The Impact of Sedentary and Physical Activity Behavior on Frailty in Middle-Aged and Older Adults

by

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ABSTRACT

Background and objectives: Physical activity and sedentary behaviors are associated with frailty. However, it is unknown if different accumulation patterns of these behaviors are linked with frailty. Four studies were conducted: the first three determined if bouts of moderate-vigorous physical activity (MVPA) and patterns of sedentary behaviors were associated with frailty, (study 1) and if sex (study 2) and CVD status (study 3) affected these associations. Study 4 systematically reviewed the evidence to determine if preoperative physical activity and sedentary behaviors were linked to post-cardiac surgical outcomes.

Methods: Study 1-3 used accelerometer data from the 2003-04/2005-06 National Health and Nutrition Examination Survey. Bouted (≥10 minutes) and sporadic (<10 minutes) durations of MVPA were analyzed based on meeting a proportion of the physical activity guidelines of 150 min/week. Prolonged sedentary behaviours were measured in bouts lasting ≥30 minutes. Breaks from sedentary behavior were any ≥1 minute interruption in sedentary time. Average intensity and duration during breaks were analyzed. Frailty was measured with a 46-item frailty index (FI). Study 4 included investigations that linked preoperative physical activity behaviors to postoperative health outcomes.

Results: The first three studies revealed that sporadic and bouted MVPA were associated with a lower FI. Meeting 1-49% of the physical activity guidelines had a protective association with frailty. Prolonged sedentary bouts had a more detrimental association with frailty in females than males. Bouted MVPA was associated with a lower FI in CVD participants but not in those without CVD. Average break intensity was associated with a lower FI across studies. Average break duration was associated with frailty in males and in those with CVD. Study 4 included 11 articles, which reported inconsistent findings in relation to self-reported physical activity behavior and postoperative outcomes in cardiac surgery patients. No studies analyzed sedentary behavior or frailty.

Conclusions: Data from this thesis suggest that bouts of MVPA and patterns of sedentary behaviors are associated with frailty, and support the need to limit extended periods of sedentary time and promote a physically active lifestyle. Studies are needed to determine if preoperative physical activity and sedentary behaviors are associated with post-cardiac surgical frailty.

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DEDICATION

I would like to dedicate all of my graduate thesis work to my family and friends. To my parents, Larry and Margaret, for supporting me through the good times and bad. To my sister Courtney who is special to me. To my grandparents, who I miss.

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CONTRIBUTION OF AUTHORS

All of the co-authors listed for each manuscript have significantly contributed to a combination of the conception, design, analysis, and interpretation of the content.

I had the primary responsibility for the conception, design, analysis, and interpretation of each study. I also drafted and revised each manuscript for the studies.

Ian Clara and Brett Hiebert were responsible for supporting the analysis of study data, and the interpretation of the study results presented in chapters 3 to 5 (Brett Hiebert also for chapter 6). They were also responsible for reviewing and critiquing the content of the draft manuscripts of those studies.

Andrew Stammers and Annette Schultz were responsible for the interpretation of the study results presented in chapters 3 to 6. They were also responsible for reviewing and critiquing the content of the draft manuscripts of those studies.

Jacqueline Hay was responsible for the interpretation of the study results presented in chapters 3 to 5. She was also responsible for reviewing and critiquing the content of the draft manuscripts of those studies.

Rakesh Arora and Navdeep Tangri were responsible for the conception and design of the study presented in chapter 6. They were also responsible for supporting the interpretation of the studies presented in chapters 3 to 6. Lastly, they reviewed and critiqued the content of the draft manuscripts for all of the studies.

Randy Fransoo, Nicholas Giacomontonio, Ansar Hassan, and Jean-Francois Légaré were responsible for supporting the design and interpretation of the study presented in chapter 6. They were also responsible for reviewing and critiquing the content of the draft manuscript for that study.

Kerry Macdonald was responsible for the development of the systematic review search in the study presented in chapter 6. She was also responsible for the analysis and interpretation of that study, as well as reviewing and critiquing the content of the draft manuscript for the study.

Andrea Szwajcer as responsible for the development of the systematic review search in the study presented in chapter 2.

Todd Duhamel was responsible for supporting the conception, design, and interpretation of the studies presented in chapters 2 to 6. He was also responsible for reviewing and critiquing the content of the draft manuscripts of those studies.

ABBREVIATIONS

AAH - African American Health Study

ADL – Activities of daily living

AF – Atrial fibrillation

ANCOVA – Analysis of covariance

BLSA II - Beijing Longitudinal Study of Aging II

BMI – Body mass index

CABG – Coronary artery bypass graft

CI – Confidence interval

COPD – Chronic obstructive pulmonary disease

CVD – Cardiovascular disease

ELANE - ELderly And their Neighborhood study

ELSA - English Longitudinal Study of Ageing

EMAS - The European Male Ageing Study

FI – Frailty index

FIBRA - Frailty syndrome in an independent urban population in Brazil study

FRAIL - Fatigue, Resistance, Ambulation, Illness, and Loss of weight scale

HDL – High density lipoprotein

Health ABC - Health, Aging and Body Composition study

HLOS – Hospital length of stay

HR – Hazard ratio

IADL – Instrumental activities of daily living

ICU – Intensive care unit

KLoSA - Korean Longitudinal Study of Aging study

KORA-Age - Cooperative Health Research in the Region of Augsburg study

LIFE - Lifestyle Interventions and Independence for Elders study

LPA – Light intensity physical activity

LTPA – Leisure time physical activity

LVEF – Left ventricular ejection fraction

MACCE – Major adverse cerebrovascular and cardiac events

MEDAS – Mediterranean diet adherence screener.

MET – Metabolic equivalent

MI – Myocardial infarction

MVPA – Moderate to vigorous intensity physical activity

NHANES - National Health and Nutrition Examination Survey

NS – Not significant

NYHA – New York Heart Association

OR – Odds ratio

PA – Physical activity

PASE – Physical activity scale for the elderly

PROSPERO - Prospective register of systematic reviews

PVD – Peripheral vascular disease

QOL – Quality of life

SALSA - San Antonio Longitudinal Study of Aging study

SB – Sedentary behaviors

SD – Standard deviation

SE – Standard error

Seniors-ENCRICA - Social Inequalities in Cardiovascular Risk Factors Among Older study Adults in Spain

STROBE - STrengthening the Reporting of OBservational studies in Epidemiology

STS – Society of Thoracic Surgeons

WHAS II - Women's Health and Aging Study II

TABLE OF CONTENTS

ABSTRACT I

ACKNOWLEDGEMENTS III

DEDICATION V

CONTRIBUTION OF AUTHORS VI

ABBREVIATIONS VIII

LIST OF TABLES XV

LIST OF FIGURES XVII

CHAPTER 1: OVERVIEW 1

Measuring biological aging 1

Phenotype and accumulation of deficits as measures of frailty 2

How Is Frailty Treated? 4

Why examine bouts of MVPA and patterns of sedentary behaviors as distinct variables and their association with frailty? 11

Sex differences and frailty, and the impact of physical activity and sedentary behaviors 12

Cardiovascular disease and frailty, and the impact of physical activity and sedentary behaviors 13

Knowledge gaps 16

Purpose of thesis 16

Changes made to the initial thesis 17

Organization of thesis and study objectives 17

References 19

CHAPTER 2: LITERATURE REVIEW 32

Methodological approach 32

Results 34

Summary and knowledge gaps 68

CHAPTER 3: THE ASSOCIATION BETWEEN BOUTS OF MODERATE TO VIGOROUS PHYSICAL ACTIVITY AND PATTERNS OF SEDENTARY BEHAVIOR WITH FRAILTY 71

Abstract 72

Publication status 73

Introduction 74

Methods 76

Results 78

Discussion 87

Supplemental methods 90

References for supplemental methods 94

CHAPTER 4: SEX-DIFFERENCES IN THE ASSOCIATION BETWEEN BOUTS OF PHYSICAL ACTIVITY AND PATTERNS OF SEDENTARY BEHAVIOR WITH FRAILTY 96

Abstract 97

Publication status 99

Introduction 100

Materials and Methods 102

Results 108

Discussion 119

CHAPTER 5: DOES THE PRESENCE OF CARDIOVASCULAR DISEASE IMPACT THE ASSOCIATION BETWEEN BOUTS OF MODERATE TO VIGOROUS PHYSICAL ACTIVITY AND PATTERNS OF SEDETNARY BEHAVIORS WITH FRAILTY? 128

Abstract 129

Publication status 131

Introduction 132

Methods 134

Results 138

Discussion 151

CHAPTER 6: SYSTEMATIC REVIEW OF PREOPERATIVE PHYSICAL ACTIVITY AND ITS IMPACT ON POST-CARDIAC SURGICAL OUTCOMES 158

Publication status 160

Other notes 160

Abstract 161

Introduction 163

Material and Methods 165

Results 168

Discussion 181

CHAPTER 7: GENERAL DISCUSSION 189

Overview of findings 189

Conceptual model of thesis findings: Take a Break from Sitting and get Moving! 194

Conclusion 204

REFERENCES 206

APPENDICES 229

Appendix 1. Frailty index variables used in the study. 230

Appendix 2. Permission to use the list of frailty index variables table. 232

Appendix 3. Permission to re-use published material for Chapter 6. 233

Appendix 4. Curriculum Vitae 234

LIST OF TABLES

Table 2.1. Characteristics of included studies 35

Table 2.2. Association between physical activity and frailty 51

Table 2.3. Association between sedentary behavior and frailty 63

Table 3.1. Characteristics of community-dwelling American adults aged 50 years or older 78

Table 3.2. Univariate, age-sex adjusted and fully adjusted multivariable linear regression models examining the individual associations between bouts of MVPA and patterns of sedentary behaviors with frailty 82

Table 3.3. Multivariable linear regression to examine the independent associations between bouts of MVPA and patterns of sedentary behaviors with frailty 83

Table 4.1. Characteristics of included sample by sex. 108

Table 4.2. Multivariable linear regression models for the frailty index examining individual MVPA and patterns of sedentary behavior variables stratified by sex 111

Table 4.3. Multivariable linear regression models for the frailty index with models examining the independent associations of bouts of MVPA and patterns of sedentary behavior stratified by sex. 114

Supplemental Table 4.1. Association between meeting a percentage of physical activity guidelines through bouted or sporadic MVPA stratified by sex, with total sedentary time removed from adjusted model 127

Table 5.1.Characteristics of included sample by cardiovascular disease status 138

Table 5.2. Multivariable linear regression models for the frailty index for individual MVPA and sedentary bout/break variables stratified by cardiovascular disease status 142

Table 5.3. Multivariable Linear regression models for the frailty index, with models determining the independent associations of bouts of MVPA and patterns of sedentary behaviors stratified by CVD status 145

Supplemental Table 5.1. Multivariable linear regression models for the frailty index with Sex/CVD status as a dummy variable 157

Table 6.1. Characteristics of included studies 169

Table 6.2. Major adverse and cerebrovascular events and postoperative events within 30 days 174

Table 6.3. Hospital length of stay, ICU length of stay, and postoperative activities of daily living and physical activity 177

Table 6.4. Newcastle-Ottawa scale risk of bias scores 180

Table 6.5. Guidelines for physical activity measurement and outcome assessment in cardiac surgery patients: limitations and opportunities for future research 181

Table 7.1. Relationship between bouts of MVPA and patterns of sedentary behaviors with frailty across 190

Table 7.2. Summary of findings from the systematic review on the impact of preoperative physical activity on post-cardiac surgical outcomes. 193

LIST OF FIGURES

Figure 1.1. Illustration of bouted and sporadic MVPA 7

Figure 1.2. Illustration of Patterns of Sedentary Behavior 10

Figure 6.1. Study flow diagram 168

Figure 7.1. Conceptual model of thesis findings 195

CHAPTER 1: OVERVIEW

Globally, the number of older adults is increasing at a rapid rate. The average life expectancy is anticipated to increase from 60 to 80 years old from 1950 to 2050.[1] In fact, by the mid-century, projections estimate that one fourth of individuals will be 60 years or older worldwide.[1] This increase in life expectancy can be attributed, at least in part, to improved survival as a result of advances in medicine and better delivery of healthcare. However, there will need to be a response to the rapidly aging population from the healthcare and public health systems because of the higher burden of chronic conditions associated with an increase in chronologic age. While over 90% of deaths in higher income countries occur in those 60 years and older are a result of non-communicable diseases, including cardiovascular disease, cancers, diabetes, and respiratory conditions,[1] the dynamics of aging are complex and chronologic age does not necessarily reflect one's physiological decline, a term commonly known as biological aging.

Measuring biological aging

It is believed that biological aging is associated with a decline in physiologic reserve and a reduced capacity to respond to stressors as a result of the accumulation of health problems or deficits.[2,3] While there is no single health indicator to accurately estimate the rate at which someone ages, it is believed that a combination of several important health-related variables, including chronic conditions, disabilities, functional capacity, and biomarkers, should be captured to measure aging.[4] However, there is no consensus as to how biological aging should be measured. In the past few decades, the term *frailty* has emerged as a concept to measure one's biological age. Conceptually, frailty is characterized by a greater vulnerability to adverse health outcomes compared to others of the same chronological age as a result of a decline in multiple physiological systems.[5] Compared to chronologic age, the literature demonstrates a stronger association between higher levels of frailty and poor health outcomes, including mortality,[6] hospitalization,[7] and the development of, or worsening disability.[7] Therefore, frailty represents a unique parameter to measure one's rate of biological aging, and importantly, their overall health status.

Despite its generally accepted conceptual definition, the operational definition and measurement of frailty is challenging. A systematic review revealed that 20 frailty instruments have been developed and tested for validity and reliability.[8] This is an important caveat for measuring frailty. While any measurement tool to assess frailty is typically associated with health outcomes, there is no widely accepted tool to measure frailty. In fact, prevalence estimates of frailty vary significantly due to the plethora of frailty tools available. A systematic review of 24 population-based studies consisting of community-dwelling adults over 65 years of age reported that the overall prevalence of frailty was 14-24%.[6] As would be expected, frailty is shown to increase with age, with estimates as low as 2-5% in 18-39 year olds, to 26-50% in adults 85 years or older.[6,9] Given these wide-ranging prevalence estimates, several health organizations seek to operationalize frailty towards a common clinical definition.[10] Two models of frailty have emerged in the scientific literature in the past 20 years as the most widely used approaches to measure frailty; the phenotype[11] and accumulation of deficits models.[12]

Phenotype and accumulation of deficits as measures of frailty

The phenotype model of frailty was developed by Fried and colleagues[11] using data from the Cardiovascular Health Study, which consisted of over 5,300 community-dwelling men and women 65 years or older in the United States. This approach views frailty as a syndrome that results from a cycle of malnutrition, weakness, slowness, exhaustion, and low energy expenditure. The phenotype model characterizes someone as frail based on the presence of three or more of the following five criteria: 1) unintentional weight loss, 2) poor hand grip strength, 3) slow gait speed, 4) exhaustion and 5) physical inactivity. Participants are generally categorized in three different risk categories based on the presence of the five criteria: 0 criterion defines someone as non-frail or robust; 1-2 criteria defines pre-frailty, and 3 or more criteria defines someone as frail.

The accumulation of deficits model views frailty as a state that arises when cellular damage goes unrepaired or unremoved, resulting in an accumulation of health deficits that negatively affects one's ability to compensate to physiologic stress.[12] This model of frailty examines the proportion of health deficits using a frailty index (FI). The first FI was first developed using the Canadian Study of Health and Aging cohort of community-dwelling men and women over the age of 65.[12] The FI is constructed using a guidelines-based approach for the inclusion of frailty deficits, where variables within the FI need to be associated with older age, poor health outcomes, cannot be prevalent in most or all individuals later in life, and cover a range of physiological systems.[13] Thus, the development of a FI is flexible to the health indicators that are available in a database, or availability of data in electronic medical records, for example. Typical FIs contain a collection of signs, symptoms, chronic conditions, activities of daily living, and laboratory variables. A FI is calculated based on the presence or absence of a deficit as a proportion of the total possible variables (e.g., 20/92 deficits would yield a frailty index of 0.22). There are no clear cut-off points established to identify someone as frail, but rather the more deficits one has, the more frail they are. The accumulation of deficits model appears to more accurately predict mortality, as compared to the phenotype model, possibly because it covers a wider range of physiological systems.[14] A recent study also suggests that a FI based on only biomarkers might provide better discrimination of mortality than those based on clinical-based deficits.[15] Moreover, the combination of biomarkers plus clinical-based deficits enhances the sensitivity of the FI.

How Is Frailty Treated?

It is estimated that 3-5% of deaths could be delayed by treating frailty.[16] At a Frailty Consensus Conference in 2011, which consisted of major societies with an interest in geriatrics, a committee of experts agreed that there is at least some evidence to support the efficacy of four treatments.[17] Specifically, the group identified a reduction in polypharmacy, vitamin D supplementation, increased caloric and protein intake, and physical activity (resistance and aerobic exercise training) as treatment strategies. The expert panel group also identified that the most consistent benefit to manage frailty is derived from physical activity-based strategies.

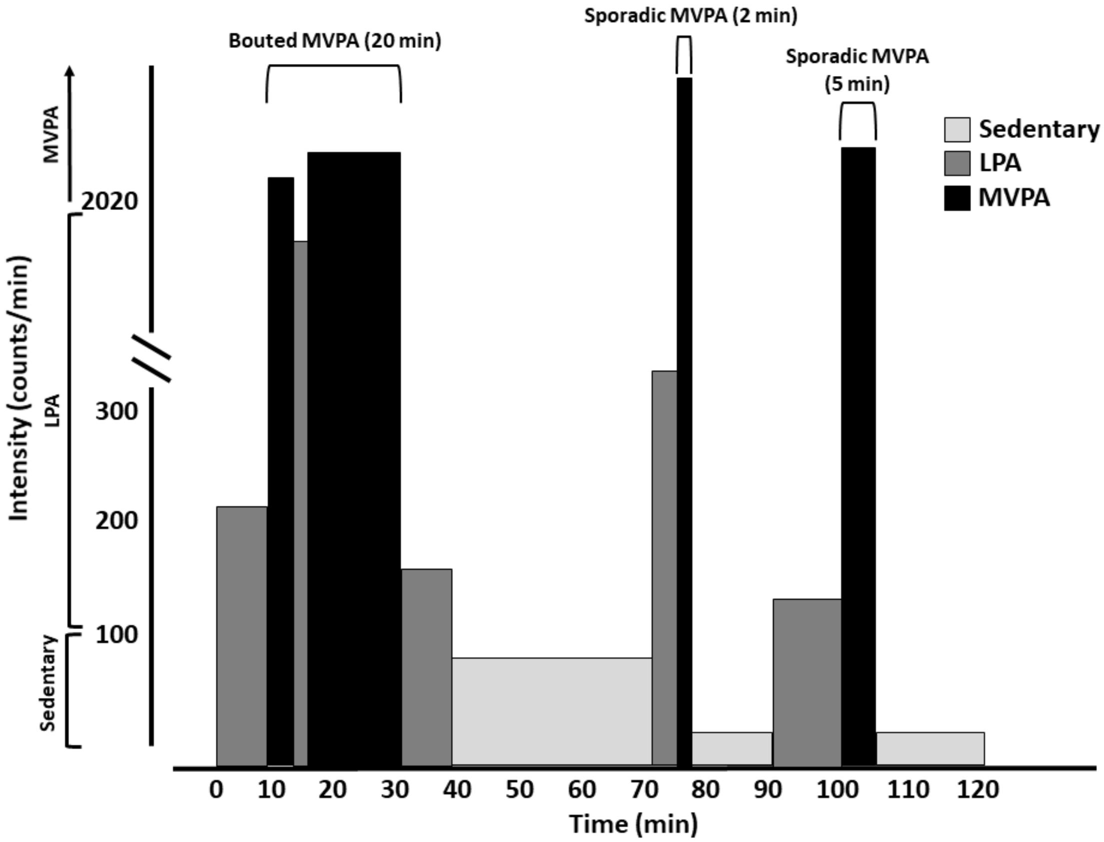
<u>The impact of physical activity on frailty</u>

Living an active lifestyle prolongs life and increases the number of disability-free years of life.[18,19] It has also been demonstrated that physical inactivity can escalate the progression of further deconditioning (i.e., frailty).[5,20] Systematic reviews of randomized trials indicate that physical activity-based strategies, typically as a part of a multi-component intervention, can improve the health of pre-frail and frail patients.[21-29] However, only eight studies included in the systematic reviews have measured a change in a validated measure of frailty pre- and post-intervention.[30-37] While those studies provide important information regarding the potential efficacy of a more physically active lifestyle for the treatment of frailty, the feasibility of implementing such interventions into healthcare practice is unclear. Furthermore, the optimal duration and intensity of physical activity required to prevent or reverse frailty is uncertain.[38] More evidence is needed concerning the impact of physical activity on frailty, and it has been suggested that more observational investigations are required to determine the dose-association between physical activity and reducing the risk of frailty.[38]

Physical activity guidelines.

Public health recommendations from North America and the World Health Organization recommend that older adults accumulate at least 150 minutes of moderate to vigorous physical activity (MVPA) in bouts of ≥10 minutes to achieve health benefits.[39-41] According to the Canadian Physical Activity Guidelines, these recommendations can be achieved through aerobic physical activity such as walking or cycling, adding bone and muscle strengthening activities at least twice per week, and balance activities for those with poor mobility. In addition, these guidelines indicate that higher physical activity levels provide additional benefits to health. However, evidence suggests that 7% of older adults, and only 3% of frail adults are physically active enough to meet these guideline recommendations.[42] Emerging evidence demonstrates that MVPA accumulated in sporadic bouts of <10 minutes are associated with improved cardio-metabolic outcomes, independent of bouted MVPA.[43] While bouted and sporadic MVPA assess the same intensity of physical activity, they are mutually exclusive in that they measure different durations of MVPA (see Figure 1.1). For example, bouted MVPA would be considered a 10 minute or longer jog or brisk walk, while sporadic MVPA could be someone climbing four flights of stairs at a brisk pace. As such, sporadic MVPA could typically be accumulated into one’s daily life may represent an alternative approach to meet the physical activity guidelines. However, whether sporadic MVPA is similarly associated with a reduction in frailty compared to bouted MVPA has yet to be determined.

Figure 1.1. Illustration of bouted and sporadic MVPA



Conceptual example of bouted and sporadic moderate-vigorous physical activity (MVPA) as measured by accelerometry over a two hour period. The light grey bars indicate sedentary time; the dark grey bars indicate light intensity physical activity (LPA) and the black bars indicate MVPA. Counts/min are registered by an accelerometer and are used to classify sedentary time, LPA, and MVPA. The counts/min cut-points are based on thresholds used in the National Health and Nutrition Examination Survey cycles 2003-04 and 2005-06 cycles (see reference by Troiano et al.[44]). Note that the bouted MVPA has two minutes of LPA embedded into the bout. This approach is typically used to define bouted MVPA in previous studies (see references by Troiano et al. and Colley et al. [44,45]). Sporadic MVPA includes any MVPA above the 2,020 counts/min threshold, with no allowable drop in intensity. Sporadic MVPA does not include bouts of MVPA that last 10 minutes or longer. Thus, bouted and sporadic MVPA are mutually exclusive.

<u>Impact of sedentary behavior on frailty.</u>

Given that few older adults are physically active enough to meet physical activity guideline recommendations, targeting reductions in sedentary behavior may also represent a strategy to prevent or reverse frailty. Sedentary behavior is distinct from physical activity behaviors, and is described as any waking activity in a seated or lying position that does not significantly increase energy expenditure beyond 1.5 metabolic equivalents.[46] There is no experimental evidence to suggest that reducing sedentary time can treat or prevent frailty. However, observational data shows that total sedentary time is associated with frailty independent of bouted MVPA.[42] In fact, evidence suggests that for every additional hour of sedentary time, the risk of developing frailty increases by 36% independent of MVPA and sociodemographic factors.[47] The literature also suggests that high amounts of total sedentary time are more detrimental in those with more severe frailty.[48] These data add to the growing body of literature which demonstrate that higher amounts of sedentary behaviors are linked to poor health outcomes despite being physically active.[49]

Sedentary behavior guidelines

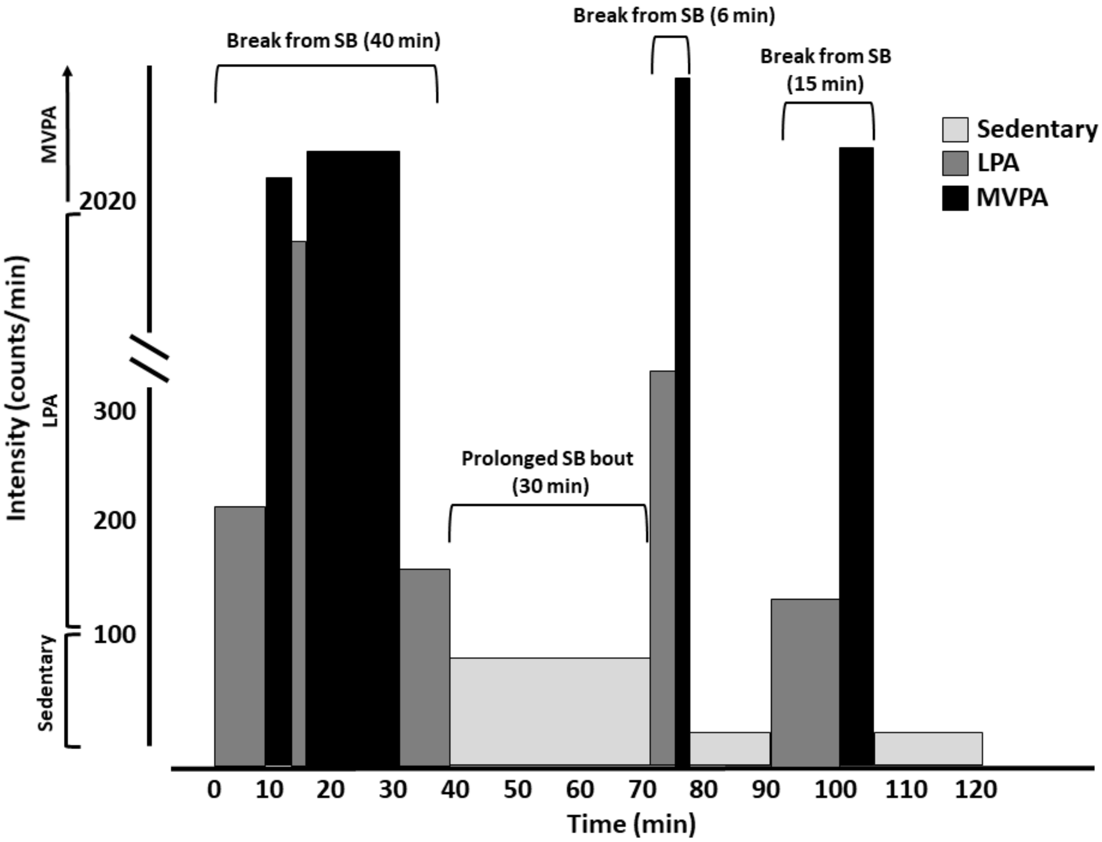
Despite the evidence showing a negative impact of higher levels of sedentary behaviors on frailty and overall health, there are few public health guidelines that provide recommendations to reduce sedentary behaviors. For example, sedentary behavior guidelines in Australia and the United Kingdom are broad in scope and suggest that adults should minimize time spent in sedentary pursuits for extended periods.[50,51] Furthermore, the 24-hour Movement Guidelines in Canada combine sleep, sedentary and physical activity behavior recommendations into a single guideline recommendation for children and youth.[52] Specifically related to sedentary behaviors, these guidelines recommend that children and youth engage in no more than 2 hours of recreational screen time per day and to limit sitting for extended periods.[52] However, public health recommendations to reduce adults' sedentary behaviors in North America are scarce. Given the broad advice provided to adults to reduce sedentary time, it is possible that more evidence is needed to inform the development of more detailed sedentary behavior recommendations for adults.

