**0.0062 (0.000067, 0.012)**	**0.0099 (0.094, 0.12)**	**0.014 (0.0092, 0.018)**	**0.018 (0.012, 0.023)**	**0.021 (0.014, 0.029)**	0.40

	Age 30	Age 40	Age 50	Age 60	Age 70	R^2
Drinking Binge Drink	-0.00056 (-0.0076, 0.0065)					0.39
Smoking Habit: Females Smoker	**0.0084 (0.0013, 0.015)**	**0.014 (0.0064, 0.021)**	**0.019 (0.0088, 0.030)**	**0.025 (0.010, 0.039)**	**0.030 (0.011, 0.049)**	0.40
Smoking Habit: Males Smoker	0.0072 (-0.00074, 0.015)					0.38

Bold p<0.05; Model 1 adjusted for Age and Sex; Model 2 further adjusted for Race, Education, and Marital Status; Model 3 further adjusted for other lifestyle behaviours. * Binge Drinking Definition: Males = 5 + alcoholic drinks on the same occasion on at least one day in the past month; Females = 4 + alcoholic drinks on the same occasion on at least one day in the past month. * Poor Sleep: Age 18-64 = <7 or >9 hours; Age 65+ = <7 or >8 hours

Table 9: Frequency of lifestyle behaviour scores by activity group

Lifestyle Behaviour Code	Total Sample N (%) N = 24,828	≥150 mins/week of MVPA N (%) N = 7,495	<150 mins/week of MVPA N (%) N= 17,333
0 – No poor behaviours	3,101 (12.5)	1996 (26.6)	3302 (19.1) *
1	9,808 (39.5)	2965 (39.6)	6527 (37.7)
2	8,432 (34.0)	1810 (24.1)	5064 (29.2) *
3	2,927 (11.8)	603 (8.0)	1940 (11.2) *
4	512 (2.1)	107 (1.4)	456 (2.6) *
5 – All poor behaviours	48 (0.2)	14 (0.2)	44 (0.3) *
* Significant difference between groups using Chi-square analysis Bonferroni post-hoc testing was conducted on significant between-group comparisons.			

Table 10: Associations between lifestyle behaviour score and frailty by sex and age in active individuals

	Age 30 β (95% CI)	Age 40 β (95% CI)	Age 50 β (95% CI)	Age 60 β (95% CI)	Age 70 β (95% CI)	R^2
≥150 mins/week of MVPA						
Model 1						
Lifestyle Behaviour Score (0-5)	**0.00035 (0.0055, 0.0094)**	**0.011 (0.0089, 0.013)**	**0.015 (0.011, 0.018)**	**0.018 (0.014, 0.022)**	**0.022 (0.016, 0.027)**	0.34
Model 2						
Lifestyle Behaviour Score (0-5)	**0.0042 (0.0020, 0.0065)**	**0.0079 (0.0056, 0.010)**	**0.012 (0.0084, 0.015)**	**0.015 (0.011, 0.020)**	**0.019 (0.013, 0.025)**	0.39
Model 3						
Lifestyle Behaviour Score (0-5)	**0.024 (0.018, 0.031)**	**0.028 (0.021, 0.034)**	**0.031 (0.024, 0.037)**	**0.034 (0.027, 0.041)**	**0.037 (0.029, 0.045)**	0.39
Bold p<0.05; Model 1 adjusted for Age and Sex; Model 2 further adjusted for Race, Education, and Marital Status; Model 3 further adjusted for all other lifestyle behaviours.						

Table 11: Association between lifestyle behaviour score and frailty, by age in inactive individuals

	Age 30 β (95% CI)	Age 40 β (95% CI)	Age 50 β (95% CI)	Age 60 β (95% CI)	Age 70 β (95% CI)	R^2
<150 mins/week of MVPA						
Model 1						
Lifestyle Behaviour Score (0-5)	**0.012 (0.010, 0.015)**	**0.017 (0.015, 0.020)**	**0.022 (0.020, 0.025)**	**0.027 (0.024, 0.030)**	**0.032 (0.028, 0.036)**	0.37
Model 2						
Lifestyle Behaviour Score (0-5)	**0.0082 (0.0058, 0.011)**	**0.013 (0.011, 0.015)**	**0.018 (0.015, 0.020)**	**0.023 (0.019, 0.026)**	**0.027 (0.023, 0.032)**	0.39
Model 3						
Lifestyle Behaviour Score (0-5)	**0.028 (0.023, 0.033)**	**0.033 (0.028, 0.037)**	**0.037 (0.032, 0.042)**	**0.042 (0.036, 0.047)**	**0.046 (0.040, 0.052)**	0.40
Bold p<0.05; Model 1 adjusted for Age and Sex; Model 2 further adjusted for Race, Education, and Marital Status; Model 3 further adjusted for all other lifestyle behaviours						