Patterns of sedentary behavior

Emerging evidence suggests that the extent to which sedentary behaviors are accumulated and interrupted are important for health. Figure 1.2 is an illustration that identifies the patterns of sedentary behaviors (i.e., prolonged sedentary bouts, and the frequency, intensity and duration of breaks in sedentary time) that will be discussed and studied in this thesis.

Prolonged bouts of uninterrupted sedentary behavior lasting at least 30 minutes increases an individual's risk of developing metabolic syndrome, independent of physical activity behavior and total sedentary time.[53] The frequency of breaking up sedentary time, that is, any ≥1 minute interruption in a bout of sedentary behavior, is linked to cardio-metabolic health. Manns et al. report that older adults who more frequently break up their sedentary time was associated with better cardio-metabolic health scores compared to those who had the fewest breaks in sedentary time.[54] Furthermore, the average intensity (measured in counts/min by accelerometry) and duration (measured in minutes) at which these breaks in sedentary time are performed were associated with a better cardio-metabolic health profile independent of total sedentary time.[54] Collectively, targeting these patterns in sedentary behaviors might be a feasible approach to implement into a frailty prevention or treatment strategy; however, it is unclear if these sedentary behavior patterns are associated with frailty.

Figure 1.2. Illustration of Patterns of Sedentary Behavior



Conceptual example of the different patterns of sedentary behaviors as measured by accelerometry over a two hour period. The light grey bars indicate sedentary time; the dark grey bars indicate light intensity physical activity (LPA) and the black bars indicate MVPA. Counts/min are registered by an accelerometer and are used to classify sedentary behaviors, LPA, and MVPA. The counts/min cut-points are based on thresholds used in the National Health and Nutrition Examination Survey cycles 2003-04 and 2005-06 cycles (see reference by Troiano et al.[44]). A break in sedentary time includes both LPA and MVPA that is bouted or sporadic. The average break duration is the sum of the duration of all breaks in sedentary time divided by the total number of breaks. Likewise, the average break intensity is the sum of intensity counts (not shown in the illustration for each break in sedentary time) divided by the total number of breaks in sedentary time. A prolonged sedentary bout is an uninterrupted period of time within the sedentary behavior threshold (0-100 counts/min) lasting at least 30 minutes or longer. This definition of prolonged sedentary behavior was adopted based on previous literature (see references by Honda et al.[53] and Diaz et al.[55]).

Why examine bouts of MVPA and patterns of sedentary behaviors as distinct variables and their association with frailty?

There is some overlap between how each physical activity and sedentary behavior variable is measured and defined. However, individually determining their relationship with frailty can provide unique insights into how public health delivered guidelines recommend increasing physical activity and to break up prolonged, uninterrupted sedentary behaviors. Specifically, it is unclear if bouted and sporadic MVPA are similarly associated with frailty, these data suggest that the North American and World Health Organization (and other) physical activity guidelines should consider that sporadic MVPA is a way to meet the 150 min/week of MVPA for health benefits.[39-41] In contrast, rather than targeting bouts of MVPA to minimize sedentary time, examining if different patterns of sedentary behaviors are associated with frailty may inform the development of health messages that distinguish between the health benefits of reducing sedentary time versus increasing physical activity. For example, a recommendation that adults limit their time spent engaging in prolonged, uninterrupted sedentary behaviors with frequent movement breaks for health benefits is one approach that may separate the health benefits of physical activity and potential harms of high levels of sedentary behavior. This approach aligns with the Australian and United Kingdom sedentary behavior recommendations for adults, as well as the 24-hour Movement guidelines for children and youth in Canada.[50-52] In addition, providing information on the potential association between the intensity and duration of breaks in sedentary time would extend current sedentary behavior guidelines and inform how intense and how long these movement breaks should be to derive health benefits. However, there are no guideline recommendations for how often to interrupt prolonged bouts of sedentary time. Furthermore, it is unclear if the intensity and duration of breaks from sedentary time are linked to improvements in frailty and overall health.

Sex differences and frailty, and the impact of physical activity and sedentary behaviors

The prevalence of frailty appears to be higher in women compared to men, but differences depend on which frailty tool is used.[56] The prevalence of frailty is approximately 13% in women 65 years or older using the phenotype model vs. 7% in men; whereas, 26% of 65 years or older women and 24% of men are classified as frail with the accumulation of deficits model.[6] While women tend to be more frail than men, they are also more likely to live longer when matched for severity of frailty.[56] It is not clear why these sex-based differences occur, but it has been posited that women have a higher physiological reserve and can tolerate higher degrees of frailty better than men.[57]

Lifestyle behaviors, including physical activity and sedentary behavior, may also provide sex-specific health outcomes in vulnerable adults. For example, there is evidence to suggest that engaging in regular physical activity improves endothelial function in older males, while these benefits are inconsistent in postmenopausal women.[58,59] This might be due to the delayed onset of endothelial functional decline that is shown in women due to their pre-menopausal cardio-protective effects.[60] Furthermore, the LIFE study (Lifestyle Interventions and Independence for Elders) provides evidence that males but not females benefitted from a structured and home-based exercise intervention for the prevention of fall-related injuries and hospitalizations.[61] However, it is unclear whether there are sex-specific benefits of a more physically active lifestyle on frailty. It is possible that women are less likely than men to engage in structured or sustained physical activities because they more often experience weakness prior to becoming frail in comparison to men.[62] As well, evidence suggests that sedentary behaviors may be more detrimental to the health of women compared to men.[63] However, the sex-based differences regarding the association of regularly breaking up prolonged bouts of sedentary time, as well as the intensity and duration of sedentary breaks with frailty needs to be investigated.

Cardiovascular disease and frailty, and the impact of physical activity and sedentary behaviors

The impact of frailty on health outcomes has been studied for several decades, but is only emerging as an important health concern in cardiovascular research.[64] Frailty is prevalent in more than a third of patients with cardiovascular disease (CVD), which is significantly higher compared to the non-CVD population.[65] Frail adults are more likely to experience adverse consequences of CVD and its management, such as acute medical problems requiring another hospitalization,[66] and in-hospital functional decline.[67] The combination of frailty and CVD appears to be more detrimental than CVD alone across disease severity, including subclinical CVD,[68] coronary artery disease,[69] cardiac surgery,[70] peripheral arterial disease,[71] heart failure,[72] and acute coronary syndromes,[73] which suggests some mechanistic link between the two and likely a bi-directional relationship.[74] Investigators have posited that frailty and CVD both arise from the activation of inflammatory pathways.[75] In fact, frailty impacts the heart by negatively altering its structure and function as a consequence of chronic inflammation.[76] Thus, if we are to improve the outcomes of frail adults with CVD, we need to begin to understand how their conditions, in combination, can be managed effectively.

While a more physically active lifestyle is known to be effective for the prevention and management of CVD,[77,78] less is known about the impact of physical activity on frailty based on the presence of CVD. One study reports that older adults at least 65 years of age with CVD had a greater associated improvement in physical function scores if they were defined as active, as compared to those who were active but without CVD.[79] By extension, these data suggest that a more physically active lifestyle may confer improvements in frailty to a greater extend in those with CVD versus those without CVD to reduce frailty. However, this possibility has yet to be determined. Furthermore, it is unknown if bouted and sporadic MVPA are similarly associated with frailty based on the presence of CVD.

Epidemiological evidence suggests that increased time spent in sedentary behaviors is independently associated with an increased risk for CVD mortality and morbid events.[80] There is also emerging evidence to suggest that breaking up sedentary time improves cardiovascular health. Specifically, a study by Garcia-Hermoso et al.[81] show that those in the highest quartile of interrupting sedentary time was independently associated with lower arterial stiffness parameters compared to those in the lowest quartile in a cohort of young and older adults without CVD. These data provide initial evidence that sedentary behavior patterns may be important for the health of patients with CVD. However, there are no investigations to date which have determined if prolonged sedentary bouts, and the frequency, intensity and duration of breaks in sedentary time are associated with frailty by CVD status.

Frailty and cardiac surgery.

There is a disproportionately high prevalence of frailty among patients with unrepaired heart disease who require cardiac surgery, and it is estimated that more than half of cardiac surgery patients are frail.[11] While cardiac surgery is generally safe and confers significant functional and quality of life benefits for older adults, patients who are frail have almost a five-fold increased odds of major postoperative cerebrovascular and cardiac events compared to their non-frail peers.[70] Frail patients are typically de-conditioned and have a reduced physiologic reserve to compensate for the stress associated with cardiac surgery. Therefore, it has been postulated that these patients could benefit from therapeutic intervention before their operative procedure as a method to reduce their operative risk. While supporting a more physically active lifestyle is intended to be a component of cardiac surgery patients' care postoperatively, little is known about the potential benefit of physical activity and harms of sedentary behaviors preoperatively. In fact, there are few randomized trials that exist which evaluate the therapeutic benefit of preoperative lifestyle modification in patients undergoing cardiac surgery.[82-84] Furthermore, the current evidence on preoperative physical activity and sedentary behaviors has not been systematically investigated, which makes drawing conclusions about the current literature a challenge. Providing data concerning the relationship between a physically active lifestyle preoperatively and outcomes of cardiac surgery patients could assist healthcare providers to evaluate who might benefit from physical activity-based approaches preoperatively.

Knowledge gaps

The associated health benefits of MVPA accumulated in bouts of 10 minutes or longer are well known.[85] Furthermore, total sedentary time appears to be independently associated with health outcomes beyond maintaining a physically active lifestyle.[49] However, the benefits of different accumulation patterns of MVPA and sedentary behavior are not as extensively studied. Specifically, the relationship between sporadic versus bouted MVPA, prolonged bouts of sedentary time, and the frequency, intensity, and duration of breaks from sedentary time with frailty have not been studied. It is also unclear whether these physical activity and sedentary behavior parameters are similarly associated with frailty in males and females, and in those with and without CVD. Lastly, there is no systematic investigation of the literature concerning the association between preoperative physical activity and sedentary behaviors on postoperative frailty and health outcomes amongst cardiac surgery patients.

Purpose of thesis

The overall aim of this thesis was to determine if alternative approaches to the accumulation of physical activity and sedentary behaviors were associated with frailty in middle-aged and older adults. Specifically, it was determined if bouts of MVPA and patterns of sedentary behaviors were associated with frailty. This thesis also investigated whether there were sex and CVD-specific associations between bouts of MVPA and patterns of sedentary behaviors with frailty. Lastly, a systematic review was completed to determine if preoperative physical activity and sedentary behaviors were linked to postoperative frailty and health outcomes after cardiac surgery.

Changes made to the initial thesis

Although we systematically searched the literature, no studies were identified that examined the impact of sedentary behaviors on post-cardiac surgical outcomes, nor did any studies test the effects of preoperative physical activity on frailty postoperatively. Therefore, those topics could not be systematically reviewed. Furthermore, in the initial thesis proposal, a randomized controlled trial examining the impact of preoperative exercise therapy on postoperative frailty in cardiac surgery patients was proposed; however, the thesis committee felt that such a project was not feasible to complete within the anticipated time of my doctoral degree. Therefore, that project was excluded from the thesis.

Organization of thesis and study objectives

This thesis is structured using the University of Manitoba Faculty of Graduate Studies grouped-based/sandwich style. The thesis itself is comprised of seven chapters. As such, the first chapter is required to have its own reference list. The reference list for chapters 2-7 are at the end of chapter 7, prior to the appendices. Given the group-based thesis style, which comprises of 4 different manuscripts (chapters 3-6), there is some overlap in the background information and methodological approach used for chapters 3-5, discussion, as well as re-defining acronyms.

Chapter 1: This chapter provided an overview of frailty, physical activity, sedentary behaviors, and the sex and CVD-differences in frailty. It also provided knowledge gaps to be tested in relation to different patterns of MVPA and sedentary behavior.

Chapter 2: This chapter comprises of a knowledge synthesis of observational studies to determine the association between physical activity and sedentary behaviors with frailty.

This synthesized evidence was explored to determine if any studies examined the association between bouts of physical activity and patterns sedentary behavior with frailty. Lastly, it was determined if there were any comparisons between sexes or in those with and without CVD in the included studies.

Chapter 3: Study 1 determined if sporadic and bouted MVPA, and if different patterns of sedentary time (i.e., prolonged bouts of sedentary time, and the frequency, intensity, and duration of sedentary breaks) were associated with frailty using the 2003-04 and 2005-06 cycles of NHANES.

Chapter 4: Study 2 aimed to identify if there are any sex differences in relation to the association between different bouts of MVPA and patterns of sedentary behavior with frailty using NHANES data.

Chapter 5: Study 3 determined if there were differences in associations between bouts of MVPA and sedentary behavior with frailty were compared in those with and without CVD using NHANES data.

Chapter 6: Study 4 was a systematic review to determine if physical activity accumulated preoperatively was associated with post cardiac-surgical outcomes.

Chapter 7: Discussion and synthesis of thesis research: An overall discussion of the findings from the four studies is provided. A conceptual model, "Take a Break from Sitting and get Moving" is proposed based on the thesis findings from the NHANES studies. Lastly, this chapter discusses possible ways in which the conceptual model could be situated in the context of supporting cardiac surgery patients to limit extended periods of sedentary time and be physically active prior to their operation.

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CHAPTER 2: LITERATURE REVIEW

The introductory chapter described the potential impact of physical activity and sedentary behaviors on frailty status. However, a noted gap was that there are few experimental studies testing the impact of physical activity interventions on the treatment and prevention of frailty, and there are no interventions targeting sedentary behaviors to reduce one's frailty status. Therefore, a systematic literature search for observational studies examining the link between physical activity and sedentary behaviours with frailty was conducted. Secondary objectives of this review were to determine if there were studies that explored the relationship between frailty and sporadic or bouted MVPA, as well as different patterns of sedentary behaviors (including prolonged bouts of sedentary time, the number of interruptions in sedentary time and the average intensity and duration of interrupting sedentary time). Finally, this review sought to determine if any studies explored sex and CVD differences in the relationship between physical activity and sedentary behavior with frailty.

Methodological approach

This literature review presents the initial results of a systematic review to examine the association between physical activity and sedentary behavior with frailty. The systematic review protocol is registered with PROSPERO: 2017:CRD42017062701. Briefly, an electronic search strategy was developed by a librarian and reviewed by a second librarian. Electronic databases were searched from inception to June 2017 for primary research studies using an observational design (cross-sectional, case-control, prospective, retrospective) and included MEDLINE, Embase, Web of Science, CINAHL, SPORTDiscus, Scopus, and the World Health Organization Clinical Trials Registry.

Participant inclusion criteria was open to any sample population, such as community-dwelling adults, or specialized populations (e.g., patients hospitalized to acute care). Frailty had to be assessed with a multicomponent measure, and the authors had to indicate that frailty was being measured as an outcome in the study. Either physical activity or sedentary behavior, or both, had to be measured as an exposure variable for inclusion. Both variables could be assessed by self-report or through an objective measurement. Statistical models amongst the individual studies had to adjust for at least one variable (e.g., age, sex) when assessing the relationship between physical activity and sedentary behaviors with frailty. If statistical models included multiple covariates, the models adjusting for the most variables were presented in this review.

A two-stage screening process was used to find articles that met the above inclusion criteria for this review. Each screening stage was conducted independently by two reviewers. Title and abstracts were initially screened for further full-text interrogation. The full-text screening revealed studies for final inclusion and qualitative synthesis. If separate articles used the same study cohort, they were included if physical activity and/or sedentary behaviors, and frailty, were assessed in a different manner.

The following data were extracted from individual studies: Study reference, study design type, study cohort name, age and sex characteristics, type of study population (e.g., community-dwelling, institutionalized), physical activity and/or sedentary behavior tool used, summary statistics of physical activity and sedentary behavior among the study participants, frailty tool used, frailty characteristics of the study sample, statistical approaches used, and covariates of statistical models. For longitudinal studies, the follow up period length and the number of frailty cases at follow up were extracted.

Results

Description of studies

After removal of duplicate articles, a total of 7975 titles and abstracts were screened to determine their eligibility. This initial screening process revealed 565 articles, which were subsequently interrogated for their eligibility by reviewing in full-text. Thirty-two studies met the inclusion criteria of assessing the association between physical activity and/or sedentary behavior with frailty, which collectively included 65,161 participants.[1-32] The sample size of studies ranged from 26[18] to 8649.[17]

Table 2.1 provides an overview of the included studies. Longitudinal studies are listed first, followed by cross-sectional studies. For longitudinal studies, the follow-up period ranged from 13 months[6] to 26 years.[9] Studies included participants from the United Kingdom,[1,12,13,16,17,28,29] the United States,[2,5,7,8,11,15,19,20,30,32] Spain,[3,4,10,12,16] Brazil,[6,18] Finland,[9] Italy,[12] Belgium,[12] Poland,[12] Sweden,[12] Hungary,[12] Estonia,[12] China,[14,27] Turkey,[21] Netherlands,[22,24] France,[23] Korea,[25] Germany,[26] and Canada.[31] Most studies included participants from a named cohort.[1-13,15-17,19-21,24-28] Data from the Social Inequalities in Cardiovascular Risk Factors Among Older Adults in Spain (Seniors-ENRICA) study[3,4,10,16] and the English Longitudinal Study of Ageing (ELSA)[13,16,17] were used multiple times, but analyzed outcomes differently. A majority of studies included community-dwelling adults (n= 23 studies),[1,3-6,8,10-21,24,27,29,31,32] and three studies contained special populations.[2,23,30] Other studies did not clearly report if special populations or community-dwellers were recruited.[7,9,22,25,26,28]

Table 2.1. Characteristics of included studies.

Reference ID /Region/ sample size	**Study cohort**	**Age/sex**	**Exposure assessment (continuous/categorical)**	**Frailty tool (continuous/categorical) and Prevalence of frailty**
Prospective Cohort studies				
Bouillon 2013[1] United Kingdom (n= 2707)	Cohort name: Whitehall II Prospective Cohort Study Cohort description: Community-dwelling adults Mean follow-up: 10.5 years	Age: 45-69 years old Sex: 27.9% female	Physical activity: (categorical) Modified Minnesota Leisure-time Physical Activity Questionnaire Sedentary time: None	Fried criteria (categorical) Frailty status at follow up reported only: *Non-frail:* 1616 (59.7%) *Pre-frail*: 1015 (37.5%) *Frail:* 76 (2.8%)
Espinoza 2012[2] United States (n= 597)	Cohort name: San Antonio Longitudinal Study of Aging (SALSA) study Cohort description: Older adults admitted to a rehabilitation outpatient clinic Mean follow-up: 6.4 years	Age: 69.6 ± 3.4 years old Sex: 55.1% female	Physical activity: (categorical) Minnesota Leisure Time Physical Activity Questionnaire Sedentary time: None	Fried criteria (categorical) Frailty status at baseline: *Non-frail:* 209 (37.4%) *Pre-frail:* 298 (53.3%) *Frail:* 52 (9.3%)

García-Esquinas 2015[3] Spain (n= 1750)	Cohort name: Social Inequalities in Cardiovascular Risk Factors Among Older Adults in Spain (Seniors-ENRICA) study Cohort description: Noninstitutionalized older adults and non-frail at baseline Mean follow-up: 3.5 years	Age: 60 years or older Sex: 51.4% female	Physical activity: (continuous) Minnesota Leisure Time Physical Activity Questionnaire Sedentary time: (continuous) Nurse's Health Study Questionnaire television viewing	Fried criteria (categorical) Frailty status at baseline: *Non-frail:* 1750 (100.0%)
Graciani 2016[4] Spain (n= 1745)	Cohort name: Social Inequalities in Cardiovascular Risk Factors Among Older Adults in Spain (Seniors-ENRICA) study Cohort description: Community-dwelling older adults and non-frail at baseline Mean follow-up: 3.5 years	Age: 60 years or older Sex: 51.5% female	Physical activity: (categorical) Unclear what tool was used. Likely based on global response to a single question. Sedentary time: None	Fried criteria (categorical) Frailty status at baseline: *Non-frail:* 1745 (100.0%)

Song 2015[5] United States (n= 1333)	Cohort name: Osteoarthritis Initiative Study Cohort description: Community-dwelling adults Follow-up: 2 years	Age: 55-83 years old Sex: 54.8% female	Physical activity: (continuous) Uniaxial accelerometer (Actigraph GT1M) Sedentary time: (continuous) Uniaxial accelerometer (Actigraph GT1M)	Combined gait speed and chair stand tests (categorical) Frailty status at baseline: *Non-frail:* 1333 (100.0%)
da Silva 2015[6] Brazil (n= 200)	Cohort name: Frailty syndrome in an independent urban population in Brazil (FIBRA) study Cohort description: Community-dwelling adults Mean follow-up: 13 months	Age: >65 years old Sex: 68.0% female	Physical activity: (categorical) Minnesota Leisure Time Physical Activity Questionnaire Sedentary time: None	Fried Criteria (categorical) Frailty status at baseline: *Non-frail:* 62 (31.0%) *Pre-frail:* 111 (55.5%) *Frail:* 27 (13.5%)

Peterson 2009[7] United States (n= 2964)	Cohort name: Health, Aging and Body Composition (Health ABC) study Cohort description: "Well functioning" adults Follow-up: 5 years	Age: 70-79 years old Sex: 51.0% female	Physical activity: (categorical) Modified Minnesota Leisure Time Physical Activity Questionnaire Sedentary time: None	Combined gait speed and chair stand tests (categorical) Frailty status at baseline: *Non-frail:* 1964 (97.3%) *Moderately frail:* 80 (4.0%) *Severely frail:* 4 (0.2%)
Ribeiro 2016[8] United States (n= 432)	Cohort name: African American Health (AAH) Study Cohort description: Community-dwelling African American adults Follow-up: 6 years	Age: 49-65 years old Sex: 63.0% female	Physical activity: (continuous) Yale Physical Activity Survey Sedentary time: (continuous) Yale Physical Activity Survey	Fatigue, Resistance, Ambulation, Illness, and Loss of weight (FRAIL) Scale (Continuous) Frailty status at baseline: Frailty scores not reported

Savela 2013[9] Finland (n= 514)	<u>Cohort name:</u> Helsinki Businessmen Study <u>Cohort description:</u> Healthy men at baseline <u>Follow-up:</u> 26 years	<u>Age:</u> 47.5 ± 4.1 years old <u>Sex:</u> 0.0% female	<u>Physical activity:</u> (continuous) Not clear. Used a global description of PA (baseline data used for analysis) based on answering yes/no to usual activities that included inactive, low, moderate, and high intensity <u>Sedentary time:</u> None	Modified Fried criteria (Categorical) <u>Frailty status at follow up only:</u> <u>*Non-frail:*</u> 201 (39.1%) <u>*Pre-frail:*</u> 265 (51.6%) <u>*Frail:*</u> 48 (9.3%)
Soler-Vila 2016[10] Spain (n= 1857)	<u>Cohort name:</u> Social Inequalities in Cardiovascular Risk Factors Among Older Adults in Spain (Seniors-ENRICA) study <u>Cohort description:</u> Noninstitutionalized older adults <u>Mean follow-up:</u> 3.5 years	<u>Age:</u> 60 years or older <u>Sex:</u> 51.3% female	<u>Physical activity:</u> None <u>Sedentary time:</u> (continuous) Nurses' Health Study questionnaire for television viewing time	Fried criteria (Categorical) <u>Frailty status at baseline:</u> <u>*Non-frail:*</u> 1857 (100.0%)

Strawbridge 1998[11] United States (n= 574)	Cohort name: Alameda County Study Cohort description: Community-dwelling adults Follow-up: 29 years	Age: 65 years or older Sex: 57.0% female	Physical activity: (categorical) Based on four items that ask how often they participated in individual PA Sedentary time: None	"1994 Frailty measure" based on 16 items assessing physical, nutritive, cognitive, and sensory functioning" (Categorical) Frailty status at follow up only: *Non-frail:* 424 (73.9%) *Frail:* 150 (26.1%)
Wade 2016[12] Italy, Belgium, Poland, Sweden, UK, Spain, Hungary, Estonia (n=2736)	Cohort name: The European Male Ageing Study (EMAS) Cohort description: Community-dwelling males Mean follow-up: 4.3 ± 0.3 years	Age: 40-79 years old Sex: 0.0% female	Physical activity: (continuous) Physical Activity Scale for the Elderly Sedentary time: None	39-item Frailty Index (Categorical) Frailty status at baseline: *Non-frail:* 2244 (82.0%) *Pre-frail:* 387 (14.1%) *Frail:* 105 (3.8%)
Wade 2017[13] England (n= 5316)	Cohort name: English Longitudinal Study of Ageing (ELSA) Cohort description: Community-dwelling adults living in private households Follow-up: 8 years	Age: 50 years or older Sex: 56.3% female	Physical activity: (continuous) Allied Dunbar Survey of Fitness Sedentary time: None	51-item Frailty Index (Categorical) Frailty status at baseline: *Non-frail or pre-frail:* 5159 (97.0%) *Frail:* 157 (3.0%)

Woo 2010[14] China (n= 3378)	Cohort name: None Cohort description: Community-dwelling adults living in Hong-Kong Follow-up: 4 years	Age: 65 years or older Sex: 51.2% female	Physical activity: (continuous) Physical Activity Scale for the Elderly Sedentary time: None	47-item Frailty Index (Continuous) Frailty status: Not reported
Xue 2008[15] United States (n= 420)	Cohort name: Women's Health and Aging Study II (WHAS II) Cohort description: Community-dwelling and cognitively intact females Follow-up: 7.5 years	Age: 70-79 years old Sex: 100.0% female	Physical activity: (categorical) Not reported. Likely Minnesota Leisure Time Physical Activity Questionnaire. Sedentary time: None	Fried Criteria (Continuous) Frailty status at baseline: *Non-frail:* 268 (63.8%) *Pre-frail:* 152 (36.2%) *Frail:* 0 (0.0%)

García-Esquinas 2017[16] Spain and England (n= 6381)	Cohort name: Study on Nutrition and Cardiovascular Risk Factors in Spain (Seniors-ENRICA), and the English Longitudinal Study of Aging (ELSA) cohorts Cohort description: Community-dwelling adults Mean follow-up: *Seniors-ENCRICA:* 3.3. ± 0.6 years *ELSA:* 3.9 ±0.2 years	Age: 50 years or older Sex: 43.1% female	Physical activity: (categorical) *Seniors-ENRICA:* Not clear. Categorized as inactive based on accumulating ≤2.5 h/week ≤2 h/week of walking in men and women, respectively. *ELSA:* Unclear. Used MET-values from an "overall measure" of physical activity. Divided into sex-specific quintiles. Sedentary time: (continuous and categorical) *Seniors-ENCRICA:* Nurses' Health Study television viewing time *ELSA:* Recall of number of hours of television watched during the week	Fried criteria (categorical) Frailty status at baseline: *Non-frail:* 6381 (100.0%)

Rogers 2017[17] England (n= 8649)	Cohort name: English Longitudinal Study of Ageing (ELSA) Cohort description: Community-dwelling adults Mean follow-up: 10 years	Age: 50 years or older Sex: 53.2% female	Physical activity: (categorical) Participants indicated how often they participated in mild, moderate, and vigorous physical activities during their leisure time Sedentary time: None	56-item Frailty Index (categorical) Frailty status at baseline: *Non-frail:* 8649 (100.0%)
Cross-sectional studies				
Bastone 2015[18] Brazil (n= 26)	Cohort name: None Cohort description: Community-dwelling adults	Age: 66-86 years old Sex: 54.8% female	Physical activity: (continuous) Triaxial accelerometer (Actigraph GT3X) Sedentary time: (continuous) Triaxial accelerometer (Actigraph GT3X)	Fried criteria (categorical) Frailty status: *Non-frail/pre-frail:* 13 (50.0%) *Frail:* 13(50.0%)

Blodgett 2015[19] United States (n= 3146)	Cohort name: National Health and Nutrition Examination Survey (NHANES) Cohort description: Community-dwelling adults	Age: 50 years or older Sex: 53.7% female	Physical activity: (continuous) Uniaxial accelerometer (Actigraph AM-7164) Sedentary time: (continuous) Uniaxial accelerometer (Actigraph AM-7164)	46-item Frailty index (continuous and categorical) Frailty status: Continuous scores not reported *Non-frail/vulnerable:* 1938 /3146 (61.6%) *Frail/most frail:* 1208/3146 (38.4%)
Cawthon 2007[20] United States (n=5993)	Cohort name: Osteoporotic Fractures in Men Study Cohort description: Community-dwelling adults	Age: 65 years or older Sex: 0.0% female	Physical activity: (continuous) Physical Activity Scale for the Elderly Sedentary time: None	Modified Fried criteria (categorical) Frailty status: Continuous scores not reported *Non-frail:* 3358 (56.0%) *Pre-frail:* 2395 (40.0%) *Frail:* 240 (4.0%)
Eyigor 2015[21] Turkey (n= 1126)	Cohort name: FrailTURK project Cohort description: Community-dwelling adults	Age: 65 years or older Sex: 65.7% female	Physical activity: (categorical) Tool not reported Sedentary time: (categorical) Tool not reported	Fried criteria (categorical) Frailty status: Continuous scores not reported *Non-frail:* 197 (17.5%) *Pre-frail:* 488 (43.3%) *Frail:* 441 (39.2%)

Gobbens 2016[22] Netherlands (n= 610)	Cohort name: None Cohort description: Unclear. "Dutch citizens completed the web-based questionnaire "Seniorenbarometer""	Age: 70.6 ± 7.3 years old Sex: 32.4% female	Physical activity: (categorical) Single question asking about frequency of participation in types of physical activities Sedentary time: None	Tillburg Frailty Indicator (continuous) Frailty status: *Total frailty score:* 3.4 ± 2.6 *Physical frailty score:* 1.5 ± 1.7 *Psychological frailty score:* 0.87 ± 1.1 *Social frailty score:* 1.0 ± 0.92
Hoogendijk 2015[23] France (n= 484)	Cohort name: None Cohort description: Patients admitted to a geriatric day hospital	Age: 83.2 ± 6.0 years old Sex: 63.0% female	Physical activity: (categorical) No tool reported. Scored as yes/no based on performing <2 hr/week of low intensity physical activity Sedentary time: None	Fried criteria and a 35-tiem Frailty Index (continuous) Frailty status: *Fried frailty status:* *Non-frail:* 35 (7.3%) *Pre-frail:* 208 (43.3%) *Frail:* 237 (50.0%) *FI frailty status:* *Total score:* 0.32 ± 0.14
Jansen 2015[24] Netherlands (n= 74)	Cohort name: ELderly And their Neighborhood (ELANE) study Cohort description: Community-dwelling adults	Age: 65 years or older Sex: 46.4% female	Physical activity: (continuous) Triaxial accelerometer (ActiGraph GT3X+) Sedentary time: (continuous) Triaxial accelerometer (ActiGraph GT3X+)	Identification Seniors At Risk – Hospitalized Patients questionnaire (categorical) Frailty status: *Non-frail:* 74 (88.0%) *Frail:* 10 (12.0%)

Ko 2016[25] Korea (n=3460)	Cohort name: Korean Longitudinal Study of Aging (KLoSA) study Cohort description: Nationally representative sample of Korean adults	Age: 45 years or older Sex: 100.0% female	Physical activity: (categorical) Single question to categorize based on exercising none or >1x/week Sedentary time: None	Geriatric Status Scale (categorical) Frailty status: *Non-frail:* 1294 (37.4%) *Incontinent:* 453 (13.1%) *Mild frailty:* 1014 (29.3%) *Moderate/Severe frailty:* 699 (20.2%)
Stephan 2016[26] Germany (n= 960)	Cohort name: Cooperative Health Research in the Region of Augsburg (KORA-Age) Study Cohort description: Randomly selected adults from the region of Augsburg, Germany	Age: 65 years or older Sex: 49.0% female	Physical activity: (categorical) Physical Activity Scale for the Elderly Sedentary time: None	31-item Frailty Index (continuous) Frailty status: *Total sample:* 0.15 ± 0.11
Woo 2015[27] China (n= 7298)	Cohort name: Beijing Longitudinal Study of Aging II (BLSA II) Cohort description: Community-dwelling adults	Age: 65 years or older Sex: 57.0% female	Physical activity: (categorical) Not reported. Exercising 0.5 hours (not clear if per week or per day) used as cut-off for active and inactive. Sedentary time: None	34-item Frailty Index (categorical) Frailty status: Prevalence of non-frail and frail could not be accurately ascertained

Young 2016[28] United Kingdom (n= 3375)	Cohort name: St. Thomas' UK Adult Twin Registry Cohort description: Monozygotic and Dizygotic twins	Age: 40-84.5 years old Sex: 100.0% female	Physical activity: (categorical) Not reported, but indicated using "questionnaire responses" based on hours spent in different types of PA during leisure time in the past week Sedentary time: None	39-item Frailty Index (continuous) Frailty status: *Total sample:* 0.13 ± 0.11
Castaneda-Gameros 2017[29] United Kingdom (n= 60)	Cohort name: None Cohort description: Community-dwelling first generation migrant women	Age: 60 years or older Sex: 100.0% female	Physical activity: (continuous) Triaxial accelerometer (Actigraph GT3X) Sedentary time: (continuous) Triaxial accelerometer (Actigraph GT3X)	Fried Criteria (continuous for analysis, categorical for reporting) Frailty status: *Non-frail:* 23 (38.3%) *Pre-frail:* 27 (45.0%) *Frail:* 10 (16.7%)

Kramer 2017[30] United States (n= 219)	Cohort name: None Cohort description: Outpatients with cardiac implantable electrical devices	Age: 60 years or older Sex: 30.0% female	Physical activity: (continuous) Accelerometer embedded in cardiac implantable electrical device (several different models used) Sedentary time: None	Study of Osteoporotic Fractures (categorical) Frailty status: *Non-frail:* 87 (39.7%) *Pre-frail:* 104 (47.5%) *Frail:* 28 (12.8%)
Roland 2012[31] Canada (n= 30)	Cohort name: None Cohort description: Community-dwelling females	Age: 50 years or older Sex: 100.0% female	Physical activity: (continuous) Triaxial accelerometer (ActiTrainer) Sedentary time: (continuous) Triaxial accelerometer (ActiTrainer)	Fried criteria (categorical) Frailty status: *Non-frail:* 12 (40.0%) *Pre-frail:* 11 (36.7%) *Frail:* 7 (23.3%)
Schwenk 2015[32] United States (n= 125)	Cohort name: None Cohort description: Community-dwelling adults recruited through primary, secondary, and tertiary health care settings	Age: 65 years or older Sex: 80.0% female	Physical activity: (continuous) Triaxial accelerometer (ActiTrainer) Sedentary time: (measured but analysis not reported in study)	Fried criteria (categorical) Frailty status: *Non-frail:* 44 (35.2%) *Pre-frail:* 60 (48.0%) *Frail:* 21 (16.8%)

PA; physical activity. MET; metabolic equivalent.

The age range of participants were 40[12] to 86[18] years old. Twenty-four studies included women and men,[1-8,10,11,13,14,16-19,21-24,26,27,30,32] five studies had women only,[15,25,28,29,31] and three studies contained men only.[9,12,20]

A series of different frailty tools were used in the studies (Table 2.1). The Fried phenotype criteria was the most commonly used frailty tool (n= 16 studies)[1-4,6,9,10,15,16,18,20,21,23,29,31,32] followed by the FI (n= 9 studies).[12-14,17,19,23,26-28] Other frailty measures included combined gait speed and chair stand testing,[5,7] the Fatigue, Resistance, Ambulation, Illness, and Loss of weight (FRAIL) Scale,[8] a 16-item scale assessing multiple frailty domains,[11] the Tillburg Frailty Indicator,[22] Identification Seniors At Risk – Hospitalized Patients questionnaire,[24] Geriatric Status Scale,[25] and the Study of Osteoporotic Fractures score.[30] Among studies that categorized participants into frailty groups, the prevalence of frailty (at baseline for longitudinal studies) ranged from 0.0%[3-5,10,16,17] to 50.0%.[18,23] Studies that had all non-frail participants at baseline were longitudinal studies. Other studies did not report frailty status[8,14] or could be adequately ascertained for the total sample.[27]

Physical activity-frailty relationship

Thirty-one studies (n=63,304) examined the relationship between physical activity and frailty (Tables 2.1 and 2.2)[1-9,11-32] Table 2.1 provides information on the physical activity tools used in the included studies. Eleven studies used a questionnaire to measure physical activity behavior,[1-3,6-8,12-14,20,26] and eight studies used accelerometry as a physical activity assessment.[5,18,19,24,29-32] Other studies (n= 12) did not clearly report what type of physical activity tool was used, or the authors of the study reported using a global assessment of physical activity based on responses to questions specifically designed for the study.[4,9,11,15-17,21-23,25,27,28] Physical activity was analyzed as a categorical response in seventeen studies[1,2,4,6,7,11,14-17,21-23,25-28] and as a continuous outcome in fourteen studies.[3,5,8,9,12,13,18-20,24,29-32] Studies using self-reported methods to measure physical activity were not clear on whether bouted or sporadic physical activity was measured. The self-report measures typically asked about the frequency and average duration of activities performed. For the studies using accelerometry, seven of eight studies were not clear if bouted or sporadic physical activity was assessed.[5,18,24,29-32] Therefore, only one study using accelerometry indicated that they measured physical activity in bouts of 10 minutes or longer.[33]

The analysis procedures and effect estimates for studies which investigated the relationship between physical activity and frailty are provided in Table 2.2. Longitudinal studies are described first, followed by cross-sectional studies. Effect estimates using an odds ratio, relative risk, or hazard ratio are listed first, followed by β-coefficients and mean differences. The proportion of frail participants at follow-up in longitudinal studies ranged from 2.8%[1] to 26.1%[11] Four studies did not report the number of frail participants at follow-up.[8,14,16,17] Sixteen studies used a longitudinal design for the assessment of physical activity and its relationship with frailty.[1-3,5-9,11-17] Fifteen studies were cross-sectional studies.[18-32] Out of the thirty-one studies, twenty-seven studies[1-4,6-9,11-14,16-19,21-23,25-32] found a statistically significant protective association between higher physical activity levels and frailty. For studies analyzing physical activity as a categorical variable and frailty as a categorical outcome, compared to inactive patients, the odds ratios or hazard ratios ranged from 0.10[13] to 0.94[4] for the active or highest active groups.

Table 2.2. Association between physical activity and frailty

Reference ID/sample size	Adjustment variables	Statistical analysis	Number frail at follow-up (prospective studies)	Effect estimates
Prospective cohort studies				
Bouillon 2013[1] (n= 2707)	Age, sex, parental/sibling history of diabetes, BMI, waist circumference, blood pressure, hypertension therapy, corticoid treatment, smoking status, fruit/vegetable consumption, fasting glucose, HDL cholesterol, Triglycerides	Multivariable logistic regression	Frail: 76 (2.8%)	OR (95% CI) for being frail (active as reference): 2.49 (2.08–2.98); $p<0.05$
Espinoza 2012[2] (n= 597)	Age, sex, ethnicity, income, education, comorbid disease, uncomplicated and complicated (macrovascular) diabetes	Generalized Estimating Equations	Frail: 76 (12.7%)	OR (95% CI) for frailty worsening vs. remaining unchanged or improving at follow up with inactive group as reference: 0.36 (0.25–0.52); $p<.001$
García-Esquinas 2015[3] (n= 1750)	Age, sex, education level	Logistic regression	Frail: 115 (6.6%)	OR (95% CI) for incident frailty for every additional 1 MET-hr/week increase: 0.94 (0.92-0.96); $p<0.05$
Graciani 2016[4] (n= 1745)	Age, sex, education, alcohol consumption, cancer, obstructive lung disease, osteomuscular disease, depression requiring treatment, IADL limitation, smoking status, healthy diet score, total cholesterol, blood pressure, fasting glucose	Cox-regression	Frail: 117 (6.7%)	HR (95% CI) compared to being inactive: Intermediate active: 0.60 (0.37-0.97); $p<0.05$ Ideal active: 0.49 (0.24-0.97); $p<0.05$
Song 2015[5] (n= 1333)	age, gender, race, marital status, education, income, BMI, comorbidity, depressive symptoms, knee and hip osteoarthritis, knee and hip symptoms, general pain, smoking status, alcohol consumption	discrete-time survival regression by applying a generalized linear model	Frail: 20.7 per 1000 person years over 2 year follow-up	HR (95% CI) for every additional hr/day increase in moderate intensity physical activity for onset of frailty: 0.18 (0.02-1.73); $p>0.05$

da Silva 2015[6] (n= 200)	Unclear. Models are at least adjusted for age and sex.	Unclear. Manuscript indicates a multinomial regression but data presented as though it is logistic regression	Pre-frail: 101 (55.5%) Frail: 28 (14.0%)	OR (95% CI) for those who improved their frailty score at follow up(frail to pre-frail, frail to non-frail, pre-frail to non-frail) based on having low activity at baseline: 0.34 (0.15-0.76); p=0.008 OR (95% CI) for those who had a worse frailty score at follow up (non-frail to frail, non-frail to pre-frail, pre-frail to frail) based on low activity at baseline: 0.96 (0.38-2.43); p=0.94
Peterson 2009[7] (n= 2964)	age, sex, race, education, marital status, smoking status, drinking status, waist circumference, and count of diagnoses	generalized estimating equation logistic regression models using an autoregressive covariance structure	Moderately frail: 262 (13.0%) Severely frail: 61 (3.0%)	ORs (95% CI) for incident moderate or severe frailty by activity category: *Volume (recommended amount as reference):* Low dose: 1.03 (0.83-1.28) *Intensity (vigorous as reference):* Sedentary: 1.10 (0.75-1.63) Light: 1.48 (0.88-1.59) Moderate: 0.91 (0.65-1.28) *Activity type (exercise active as reference):* Sedentary: 1.45 (1.04-2.01) Lifestyle active: 1.08 (0.83-1.41) ORs (95% CI) for incident severe frailty in moderately frail at baseline (n=410): *Volume (recommended amount as reference):* Low dose: 0.97 (0.55-1.70) *Intensity (vigorous as reference):*

				Sedentary: 1.47(0.58–3.73) Light: 1.31 (0.58–2.95) Moderate: 0.66 (0.22–1.98) *Activity type (exercise active as reference):* Sedentary: 2.80 (0.98–8.02) Lifestyle active: 2.81 (1.22–6.43)
Savela 2013[9] (n= 514)	Baseline age, BMI, smoking status, blood pressure, alcohol consumption, and comorbidity index at follow up	Multinomial logistic regression	Pre-frail: 265 (51.6%) Frail: 48 (9.3%)	OR (95% CI) for being pre-frail at follow up (low activity as reference): Moderate activity: 1.00 (0.57–1.78) High activity: 0.57 (0.31–1.03) OR (95% CI) for being frail at follow up (low activity as reference): Moderate activity: 0.75 (0.32–1.74); p>0.05 High activity: 0.23 (0.08–0.65); p<0.05
Strawbridge 1998[11] (n= 574)	Age, sex, race, education, chronic conditions	Multivariable logistic regression	Frail: 150 (26.1%)	OR (no 95% CI reported) for being frail at follow up (reference are those who were always active at each time point) Inactive for one follow up time point: 2.18; p<0.05 Inactive at two or three follow up time points: 1.95; p<0.05
Wade 2016[12] (n=2736)	Age, centre, BMI, smoking status, depression, pain status	Logistic regression and negative binomial regression	Frail: 112 (4.3%)	OR (95% CI) for being frail at follow up based on continuous PASE scores:

				0.99 (0.98-0.99); p<0.05 Incident rate ratios (95% CI) for being frail at follow up based on continuous PASE scores: 0.99 (0.99-1.00): p>0.05
Wade 2017[13] (n= 5316)	Logistic regression analysis: Age, sex, BMI, smoking status, depressive symptoms, occupation, income, pain status Negative binomial regression analysis: Age, sex, BMI, smoking status, depressive symptoms, occupation, income, pain status, FI at baseline	Logistic regression and negative binomial regression	Frail: 328 (6.4%)	OR (95% CI) for being frail at follow up (high activity as reference, n=4601): Moderate: 1.71 (1.06-2.76); p<0.05 Low: 3.31 (2.01-5.43); p<0.001 Sedentary: 9.54 (4.94-18.42); p<0.001 Incident rate ratios (95% CI) for being frail at follow up (high activity as reference, n= 4733): Moderate: 1.13 (1.08-1.17); p<0.001 Low: 1.17 (1.12-1.23); p<0.001 Sedentary: 1.15 (1.04-1.27); p<0.001
Xue 2008[15] (n= 420)	Age, Race, Education, Comorbidity	Discrete-time proportional hazard models	Frail: 38 (9.0%)	HR (95% CI) for being frail at follow up in those who were inactive at baseline compared to those who were non-frail at baseline: 2.48 (0.93-6.60); p=0.07

García-Esquinas 2017[16] (n= 6381)	Age, sex, education, BMI, tobacco consumption, PA, CVD, diabetes, chronic lung disease, osteomuscular disease, total energy intake (Seniors-ENCRICA only), MEDAS index (Seniors-ENCRICA only).	Random effects meta-analysis from logistic regression results of both cohorts	Not reported	OR (95% CI) for incident frailty stratified by tertiles of TV viewing time (lowest tertile as reference): **Seniors-ENRICA cohort** 2.1-3 hr/day of TV viewing time: *Inactive:* 1.21 (0.71, 2.07); p>0.05 *Active:* 1.09 (0.28, 4.19); p>0.05 >4 hr/day of TV viewing time: *Inactive:* 1.62 (1.01, 2.58); p<0.05 *Active:* 1.13 (0.29, 4.33); p>0.05 **ELSA cohort** 3.7-5.6 hr/day (women); 3-5 hr/day (men) *<10 MET-hr/wk:* 0.84 (0.49, 1.45); p>0.05 *10-16 MET-hr/wk:* 1.30 (0.67, 2.53); p>0.05 *>16 MET-hr/wk:* 1.04 (0.23, 4.73); p>0.05 >5.6 hr/day (women); >5 hr/day (men): *<10 MET-hr/wk:* 1.06 (0.63, 1.78); p>0.05 *10-16 MET-hr/wk:* 1.41 (0.74, 2.68); p>0.05 *>16 MET-hr/wk:* 4.89 (1.46, 16.4); p<0.05
Ribeiro 2016[8] (n= 432)	Age, sex, frailty scores at baseline, fruit and vegetable intake, all physical activity variables	Residual change score linear regression	Not reported	β-coefficients (SE) for FRAIL scale residual change scores: Leisure walking: -0.04 (0.01); p<0.05

Woo 2010[14] (n= 3378)	Age, sex, socioeconomic status and living district	Path analysis	Not reported	Standardized β-regression coefficient (no SE or 95% CI reported) for the log FI and the PASE score as a continuous measure: -0.1070; p<0001
Rogers 2017[17] (n= 8649)	Main effects for survey wave, age, cohort (divided into 5 year age groups), baseline PA; two way interaction terms (wave x age cohort; wave x PA; age cohort x PA); and three-way interactions (age cohort x wave x PA). Quadratic term added for time and age	Multilevel growth curve models	Not reported. Frailty analyzed as a continuous outcome	β-coefficient (95% CI) for trajectories of frailty using the two-way interaction term for survey wave and PA for each 5 year age group (sedentary group as reference): <u>50-54 years:</u> *Mild:* -0.006 (-0.017, 0.016); p=0.95 *Moderate*: -0.021 (-0.036, -0.007); p= 0.004 *Vigorous:* -0.031 (-0.046, -0.016); p<0.0001 <u>55-59 years:</u> *Mild:* 0.009 (-0.007, 0.026); p=0.30 *Moderate:* -0.009 (-0.024, 0.005); p=0.21 *Vigorous:* -0.025 (-0.040, -0.011); p=0.001 <u>60-64 years:</u> *Mild:* 0.013 (-0.004, 0.030); p=0.12 *Moderate:* -0.007 (-0.021, 0.008); p=0.38 *Vigorous:* -0.019 (-0.035, -0.004); p=0.012 <u>65-69 years:</u> *Mild:* -0.008 (-0.024, 0.008); p=0.31 *Moderate:* -0.034 (-0.047, -0.021); p<0.0001 *Vigorous:* -0.040 (-0.054, -0.027); p<0.0001 <u>70-74 years:</u> *Mild:* 0.001 (-0.017, 0.018); p=0.95 *Moderate:* -0.028 (-0.044, -0.012); p=0.001 *Vigorous:* -0.036 (-0.053, -0.019); p<0.0001 <u>75-79 years:</u>

				Mild: -0.005 (-0.015, 0.023); p=0.64 *Moderate:* -0.024 (-0.042, -0.007); p=0.005 *Vigorous:* -0.044 (-0.062, -0.025); p<0.0001 80+ years: *Mild:* -0.014 (-0.031, 0.004); p=0.13 *Moderate:* -0.039 (-0.054, -0.023); p<0.0001 *Vigorous:* -0.061 (-0.081, -0.042); p<0.0001
Cross-sectional studies				
Bastone 2015[18] (n= 26)	Number of chronic conditions	Multivariable logistic regression	N/A	Light intensity (per min/day): OR (95% CI) for being frail: 0.98804 (0.977476–0.998718); p<0.05 Moderate intensity (per min/day): OR (95% CI) for being frail: 0.893769 (0.818946–0.975429); p<0.05 Steps (per day): OR for being frail: 0.999012 (95% CI: 0.998196–0.999829); p<0.05
Eyigor 2015[21] (n= 1126)	Depressive symptoms, ambulation, fatigue, use of prescription drugs, sex, sedentary, hearing problems, admission to emergency service, malnutrition,	Multinomial logistic regression analysis		OR (95% CI) for frailty (unclear what reference group is and if for being frail): 4.378 (2.010-9.536); p<0.0001
Ko 2016[25] (n=3460)	Not clear. Each variable served as a risk factor: Age, education, family assets, marital status, living arrangement, region, smoking status, alcohol consumption, weight loss, depression	Multinomial logistic regression		OR (95% CI) for being moderate-severely frail compared to the Non-frail group: 1.57 (1.17-2.10); p<0.01

Woo 2015[27] China (n= 7298)	Age, sex, marital status, education, alcohol consumption, chronic conditions, prescription drug use	Logistic regression		OR (95% CI) for being frail with active group as reference: Beijing urban group: 1.75 (1.49-2.05); p<0.05 Hong Kong group: 1.71 (1.41-2.07); p<0.05
Kramer 2017[30] (n= 219)	Age, BMI, quality of life	Multinomial linear regression		OR (95% CI) for every additional hour increase in PA per day: For being frail: 0.71 (0.50-0.99); p<0.05 For being pre frail: 0.81 (0.67-0.99); p<0.05
Schwenk 2015[32] (n= 125)	Age	Multinomial logistic regression		OR (95% CI) for being pre-frail per 100 steps/day: 0.97 (.96 – .99); p<0.0001 OR (95% CI) for walking bout duration variability (sec): Pre-frail vs. non-frail: 0.97 (0.93 – 1.002); p>0.05 Frail vs. pre-frail: 0.90 (0.83 – 0.99); p<0.05
Blodgett 2015[19] (n= 3146)	Age, sex, accelerometer wear time, race, marital status, total sedentary time	Multivariable linear regression	N/A	MVPA (hr/day): β-coefficient (SE): −0.045 (0.009); p<0.001

Gobbens 2016[22] (n= 610)	Not clear, but assuming age, sex, marital status, education, income, multi morbidity, smoking, alcohol consumption, vegetable and fruit intake, eating breakfast, teeth brushing	Multivariable linear regression		β-coefficient (SE) for being inactive: Total frailty: 0.394 (0.274); p=0.151. Physical frailty: 0.420 (0.173); p=0.016 Psychological frailty: -0.030 (0.120); p=0.806 Social frailty: 0.003 (0.104); p=0.978
Hoogendijk 2015[23] (n= 484)	Age, sex, education	Multivariable linear regression		β-coefficient (SE) for the FI and being inactive: 0.106 (0.011); p<0.001
Jansen 2015[24] (n= 74)	Age, sex, self-reported health status	Bootstrapped linear regression		β-coefficient (95% CI) for how many minutes spent in physical activity intensities, with non-frail as reference category: Light intensity (min/week): -31.183 (-249.189, 219.499); p=0.790 MVPA (min/week): -5.214 (-13.778, 3.116); p=0.187 MET-minutes/week: -645.342 (-1720.834, 475.839); p= 0.221

Stephan 2016[26] (n= 960)	Age, sex, BMI, smoking status, alcohol consumption, marital status, income, education	Negative binomial regression		β-coefficient (95% CI) for FI based on LTPA quartiles (1st quartile as reference group): <u>2nd quartile:</u> −0.17 (−0.27, −0.07); p=0.0011 <u>3rd quartile:</u> −0.27 (−0.38, −0.17); p<0.001 <u>4th quartile:</u> −0.36 (−0.47, −0.25); p<0.001 β-coefficient (95% CI) for FI based on household PA quartiles (1st quartile as reference group): <u>2nd quartile</u>: −0.17 (−0.27, −0.07); p=0.0011 <u>3rd quartile:</u> −0.27 (−0.38, −0.17); p<0.001 <u>4th quartile:</u> −0.36 (−0.47, −0.25); p<0.001
Young 2016[28] (n= 3375)	Age and "other covariates"	Multiple linear regression with a square root transformation to the FI		Unstandardized regression coefficients (no SE or 95% CI reported) for the continuous square root transformed FI (inactive as reference group): <u>Light:</u> -0.038; p<0.001 <u>Moderate:</u> -0.062; p<0.001 <u>Vigorous:</u> -0.086; p<0.001

Castaneda-Gameros 2017[29] (n= 60)	Age, marital status, number of comorbidities, index of multiple deprivation, BMI, religion, accelerometer wear time, MVPA	Linear regression		β-coefficient (SE) for continuous Fried frailty score excluding self-report PA; <u>MVPA log transformed:</u> -0.54 (0.24); p=0.04
Cawthon 2007[20] (n= 5993)	Age-adjusted means	Least square means	N/A	<u>Mean PASE score (95% CI):</u> Non-frail: 173.0 (170.9-175.0) Pre-frail: 117.8 (115.4-120.2) Frail: 62.9 (55.3-70.6)*
Roland 2012[31] (n= 30)	Age	Two-way ANCOVA		ANCOVA results presented in previous column (Non-frail had higher total step counts/day and % time in light intensity PA than Frail participants) <u>Total step counts (per day):</u> *Non-frail*: 5624 ± 3309* *Pre-frail:* 3019 ± 3290 *Frail:* 1636 ± 1599 <u>% time spent in light intensity PA:</u> *Non-frail*: 39.4 ± 7.4* *Pre-frail*: 28.6 ± 10.2 *Frail*: 25.2 ± 8.2

BMI; body mass index. SD; standard deviation. HDL; high density lipoprotein. OR; odds ratio. CI; confidence interval. MET; metabolic equivalent. IADL; instrumental activities of daily living. NS; not significant. HR; hazard ratio. FI; frailty index. PA; physical activity. PASE; physical activity scale for the elderly CVD; cardiovascular disease. TV; television. RR; relative risk. Seniors-ENRICA; Social Inequalities in Cardiovascular Risk Factors Among Older Adults in Spain. MEDAS; Mediterranean diet adherence screener. ELSA; English Longitudinal Study on Aging. SE; standard error. N/A; not applicable. MVPA; moderate-vigorous physical activity. LTPA; leisure-time physical activity. ANCOVA; analysis of covariance.
*Statistically significantly different between non-frail and frail and/or non-frail and pre-frail/frail or across frailty groups

No studies found a non-significant association when physical activity and frailty were analyzed as categorical responses. Five studies[3,12,18,30,32] that examined physical activity as a continuous variable and frailty as a categorical outcome reported a significant dose-response; whereas, there was no dose-response detected in one study.[5] When physical activity was assessed categorically and frailty assessed as a continuous outcome (n= 6 studies), all six studies found a significant association between the most active vs. least active group.[8,17,22,23,26,28] Five studies found an associated lower frailty score when assessed as a continuous outcome and when physical activity was assessed as a continuous exposure.[14,19,20,29,31] One study found no association between physical activity levels and frailty when both parameters were measured as continuous outcomes.[24]

Sedentary behavior-frailty relationship

Eleven studies (n= 16,340) investigated the link between sedentary behaviors and frailty status.[3,5,8,10,16,18,19,21,24,29,31] Table 2.1 describes the manner in which sedentary behavior was measured amongst the included studies. Four studies measured sedentary time by questionnaire[3,8,10,16] and six studies by accelerometry.[5,18,19,24,29,31] One study did not report the tool used to measure sedentary time.[21] Of the studies using self-report measures, three studies measured television viewing time only.[3,10,16] Sedentary time was analyzed as a categorical response in two studies[16,21] and as a continuous response in ten studies.[3,5,8,10,16,18,19,24,29,31]

The analytical approach and outcomes describing the association between sedentary behaviors with frailty in the reviewed papers are provided in Table 2.3.

Table 2.3. Association between sedentary behavior and frailty

Reference ID/sample size	**Adjustment variables**	**Statistical analysis**	**Number frail at follow up (prospective studies)**	**Effect estimates**
Prospective cohort studies				
García-Esquinas 2015[3] Spain (n= 1750)	Age, sex, education level	Logistic regression	Frail: 115 (6.6%)	OR (95% CI) for every additional hour/day increase in television viewing: 1.02 (1.01-1.04)
Song 2015[5] (n= 1333)	age, gender, race, marital status, education, income, BMI, comorbidity, depressive symptoms, knee and hip osteoarthritis, knee and hip symptoms, general pain, smoking status, alcohol consumption, moderate intensity physical activity	discrete-time survival regression by applying a generalized linear model	Frail: 20.7 per 1000 person years over 2 year follow-up	HR (95% CI) for every hour/day increase in total sedentary time for onset of frailty: 1.36 (1.02-1.79); p=0.033 HR (95% CI) for every 10% increase in time spent sedentary during waking time: 1.55 (1.04-2.32); p=0.033
Soler-Vila 2016[10] (n= 1857)	Age, number of frailty criteria (0, 1 or 2) at baseline	Multivariable logistic regression	Frail: 133 (7.2%)	OR (95% CI) for incident frailty by sex: Watching TV (hr/wk): Males: 1.11 (0.96-1.29) Females: 1.13 (1.03-1.23) Seated in transportation (hr/wk): Males: 1.01 (0.59-1.75) Females: 0.55 (0.24-1.26) Reading (hr/wk): Males: 0.78 (0.60-1.00) Females: 0.84 (0.67-1.06) Listening to music (hr/wk): Males: 0.61 (0.30-1.24) Females: 0.88 (0.62-1.26)

García-Esquinas 2017[16] (n= 6381)	Age, sex, education, BMI, tobacco consumption, PA, CVD, diabetes, chronic lung disease, osteomuscular disease, total energy intake (Seniors-ENCRICA only), MEDAS index (Seniors-ENCRICA only).	Random effects meta-analysis from logistic regression results of both cohorts	Not reported	Random-effect meta-analysis OR (95% CI) for incident frailty based on tertiles of TV viewing time (lowest tertile as reference): Tertile 2: 1.10 (0.80-1.51); p>0.05 Tertile 3: 1.47 (1.09-1.97); p<0.05 Random effects meta-analysis OR (95% CI) per hour increase in in TV viewing time (hr/day): 1.05 (0.95-1.13); p>0.05
Ribeiro 2016[8] (n= 432)	Age, sex, frailty scores at baseline, fruit and vegetable intake, all physical activity variables	Residual change score linear regression	Not reported	β-coefficient (SE): Sitting (every hr/day increase): 0.10 (0.05); p=0.02
Cross-sectional studies				
Bastone 2015[18] (n= 26)	Number of chronic conditions	Multivariable logistic regression	N/A	Total sedentary time (per min/day): OR (95% CI) for being frail: 1.010916 (95% CI: 1.00127–1.020655); p<0.05
Eyigor 2015[21] (n= 1126)	Depressive symptoms, ambulation, fatigue, use of prescription drugs, sex, recreational walking, hearing problems, admission to emergency service, malnutrition	Multinomial logistic regression analysis	N/A	OR (95% CI) for frailty (reference group unclear; likely compared to recreational walkers): 11.880 (5.415- 26.065); p<0.0001
Blodgett 2015[19] (n= 3146)	Age, sex, accelerometer wear time, race, marital status, MVPA	Multivariable linear regression	N/A	Total sedentary time (per hr/day): β-coefficient (SE): 0.016 (0.002) p<0.001
Jansen 2015[24] (n= 74)	Age, sex, self-reported health status	Bootstrapped linear regression	N/A	β-coefficient (95% CI) for how many minutes spent in sedentary behavior: -5.499 (-88.958, 63.011); p= 0.873

Castaneda-Gameros 2017[29] (n= 60)	Age, marital status, number of comorbidities, index of multiple deprivation, BMI, religion, accelerometer wear time, MVPA	Linear regression	N/A	β-coefficient (SE) for continuous Fried frailty score excluding self-report PA; <u>SB time (min/day):</u> -0.00 (0.00); p=0.79
Roland 2012[31] (n= 30)	Age	Two-way ANCOVA	N/A	ANCOVA results presented in previous column (Non-frail had lower total percent time spent in SB than frail participants) <u>% time spent in SB:</u> <u>*Non-frail:*</u> 49.39 ± 9.5* <u>*Pre-frail:*</u> 66.4 ± 14.6 <u>*Frail:*</u> 71.9 ± 11.3

OR; odds ratio. CI; confidence interval. BMI; body mass index. HR; hazard ratio. TV; television. PA; physical activity. CVD; cardiovascular disease. Seniors-ENRICA; Social Inequalities in Cardiovascular Risk Factors Among Older Adults in Spain. MEDAS; Mediterranean diet adherence screener. ELSA; English Longitudinal Study on Aging. SE; standard error. MVPA; moderate-vigorous physical activity. SB; sedentary behavior. ANCOVA; analysis of covariance.

Longitudinal designs are listed first, followed by cross-sectional studies. Effect estimates using an odds ratio, relative risk, hazard ratio are listed first, followed by β-coefficients and mean differences. Five studies used a longitudinal design[3,5,8,10,16] and six studies were cross-sectional.[18,19,21,24,29,31] The proportion of frail participants at follow-up ranged from 6.6%[3] to 7.2%.[10] Two studies did not report frailty status at follow up.[8,16] Nine out of eleven studies found a significant detrimental association between higher levels of sedentary time and frailty.[3,5,8,10,16,18,19,21,31] The two non-significant studies had sample sizes that were less than 100, and used cross-sectional designs.[24,29] For studies analyzing sedentary time as a categorical response and frailty as a categorical outcome, compared those categorized as accumulating the least amount of sedentary time, the odds ratios or hazard ratios ranged from 1.47[16] to 11.88[21] for individuals categorized in the highest sedentary group. Five out of six studies that examined sedentary behavior as a continuous exposure and frailty as a categorical outcome found a significant dose response relationship with higher levels of sedentary time and higher frailty scores.[3,5,10,18,19] The largest study (n= 6381) that combined the Seniors-ENRICA and ELSA cohorts found a significant detrimental association with frailty across tertiles of television viewing time, while the television viewing score as a continuous variable was non-significant.[16] One study found that the age-adjusted percentage of time spent in sedentary behavior was higher in frail versus non-frail participants.[31] Three studies found a significant detrimental association between higher levels of sedentary time and frailty when both were assessed continuously,[8,19,31] while two studies did not.[24,29]

Secondary outcomes

Sex-specific associations between physical activity and sedentary behaviors with frailty

One study examined if there was a sex-specific association between physical activity and frailty,[26] and two studies examined the differential association between sedentary behavior and frailty by sex.[10,16] For physical activity behavior in the study by Stephan et al.,[26] they report that while females had a higher FI score, adding a sex-specific interaction term to their negative binomial regression model was not statistically significant for either leisure time physical activity or household physical activity. Those authors did not provide results from a sex-stratified analysis.

Soler-Vila and colleagues[10] provide a stratified analysis by sex for the relationship between sedentary behavior and frailty. Their study revealed a detrimental association with higher levels of television viewing time, measured in hours per week, in females (hazard ratio for incident frailty: 1.13 (95% CI, 1.03-1.23) but not males (hazard ratio: 1.11 (95% CI, 0.96-1.29). No interaction term by sex was included in that study. The study by Garcia-Esquinas et al.[16] included a stratified analysis by sex for tertiles of television viewing time and incident frailty, and included a sex interaction term. Data are provided for both cohorts used in that study (Seniors-ENRICA and ELSA). In their stratified analyses, they showed no significant association between sedentary time and frailty in men or women. There was also no significant sex-interaction effect in the models.

CVD-specific associations between physical activity and sedentary behaviors with frailty

No studies evaluated if the presence of pre-existing CVD modified the association between physical activity or sedentary behaviors with frailty.

Relationship between bouts of physical activity and patterns of sedentary behaviors with frailty

No studies determined if bouted or sporadic physical activity were similarly associated with frailty.

No studies measured if the frequency and intensity of breaks from sedentary time were associated with frailty. Measures of the average length of sedentary bouts and average duration of breaks from sedentary time were measured in the study by Schwenk et al.[32] In their study, they completed age-adjusted logistic regression to determine if the average duration of walking, standing, and in a lying position were associated with frailty. The authors did not report the odds ratios for average duration of standing or in a lying position, but reported that there was no statistically significant association between those variables with frailty. The average bout duration of walking (per second) was significantly associated frailty versus pre-frailty according to the Fried criteria (odds ratio: 1.11 (95% CI, 1.01-1.20).[32] No significant association was found in the age-adjusted model for average walking bout duration and being pre-frail versus non-frail.

Summary and knowledge gaps

This systematic search of the literature revealed that previous investigations generally found a protective association between a more physically active lifestyle and frailty. Furthermore, the majority of studies indicated a significant detrimental association between higher levels of sedentary behaviors and frailty. However, there was significant heterogeneity in the way in which physical activity, sedentary behavior, and frailty were measured. These methodological differences make it difficult to quantitatively pool the evidence concerning these relationships.

There were no studies that determined if bouted or sporadic MVPA were similarly associated with frailty. North American and World Health Organization physical activity guidelines recommend that older adults accumulate at least 150 minutes through bouted MVPA.[34-36] However, meeting these guideline recommendations may not be feasible for the frail adult.[19,24] Meeting the physical activity guidelines through sporadic MVPA may be a more feasible approach to improve frailty status among older adults, but this possibility needs further exploration.

This knowledge synthesis also revealed the lack of data describing the relationships between patterns sedentary behaviors with frailty. Only one study reported that the average duration of walking behavior was associated with a lower odds of frailty.[32] However, that study only adjusted for age in their statistical model and did not control for other patterns of physical activity or sedentary behaviors. Targeting reductions in prolonged sedentary behaviors may be a feasible strategy to influence frailty status than adopting and sustaining a more physically active lifestyle. However, this review found that studies only examined total sedentary time rather than a collection of sedentary behavior parameters. The way in which sedentary time is interrupted may be important for health benefits, as evidence suggests that the intensity and duration of breaks in sedentary time are associated with cardio-metabolic outcomes in older adults.[37] Even so, the possibility that breaking up prolonged sedentary time with higher intensity breaks of longer duration to reduce frailty remains to be investigated. Such data may help inform the development of public health recommendations to reduce sedentary behaviors in adults.

This knowledge synthesis found that few studies have determined if there are sex differences in the association between physical activity and sedentary behaviors with frailty. In fact, only three studies evaluated if there are sex differences in the association between physical activity (n= 1 study) and sedentary time (n= 2 studies) with frailty. Only one study found that longer self-reported television viewing time was associated with incident frailty in females, but not males.[10] Therefore, more evidence is needed to determine if there are sex differences in the association between physical activity and sedentary behaviors with frailty. These data may be important to provide more tailored recommendations for females and males that might be more achievable and sustainable in the frail adult.

No studies determined if CVD status affected the physical activity/sedentary behavior and frailty relationship. It is known that there is a bi-directional relationship between frailty and CVD as they both develop as a consequence of the activation of inflammatory pathways.[38,39] Given these unique consequences and the mechanistic link between frailty and CVD, it is important to determine if physical activity and sedentary behaviors are differentially associated with frailty.

CHAPTER 3: THE ASSOCIATION BETWEEN BOUTS OF MODERATE TO VIGOROUS PHYSICAL ACTIVITY AND PATTERNS OF SEDENTARY BEHAVIOR WITH FRAILTY

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Abstract

Background: This study determined if bouts of moderate-vigorous physical activity (MVPA) and patterns of sedentary behavior are associated with frailty.

Method: Accelerometry from community-dwelling adults ≥50 years old (n=2317) enrolled in the 2003-04/2005-06 National Health and Nutrition Examination Survey were used. Bouted (≥10 minutes) and sporadic (<10 minutes) durations of MVPA were analyzed based on meeting 0%, 1-49%, 50-99%, and ≥100% of physical activity guidelines (150 min/week of MVPA). Prolonged sedentary behavior were bouts lasting ≥30 minutes. Breaks from sedentary behavior were defined as any ≥1 minute interruption in sedentary behavior. Average intensity (counts/min) and duration (minutes) during breaks were also analyzed. Frailty was measured with a 46-item frailty index.

Results: Linear regression models adjusting for demographics, total sedentary time and accelerometer wear time indicated that meeting any percentage of the activity guidelines with bouted and sporadic MVPA was associated with a lower frailty index. This relationship peaked at meeting 50-99% of guidelines and was associated with a 1.5 and 2.0 point lower frailty index scores for bouted and sporadic MVPA, respectively. Two additional prolonged sedentary behaviour bouts/day were associated with an additional frailty index deficit while every additional 100 counts/min in average break intensity and every two minutes in average break duration were associated with one less deficit. Total sedentary breaks were not associated with frailty.

Conclusion: These population-level data are the first to show that different patterns of MVPA and sedentary behaviour are associated with frailty. Interventions are needed to determine if modifying these parameters reduce frailty.

Publication status

This study has been submitted to Experimental Gerontology. Revisions have been requested.

Introduction

Globally, the number of older adults is increasing.[40] With aging comes a milieu of complications that coexist on various levels, including differences in biology, the presence of morbidities, functional status, and lifestyle, which results in some adults having a more favorable health prognosis than others despite being the same age.[41] These differences can be referred to as *frailty*. Frailty is characterized by a decrease in reserve and resistance to stressors as a consequence of the dysfunction of physiological systems that leaves an individual vulnerable to stressors.[42] Independent of age, frailty is linked to poor health outcomes and increased healthcare expenditures.[43,44] Therefore, strategies are needed to prevent the onset of worsening health in this vulnerable population.

It is recommended that physical activity should be a part of treatment and prevention strategies to combat frailty.[45] Evidence from randomized trials indicate that physical activity, either in isolation or as part of a multicomponent intervention, has the potential to prevent or reverse frailty.[46] However, the amount and intensity of physical activity required to positively influence frailty is not clear.[47] North American and World Health Organization physical activity guidelines recommend that older adults accumulate at least 150 minutes of moderate to vigorous intensity physical activity (MVPA) in continuous bouts of $\geq$10 minutes per week.[34-36] However, meeting these guideline recommendations may not be feasible for the frail adult.[19,24] Evidence suggests that sporadic MVPA is associated with improved cardio-metabolic outcomes, independent of bouted MVPA.[48] Meeting the physical activity guidelines through sporadic MVPA may be a more feasible approach to improve frailty among older adults, but this possibility has not been explored.

Targeting sedentary behavior may represent a feasible strategy to improve frailty in older adults. In fact, total sedentary time is linked to higher levels of frailty independent of one's physical activity behaviors.[19] Sedentary behaviors are viewed as a distinct class of behavior from that of a lack of physical activity, and have been defined as any waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents while in a seated or reclining position.[49] However, the manner in which to reduce total sedentary time that influences frailty needs further investigation. Evidence suggests minimizing prolonged bouts of sedentary time as a way to improve cardio-metabolic outcomes.[50] Furthermore, the way in which sedentary time is interrupted may be important for health benefits, as evidence shows that the intensity and duration of breaks in sedentary time are associated with cardio-metabolic outcomes in older adults.[37]

Providing evidence concerning the degree to which different patterns of physical activity and sedentary behavior influence frailty might inform novel and feasible approaches to target frailty in adults. Therefore, the objectives of this study are to determine if sporadic and bouted MVPA are similarly associated with frailty. As well, this study determined if prolonged bouts of sedentary time, and if the frequency, intensity and duration of breaks from sedentary time are associated with frailty.

Methods

Additional details of the study methodology can be found in the supplemental content. Data from the National Health and Nutrition Examination Survey (NHANES) cycles 2003-2004 and 2005-2006 were used. Participants aged 50-85 years old were included in the study who wore an accelerometer for ≥4 days, at least 10 hours/day.

Frailty was measured using an accumulation of deficits model frailty index (FI) that has previously been used in NHANES.[19] The FI consisted of 46 health deficits, including signs, symptoms, chronic conditions, impairments in activities of daily living, and laboratory variables (see Appendix 1). Participants were excluded if they were missing >20% FI variables. The FI was converted into a score from 0-100.

The amount of MVPA was measured with hip-mounted Actigraph accelerometers over a 7-day period, as well as sedentary behaviors over each minute. The thresholds for sedentary behavior and MVPA were <100 counts/min and >2020 counts/min, respectively. MVPA was classified as bouted or sporadic. Bouted MVPA was defined as activity accumulated in ≥10 minutes, with two allowable consecutive minutes out of 10 minutes to drop below the MVPA intensity threshold. Sporadic MVPA was classified as any MVPA accumulated in <10 minutes with no allowable drop in intensity.

Prolonged sedentary bouts were defined as sedentary time accumulated in ≥30 minutes without interruption. A break from sedentary time was defined as any ≥1 minute interruption in sedentary time. The average intensity, measured in counts/min, and duration of sedentary breaks, measured in minutes, were also captured.

Statistical analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina) and used SAS survey procedures. Mean ± standard error and frequency (percent) are provided for continuous and categorical variables, respectively. Descriptive variables between included and excluded participants were compared with a t-test or Chi-square test for continuous and categorical variables, respectively.

Simple linear regression was first used to determine the association between bouted and sporadic MVPA, as well as the sedentary bout and break variables, with frailty. Bouted and sporadic MVPA were converted into four groups based on meeting a percentage of the physical activity guidelines of 150 minutes of MVPA per week: 0%, 1-49%, 50-99%, and ≥100% of the aerobic component of the North American and World Health Organization physical activity guidelines. Multivariable linear regression models were subsequently used. An age, sex, and accelerometer wear time adjusted model was initially completed for each physical activity and sedentary bout/break variable individually to determine their association with frailty, followed by a fully adjusted model. Fully adjusted models controlled for age, sex, ethnicity, education, income, marital status, smoking status, alcohol consumption, body mass index, total sedentary time, and total accelerometer wear time. Subsequently, the bouted and sporadic MVPA groups were added to a fully adjusted model, and the prolonged sedentary bout and break variables in a separate model. Lastly, the bouted MVPA group variable and sedentary bout and break variables were included in a fully adjusted model. Sporadic MVPA was excluded from the fully adjusted model due to the high correlation ($r>0.75$) with average break intensity. An alpha of 0.05 was used to test for statistical significance.

Results

Study population

Of the 20470 participants available in the 2003-06 NHANES cohorts, 3177 were ≥50 years old and had valid accelerometer data. After removing participants who were missing more than 20% of FI data and missing covariates (n= 860), a total of 2317 individuals were eligible for analysis. Descriptive variables between those who were included in the analyses versus those who were excluded (n= 252) and were ≥50 years old with valid accelerometer and FI data are available in Table 3.1. Compared to the included sample, excluded participants were not different except for race/ethnicity, and their average break intensity was lower.

Table 3.1. Characteristics of community-dwelling American adults aged 50 years or older

Variable	Included sample n=2317 Mean (SE) or n and frequency (%)	Excluded sample n=252 Mean (SE) or n and frequency (%)	p-value
Age	67.4 (0.32)	68.8 (0.90)	0.1484
Frailty index	0.22 (0.004)	0.23 (0.010)	0.3022
Gender (% female)	1143 (49.3%)	126 (50.0%)	0.5869
Weight (kg)	80.02 (0.50)	78.56 (1.87)	0.4557
Body Mass Index (kg/m^2)	28.56 (0.18)	28.60 (0.53)	0.2879
Race/ethnicity			**<.0001**
Mexican American	**424 (18.3%)**	**37 (14.7%)**	
Other Hispanic	**39 (1.7%)**	**5 (2.0%)**	
Non-Hispanic white	**1408 (60.8%)**	**142 (56.3%)**	
Non-Hispanic black	**385 (16.6%)**	**45 (17.9%)**	
Other	**61 (2.6%)**	**23 (9.1%)**	
Education			0.2984
Less than 12th grade	804 (34.7%)	105 (41.7%)	
High school/GED equivalent	584 (25.2%)	60 (23.8%)	
Some college	528 (22.8%)	45 (17.9%)	
College grad or higher	401 (17.3%)	38 (15.1%)	
Marital status			0.0822
Married/common law	1442 (62.2%)	139 (55.2%)	
Widowed	477 (20.6%)	74 (29.3%)	

Divorced/separated	311 (13.4%)	27 (10.7%)	
Never married	87 (3.8%)	11 (4.4%)	
Annual household income*			
<$20,000	695 (30.0%)		
$20,000-$34,999	640 (27.6%)		
$35,000-$54,999	467 (20.2%)		
$55,000-$74,999	197 (8.5%)		
>=$75,000	318 (13.7%)		
Alcohol intake*			
Does not drink	1902 (82.1%)		
<1 drink/day	258 (11.1%)		
1-2 drinks/day	76 (3.3%)		
>2 drinks/day	81 (3.5%)		
Smoking status			0.4813
Non-smoker	1012 (44.1%)	121 (48.0%)	
Previous smoker	969 (41.8%)	90 (35.7%)	
Current smoker	327 (14.1%)	40 (15.9%)	
Bouted MVPA (min/week)	29.75 (2.09)	32.05 (6.12)	0.7417
Sporadic MVPA (min/week)	52.68 (1.78)	47.60 (4.53)	0.3353
Meeting guidelines of 150 min/week with bouted MVPA			0.8442
≥100% of guidelines	150 (5.8%)	16 (6.3%)	
50-99% of guidelines	162 (6.3%)	16 (6.3%)	
1-49% of guidelines	443 (17.2%)	37 (14.7%)	
0% of guidelines	1815 (70.6%)	183 (72.6%)	
Meeting guidelines of 150min/week with sporadic MVPA			0.5182
≥100% of guidelines	173 (6.7%)	14 (5.5%)	
50-99% of guidelines	364 (14.2%)	39 (15.4%)	
1-49% of guidelines	1726 (67.2%)	162 (64.2%)	
0% of guidelines	307 (11.9%)	37 (14.7%)	
Total sedentary time (hr/day)	8.77 (0.05)	9.13 (0.22)	0.1226
Sedentary bouts lasting ≥30 min (per day)	3.60 (0.04)	3.90 (0.18)	0.1367
Number of breaks from sedentary time (per day)	87.66 (0.55)	86.83 (1.36)	0.5786
Avg break intensity (counts/min)	**414 .06 (2.69)**	**395.43 (7.50)**	**0.0373**
Avg break duration (min)	3.70 (0.04)	3.56 (0.12)	0.3311

MVPA; Moderate-vigorous physical activity
Bold indicates statistical significance
*Due to the high number of missing values for household income (n=129) and alcohol consumption (n=99) for the excluded group, these data were not summarized and compared to the eligible group.

For the included sample, the average age was 67 and 49% were female. The average

FI was 0.22±0.004. The majority of individuals were Caucasian, did not drink alcohol and most were either non-smokers or had quit smoking. Participants, on average, wore the accelerometer for 6.30±0.03 days, 14.1±0.06 hours/day. The eligible sample accumulated about 30 and 50 minutes/week of bouted and sporadic MVPA, respectively. Nearly 6% of the cohort achieved the physical activity guidelines of 150 minutes/week with bouted MVPA, and almost 7% met the guidelines through sporadic MVPA. Participants were sedentary approximately 9 hours/day.

Association of bouts of MVPA and Frailty

The univariate and multivariable linear regression models testing bouted and sporadic MVPA variables individually can be viewed in Table 3.2. Compared to those meeting 0% of the physical activity guidelines, meeting a higher percentage of the guidelines through bouted and sporadic MVPA had a protective association with frailty in the univariate, age, sex, and accelerometer adjusted, and the fully adjusted models. The bouted and sporadic MVPA group estimates were similar for those meeting 50-99% and ≥100% of the physical activity guidelines when compared against those meeting 0% of the guidelines.

Table 3.2 shows the adjusted models when bouted and sporadic MVPA were combined into a single model (Model 1). Compared to those meeting 0% of the physical activity guidelines, achieving any percentage of the guidelines was independently associated with a lower FI. Estimates were similar between meeting 50-99% or ≥100% of the guidelines for both bouted and sporadic MVPA. After adding the sedentary behavior pattern variables to a model with bouted MVPA (Model 3), the protective association between bouted MVPA with frailty by meeting a higher percentage of the physical activity guidelines was attenuated (Table 3.3).

Table 3.2. Univariate, age-sex adjusted and fully adjusted multivariable linear regression models examining the individual associations between bouts of MVPA and patterns of sedentary behaviors with frailty.

Variables	Univariate			Age, sex and accelerometer wear time adjusted			Fully adjusted		
PHYSICAL ACTIVITY VARIABLES	**β-coefficient**	**SE**	**P-value**	**β-coefficient**	**SE**	**P-value**	**β-coefficient**	**SE**	**P-value**
Meeting guidelines of 150 min/week with bouted MVPA									
≥100% guidelines	-8.813	1.006	<.0001	-7.898	0.947	<.0001	-4.059	0.964	0.0002
50-99% guidelines	-8.753	0.838	<.0001	-6.849	0.868	<.0001	-3.648	0.777	<.0001
1-49% guidelines	-6.124	0.749	<.0001	-4.761	0.757	<.0001	-2.596	0.586	0.0001
0% guidelines		Ref.			Ref.			Ref.	
Meeting guidelines of 150min/week with sporadic MVPA									
≥100% guidelines	-14.291	1.472	<.0001	-12.156	1.610	<.0001	-5.824	1.702	0.0018
50-99% guidelines	-12.581	1.112	<.0001	-10.610	1.301	<.0001	-5.716	1.336	0.0002
1-49% guidelines	-6.696	0.893	<.0001	-5.815	1.008	<.0001	-3.737	1.116	0.0022
0% guidelines		Ref.			Ref.			Ref.	
SB BOUT/BREAK VARIABLES									
SB bouts lasting ≥30min (per day)	1.561	0.192	<.0001	1.782	0.200	<.0001	0.623	0.217	0.0075
Breaks in SB (every 10 per day)	-0.958	0.172	<.0001	-0.302	0.234	0.2071	-0.076	0.181	0.6783
Avg break intensity (per 100 counts/min)	-4.505	0.295	<.0001	-4.392	0.393	<.0001	-2.464	0.389	<.0001
Avg break duration (min)	-3.209	0.259	<.0001	-2.863	0.253	<.0001	-1.623	0.392	0.0003

Estimates of the regression coefficient are provided, with standard error and p-value. SB, Sedentary behavior; SE, standard error; MVPA, moderate-vigorous physical activity.

Model 1: No adjustment

Model 2: Adjusted for age and sex, and accelerometer wear time

Model 3: Adjusted for age, sex, ethnicity, education, annual household income, marital status, smoking status, alcohol consumption, BMI, total sedentary time, and accelerometer wear time

Table 3.3. Multivariable linear regression to examine the independent associations between bouts of MVPA and patterns of sedentary behaviors with frailty.

Variables	Model 1			Model 2			Model 3		
PHYSICAL ACTIVITY VARIABLES	**β-coefficient**	**SE**	**P-value**	**β-coefficient**	**SE**	**P-value**	**β-coefficient**	**SE**	**P-value**
Meeting guidelines of 150 min/week with bouted MVPA									
≥100% guidelines	-3.623	0.934	0.0005				-2.242	0.895	0.0179
50-99% guidelines	-3.304	0.798	0.0003				-2.804	0.866	0.0029
1-49% guidelines	-2.225	0.544	0.0003				-1.829	0.498	0.0009
0% guidelines	Reference.						Reference.		
Meeting guidelines of 150min/week with sporadic MVPA									
≥100% guidelines	-4.868	1.678	0.0069						
50-99% guidelines	-4.886	1.276	0.0006						
1-49% guidelines	-3.417	1.121	0.0048						
0% guidelines	Reference.								
SB BOUT/BREAK FROM SB VARIABLES									
SB bouts lasting ≥30min (per day)				1.140	0.297	0.0006	1.135	0.301	0.0007
Breaks from SB (every 10 per day)				-0.061	0.249	0.8087	-0.067	0.244	0.7853
Avg break intensity (per 100 counts/min)				-2.108	0.444	<.0001	-1.749	0.474	0.0009
Avg break duration (min)				-1.342	0.432	0.0041	-1.314	0.433	0.0050

Estimates of the regression coefficient are provided, with standard error and p-value. SB, Sedentary behavior; SE, standard error; MVPA, moderate-vigorous physical activity.

*All models are adjusted for age, sex, ethnicity, education, annual household income, marital status, smoking status, alcohol consumption, BMI, total sedentary time, and accelerometer wear time. Models are also adjusted for variables within the specific models presented

Model 1: Fully adjusted with physical activity variables only

Model 2: Fully adjusted with sedentary bout and break variables only

Model 3: Fully adjusted with bouted MVPA and sedentary bout and break variables

Association of Sedentary Behavior Patterns and Frailty

The univariate, age, sex and accelerometer wear time adjusted, and the fully adjusted model for individual sedentary behavior pattern variables are shown in Table 3.2. All sedentary behavior pattern variables were significantly associated with frailty in the univariate and age, sex, and accelerometer wear time adjusted models. Higher levels of prolonged sedentary bouts were detrimentally associated with frailty, while a higher frequency, intensity, and duration of sedentary breaks had a protective association with frailty. In the fully adjusted model, all sedentary behavior pattern variables were significantly associated with frailty except for the frequency of sedentary breaks. The relationship between prolonged sedentary bouts, and the average intensity and duration during sedentary breaks with frailty was attenuated, although still statistically significant in the fully adjusted models. After adding bouted MVPA to a fully adjusted model with the sedentary behavior pattern variables (Table 3.3, model 3), the strength of association between average break intensity and frailty was mitigated. The β-coefficients in this model for prolonged sedentary bouts and average break duration were similar in as in Model 2 in Table 3.3. The strength of association between prolonged sedentary bouts and average break duration with frailty in Model 3 were similar as in Model 2.

Sensitivity analysis adding total number of accelerometer wear days as a covariate

The total number of accelerometer wear days was added to the fully-adjusted models examining the independent associations between bouts of MVPA and patterns of sedentary behaviors. Adding total accelerometer wear days did not significantly influence the estimates in either fully adjusted model (data not shown).

Discussion

This representative study of ambulatory community-dwelling American adults ≥50 years old demonstrated that different patterns of physical activity and sedentary behavior are associated with frailty independent of demographic and behavioral variables, total sedentary time, and accelerometer wear time. Meeting a smaller percentage of the physical activity guidelines through bouted or sporadic moderate to vigorous physical activity was significantly associated with a lower FI, with the strength of the association being similar in those meeting 50-99% and ≥100% of the guidelines. Collectively, this information provides the basis for the development of strategies and guidelines to improve frailty status that might be more feasible for older adults.

To the author's knowledge, this is the first study to examine the associations between bouts of moderate to vigorous physical activity, patterns of sedentary behaviors, and frailty. In this study, few older adults met the physical activity guidelines of 150 minutes/week of MVPA, either with bouted or sporadic MVPA, which corroborates with previous studies.[19,51] Meeting a low percentage (1-49%) of the physical activity guidelines with bouted or sporadic MVPA was associated with a lower frailty score when examined in isolation and when also adjusted in a combined model (Table 3.2 and Table 3.3). The strength of the association was also not increased in those meeting ≥100% of the guidelines compared to meeting 50-99% of the guidelines. These data align with previous observational evidence concerning the health benefits of lower amounts of physical activity.[52] It is unclear, however, why no additional benefit was observed in participants achieving higher amounts of MVPA beyond the recommended guidelines and frailty. A recent study that pooled 11 different cohorts (n=63,591) found that individuals who reported accumulating 1-149 minutes per week of moderate intensity or 1-74 minutes per week of vigorous intensity physical activity had a similar lower risk in all-cause and cardiovascular mortality compared to those achieving ≥150 minutes of MVPA per week.[53] Collectively, these data suggest that lower quantities of MVPA are linked to improved health outcomes, and importantly lower amounts of physical activity may be more achievable in the frail adult. It is important to test the efficacy of implementing lower amounts of MVPA to improve frailty status, as randomized trials typically provide a larger dose of physical activity than was identified to be beneficial in the present study.[46]

Sporadic MVPA, which is defined as a duration of MVPA lasting less than 10 minutes, appeared to have a stronger association with a lower FI, as compared to bouted MVPA. This is a novel finding that could inform physical activity guidelines for older adults, which currently recommend that MVPA should be accumulated in bouts of 10 minutes or longer for health benefits.[34-36] More data are needed concerning the relationship between sporadic MVPA on other health outcomes of adults to support the implementation of sporadic MVPA as a guideline recommendation.

Previous studies demonstrate that sedentary behavior is associated with frailty independent of MVPA.[5,16,19] The present study extends those findings by demonstrating that prolonged bouts of sedentary time were associated with higher FI scores independent of total sedentary time. Thus, the finding that uninterrupted sedentary time lasting ≥30 minutes was associated with increased frailty levels independent of total sedentary time and bouted MVPA is novel and in keeping with other investigations examining prolonged bouts of sedentary time and health outcomes, including metabolic syndrome and physical function.[54,55] There is no universally accepted definition of prolonged sedentary time.[49] The 30 minute threshold was chosen as it seems to be the most consistently used in previous studies.[54-56] Further research is needed to develop a uniform definition of prolonged sedentary time.

Prolonged sedentary time was consistently associated with higher FI scores; whereas, average break intensity and average break duration were associated lower levels of frailty in all linear regression models, independent of bouted MVPA, total sedentary time, and total number of sedentary breaks (Table 3.3). In fact, this study is the first to show that prolonged sedentary time and the intensity and duration of breaks from sedentary time may be linked to frailty. From a clinical relevance standpoint, the data in the present study show that even two additional prolonged bout of sedentary time per day was independently associated with an additional FI deficit, while for every additional 100 counts/min in average break intensity and about every two minute duration increase in breaks from sedentary time as associated with one fewer FI deficits.

In this study, the total number of breaks from sedentary time were not significantly associated with frailty when controlling for bouted MVPA and other sedentary accumulation pattern variables (Table 3.2 and Table 3.3). These data contrast previous findings which indicated that total sedentary breaks are associated with cardio-metabolic outcomes in older adults.[37,50] These divergent findings may be a result of examining different outcomes (i.e., frailty versus cardio-metabolic outcomes) or possibly controlling for different covariates between the present study and previous findings. Even so, interrupting total and prolonged sedentary time may be a feasible approach to improve frailty status or in those who require assistance with walking or who are fatigued, as these populations tend to live a sedentary lifestyle.[57]

In regards to the implications of the findings in the present study, they may assist in developing novel lifestyle approaches in clinical practice to treat or prevent frailty. To the authors' knowledge, there are no experimental studies that have focused on interrupting extended periods of uninterrupted sedentary time to modify frailty. Such an approach may be used in isolation or in conjunction with physical activity-based interventions that have been delivered in previous studies.[46] If this approach could improve frailty and reduce fatigue, it might be more likely that these individuals could become more physically active for further health benefits.[58]

Another implication of the study findings suggest that public health recommendations should focus on messaging the benefits of a more physically active lifestyle in conjunction with reducing extended periods of sedentary time. In fact, there are no guidelines for older adults that provide recommendations to reduce their sedentary behaviors in North America. It is envisioned such recommendations could be made after further research into the sedentary behavior-frailty relationship is conducted. These future investigations are likely to be endorsed by geriatric and exercise physiology-based governing bodies.

Limitations

The results of this cross-sectional study are limited by potential confounding, and cannot draw conclusions towards the temporal association or causality between different patterns of physical activity or sedentary behavior with frailty. Despite the advantages of accelerometers over self-reported measures of physical activity, the accelerometers used in NHANES are uniaxial which can only accurately capture movement in the vertical plane. Given that activities of daily living are not limited to single-plane movements, this study may have underestimated physical activity levels.[59] Standard cut-points to classify intensity of physical activity and sedentary time for NHANES were used, which may have resulted in an underestimation of MVPA achieved in the study cohort. This approach was chosen because defining thresholds for sedentary behavior and intensity of physical activity in older adults is a challenge due to the heterogeneity in physical abilities of older adults, and there is no consensus on age or physical ability-specific intensity cut points to use.[60]

Conclusion

This study found that different accumulation patterns of physical activity and sedentary behavior are associated with frailty. The implementation of a “sitting less and moving more” strategy to prevent or treat frailty with sporadic or bouted physical activity and breaking up prolonged sedentary time with light to vigorous intensity bouts should be explored through an experimental approach to test its efficacy.

Supplemental methods

Design

Cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) cycles 2003-2004 and 2005-2006 were used. NHANES is a nationally representative sample of non-institutionalized Americans 3-85 years old. Sampling was conducted using a multistage probability sampling approach, and consisted of four stages: 1) primary sampling units were selected by single counties or groups of counties with probability proportional to a measure of size; 2) primary sampling units were divided into segments; 3) households in each segment were randomly selected (oversampling of age, ethnic, and income groups led to higher probability of selection in these groups); 4) individuals were chosen to participate in NHANES from all persons residing in selected households and were drawn at random within designated age-sex-ethnicity screening sub-domains.

The data collection strategy for NHANES consists of a home interview to collect demographic, socioeconomic, dietary, and health-related data conducted by trained personnel. Medical personnel conduct the examination component, including medical, dental, and physiological measurements. All participants in NHANES provide consent to participate and the survey is approved by the Institutional Review Board of the Centers for Disease Control and Prevention. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed for reporting of the study.[1]

Participants

Participants ≥50 year old were included if they wore an accelerometer for a minimum of 4 days on at least 10 hours per day. The purpose of choosing a slightly younger population (i.e. minimum 50 years) is because emerging evidence suggests that frailty can manifest in earlier adulthood.[2, 3] Participants were excluded if they did not have sufficient data to measure frailty (described below).

Frailty measure

A Frailty index (FI) that was previously developed in NHANES using the accumulation of deficits model of frailty was used.[4] The FI is calculated as a ratio of the number of deficits present out of the total number of possible deficits. For example, if someone scores a 10 out of a possible 50 deficits, their frailty index would be 0.2. The items included in a FI are not standardized, but follow a guidelines-based system by Searle and colleagues.[5] Variables must increase with age, be associated with poor outcomes, cover a range of physiological systems, cannot be too uncommon (<1%) or too common (>80% by age 80), and more than 20% of variables cannot be missing for an individual.[4] A 46-item FI using self-reported measures and laboratory variables was used (see Appendix 1). All variables included in the FI were recoded to indicate the absence (i.e., 0) or the presence (i.e., 1) of a health-deficit. For variables with intermediate responses, such as a cataract surgery on no eyes, one eye, or two eyes, a score of 0, 0.5, or 1, respectively, was assigned.

Physical activity and sedentary behavior measures

Minute-by-minute MVPA and sedentary behaviour parameters were measured using hip-mounted, uniaxial, Actigraph accelerometers over a 7-day period. Accelerometers do not display data immediately to the user thus blinding them to the data collected while wearing the monitor. Participants were instructed to wear the accelerometer during their waking hours, but not to wear the device during bathing or swimming activities. Cut-points for intensity were used based on previous literature in NHANES.[6] Specifically, sedentary time was classified based on accumulating 0-100 counts/min and MVPA cut-points were ≥2020 counts/min.

Bouted and sporadic MVPA were calculated separately. Bouted activity was defined as physical activity accumulated in ≥10 minutes, with two allowable consecutive minutes out of 10 minutes to drop below the MVPA intensity threshold in to light intensity physical activity. Sporadic MVPA was defined as any MVPA accumulated in <10 minute bouts. There were no allowable minutes for sporadic activity to drop below the MVPA intensity threshold.

Different patterns in sedentary time were also explored, including the total number of interruptions in sedentary time, the average break intensity, and average break duration. Also, the total number of prolonged sedentary bouts, which were defined as sedentary time accumulated in ≥30 minutes without interruption (i.e., going above 100 counts/min) were examined. There is no agreed upon definition of prolonged sedentary time; however, the 30 minute cut-off was chosen based on previous studies.[7, 8]

Statistical analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina) and used SAS survey procedures to account for the complex survey design of NHANES. Differences in descriptive variables were compared for those who were eligible versus those who did not meet the study inclusion criteria using a t-test for continuous variables and a Chi-square test for categorical variables. Mean ± standard error and frequency (percent) are provided for continuous and categorical variables, respectively. Multivariable linear regression models were used to determine the association between bouted and sporadic MVPA, as well as the different patterns in sedentary behavior, with the FI. The FI was converted into a score from 0-100 using the 46 FI deficits.

Bouted and sporadic MVPA did not meet linear regression assumptions and were therefore converted into four different groups based on meeting a percentage of the physical activity guidelines of 150 minutes of MVPA per week: meeting 1) 0%, 2) 1-49%, 3) 50-99%, and 4) ≥100% of guidelines. For the sporadic MVPA groups the 0% guideline group was defined as accumulating less than one minute per day because >99% of participants accumulated at least one minute of sporadic MVPA.

Several multivariable linear regression models were completed. Univariate as well as an age and sex-adjusted model were undertaken for each individual physical activity and sedentary behavior pattern variable (see Appendix 1). The remaining models were adjusted for age, sex, ethnicity, education, household income, marital status, smoking status, alcohol consumption, body mass index, total sedentary time, and accelerometer wear time. Subsequently, the bouted and sporadic MVPA categories were included in one model. The sedentary behavior pattern variables were also included in a separate model (i.e., number of breaks in sedentary time, average break intensity and average break duration, and prolonged sedentary time). Lastly, the bouted MVPA group and sedentary bout and break variables were included in a fully adjusted model. Sporadic MVPA was excluded due to the high correlation with average break intensity and high variance inflation when included. An alpha of 0.05 was used to test for statistical significance. An alpha of 0.05 was used to determine statistical significance.

References for supplemental methods

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CHAPTER 4: SEX-DIFFERENCES IN THE ASSOCIATION BETWEEN BOUTS OF PHYSICAL ACTIVITY AND PATTERNS OF SEDENTARY BEHAVIOR WITH FRAILTY

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Abstract

Objective: This study determined if there are sex differences in the association between bouts of moderate-vigorous physical activity (MVPA) and patterns of sedentary behavior (SB) with frailty.

Method: Accelerometry from individuals ≥50 years old from the National Health and Nutrition Examination Survey (2003-04/2005-06 cycles) were included. Bouted and sporadic MVPA were defined as accumulating MVPA in ≥10 minute or <10 minute durations. MVPA was analyzed based on meeting 0%, 1-49%, 50-99%, and ≥100% of the physical activity guidelines of 150 min/week. A duration of ≥30 minutes defined prolonged SB. Breaks in SB were defined as any ≥1 minute interruption in SB. Average break intensity and duration of breaks in SB were analyzed. A 46-item frailty index (FI) quantified frailty. Multivariable linear regression was used. Models adjusted for demographics, total sedentary time, and accelerometer wear time.

Results: There were 1143 females and 1174 males available for analysis. Bouted MVPA was associated with a lower FI; the strengths of associations peaked at meeting 50-99% of the guidelines in females and ≥100% in males. No significant sex-interaction was detected for bouted MVPA. Meeting a higher proportion of the guidelines through sporadic MVPA was significantly associated with a lower FI in males only. No sex-interaction effect was found. Prolonged SB bouts were associated with worse frailty in females but not males ($p<0.05$ sex-interaction). Higher average break intensity was associated with a lower FI in both sexes, whereas, total sedentary breaks were not. Average break duration was associated with frailty in males. No sex-interaction was found.

Conclusion: This study found that prolonged SB were more detrimentally associated with frailty in females than males, which could influence tailored movement prescriptions and guideline development.

Publication status

This study is to be submitted to Experimental Gerontology in February 2018.

Introduction

Advances in modern medicine have resulted in a prolonged life expectancy globally, enabling older people themselves to live longer.[61] However, these benefits in prolonged life have not been experienced to a similar extent by females and males.[61] Women tend to live longer than men, but they usually experience more functional limitations, co-morbidities, and poorer self-rated health during their lives.[62] More recently, frailty has emerged as a way to quantify individual heterogeneity in health and survival across the lifespan and may serve as a useful model to investigate these sex differences in survival and health.[63] In fact, women are shown to be more frail than men at any age even though they tolerate a higher degree of frailty.[64]

This female-male health-survival paradox remains to be fully elucidated, but it is posited that biological differences, such as hormones (e.g., favorable impact of estrogen), a more robust immune system, and genetic influences allow women to live longer and tolerate a poorer frail state than men.[65] Lifestyle behaviors, including the relationship between physical activity and sedentary behaviors, may interact with these biological differences that may result in sex-specific outcomes and a different risk state. For example, engaging in regular physical activity improves endothelial function in older males, while these benefits are inconsistent in postmenopausal women.[66,67] This lack of physiologic adaptation might be due to the delayed onset of decline in endothelial function that is shown in women due to their pre-menopausal protective effects.[68] Furthermore, the Lifestyle Interventions and Independence for Elders (LIFE) study provides evidence that males, but not females, benefitted from a structured and home-based exercise intervention for the prevention of fall-related injuries and hospitalizations.[69] However, it is unclear whether there are sex-specific benefits of a more physically active lifestyle on frailty.

Women might be less likely than men to engage in structured or sustained physical activities because they tend to experience weakness prior to becoming frail in comparison to men.[70] This is a concern because the aerobic component of the North American and World Health Organization physical activity guideline recommendations indicate that older adults should engage in at least 150 minutes of moderate to vigorous physical activity (MVPA) per week in bouts of at least 10 minutes for health benefits.[34-36] Promoting the accumulation of MVPA in shorter, sporadic bouts is intriguing because it could inform strategies to improve frailty in both women and men.

Accumulating more sedentary time is shown to be associated with worse frailty, independent of MVPA.[5,19] Recent evidence suggests that regularly interrupting extended periods of sedentary time with more intense and longer duration breaks may positively influence cardiovascular health.[37,71] Whether these benefits extend to reducing frailty remains to be investigated. Furthermore, there are no sex-specific data on the associations of different accumulation patterns of sedentary behavior with frailty.

Providing data concerning the sex-specific associations between bouts of MVPA and patterns of sedentary time could inform tailored public health recommendations for females and males that might initially be more achievable and sustainable in the frail adult. Collectively, the objectives of this study are to determine if sex differences exist in the associations between sporadic and bouted MVPA, as well as prolonged sedentary time, breaks in sedentary time, and the average intensity and duration during breaks from sedentary time, with frailty.

Materials and Methods

This study report follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[72]

Design

This study is a secondary analysis of cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) cycles 2003-2004 and 2005-2006. The data collection strategy for NHANES consists of a home interview to collect demographic, socioeconomic, dietary, and health-related data conducted by trained personnel. Medical personnel conduct the examination component, including medical, dental, and physiological measurements.

The multistage probability sampling design of NHANES is intended to capture a representative sample of community-dwelling children and adults living in the United States. Particular groups were oversampled in NHANES cycles used in the present study, including those of lower income, older adults ≥60 years old, African Americans, and Mexican Americans.

Unique to the 2003-2004 and 2005-2006 NHANES cycles were the collection of minute-by-minute objectively measured physical activity by accelerometry over a 7 day period. NHANES provided a hip-mounted, uniaxial Actigraph accelerometer (model 7164) to a selection of participants. Accelerometers capture the amount and intensity of physical activity, as well as sedentary time, and are considered the gold standard for measurement of physical activity in field settings.[73] All participants in NHANES provide consent to participate and the survey was approved by the Institutional Review Board of the Centers for Disease Control and Prevention.

Participants

Ambulatory participants who were ≥50 years old were included in the present analysis. The intention of choosing a population aged 50 years and older is based on evidence suggesting that frailty can manifest in early adulthood.[74,75] Participants were excluded if they did not wear their accelerometer for a minimum of 4 out of 7 days for at least 10 hours per day, which is a recommended approach to capture physical activity behaviors in adults.[76] Participants were also excluded if they were missing covariates (i.e., age, race/ethnicity, income, marital status, education, alcohol consumption, smoking status, body mass index, total sedentary time, and accelerometer wear time) and had insufficient data to measure frailty. Therefore, a complete case analysis was performed. Details on the measurement of frailty are described later.

Accelerometer assessment

Participants were instructed to wear the accelerometer during their awake hours, but not to wear the device during bathing or swimming activities. Accelerometers in NHANES capture the intensity of physical activity and time spent in sedentary behavior by registering accelerations in the vertical plane in the form of counts per minute. Accelerometer cut-points in the form of counts/min can therefore be used to classify physical activity intensity. Cut-points for intensity were used based on previous literature in NHANES.[76] To determine if participants wore the accelerometer for at least 10 hours per day, accelerometer wear and non-wear time were captured. Specifically, accelerometer non-wear time was defined by an interval of time lasting at least 60 consecutive minutes with 0 intensity counts/min, and an allowance of up to 2 minutes to go above 1-100 counts/min. Participants in the study were blinded to data derived from accelerometers while wearing the monitor.

Bouted and sporadic MVPA

A cut-point of ≥2020 counts/min was used to classify MVPA intensity. Bouted and sporadic MVPA were calculated separately. Bouted activity was defined as physical activity accumulated in ≥10 minutes, with two allowable consecutive minutes out of 10 minutes to drop below the MVPA intensity threshold. Sporadic MVPA was defined as any MVPA accumulated in <10 minute bouts with no allowable minutes to fall below the MVPA intensity threshold.

Prolonged bouts and breaks in sedentary time

Sedentary time was defined as accelerometer counts of <100 counts/min. Prolonged bouts of sedentary time were defined as any uninterrupted duration of time within the sedentary behavior threshold lasting ≥30 minutes. There is no accepted definition of prolonged sedentary time in the research literature; therefore, the 30 minute or longer time period was selected based on its use in previous studies.[54,77] A break in sedentary time was defined as any duration of time lasting one minute or longer above the 100 counts/min sedentary time threshold. Breaks in sedentary time were further characterized by their average duration in minutes and average intensity in counts/min.

Frailty assessment

Frailty has been previously measured within NHANES by using a 46-item frailty index (FI) with the accumulation of deficits model.[19] This FI was used in the present study (see Appendix 1). A FI is the sum of deficits present and divided by the total number of possible deficits. For example, someone with 13 out of a possible 46 deficits would score a 0.28. The approach used to develop an FI in NHANES was based on guidelines developed by Searle et al.[78] Specifically, the prevalence of deficits should increase with age, are linked to health outcomes, and are not prevalent in most or all older adults. However, the deficits should not be uncommon. Participants were excluded from analysis if they were missing more than 20% of FI variables. This approach to missing FI values has been used previously and provides a stable FI that is linked to mortality despite using different variables.[78] Individual FI variables with intermediate responses were coded with a score of 0, 0.5, and 1. The FI was converted into a score from 0-1 to 0-100 to improve the interpretability of β-coefficients. This approach has been used previously.[79]

Statistical analysis

All analyses were performed using the survey procedures in SAS 9.4 (SAS Institute, Cary, North Carolina) to account for the complex sampling design used by NHANES. Descriptive variables are presented as mean ± standard error, or frequency (percent) for continuous and categorical variables, respectively. An independent t-test and Chi-square test were used to compare differences between females and males for continuous and categorical descriptive variables, respectively.

Separate linear regression models were conducted for females and males, followed by a model testing for sex interactions with each physical activity and sedentary variable. Simple linear regression was initially used, followed by multivariable linear regression. All variables were individually inputted into an age and accelerometer wear time adjusted model, and subsequently inputted into a fully adjusted model. Covariates in the fully adjusted models included age, ethnicity, education, annual household income, marital status, smoking status, alcohol consumption, body mass index, total sedentary time, and accelerometer wear time.

The bouted and sporadic MVPA variables were both included in a fully adjusted model to determine if bouted MVPA was associated with frailty independent of sporadic MVPA, and vice versa. The linear regression assumptions were not met for bouted and sporadic MVPA. Therefore, participants were categorized based on meeting 0%, 1-49%, 50-99% or 100% or more of the physical activity guidelines through bouted or sporadic MVPA. There were only four participants who accumulated 0 min/week (i.e., met 0% of the guidelines) for sporadic MVPA. Therefore, to maximize statistical power in this group, those accumulating, on average, less than one minute per day throughout their accelerometer wear time were defined as meeting 0% of the guidelines through sporadic MVPA. The sedentary behavior pattern variables were added to a model with bouted MVPA to determine if bouted MVPA was independently associated with frailty. Sporadic MVPA was not included in the final model because it had a high correlation with average break intensity ($r>0.75$). Light intensity physical activity was not included in the present analysis due to its high variance inflation (18.1) when added to the fully adjusted linear regression models.

The sedentary behavior pattern variables, including prolonged sedentary behavior, total breaks in sedentary time, and the average intensity and duration were included in a fully adjusted model to determine their independent relationships with frailty. As described previously, bouted MVPA was included in a model with the sedentary behavior pattern variables to a fully adjusted model.

An alpha of 0.05 was used to determine statistical significance. Complete case analyses were conducted in the present study.

Results

Female and Male Descriptive Variables

Valid accelerometer data were available in 3177 participants who were 50 years or older. After removal of those with missing covariates and those having more than 20% FI variables absent, 2317 participants were available for analysis. Table 4.1 includes descriptive variables between males and females.

Table 4.1. Characteristics of included sample by sex.

Variable	Females n= 1143 Mean (SE) or n and frequency (%)	Males n=1174 Mean (SE) or n and frequency (%)	p-value
Age	67.88 (0.40)	66.83(0.33)	0.0107
Frailty index	0.23 (0.005)	0.21 (0.004)	0.0006
Weight (kg)	74.21 (0.67)	87.04 (0.63)	<0.0001
Body Mass Index (kg/m^2)	28.66 (0.26)	28.45 (0.19)	0.2928
Race/ethnicity			0.9852
Mexican American	212 (18.5%)	212 (18.1%)	
Other Hispanic	19 (1.7%)	20 (1.7%)	
Non-Hispanic white	691 (60.5%)	717 (61.1%)	
Non-Hispanic black	189 (16.5%)	196 (16.7%)	
Other	32 (2.8%)	29 (2.5%)	
Education			0.0031
Less than 12th grade	384 (33.6%)	420 (35.8%)	
High school/GED equivalent	317 (27.7%)	267 (22.7%)	
Some college	270 (23.6%)	258 (22.0%)	
College grad or higher	172 (15.0%)	229 (19.5%)	
Marital status			<0.0001
Married/common law	556 (48.6%)	886 (75.5%)	
Widowed	355 (31.1%)	122 (10.4%)	
Divorced/separated	183 (16.0%)	128 (10.9%)	
Never married	49 (4.3%)	38 (3.2%)	
Annual household income			0.0054
<$20,000	378 (33.1%)	317 (27.0%)	
$20,000-$34,999	314 (27.5%)	326 (27.8%)	
$35,000-$54,999	228 (19.9%)	239 (20.4%)	

$55,000-$74,999	86 (7.5%)	111 (9.5%)	
>=$75,000	137 (12.0%)	181 (15.4%)	
Alcohol intake			<0.0001
Does not drink	1038 (90.8%)	864 (73.6%)	
<1 drink/day	82 (7.2%)	176 (15.0%)	
1-2 drinks/day	12 (1.0%)	64 (5.5%)	
>2 drinks/day	11 (1.0%)	70 (6.0%)	
Smoking status			<0.0001
Non-smoker	669 (58.5%)	352 (30.0%)	
Previous smoker	350 (30.6%)	619 (52.7%)	
Current smoker	124 (10.8%)	203 (17.8%)	
Bouted MVPA (min/week)	27.34 (1.75)	32.67 (2.89)	0.0822
Sporadic MVPA (min/week)	38.62 (1.78)	69.66 (2.13)	<0.0001
Meeting guidelines of 150 min/week with bouted MVPA			0.0068
Meeting ≥100% of guidelines	55 (4.8%)	79 (6.7%)	
Meeting 50-99% of guidelines	64 (5.6%)	82 (7.0%)	
Meeting 1-49% of guidelines	182 (15.9%)	224 (19.1%)	
Meeting 0% of guidelines	842 (73.7%)	789 (67.2%)	
Meeting guidelines of 150min/week with sporadic MVPA			<0.0001
Meeting ≥100% of guidelines	36 (3.1%)	123 (10.5%)	
Meeting 50-99% of guidelines	111 (9.7%)	214 (18.2%)	
Meeting 1-49% of guidelines	838 (73.3%)	728 (61.8%)	
Meeting 0% of guidelines	158 (13.8%)	111 (9.5%)	
Total sedentary time (hr/day)	8.65(0.06)	8.92 (0.08)	0.0027
Prolonged sedentary bouts (per day)	3.38 (0.07)	3.86 (0.06)	<0.0001
Breaks in sedentary time (per day)	89.91 (0.59)	84.94 (0.82)	<0.0001
Avg break intensity (counts/min)	390.79 (3.14)	442.16 (2.92)	<0.0001
Avg break duration(min)	3.62 (0.05)	3.80 (0.05)	0.0019

Data are expressed as mean ± standard error or frequency (percent).

There were a total of 1143 females and 1174 males included in the present study. Females were approximately one year older than males (68 vs. 67 years old), had a higher FI (0.23 vs. 0.21), lower body weight (74 kg vs. 87 kg), but a similar body mass index. Females were more likely to have high school education, less likely to be married/common law, and have a lower income than males. Males were more likely to have a college education or higher, but more likely to drink any amount of alcohol, and had a higher prevalence of being either current or previous smokers, as compared to females.

For bouted MVPA, females accumulated 27 min/week and 4.8% met the aerobic component of the North American and World Health Organization physical activity guidelines, while males accumulated almost 33 min/week and 6.7% met the guidelines (Table 4.1). Females accumulated 39 min/week and 3.1% met the physical activity guidelines through sporadic MVPA, while males achieved 70 min/week of sporadic MVPA and 10.5% met the guidelines through sporadic MVPA. Males accumulated more total sedentary time, had more prolonged bouts of sedentary behavior lasting 30 minutes or longer per day, and had fewer total breaks in sedentary behavior per day, as compared to females. During breaks from sedentary time, the average intensity was higher and the duration was longer in males compared to females.

MVPA and Frailty

Univariate analysis demonstrated that meeting a higher percentage of the physical activity guidelines with bouted or sporadic MVPA was significantly associated with a lower FI in both females and males (Table 4.2). A statistically significant sex-interaction was detected for bouted MVPA and showed a stronger relationship in females than males at meeting 1-49% or 50-99% of the physical activity guidelines. The age and accelerometer wear time adjusted models showed similar protective strength in association with frailty as in the univariate model. No sex-interactions were found for bouted or sporadic MVPA in this model. For the fully adjusted models, bouted MVPA was significantly associated with lower frailty scores in females and males (Table 4.2).

Table 4.2. Multivariable linear regression models for the frailty index examining individual MVPA and patterns of sedentary behavior variables stratified by sex.

Variables	Univariate				Age and accelerometer wear time adjusted				Fully adjusted			
	Female		Male		Female		Male		Female		Male	
	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE
PHYSICAL ACTIVITY VARIABLES												
Meeting guidelines of 150 min/week with bouted MVPA												
≥100% guidelines	**-8.481**	**1.408**	**-9.074**	**1.302***	**-7.202**	**1.383**	**-8.601**	**1.249**	**-3.202**	**1.350**	**-4.824**	**1.259**
50-99% guidelines	**10.276**	**0.771**	**-6.897**	**1.402**	**-8.164**	**0.941**	**-5.742**	**1.282**	**-5.029**	**1.010**	**-3.418**	**1.308**
1-49% guidelines	**-7.107**	**1.185**	**-4.761**	**1.003**	**-5.342**	**1.264**	**-4.038**	**1.007**	**-2.559**	**1.054**	**-2.912**	**0.845**
0% guidelines	*Reference*				*Reference*				*Reference*			
Meeting guidelines of 150min/week with sporadic MVPA												
≥100% guidelines	**-12.325**	**2.560**	**-15.204**	**1.358**	**-9.895**	**2.722**	**-15.404**	**1.610**	-0.104	3.041	**-8.574**	**1.906**
50-99% guidelines	**-12.216**	**1.844**	**-12.987**	**1.020**	**-9.093**	**1.953**	**-13.054**	**1.423**	-2.333	1.703	**-8.154**	**1.672**
1-49% guidelines	**-6.017**	**1.216**	**-7.775**	**1.208**	**-4.410**	**1.385**	**-7.926**	**1.296**	-1.179	1.306	**-5.638**	**1.407**
0% guidelines	*Reference*				*Reference*				*Reference*			
SB BOUT/BREAK FROM SB VARIABLES												
SB bouts lasting ≥30min (per day)	**2.341**	**0.303**	**1.005**	**0.227***	**2.416**	**0.302**	**1.116**	**0.253***	**1.339**	**0.278**	-0.191	0.329*
Breaks from SB (every 10 per day)	**-1.575**	**0.256**	**-0.458**	**0.209***	**-0.775**	**0.305**	0.282	0.296*	**-0.345**	**0.244**	0.270	0.221*
Avg break intensity (per 100 counts/min)	**-5.148**	**0.562**	**-3.936**	**0.395**	**-4.678**	**0.625**	**-4.318**	**0.531**	**-2.390**	**0.691**	**-2.760**	**0.490**
Avg break duration (min)	**-3.483**	**0.392**	**-2.829**	**0.392**	**-3.063**	**0.381**	**-2.691**	**0.379**	-0.916	0.490	**-2.121**	**0.518**

Estimates of the regression coefficient are provided, with standard errors

Bold indicates p-values <0.05
*Indicates significant sex-interaction
Model 1: No adjustment
Model 2: Adjusted for age and accelerometer wear time
Model 3: Adjusted for age, ethnicity, education, annual household income, marital status, smoking status, alcohol consumption, BMI, total sedentary time, and accelerometer wear time

A graded response was observed between the 1-49%, 50-99%, and ≥100% groups in males, while the strength of association peaked at 50-99% in females. No significant sex-interaction was found for bouted MVPA. There was a significant beneficial association between meeting any percentage of the physical activity guidelines through sporadic MVPA and frailty in males, but not females. The strength of association in males peaked at meeting 50-99% of the guidelines in males. There was no statistically significant sex-interaction effect between females and males for sporadic MVPA.

Table 4.3 provides a fully adjusted model, which combined bouted and sporadic MVPA in a single model (Model 1). This model showed that meeting any percentage of the MVPA guidelines through bouted MVPA was associated with lower frailty levels in females and males. The strength of association peaked at 50-99% in females and at ≥100% in males. No sex-interaction effect was found for bouted MVPA. There was a significant association between sporadic MVPA and reduced frailty in males but not females in the stratified analysis. No significant sex-interaction effect was found for sporadic MVPA. An additional analysis (see supplementary Table 4.1) with total sedentary time removed from Model 1 was conducted because it was suspected that total sedentary time attenuated the response of sporadic MVPA. Bouted MPVA remained significantly associated with frailty when meeting any percentage of the guidelines in both sexes. No significant sex-interaction was found for bouted MVPA. This analysis also demonstrates that sporadic MVPA was significantly associated with a lower FI when meeting any percentage of the physical activity guidelines in both sexes. The strength of association peaked when meeting ≥100% of the guidelines in females and males. There was no significant sex-interaction effect for sporadic MVPA.

Table 4.3. Multivariable linear regression models for the frailty index with models examining the independent associations of bouts of MVPA and patterns of sedentary behavior stratified by sex

Variables	Model 1				Model 2				Model 3			
	Females		Males		Females		Males		Females		Males	
	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE
PHYSICAL ACTIVITY VARIABLES												
Meeting guidelines of 150 min/week with bouted MVPA												
≥100% guidelines	**-3.145**	**1.361**	**-4.342**	**1.255**					-1.889	1.357	**-3.079**	**1.274**
50-99% guidelines	**-4.961**	**0.994**	**-2.966**	**1.328**					**-4.094**	**0.919**	**-2.796**	**1.344**
1-49% guidelines	**-2.523**	**1.070**	**-2.434**	**0.901**					-1.266	1.082	**-2.159**	**0.840**
0% guidelines	*Reference*								*Reference*			
Meeting guidelines of 150min/week with sporadic MVPA												
≥100% guidelines	0.708	3.068	**-7.415**	**1.971**								
50-99% guidelines	-1.477	1.653	**-7.303**	**1.741**								
1-49% guidelines	-0.918	1.333	**-5.299**	**1.446**								
0% guidelines	*Reference*											
SB BOUT/BREAK FROM SB VARIABLES												
SB bouts lasting ≥30min (per day)					**2.115**	**0.366**	0.041	0.494*	**2.110**	**0.369**	0.035	0.486*
Breaks from SB (every 10 per day)					0.102	0.320	-0.435	0.290	0.122	0.317	-0.454	0.282
Avg break intensity (per 100 counts/min)					**-2.461**	**0.710**	**-2.273**	**0.528**	**-2.102**	**0.751**	**-1.836**	**0.547**
Avg break duration (min)					-0.727	0.582	**-1.562**	**0.457**	-0.722	0.587	**-1.517**	**0.469**

Estimates of the regression coefficient are provided, with standard errors
Bold indicates p-values <0.05
*Indicates statistically significant sex-interaction effect (p<0.05)

All models are adjusted for age, ethnicity, education, annual household income, marital status, smoking status, alcohol consumption, BMI, total sedentary time, and accelerometer wear time. Models are also adjusted for variables within the specific models presented

Model 1: All physical activity and sedentary bout/break variables.

Model 2: Sex comparison of estimates with all physical activity and sedentary bout/break variables

Model 3: Sex comparison of estimates with bouted physical activity and all sedentary bout/break variables

The addition of the sedentary behavior pattern variables to a fully adjusted model with bouted MVPA showed that only females achieving 50-99% of the physical activity guidelines through bouted MVPA was associated with a lower FI compared to those meeting 0% of the guidelines (Model 3, Table 4.3). In males, meeting any percentage of the guidelines through bouted MVPA had a similar protective association with frailty, as compared to those meeting 0% of the guidelines. There was no sex-interaction effect for bouted MVPA

Sedentary Behavior Patterns and Frailty Relationship

The univariate, age-accelerometer wear time, and fully adjusted analyses comparing the relationship between individual sedentary behavior pattern variables with frailty are shown in Table 4.2. All variables were significantly associated with frailty in both females and males in the univariate analyses. Significant sex-interactions were detected for prolonged bouts of sedentary time and total breaks from sedentary time. The relationships between the sedentary behavior pattern variables with frailty remained statistically significant in the age and accelerometer wear time adjusted models, except for total breaks in sedentary time for males. There were significant sex-interaction effects for prolonged bouts of sedentary time and the frequency of breaks from sedentary time. This interaction demonstrated a stronger detrimental association with frailty for prolonged sedentary bouts and a beneficial association with frailty for total sedentary breaks in females compared to males. In the fully adjusted models, prolonged bouts of sedentary time and total breaks from sedentary time were significantly associated with frailty in the fully adjusted models for females, but not in males. There was a significant sex-interaction for both prolonged sedentary bouts and total breaks from sedentary time.

Average break intensity was significantly associated with a lower FI in both sexes. No sex-interaction effect was found. Average break duration was associated with a lower FI in males, but not females. There was no significant sex-interaction effect for average break duration.

Table 4.3 includes data for a fully adjusted model that combined prolonged sedentary bouts, and the frequency, intensity and duration of breaks from sedentary time (Model 2), and a model that included bouted MPVA with the sedentary behavior pattern variables (Model 3) stratified by sex. In model 2, prolonged sedentary bouts were associated with a higher FI score in females but not males. A statistically significant sex-interaction effect was found, with the strength of relationship being higher in females versus males. Total breaks from sedentary time were not associated with frailty in either sex. Average break intensity remained significantly associated with lower frailty in females and males. No significant sex-interaction was found. The duration of breaks from sedentary time were significantly associated with lower frailty levels in males only. No significant sex-interaction was found for average sedentary break duration. When bouted MVPA was added to the fully adjusted model with the sedentary behavior pattern variables, prolonged sedentary bouts remained significantly associated with a higher FI in females only. The sex-interaction effect remained significant as in previous models, showing that prolonged sedentary bouts were significantly associated with a higher FI in females, but not males. The frequency of breaks from sedentary time were not associated with frailty in both sexes. Average break intensity was associated with a lower FI in both sexes. No significant sex-interaction effect was found for average break intensity. In males, average break duration was associated with lower frailty levels. There was no statistically significant sex-interaction effect.

Sensitivity analysis adding total number of accelerometer wear days as a covariate

The total number of accelerometer wear days was added to the sex-stratified, fully-adjusted models examining the independent associations between bouts of MVPA and patterns of sedentary behaviors. In general, adding total accelerometer wear days did not significantly influence the estimates in either fully adjusted model for either sex (data not shown). However, the estimates for bouted MVPA in the fully adjusted for females was attenuated. Furthermore, the average break duration-frailty association was attenuated in males.

Discussion

Overall findings

The purpose of this study was to determine if there were sex differences in the association between patterns of physical activity and sedentary behavior with frailty. In general, the stratified analysis by sex in the present study suggests MVPA is more consistently associated with frailty in males, as compared to females. In fact, the stratified analyses indicated that sporadic MVPA was only significantly associated with a lower FI in males. However, the analysis which removed total sedentary time as a covariate showed a beneficial association of sporadic MVPA on frailty status in females. Interestingly, prolonged, uninterrupted bouts of sedentary time were linked to higher levels of frailty in females, but not males, and showed that females had an associated higher FI than males. This study is the first to show this sex-specific association. In both sexes, the intensity of breaks from sedentary time were significantly associated with lower levels of frailty, while the frequency and duration of breaks were not when stratified by sex. Overall, these data have implications for tailored recommendations and guideline development in female and male adults.

Bouted and sporadic MVPA

The present study showed that males were more likely to meet the aerobic component of the North American and World Health Organization physical activity guidelines of 150 minutes per week or more through bouted or sporadic MVPA. However, only 4.8% and 3.1% of females and 6.7% and 10.5% of males met the guidelines through bouted or sporadic MVPA, respectively (Table 4.1). These data are in line with previous studies.[33,51,76] While females and males accumulated a similar amount of bouted MVPA, men accumulated an additional 30 min/week of sporadic MVPA compared to females (39 min/week vs. 70 min/week). These data are in contrast with a previous study in Japanese adults 70-79 years old, which indicated that women accumulate more sporadic MVPA than men.[80] One possibility is that the differences in classification of physical activity intensity between studies. Specifically, that study used software-derived metabolic equivalents to classify intensity; whereas, the present study the use of standard NHANES cut-points determined physical activity intensity.

The fully adjusted multivariable models (Tables 4.2 and 4.3) showed that bouted MVPA was associated with frailty in both sexes after adjusting for covariates. The sex-stratified multivariable linear regression models showed that sporadic MVPA was associated with a lower frailty score in males but not females independent of bouted MVPA. A post-hoc analysis revealed (supplemental Table 4.1) that after removal of total sedentary time from the model, sporadic MVPA became significantly associated with lower frailty levels in females, suggesting that sedentary time may be more important in females than the accumulation of sporadic MVPA (see the study implications below for further discussion) for associated reductions in frailty. The lack of significance between sporadic MVPA and frailty in the original model (Table 4.3, model 1) suggests that sporadic MVPA might still be important in females, but there might be a stronger association in males. These data are in contrast with the study by Glazer et al.[81] who found that the association between sporadic MVPA and cardiovascular risk factors was stronger in women compared to men in a middle-aged cohort, although there was no test for a sex-interaction effect. When a fully adjusted model was completed (data not shown) with all participants and adjusting for sex, sporadic MVPA remained statistically significant, but the strength of association with frailty across all MVPA categories (i.e., meeting 1-49%, 50-99%, and ≥100% of guidelines) was attenuated. A possibility is that the present study was not statistically powered to detect sex-interactions across the sporadic MVPA categories, as there were few females who met ≥100% (n= 36) of the guidelines through sporadic MVPA (Table 4.1). These data suggest that, even though sex-stratified analyses showed that males appeared to have associated lower FI scores by meeting a higher percentage of physical activity guidelines through sporadic MVPA, meeting national physical activity guidelines through bouted or sporadic MVPA is likely important regardless of sex.

Patterns of sedentary behavior

Previous investigations have shown sex-differences in the association between television viewing time and total sedentary time with health outcomes independent of physical activity, demonstrating that sedentary behaviors are more detrimental to females' cardio-metabolic health than males.[82,83] This study adds to that literature, indicating that prolonged bouts of sedentary time are associated with worsening frailty in females but not males independent of demographics, the frequency, intensity and duration of breaks in sedentary time, total sedentary time, and bouted MVPA. To the authors' knowledge, this study is the first to show this relationship with frailty. To place these data in context, every additional prolonged sedentary bout lasting 30 minutes or longer was associated with approximately one additional FI deficit in females. Previous studies testing the associations between prolonged, uninterrupted sedentary time found no sex-interaction effects with the development of the metabolic syndrome in office workers 20-64 years old or with arterial stiffness in the EVIDENT study (Physical Exercise, Fitness and Dietary Pattern and Theirs Relationship With Blood Pressure Circadian Pattern, Augmentation Index and Endothelial Dysfunction Biological Markers) Spanish cohort 20-80 years old.[54,84] The contrasting findings between the present study and those previous studies might be due to the older age group chosen for the present study. Katzmarzyk and colleagues report significantly higher rates of mortality in older (≥60 years old) versus younger (<59 years old) adults with increasing levels of sitting time.[85] Therefore, it can be speculated that prolonged sedentary bouts are more detrimental in older females than males. These data are significant because women tend to accumulate more health deficits at a faster rate later in life than males.[86] By extension, if women can reduce the amount of uninterrupted sedentary time they accumulate over time, it might be possible to slow the rate of deficit accumulation. However, testing this possibility requires a study using a longitudinal design or experimental approach.

The intensity of breaks from sedentary time in this study were demonstrated to be associated with a lower FI, while the total number of breaks in sedentary time were not. The present study found that, regardless of sex, there was almost one fewer FI deficits associated with every additional 100 counts per minute in average break intensity even with controlling for the other sedentary pattern variables (i.e., prolonged sedentary bouts, total sedentary breaks, and average break duration) and bouted MPVA (Table 4.3). Manns et al.[37] conducted a similar study to test the relationship between the frequency, intensity and duration of sedentary breaks on cardio-metabolic health in older adults. This study adds to the literature indicating that average break intensity may be associated with lower frailty levels despite participating in longer durations of MVPA and prolonged, uninterrupted sedentary time. It is important to note that the average intensity during breaks in sedentary time were classified in the light intensity threshold in both females (391 counts/min) and males (442 counts/min) suggesting that short interruptions in sedentary time of lighter intensity may be sufficient for a protective association with the FI. Further research should test the impact of different intensity thresholds of sedentary breaks and their associated benefits with frailty and other health parameters. The present study found a significant association between average break duration and lower frailty scores in only males when controlling for other sedentary behavior pattern variables. However, there was no sex-interaction effect detected. More studies are needed, likely with a larger sample size, to confirm these findings.

<u>Study implications</u>

This investigation examining bouts of MVPA and patterns of sedentary behavior, and their association with frailty have several implications to inform future research and may inform clinical and public health recommendations. First, in regards to physical activity, more research is needed using longitudinal designs with larger sample sizes to determine if there are any sex-differences in the benefits of bouted and sporadic MVPA to attenuate frailty. The feasibility of continuously measuring physical activity by objective assessment over time may be a challenge. The data in the present study suggest that North American and World Health Organization physical activity guidelines,[34-36] which currently recommend that MVPA should be accumulated in bouts of 10 minutes or longer, may need to be inclusive of any type of MVPA (i.e., sporadic or bouted) for health benefits in adults of both sexes. However, further research through prospective examinations are needed to support this recommendation. Another important finding was that even meeting a lower proportion of the guidelines (i.e., 1-49%) through bouted (females and males) or sporadic (males only) MVPA was associated with a lower FI. These data suggest that a lower dose of MVPA, either in bouts of 10 minute or longer or sporadically, might lead to significant health benefits.

Another implication of these findings concern the detrimental association between the accumulation of prolonged sedentary bouts and frailty. While there are physical activity guideline recommendations for adults, no public health guidelines for sedentary behavior exist for adults in North America. The United Kingdom and Australia provide broad recommendations for reducing prolonged sitting, but are silent on how much uninterrupted sitting needs to be reduced for health benefits.[87,88] These data add to the current literature indicating that prolonged, uninterrupted sedentary time is more detrimentally associated with frailty in females than males which could inform the development of more detailed sedentary behavior guidelines. In fact, a previous study by Healy et al.[82] also indicated sex-specific associations with higher levels of television viewing time with poor cardiovascular health scores, despite meeting physical activity guideline recommendations. It is unclear why this sex-specific difference exists. It is possible that there are underlying biological differences between females and males concerning the adverse effects of sedentary behaviors. Evidence to support this notion comes from data by Blanc et al.[89] who demonstrated that 6 days of bed rest resulted in more pronounced insulin resistance of the liver in women, as well as a greater shift towards lipogenic activity, as compared to males. Thus, it is possible that in the present study that higher levels of prolonged, uninterrupted, sedentary behaviors altered female's metabolism, which could lead to a more severe frail state. However, this possibility needs to be tested in a future study.

The clinical relevance of the present findings are of equal importance. Data from previous studies assessing the relationship between increasing levels in the FI show that, for every 0.1 increase in the FI (approximately 5 FI deficits in the present study), there was a 13% increased risk in eight-year mortality after adjusting for age and sex.[90] Smaller differences in the FI, including a 0.01 point increase (corresponding to 0.5 FI deficits in the present study confer to a 3.6% and 2.0% increased risk of two and six year mortality, respectively.[91,92] Thus, the findings in the present study are of significant value. For example, males who met 100% of the physical activity guidelines through bouted or sporadic MVPA had 2 and 3.5 fewer deficits, respectively (Table 4.3, model 1). Whereas, females had about 1.5 fewer deficits among those who met the guidelines through bouted MVPA (Table 4.3, model 1). Notably, every additional prolonged bout of sedentary time lasting at least 30 minutes in this study was associated with one less FI deficit in females. However, that result should be interpreted with caution, as the directionality of the relationship cannot be determined in this cross-sectional study.

Strengths and limitations

A strength of this study was the analysis of different patterns of physical activity and sedentary behaviors in a representative sample of non-institutionalized U.S. citizens aged 50 years or older. Another strength of the study was the use of objective assessment of physical activity and sedentary behaviors by accelerometry. However, it should be noted that the accelerometers used in the present study may not accurately capture all types of movements, especially activities of daily living. Consequently, this may have underestimated time spent in those activities.[59] Other modes of physical activity, such as swimming, cycling, and resistance exercise are not accurately captured by accelerometry.

Furthermore, the accelerometer cut-points used to define sedentary and physical activity thresholds may have resulted in an underestimation of MVPA and an overestimation of sedentary time.[60] More research is needed to determine accelerometer intensity thresholds specific to older (and frail) adults. An individualized cut-point approach may lead to the most accurate estimations of physical activity and its intensity, but the feasibility of this method is unclear in population-based studies. Lastly, this study may have been underpowered to detect sex-differences across different patterns of physical activity and sedentary behaviors with frailty.

Conclusions

This study found sex-differences in the relationship between different accumulation patterns of physical activity and sedentary behaviors with frailty. The accumulation of sporadic MVPA might be more important in males to reduce frailty, while prolonged, uninterrupted sedentary behaviors were more detrimental to frailty status in females. More research is needed to determine if there are sex-differences in the relationship between patterns of MVPA, sedentary behaviors, with the development of frailty.

Supplemental Table 4.1. Association between meeting a percentage of physical activity guidelines through bouted or sporadic MVPA stratified by sex, with total sedentary time removed from adjusted model.

Variables	Females		Males		
	β-coefficient	SE	β-coefficient	SE	P-value for sex interaction
Meeting guidelines of 150 min/week with bouted MVPA					0.339
>=100% guidelines	**-4.505**	**1.302**	**-4.624**	**0.887**	
50-99% guidelines	**-5.857**	**1.027**	**-4.310**	**0.805**	
1-49% guidelines	**-3.328**	**1.091**	**-2.864**	**0.584**	
0% guidelines		*Reference*			
Meeting guidelines of 150min/week with sporadic MVPA					0.620
>=100% guidelines	**-7.353**	**2.897**	**-9.339**	**1.582**	
50-99% guidelines	**-5.947**	**1.900**	**-8.002**	**1.231**	
1-49% guidelines	**-3.555**	**1.495**	**-4.904**	**1.043**	
0% guidelines		*Reference*			

Estimates of the regression coefficient are provided, with standard error
Bold indicates p-values <0.05
*Model is adjusted for age, ethnicity, education, annual household income, marital status, smoking status, alcohol consumption, BMI, and accelerometer wear time. Models are also adjusted for variables within the specific models presented

CHAPTER 5: DOES THE PRESENCE OF CARDIOVASCULAR DISEASE IMPACT THE ASSOCIATION BETWEEN BOUTS OF MODERATE TO VIGOROUS PHYSICAL ACTIVITY AND PATTERNS OF SEDETNARY BEHAVIORS WITH FRAILTY?

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Abstract

Objective: The prevalence of frailty is higher in the cardiovascular disease (CVD) versus the non-CVD population. This study determined if moderate-vigorous physical activity (MVPA) bouts and patterns of sedentary behavior (SB) are differently associated with frailty by CVD status.

Method: Accelerometry in adults ≥50 years old from the 2003-04/2005-06 National Health and Nutrition Examination Survey were used. Bouted and sporadic MVPA in ≥10 minute or <10 minute bouts were assessed based on meeting a percentage of the physical activity guidelines of 150 min/week. SB patterns included: prolonged SB lasting ≥30 minutes, frequency, intensity, and duration of breaks from SB. A 46-item frailty index defined frailty. Multivariable linear regression was used and controlled for demographics, total sedentary time, and accelerometer wear time.

Results: There were 827 CVD-free participants and 1490 with CVD. Meeting a higher percentage of the physical activity guidelines through bouted MVPA was associated with lower frailty in CVD-only participants ($p<0.05$ for CVD-interaction). Sporadic MVPA was associated with reduced frailty in both groups. Prolonged SB was associated with worse frailty in CVD participants only. There was no CVD-prolonged SB interaction. Total SB breaks were not associated with frailty. Average break intensity had a protective association from frailty in both groups. The duration of breaks in SB were associated with lower frailty CVD participants only. No CVD-interaction was found for duration of sedentary breaks.

Conclusion: Insufficient MVPA and prolonged SB are detrimental despite CVD status; however, bouted MVPA may provide an additional protective association with frailty in those with CVD.

Publication status

This study will be submitted to Medicine & Science in Sport & Exercise February 2018.

Introduction

Frailty, a term used to describe someone who cannot optimally cope with stressors due to reductions in physiologic reserve, is associated with higher rates of mortality, hospitalization and in-hospital functional decline.[93-95] Given a rapidly aging population, frailty has emerged as a major health concern in those with cardiovascular disease (CVD), and major scientific bodies recognize its importance in the cardiovascular care of adults.[96,97] In fact, it is estimated that one third of patients with CVD are frail, which is significantly higher than the general, non-CVD, community dwelling population.[95] The presence of both frailty and CVD are likely to arise due to the activation of inflammatory pathways, and it has been suggested that there is a bi-directional relationship between the two as a consequence of this shared pathophysiological process.[38,39] Given these unique consequences and the mechanistic link between frailty and CVD, it is imperative that these conditions are managed effectively so as to improve patient outcomes.

A more physically active lifestyle provides significant health benefits in those with and without CVD.[98,99] However, most adults are not physically active enough to meet the North American and World Health Organization recommended 150 minutes of moderate to vigorous physical activity in 10-minute bouts or longer (bouted MVPA) for health benefits.[34-36] There are studies providing evidence to support the beneficial associations between MVPA accumulated sporadically in less than 10 minute bouts and cardio-metabolic health.[48,81] However, it is unclear if bouted and sporadic MVPA are differentially associated with frailty in those with and without CVD.

Recent observational evidence suggests that reducing total sedentary time is important for reducing the risk of CVD mortality and morbid events beyond that of living a physically active lifestyle.[100] Interestingly, regularly breaking up sedentary time, and the duration and intensity of those breaks, have been shown to be associated with better cardiovascular health in older adults.[37] However, the evidence is silent about the differential associations between patterns of sedentary behaviors and frailty in those with and without CVD. Generating new data concerning CVD-specific associations between different patterns of physical activity and sedentary behaviors with frailty could inform lifestyle therapies in those with and without CVD. Given that frailty is becoming a recognized problem in patients with CVD that warrants investigation into therapeutic alternatives, these data may inform the clinical management of CVD in frail or non-frail patients.[96,101]

The objectives of this study are to determine if there are differential associations between sporadic and bouted MVPA, as well as prolonged sedentary time, and the frequency, intensity and duration of breaks from sedentary time with frailty, among those with and without CVD.

Methods

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used to generate the study report of this secondary, cross-sectional analysis.[72]

Data from the 2003-04 and 2005-06 National Health and Nutrition Examination Survey (NHANES) were used. NHANES uses a complex multistage probability sampling approach to provide demographic, socioeconomic, behavioral, and health-related information on individuals three years or older. Participants of lower income, adults 60 years or older, African Americans, and Mexican Americans were oversampled in the NHANES cycles used in the present study.

Ambulatory participants who were at least 50 years old and wore a uniaxial, hip-mounted accelerometer (Actigraph model 7164) for at least 4 out of 7 days, 10 hours per day, were included in this study. Individuals were separated by the presence of CVD. There is no standard definition in NHANES to define the presence of CVD. Therefore, in the present study, individuals with CVD were defined as responding positively to at least one of the following: having a healthcare provider indicate that they have high blood pressure, heart disease, heart failure, or angina, or had a previous myocardial infarction or stroke. Participants were excluded if they did not have sufficient data to assess frailty (details are described below) and were missing covariates. Therefore, a complete case analysis was performed. The Institutional Review Board of the Centers for Disease Control and Prevention approved the NHANES study.

The accumulation of deficits model was used to measure frailty based on an approach that was previously developed in NHANES (See Appendix 1).[33,102] This frailty measure used a guidelines-based approach to develop a frailty index (FI).[103] A FI typically consists of signs, symptoms, chronic conditions, physical and cognitive impairments, self-rated health, and biomarkers.[103] A FI is the ratio of health deficits present, and can either be measured on a 0-1 or 0-100 scale for the presence versus absence of FI deficits. The present study used a 0-100 scale for enhancing interpretability of analyses. Forty-six items were included in the FI (see Appendix 1). Note that CVD-related deficits are included in the FI. Those missing more than 20% of FI data were excluded from the study. Searle et al. report that the FI provides stable estimates of frailty for participants with 80% of FI deficits included.[103]

Minute-by-minute accelerometry were used to assess MVPA and sedentary behaviors. Physical activity intensity cut-points for MVPA were ≥2020 counts/min and time spent in sedentary behaviors had a threshold of 0-100 counts/min. Accelerometer wear time was determined by subtracting non-wear time from a 24-hour period. Non-wear time was defined as 60 consecutive minutes or longer of 0 intensity counts, with an allowable two minutes to reach 1-100 counts/min. Bouted MVPA was defined as any continuous amount of MVPA lasting at least 10 minutes, with 2 allowable minutes to drop below the moderate intensity threshold for every 10 minute block of activity. Sporadic MVPA was defined as any MVPA lasting 1-9 minutes, with no allowable interruption below the moderate intensity threshold.

Prolonged sedentary bouts, and the frequency, intensity, and duration of breaks from sedentary time were analyzed. A prolonged sedentary bout was defined as sedentary time lasting at least 30 minutes without going above the sedentary time threshold of 0-100 counts/min. A break in sedentary time was defined as an interruption sedentary time.

The intensity and duration of breaks in sedentary time were measured in counts/min and minutes, respectively.

<u>Statistical analysis</u>

To account for the complex survey approach used in NHANES, the SAS 9.4 (SAS Institute, Cary, North Carolina) survey procedures were used. Mean (standard error) and frequencies (percent) are provided for continuous and categorical descriptive variables, respectively. Independent t-tests and Chi-square tests were used to compare differences between those with and without CVD for continuous and categorical outcomes, respectively.

Univariate and Multivariable linear regression analyses were performed to determine the associations between bouted and sporadic MVPA and sedentary behavior patterns with the FI. All analyses were initially stratified by CVD status, followed by a test for a CVD-interaction. Initial CVD-stratified multivariable models adjusted for age, sex, and accelerometer wear time, followed by a fully adjusted model. Fully adjusted models controlled for age, sex, ethnicity, education, income, marital status, smoking status, alcohol consumption, body mass index, total sedentary time, and accelerometer wear time. All physical activity and sedentary pattern variables were initially analyzed individually.

For bouted and sporadic MVPA, individuals were categorized based on meeting a percentage of the aerobic component of the North American and World Health Organization physical activity guidelines: 0%, 1-49%, 50-99% and ≥100% to categorize participants within clinically meaningful cut-points. Only four individuals accumulated zero minutes of sporadic MVPA. Therefore, the 0% sporadic MVPA group represents those who did not accumulate at least one minute per day of sporadic MVPA during their accelerometer wear time to increase the sample size within this group. Fully adjusted models were subsequently completed with bouted and sporadic MVPA in one model. Next, the sedentary behavior pattern variables were added to a fully adjusted model with bouted MVPA. Sporadic MVPA was excluded from that analysis due to its strong correlation ($r>0.75$) with average break intensity. The analyses in this study excluded light intensity physical activity as a covariate because it had significant collinearity (variance inflation factor of 18.1) in the linear regression models.

Prolonged sedentary bouts and the frequency, intensity, and duration of breaks in sedentary time were initially analyzed in a univariable, age, sex, and fully adjusted model individually. In a second model, all sedentary behavior pattern variables were included in a single model. As described above, bouted MVPA was added to a fully adjusted model with the sedentary behavior pattern variables. A p-value of 0.05 was used to determine statistical significance.

Results

Descriptive statistics

From 3177 participants who were at least 50 years or older with valid data from accelerometry, no missing covariates, and missing less than 20% FI variables,[103] there were 1490 individuals defined as having CVD and 827 without CVD with complete data (Table 5.1). Compared to participants without CVD, those with CVD were older (66 vs. 68 years old), had a higher FI (0.16 vs. 0.25), were heavier (76 vs. 83 kg) had a higher body mass index (27 vs. 30), were more likely to be Non-Hispanic Black, generally had a lower education and income, and were current smokers. Those with CVD were less active than those without CVD, as they accumulated about half the amount of bouted (22 vs. 42 min/week) and 21 min/week less sporadic MVPA (45 vs. 66 min/week) than those without CVD. People without CVD were more likely to meet the physical activity guidelines through bouted (4.6% vs. 7.9%) or sporadic (4.8% vs. 10.6%) MVPA. In general, CVD participants had a higher amount of total sedentary time, accumulated more prolonged bouts of sedentary time, and had a lower frequency, intensity and duration of breaks in sedentary time than CVD-free participants.

Table 5.1. Characteristics of included sample by cardiovascular disease status

Variable	No CVD n=827 Mean (SE) or n and frequency (%)	CVD n= 1490 Mean (SE) or n and frequency (%)	p-value
Age	65.85 (0.51)	68.34 (0.31)	<0.0001
	411 (49.7%)	732 (49.1%)	0.7925
Frailty index	0.16 (0.003)	0.25 (0.005)	<0.0001

Weight (kg)	75.56 (0.73)	82.73 (0.59)	<0.0001
Body Mass Index (kg/m^2)	26.85 (0.26)	29.60 (0.19)	<0.0001
Race/ethnicity			<0.0001
Mexican American	175(21.2%)	249 (16.7%)	
Other Hispanic	15 (1.8%)	24 (1.6%)	
Non-Hispanic white	514 (62.2%)	894 (60.0%)	
Non-Hispanic black	96 (11.6%)	289 (19.4%)	
Other	27 (3.3%)	34 (2.3%)	
Education			0.0001
Less than 12th grade	271 (32.8%)	533 (35.8%)	
High school/GED equivalent	199 (24.1%)	385 (25.8%)	
Some college	174 (21.0%)	354 (23.8%)	
College grad or higher	183 (22.1%)	218 (14.6%)	
Marital status			0.6814
Married/common law	521 (63.0%)	921 (61.8%)	
Widowed	165 (20.0%)	312 (20.9%)	
Divorced/separated	106 (12.8%)	205 (13.8%)	
Never married	35 (4.2%)	52 (3.5%)	
Annual household income			0.0339
<$20,000	215 (26.0%)	480 (32.2%)	
$20,000-$34,999	238 (28.8%)	402 (27.0%)	
$35,000-$54,999	175 (21.2%)	292 (19.6%)	
$55,000-$74,999	73 (8.8%)	124 (8.3%)	
>=$75,000	126 (15.2%)	192 (12.9%)	
Alcohol intake			0.0734
Does not drink	686 (83.0%)	1216 (81.6%)	
<1 drink/day	76 (9.2%)	182 (12.2%)	
1-2 drinks/day	30 (3.6%)	46 (3.1%)	
>2 drinks/day	35 (4.2%)	46 (3.1%)	
Smoking status			0.0174
Non-smoker	368 (44.5%)	653 (43.8%)	
Previous smoker	322 (38.9%)	647 (43.4%)	
Current smoker	137 (9.2%)	190 (12.8%)	
Bouted MVPA (min/week)	41.76 (3.00)	22.47 (2.40)	<0.0001
Sporadic MVPA (min/week)	65.83 (3.83)	44.70 (2.18)	<0.0001
Meeting guidelines of 150 min/week with bouted MVPA			<0.0001
Meeting ≥100% of guidelines	65 (7.9%)	69 (4.6%)	
Meeting 50-99% of guidelines	78 (9.4%)	68 (4.8%)	
Meeting 1-49% of guidelines	176 (21.3%)	230 (15.4%)	
Meeting 0% of guidelines	508 (61.4%)	1123 (75.4%)	
Meeting guidelines of 150min/week with sporadic MVPA			<0.0001
Meeting ≥100% of guidelines	88 (10.6%)	71 (4.8%)	
Meeting 50-99% of guidelines	147 (17.8%)	178 (11.9%)	
Meeting 1-49% of guidelines	526 (63.6%)	1038 (69.7%)	

Meeting 0% of guidelines	66 (8.0%)	203 (13.6%)	
Total sedentary time (hr/day)	8.54 (0.08)	8.91 (0.05)	0.0007
Prolonged sedentary bouts (per day)	3.31 (0.08)	3.77 (0.05)	<0.0001
Number of breaks in sedentary time (per day)	89.81 (0.84)	86.35 (0.60)	0.0003
Avg break intensity (counts/min)	433.07 (3.96)	402.52 (3.19)	<0.0001
Avg break duration (min)	3.97 (0.07)	3.54 (0.04)	<0.0001

Data are expressed as mean ± standard error or frequency (percent).

MVPA-frailty relationship

Univariate and multivariable linear regression models stratified by CVD status are provided in Table 5.2. These models show results for MVPA and sedentary pattern variables individually. Univariate analyses demonstrated that, in both groups, achieving a higher amount of bouted and sporadic MVPA as assessed by meeting a percentage of the physical activity guidelines are associated with a lower FI. Meeting 1-49% of the guidelines through bouted MVPA was not associated with a lower FI in those without CVD. A significant CVD-interaction was found for bouted and sporadic MVPA, with a stronger association with frailty in those with CVD.

The models adjusting for age, sex, and accelerometer wear time for bouted and sporadic MVPA analyzed separately are shown in Table 5.2. The strength of associations for bouted and sporadic MVPA was attenuated in both CVD and non-CVD groups. The CVD-interaction with bouted and sporadic MVPA remained statistically significant.

Fully adjusted models examining bouted and sporadic MVPA individually are found in Table 5.2. For bouted MVPA, there was a significant protective association with frailty in participants with CVD, but not in those without CVD. The CVD-interaction remained statistically significant, which showed an associated lower FI in those with

CVD. Sporadic MVPA was associated with lower frailty scores for both groups. The CVD-interaction was still significant as in the univariate and age, sex, and accelerometer wear time models. However, the strength of association with reduced frailty in that model was stronger in those without CVD.

Table 5.2. Multivariable linear regression models for the frailty index for individual MVPA and sedentary bout/break variables stratified by cardiovascular disease status.

Variables	Univariate				Age and accelerometer wear time adjusted				Fully adjusted			
	CVD		No CVD		CVD		No CVD		CVD		No CVD	
	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE
PHYSICAL ACTIVITY VARIABLES												
Meeting guidelines of 150 min/week with bouted MVPA												
>=100% guidelines	**-9.081**	**1.384**	**-4.525**	**1.325***	**-8.522**	**1.407**	**-4.024**	**1.250***	**-5.405**	**1.361**	-1.944	1.276*
50-99% guidelines	**-10.915**	**1.162**	**-3.283**	**0.916**	**-9.252**	**1.130**	**-2.434**	**1.119**	**-5.615**	**1.177**	-1.417	1.100
1-49% guidelines	**-7.191**	**0.880**	**-2.240**	**1.326**	**-5.696**	**0.904**	-1.655	1.117	**-3.626**	**0.836**	-0.211	1.041
0% guidelines	Reference				Reference				Reference			
Meeting guidelines of 150min/week with sporadic MVPA												
>=100% guidelines	**-13.972**	**1.287**	**-9.771**	**1.948***	**-12.059**	**1.662**	**-9.612**	**1.892***	**-5.936**	**1.707**	**-6.167**	**1.857***
50-99% guidelines	**-12.047**	**1.237**	**-9.122**	**1.387**	**-9.775**	**1.503**	**-8.900**	**1.667**	**-4.808**	**1.507**	**-6.110**	**1.591**
1-49% guidelines	**-5.659**	**1.012**	**-6.018**	**1.485**	**-4.949**	**1.084**	**-5.963**	**1.494**	**-2.640**	**1.080**	**-4.789**	**1.413**
0% guidelines	Reference				Reference				Reference			
SB BOUT/BREAK FROM SB VARIABLES												
SB bouts lasting ≥30min (per day)	**1.396**	**0.252**	**1.007**	**0.290**	**1.632**	**0.208**	**1.254**	**0.286**	**0.767**	**0.307**	0.335	0.377
Breaks from SB (every 10 per day)	**-0.857**	**0.223**	-0.500	0.288	-0.414	0.271	-0.005	0.310	-0.189	0.245	-0.015	0.281
Avg break intensity (per 100 counts/min)	**-4.505**	**0.295**	**-2.422**	**0.427***	**-4.627**	**0.465**	**-2.783**	**0.457***	**-2.619**	**0.494**	**-1.672**	**0.540***
Avg break duration (min)	**-3.812**	**0.350**	**-1.521**	**0.304***	**-3.397**	**0.361**	**-1.469**	**0.300***	**-2.034**	**0.490**	-0.667	0.390*

Estimates of the regression coefficient are provided, with standard errors

Bold indicates p-values <0.05

*Indicates statistically significant CVD-interaction (p<0.05)

Model 1: No adjustment
Model 2: Adjusted for age and accelerometer wear time
Model 3: Adjusted for age, ethnicity, education, annual household income, marital status, smoking status, alcohol consumption, BMI, total sedentary time, and accelerometer wear time

A fully adjusted model with bouted and sporadic MVPA added to a single model demonstrated that there was a protective association from frailty amongst those meeting a higher percentage of the physical activity guidelines through bouted MVPA for CVD participants only. There was a peak in the strength of association at meeting 50-99% of the guidelines. A statistically significant CVD-interaction was found and showed that those with CVD and meeting at least 1-49% of the physical activity guidelines was associated with a lower FI compared to those meeting 0% of the guidelines. Meeting a higher percentage of the guidelines through sporadic MVPA was associated with a lower FI to a similar extent in both groups. No significant CVD-interaction was found.

A fully-adjusted model combining bouted MVPA, prolonged bouts of sedentary time, and the frequency, intensity, and duration of breaks from sedentary time are shown in Table 5.3 (Model 3). Bouted MVPA was significantly associated with a lower FI in CVD participants only. The CVD-interaction for bouted MVPA remained statistically significant between the groups, showing that bouted MVPA was more strongly associated with a lower frailty scores in the CVD versus non-CVD participants.

Table 5.3. Multivariable Linear regression models for the frailty index, with models determining the independent associations of bouts of MVPA and patterns of sedentary behaviors stratified by CVD status.

	Model 1				Model 2				Model 3			
Variables	**CVD**		**No CVD**		**CVD**		**No CVD**		**CVD**		**No CVD**	
	β-coefficient	**SE**	**β-coefficient**	**SE**	**β-coefficient**	**SE**	**β-coefficient**	**SE**	**β-coefficient**	**SE**	**β-coefficient**	**SE**
PHYSICAL ACTIVITY VARIABLES												
Meeting guidelines of 150 min/week with bouted MVPA												
>=100% guidelines	**-5.018**	**1.360**	-1.391	1.298*					**-3.489**	**1.431**	-0.616	1.324*
50-99% guidelines	**-5.349**	**1.187**	-1.003	1.114					**-4.966**	**1.195**	-0.607	1.139
1-49% guidelines	**-3.285**	**0.843**	0.277	1.060					**-3.011**	**0.820**	0.559	1.032
0% guidelines	Reference								Reference			
Meeting guidelines of 150min/week with sporadic MVPA												
>=100% guidelines	**-4.885**	**1.727**	**-5.994**	**1.911**								
50-99% guidelines	**-3.739**	**1.510**	**-5.905**	**1.605**								
1-49% guidelines	**-2.296**	**1.067**	**-4.740**	**1.419**								
0% guidelines												
SB BOUT/BREAK FROM SB VARIABLES												
SB bouts lasting ≥30min (per day)					**1.370**	**0.429**	0.528	0.490	**1.413**	**0.428**	0.533	0.494
Breaks from SB (every 10 per day)					0.018	0.336	-0.148	0.405	0.033	0.331	-0.147	0.404
Avg break intensity (per 100 counts/min)					**-2.212**	**0.540**	**-1.611**	**0.574***	**-1.721**	**0.540**	**-1.563**	**0.583**
Avg break duration (min)					**-1.632**	**0.531**	-0.489	0.461	**-1.593**	**0.526**	-0.504	0.462

Estimates of the regression coefficient are provided, with standard errors
Bold indicates p-values <0.05
*Indicates statistically significant CVD-interaction (p<0.05)

All models are adjusted for age, ethnicity, education, annual household income, marital status, smoking status, alcohol consumption, BMI, total sedentary time, and accelerometer wear time. Models are also adjusted for variables within the specific models presented
Model 1: All physical activity and sedentary bout/break variables.
Model 2: Sex comparison of estimates with all physical activity and sedentary bout/break variables
Model 3: Sex comparison of estimates with bouted physical activity and all sedentary bout/break variables

Sedentary behavior patterns and frailty

In the univariate models examining sedentary pattern variables individually, prolonged sedentary time was detrimentally associated with frailty in both groups (Table 5.2). No significant CVD-sedentary time interaction was found. The frequency of breaks from sedentary time were associated with lower FI scores in those with CVD only. However, there was no significant CVD-interaction for breaks from sedentary time. Both the intensity and duration of breaks from sedentary time were associated with a lower FI in both groups. There was a statistically significant CVD-interaction found for both variables, with a stronger protective relationship with frailty state in those with CVD.

The age, sex, and accelerometer wear time adjusted models showed that all of the sedentary behavior pattern variables remained significantly associated with frailty (directionality remained the same) except that the frequency of breaking up sedentary time was no longer associated with lower frailty levels in those with CVD. The CVD-sedentary behavior interaction remained statistically significant for the intensity and duration of breaks in sedentary time.

Fully adjusted stratified models for each individual sedentary behavior pattern variables are found in Table 5.2. The accumulation of prolonged sedentary bouts of at least 30 minutes were associated with high FI scores in CVD participants only. There was no significant CVD-interaction found. Total breaks in sedentary time were not associated with frailty in both groups. The intensity of breaks from sedentary time was associated with a lower FI in both groups. A significant CVD-interaction was found; the CVD groups' average break intensity had a stronger protective association with frailty. The duration of breaks in sedentary time were not associated with frailty in non-CVD participants in the fully-adjusted model. Those with CVD had a significant protective association with frailty. There was a significant CVD-interaction found, with a stronger association in those with CVD.

Table 5.3 displays the results from fully adjusted models combining the patterns of sedentary behavior variables in a single model (Model 2). Prolonged bouts of sedentary time were significantly associated with higher FI scores in CVD participants only. However, no statistically significant CVD-interaction was found. Total breaks in sedentary time were not associated with frailty in either group. The intensity of breaks in sedentary time had a protective association with frailty in those with and without CVD. A significant CVD-interaction was found, where there was a stronger association with lower FI scores amongst those with CVD. The duration of breaks from sedentary time were associated with lower frailty levels scores in CVD participants only. However, there was no significant CVD interaction found.

The fully-adjusted model with bouted MVPA added to the sedentary behavior pattern variables showed that prolonged sedentary bouts were not associated with frailty in those without CVD (Table 5.3, Model 3). In contrast, there was a significant detrimental association with frailty amongst those without CVD. There was no statistically significant CVD-interaction for prolonged sedentary bouts between groups. Total sedentary breaks had a non-significant association with the FI for both groups. Average break intensity was associated with reduced frailty in both groups. In this model, there was no significant CVD-interaction with average break intensity. For participants with CVD, the duration of breaks from sedentary time was significantly associated with a lower FI, but not for those without CVD. No significant CVD-interaction was found for average break duration.

Post-hoc analyses

Additional fully adjusted analyses (see Supplementary Table 5.1) that included a dummy variable based on the presence of CVD in males and females (i.e., females/no CVD, females/CVD, males/no CVD, and males/CVD) was conducted. A stratified analysis by sex and CVD status could not be performed due to the low sample sizes in those meeting at least 100% of the physical activity guidelines for males and females. Model 1 containing a fully adjusted model that combined bouted and sporadic MVPA showed similar protective associations with frailty when the sex-CVD status dummy variable was included, as compared to the stratified analyses in Tables 5.2 and 5.3. Model 2 shows that prolonged sedentary bouts, and the average intensity and duration of breaks in sedentary time were associated with higher and lower FI scores, respectively. Total breaks in sedentary time were not associated with frailty. Model 3 combined bouted MVPA to the sedentary behavior pattern variable model. The beneficial association of bouted MVPA with lower frailty levels was significant, but the strength of association was attenuated, as compared to Model 1. Prolonged sedentary bouts remained associated with a higher FI, while the intensity and duration of breaks in sedentary time had a protective association with frailty as in previous models. Total number of breaks in sedentary time were not associated with frailty.

The total number of accelerometer wear days was added to the CVD-stratified, fully-adjusted models examining the independent associations between bouts of MVPA and patterns of sedentary behaviors. Adding total accelerometer wear days did not significantly influence the estimates in either fully adjusted model (data not shown).

Discussion

Due to an aging population, there is an increasing number of patients with CVD who are frail, making the findings in the present study relevant for informing novel frailty treatment and prevention strategies by CVD status. The present study has demonstrated that patterns of MVPA and sedentary behaviors are differentially associated with frailty by CVD status. A key finding of the present study was that MVPA accumulated in at least 10 minute bouts had a protective association with frailty in those with CVD only. Even so, sporadic MVPA accumulated in less than 10 minute bouts was similarly associated with frailty despite CVD status, and appeared to have a stronger protective association with frailty compared to bouted MVPA. Prolonged time spent in sedentary behaviors was associated with higher FI scores in participants with CVD; however, there was no significant association in those without CVD after controlling for other sedentary pattern variables. Despite CVD status, it appears that the average intensity at which breaks from sedentary time are performed were consistently associated with lower frailty scores. Overall, these findings extend our understanding of the benefits of physical activity and the consequences of sedentary behaviors with frailty and highlight important differences by CVD status.

<u>Bouts of MVPA</u>

The North American and World Health Organization physical activity guidelines recommend that adults accumulate at least 150 min/week of MVPA in 10 minute bouts or longer for health benefits.[34-36] Similar recommendations are provided to adults with CVD, although are silent on the way in which MVPA should be accumulated.[104] Interestingly, the present study provides evidence that participants with CVD had a protective association with frailty through bouted MVPA; whereas, there was no significant association found in those without CVD. It is unclear why bouted MVPA was only significant in those with CVD, but there is likely a mechanistic link between longer physical activity duration and cardiovascular health. The authors speculate that the more damaged endothelium in patients with CVD compared to those without CVD may have benefitted from improved vascular function from longer bouts of MVPA.[105] However, further evidence is needed to identify the differences in the link between bouted MVPA and frailty by CVD status.

The present study shows a similar protective association between sporadic MVPA and frailty despite CVD status. This finding confirms that of a comprehensive review of interventional studies and previous epidemiological studies comparing the link between shorter versus longer bouts of physical activity on cardiovascular health.[48,81,106] An interesting finding in the present study is that meeting less than half of the physical activity guidelines through sporadic MVPA was associated with clinically relevant associated lower FI scores. Specifically, a β-coefficient of ±2.17 represents a one FI deficit difference in the present study. Therefore, compared to those meeting 0% of the physical activity guidelines, participants with CVD had one fewer FI deficits meeting 1-49% of the guidelines, and there were two fewer FI deficits in those without CVD. These data suggest that current physical activity recommendations should include sporadic MVPA for health benefits, and that lower amounts of MVPA may be protective from a higher frailty score. These recommendations are supported by Powell and colleagues in their review, who suggest that the total accumulation of physical activity is more important than the duration of physical activity bouts for health benefits.[107]

<u>Sedentary behavior patterns</u>

Independent of physical activity behaviors, high amounts of sedentary time are linked to a higher risk of mortality.[108] Other investigations indicate that total sedentary time is associated with frailty independent of a person's MVPA levels.[5,33] However, to the authors' knowledge, no studies have investigated the relationship between different patterns of sedentary behaviors with frailty by CVD status. This study found that prolonged, uninterrupted time spent in sedentary behaviors was associated with a higher accumulation of FI deficits in those with CVD independent of bouted MVPA and the total accumulation of sedentary time. This finding is novel and could inform sedentary behavior reduction recommendations for individuals with and without CVD. While there are sedentary behavior guidelines in Canada for children and youth,[109] there are no guideline recommendations for adults to reduce the time spent in sedentary behaviors in North America. Sedentary behavior guidelines in Australia and the UK are broad in scope and suggest that adults should minimize time spent in sedentary pursuits for extended periods.[87,88] Scientific entities, such as the American Heart Association, and the Sedentary Behavior Research Network are calling for more research concerning the link between sedentary behaviors and health outcomes, along with potential mechanisms.[49,100] Therefore, the present findings are relevant to inform clinical and public health recommendations to reduce time spent in sedentary behaviors.

<u>Future research and study implications</u>

Further research is needed to understand and explain the relationships between patterns of sedentary behaviors and frailty, and to determine if the implementation of a targeted approach to reduce prolonged sedentary behaviors leads to better health outcomes (i.e., reductions in frailty). For example, a prolonged sedentary behavior reduction strategy could be implemented into the current standard of care for patients who have experienced a cardiovascular event (i.e., cardiac rehabilitation). Evidence to inform such a strategy comes from Bond and colleagues, who found that short, three minute breaks every 30 minutes is superior to reducing sedentary time compared to 12 minute sedentary breaks every 60 minutes in overweight and obese adults (47 vs. 26 min/day).[110] To complement that evidence, it should be determined if more intense breaks of longer duration can support reductions in sedentary time, along with deriving significant health outcomes as was found in the present study.

In addition to informing novel treatment and prevention strategies for frailty by CVD status, future research should use longitudinal designs to investigate the relationship between physical activity and sedentary behavior patterns with the development of frailty. Studies should also determine the association between bouts of physical activity and patterns of sedentary behavior across frailty severity, as evidence suggests that total sedentary time, despite meeting physical activity guidelines, is associated with a higher risk of mortality in more frail groups, but not in the least frail group.[111]

These data have implications for governing bodies from exercise physiology, geriatrics, and cardiovascular medicine. Specifically, these data suggest that these agencies need to focus not only on promoting an active lifestyle, but also to reduce extended periods of sedentary time. This type of "two pronged" approach could lead to additional health benefits compared to previous approaches targeting only physical activity, and should be tested through experimental studies in both the CVD and non-CVD population.

Limitations

There are limitations to consider with the use of accelerometer to classify intensity of physical activity and sedentary behaviors. Specifically, the accelerometer cut-points used may not be appropriate for the cohort studied that might lead to potential inaccurate estimates of MVPA and sedentary time. Standard accelerometer cut-points typically used in NHANES were chosen because to date there is no consensus on appropriate cut-points to use in an older population.[60] Accelerometer data reduction procedures used by other studies in older adults were mostly followed based on a systematic review by Migueles et al who conducted a systematic review on accelerometer processing criteria, which enhances the comparability of the present study to other studies.[112] The accelerometers used in NHANES may not accurately capture all movements of activities of daily living, possibly underestimating physical activities in the present study.[59] With regards to CVD, there was no standard definition in NHANES to separate groups by CVD status. Furthermore, the FI included health deficits related to CVD, making those with CVD simply having a higher FI because those deficits were included. However, when CVD-related deficits were removed, the average FI did not change between groups, and the estimates of association between bouts of MVPA and patterns of sedentary behavior with frailty were not affected. Lastly, this cross-sectional study could not determine if higher frailty was a consequence of CVD, or vice versa. Given the bi-directional relationship between CVD and frailty, a prospective study is needed.[39] Similarly, people with more severe frailty could have been unable to participate in MVPA and would in turn engage in higher amounts of sedentary time.

Conclusions

These data suggest that sporadic MVPA is equally important to reduce frailty despite CVD status, while bouted MVPA was associated with reductions in frailty in CVD patients only. Breaking up sedentary time with light to vigorous intensity breaks resulted in significant associated reductions in frailty in those with and without CVD, which may help inform the development of CVD-specific and general public health sedentary behavior guideline recommendations.

Supplemental Table 5.1. Multivariable linear regression models for the frailty index with Sex/CVD status as a dummy variable

Variables	Model 1		Model 2		Model 3	
	β-coefficient	SE	β-coefficient	SE	β-coefficient	SE
PHYSICAL ACTIVITY VARIABLES						
Meeting guidelines of 150 min/week with bouted MVPA						
>=100% guidelines	**-3.248**	**1.081**			**-2.025**	**1.077**
50-99% guidelines	**-3.153**	**0.939**			**-2.664**	**0.983**
1-49% guidelines	**-1.936**	**0.534**			**-1.578**	**0.475**
0% guidelines	*Reference*				*Reference*	
Meeting guidelines of 150min/week with sporadic MVPA						
>=100% guidelines	**-4.567**	**1.373**				
50-99% guidelines	**-4.431**	**1.053**				
1-49% guidelines	**-3.184**	**1.014**				
0% guidelines	*Reference*					
SB BOUT/BREAK FROM SB VARIABLES						
SB bouts lasting ≥30min (per day)			**0.960**	**0.248**	**0.963**	**0.252**
Breaks from SB (every 10 per day)			-0.201	0.222	-0.195	0.218
Avg break intensity (per 100 counts/min)			**-2.127**	**0.371**	**-1.796**	**0.410**
Avg break duration (min)			**-0.986**	**0.357**	**-0.969**	**0.359**

Estimates of the regression coefficient are provided, with the lower and upper 95% confidence intervals for the estimates in parentheses)
Bold indicates p-values <0.05
*All models are adjusted for age, sex, ethnicity, education, annual household income, marital status, smoking status, alcohol consumption, BMI, total sedentary time, and accelerometer wear time. Models are also adjusted for variables within the specific models presented
Model 1: All physical activity and sedentary bout/break variables.
Model 2: Sex comparison of estimates with all physical activity and sedentary bout/break variables
Model 3: Sex comparison of estimates with bouted physical activity and all sedentary bout/break variables

CHAPTER 6: SYSTEMATIC REVIEW OF PREOPERATIVE PHYSICAL ACTIVITY AND ITS IMPACT ON POST-CARDIAC SURGICAL OUTCOMES

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Publication status

This study has been published in BMJ Open.[113]

Other notes

This systematic review was used to inform a CIHR operating grant (grant number: 326290) to complete a randomized controlled trial to determine if preoperative rehabilitation is superior to standard care for reducing prolonged hospital length of stay and frailty prior to cardiac surgery.[114]

Abstract

Objectives: The objective of this systematic review was to study the impact of preoperative physical activity levels on adult cardiac surgical patients' postoperative: 1) major adverse cardiac and cerebrovascular events (MACCE), 2) adverse events within 30 days, 3) hospital length of stay (HLOS), 4) intensive care unit length of stay (ICU LOS), 5) activities of daily living (ADLs), 6) quality of life, 7) cardiac rehabilitation attendance, and 8) physical activity behavior.

Methods: A systematic search of MEDLINE, Embase, AgeLine, and Cochrane library for cohort studies was conducted.

Results: Eleven studies (n=5,733 patients) met the inclusion criteria. Only self-reported physical activity tools were used. Few studies used multivariate analyses to compare active versus inactive patients prior to surgery. When comparing patients who were active versus inactive preoperatively, there were mixed findings for MACCE, 30 day adverse events, HLOS, and ICU LOS. Of the studies which adjusted for confounding variables, five studies found a protective, independent association between physical activity and MACCE (n= 1), 30 day postoperative events (n= 2), hospital length of stay (n= 1), and ICU length of stay (n= 1), but two studies found no protective association for 30 day postoperative events (n= 1) and postoperative ADLs (n= 1). No studies investigated if activity status before surgery impacted quality of life or cardiac rehabilitation attendance postoperatively. Three studies found that active patients prior to surgery were more likely to be inactive postoperatively.

Conclusion: Due to the mixed findings, the literature does not presently support that self-reported preoperative physical activity behavior is associated with postoperative cardiac-

surgical outcomes. Future studies should objectively measure physical activity, clearly define outcomes, and adjust for clinically relevant variables.

Registration: PROSPERO number CRD42015023606.

Introduction

Recent reports suggest that more than half of cardiac surgeries are being performed on older adults who are more likely to be frail and have multiple co-morbidities.[115] While cardiac surgery has been shown to improve the outcomes of these patients, more than 75% of major perioperative complications and deaths occur in older adults.[116,117] Before surgery, many of these patients are de-conditioned and have diminished resilience in the face of major stressors such as cardiac surgery, and it has been postulated that they could benefit from a therapeutic intervention prior to their major surgical procedure in order to reduce their operative risk. However, little information exists to evaluate the benefit of preoperative risk reduction strategies for the older cardiac surgery patient.

Adopting and sustaining a more physically active lifestyle is typically intended to be a part of an interdisciplinary rehabilitation plan that is instituted postoperatively and has been shown to reduce the risk of cardiac mortality and hospital admissions and improve health-related (QOL) in patients.[118] Importantly, older adults who sustain a physically active lifestyle after a postoperatively exercise-based rehabilitation program can continue to improve their functional walking status.[119] However, evidence suggests that cardiac surgery patients are highly sedentary during the preoperative period, especially in older adults.[120] Furthermore, few randomized controlled trials exist which evaluate the therapeutic benefit of preoperative lifestyle modification in patients undergoing cardiac surgery.[121-123] Information regarding the link between preoperative physical activity and postoperative health outcomes in cardiac surgery patients would be valuable for healthcare providers to assist them in selecting patients who might benefit from preoperative exercise therapy.

The purpose of this systematic review was to compare the following postoperative outcomes between cardiac surgery patients defined as physically active prior to surgery and those who were defined as physically inactive preoperatively: 1) major adverse cerebrovascular and cardiovascular events (MACCE) 2) 30-day adverse events as defined by the Society of Thoracic Surgeons (STS)[10] 3) hospital length of stay, 4) Intensive Care Unit (ICU) length of stay, 5) health-related QOL, 6) activities of daily living (ADL) 7) cardiac rehabilitation attendance and 8) physical activity levels postoperatively.

Material and Methods

The protocol for this systematic review has been described in PROSPERO: CRD42015023606. Note the following *ad-hoc* changes to the previous protocol: ICU length of stay and postoperative physical activity as additional outcomes were explored in this systematic review.

Eligibility criteria

Eligible studies included cohort studies which examined adult (>18 years) cardiac surgery patients undergoing coronary artery bypass grafting (CABG), aortic or mitral valve repair/replacement, transcatheter aortic valve implantation, or combined procedures. Studies with patients undergoing congenital cardiac surgery, heart transplantation or left ventricular assist device implantation procedures were excluded. Studies could compare physically active versus inactive patients prior to cardiac surgery on the basis of subjective (e.g., questionnaire) or objective (e.g., pedometer, accelerometry) assessments of physical activity.

Eligible studies had to compare at least one of the following postoperative outcomes: MACCE defined as death, stroke, myocardial infarction, and the need for emergency cardiac surgery; 30-day adverse events as defined by the STS,[124] including an unexpected return to the operating room, complications due to pulmonary, cardiovascular, gastrointestinal, hematological, urologic, infection, and neurological deficits, other important miscellaneous outcomes (e.g., unexpected admission to ICU, or other events requiring admission to operating room requiring anesthesia; hospital length of stay; ICU length of stay; health-related QOL with any assessment tool; ADLs using any evaluation strategy; cardiac rehabilitation attendance; and physical activity behavior using either subjective or objective forms of assessment.

Search strategy

The search strategy was completed by a librarian and reviewed by a second librarian. The search included keywords and controlled vocabulary. English language limits were applied. Databases used included MEDLINE, Embase, AgeLine, and Cochrane Library (CDSR, CENTRAL, DARE) and articles were searched from inception to December 2016. The MEDLINE strategy was registered and published online in PROSPERO (http://www.crd.york.ac.uk/PROSPEROFILES/23606_STRATEGY_20150518.pdf) and is available as Supplemental Digital Content. The search was validated through a cross-check of references of studies selected for inclusion. In addition, conference abstracts were hand searched using the Internet. Attempts were made to contact authors of conference abstracts to determine if their findings were published in a peer-reviewed journal.

Study selection

The title, abstract and full-text article screening processes were independently completed by two reviewers. A training exercise for the title and abstract phase was conducted by the independent reviewers using a random sample of 100 titles and abstracts. Discrepancies in studies for inclusion were resolved by discussion of the two reviewers. The final observed agreement was 98% with a kappa statistic of 0.47 for the title and abstract screen. One training exercise of 10 randomly selected articles was completed for the full-text screen. Discrepancies for inclusion were resolved through discussion. The observed agreement for the full-text screen was 96% with a kappa statistic of 0.83.

Data abstraction

Two reviewers independently extracted relevant data for the selected outcomes described above. Discrepancies in the data extraction procedure were resolved through discussion. Data abstraction items included study characteristics (e.g., authors, year of publication, sample size, follow up time points if relevant), patient characteristics (e.g., age, sex, surgery type), physical activity tool used, and the outcomes which were measured.

Risk of bias assessment

Two reviewers independently reviewed the risk of bias of each included study using the Newcastle-Ottawa Scale.[125] Items within this tool assess the risk of bias associated with selection of participants, comparability (e.g., study authors controlled for patient demographics and clinical characteristics), and outcome assessment (e.g., data collection method for outcome, sufficient follow-up, and adequacy of follow up of cohorts). Each study was given a score within each category (Selection: 0-4; Comparability: 0-2; and Outcome: 0-3) and an overall score ranging from 0-9. A score of zero suggests an increased risk of bias and a higher score suggests a lower risk of bias.

Quantitative synthesis

Due to the significant heterogeneity between studies in terms of physical activity assessment tools used and outcomes assessed, meta-analyses were not performed.

Results

The literature search results are shown in Figure 6.1. After removing duplicates, 5722 articles were title and abstract screened. A total of 137 articles were then assessed in full-text. Eleven studies met the eligibility criteria for the final analysis, and they included a total of 5,733 patients.[126-136] An overview of the included studies can be viewed in Table 6.1.

Figure 6.1. Study flow diagram.

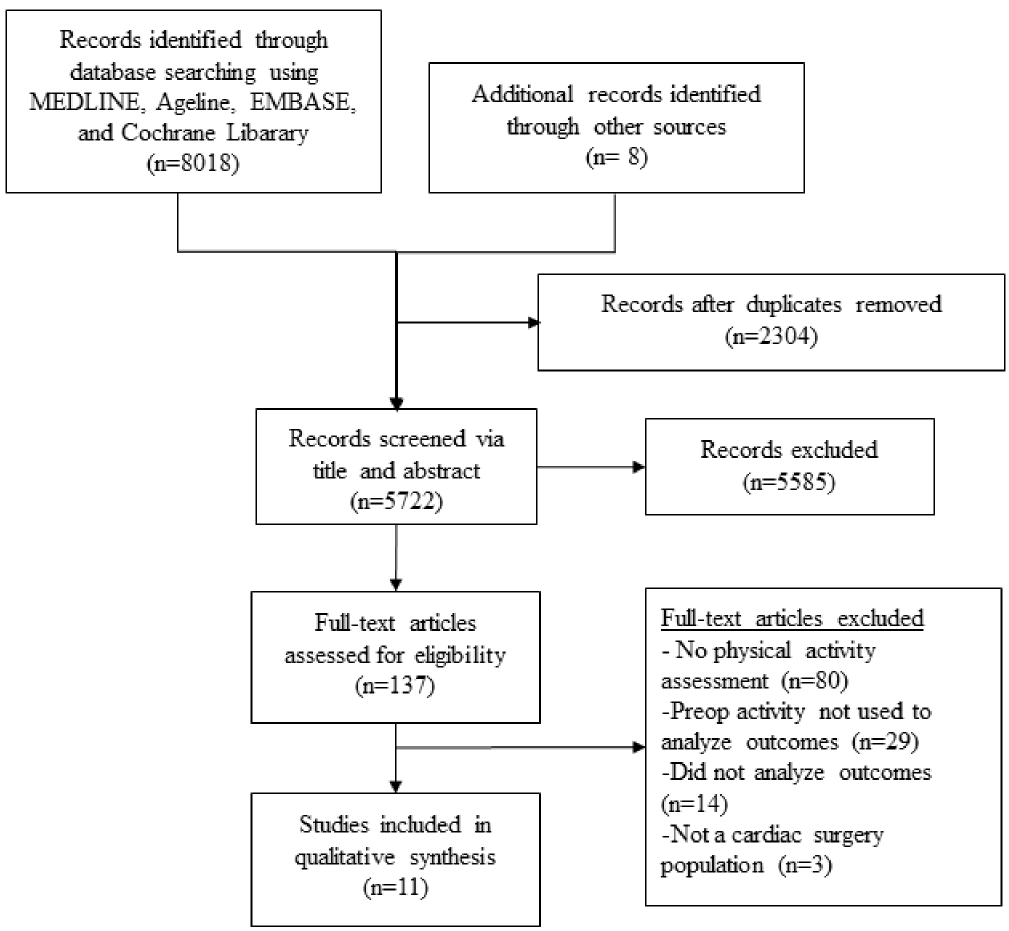

Table 6.1. Characteristics of included studies

First author, year	Study Population	Country	Participants at follow-up	Physical Activity Assessment	Longest follow-up	Main findings
Giaccardi, 2011[132]	All patients ≥ 65 years undergoing CABG and/or valve procedures (total sample: 74.1 ± 5.8 years old); 43% female	Italy	158	Harvard Alumni Questionnaire	Four weeks postoperatively	Physical activity had an independent association with postoperative atrial fibrillation within 30 days.
Markou, 2007[126]	Elective CABG patients (Active: 64.4 ± 9.4, Inactive: 63.8 ± 9.0 years old); % female not reported	Netherlands	428	The Corpus Christi Heart Project	One year	Inactive vs. Active group had significantly more peri-operative MIs, but not reoperations, ICU LOS, HLOS, or postoperative complications at one year. Inactive group was more likely than Active group to be physically active at one year.
Nery, 2007[127]	All patients undergoing CABG (Active: 63 ± 11, Inactive 66 ± 14 years old); 42% female	Brazil	55	Structured Questionnaire confirmed by Minnesota Leisure Time Physical Activity Questionnaire	One year	Inactive vs. Active group had significantly longer HLOS and more postoperative events at one year.
Markou, 2008[128]	Elective CABG patients (64.3 ± 9.04 years old); 18% female	Netherlands	568	The Corpus Christi Heart Project	One year	Inactive vs. Active group were more likely to be more physically active one year postoperatively.
Martini, 2010[129]	Elective CABG patients (Active: 60 ± 10, Inactive: 62 ± 10 years old); 34% female	Brazil	185	Baecke Usual Physical Activity Questionnaire	Two years	Inactive vs. Active group did not have significantly different MACCE outcomes at two years.

Nery, 2010[130]	Elective CABG patients (Active: 60 ± 10, Inactive: 62 ± 10 years old); 34% female	Brazil	202	Baecke Usual Physical Activity Questionnaire	Hospital discharge	Inactive vs. Active group had more postoperative events within 30 days and a longer HLOS.
Rengo, 2010[131]	Acute or elective CABG patients ≥ 70 years (Active: 72.3 ± 3.2, Inactive: 76.1 ± 3.9 years old); 34% female	Italy	587	Physical Activity Scale for the Elderly	Mean 44.3 ± 21.0 months	Physical activity had an independent and dose association with cardiac and all-cause mortality five years postoperatively.
Cacciatore, 2012[133]	All patients ≥ 65 years undergoing CABG and/or valve procedures (72.9 ± 4.8 years old); 48% female	Italy	250	Physical Activity Scale for the Elderly	Hospital discharge	Physical activity was independently associated with reduced prolonged ICU LOS. Physical activity was not independently associated with postoperative ADLs.
Noyez, 2013[134]	Elective CABG and/or valve patients (69.7 ± 10.1 years old);	Netherlands	3150	The Corpus Christi Heart Project	30 days postoperatively	Physical activity was not independently associated with hospital or 30 day mortality. Inactive vs. Active group had a significantly longer ICU LOS.
Min, 2015[135]	Elective CABG and/or valve patients ≥ 65 years (74.7 ± 5.9 years old)	United States of America	62	The Health and Retirement Survey	4-6 months	Inactive vs. Active group had significantly higher postoperative physical activity up to 6 months postoperatively.
van Laar[136]	Patients ≥75 years undergoing elective isolated aortic valve replacement (79.5 ± 2.8 years old); 59% female	Netherlands	115	The Corpus Christi Heart Project	2 years postoperatively	Inactive vs. Active group had significantly higher mortality rates 2 years postoperatively.

In the studies by Markou et al.,[126,128] Nery et al.,[127,130] Martini et al.,[129] they evaluated CABG only patients. Rengo et al.,[131] Giaccardi et al.,[132] Cacciatore et al.,[133] Noyez et al.,[134] and Min et al.[135] evaluated both CABG and/or valve procedures, and van Laar et al.[136] evaluated isolated aortic valve repair patients. The average age of participants in different studies ranged from 60 years (Martini and Nery et al.[129,130]) to 75 years (Rengo, Giaccardi, Min, and van Laar et al[131,132,135,136]). Rengo et al.,[131] Giaccardi et al.,[132] Min et al.,[135] and van Laar et al.[136] excluded patients with physical impairments or with New York Heart Association heart failure class IV symptoms (severe cardiac symptoms) but in general exclusion criteria were not explicitly reported. Studies were conducted in the Netherlands (Markou et al.,[126,128] Noyez et al.,[134] and van Laar et al.[136]), Brazil (Nery et al.,[127,130] and Martini et al.[129]), Italy (Rengo et al.,[131] Giaccardi et al.,[132] and Cacciatore et al.[133]), and the United States (Min et al.[135]). Two studies by Nery et al.[127] and Martini et al.[129] used the same patient sample, but examined different outcomes. The sample size of studies ranged from 35 in the Min et al.[21] study to 3150 in the Noyez et al.[134] study

Physical activity tools

The physical activity assessments in each study were based on self-reported assessment tools. The timing of the physical activity assessments prior to surgery was not reported by Cacciatore et al.,[133] Nery et al.,[127,130] Markou et al.,[126,128] or by Martini et al.[129] Rengo et al.[131] reported the timing of their physical activity assessment, which was within 35±6 days prior to surgery. Noyez et al., and van Laar et al. measured activity the day before surgery.[134,136] Min and colleagues measured physical activity four weeks prior to the patients' surgical procedure.[21] Finally, Giaccardi et al. measured preoperative physical activity levels approximately one week following surgery.[132]

Four studies used the Corpus Christi Heart Project questionnaire[126,128,134,136] which asks participants about their typical physical activity behaviors over the past year during their leisure time. Participants were categorized into a sedentary group if they accumulated less than 30 minutes per day of light intensity activity, or into an active group if they accumulated at least one session per week of dynamic activity lasting ≥15 minutes marked by moderate intensity. Nery et al.,[127,130] and Martini et al.[129] used a structured questionnaire confirmed by the Minnesota Leisure Time Physical Activity Questionnaire[127,130] or the Baecke Usual Physical Activity questionnaire.[129,130] Both physical activity tools ask participants to recall their usual activities 12 months prior and determine the frequency, intensity, and time of activity. Participants were categorized into an inactive group if they engaged only in light intensity (<3 metabolic equivalents) activity or into an active group if they achieved ≥3 metabolic equivalents. Rengo et al.[131] and Cacciatore et al.[133] used the Physical Activity Scale for the Elderly, which is a 7-day recall of a participants' frequency, intensity, duration, and type of activity. Participants receive a total score from 0-400. Rengo et al.[131] separated participants by inactive and active groups using the median score, whereas Cacciatore et al.[133] used the continuous measure. The Harvard Alumni Questionnaire was implemented by Giaccardi and colleagues[132] which measures the typical weekly amount and intensity of physical activity over the past year. Participants were categorized as inactive if they participated in <1 hour per week of light activity and as active if they participated in either ≥4 hours of light or more than 1-2 hours of moderate activity per week. In the study by Min et al.,[21] the physical activity-related questions were used from the Health and Retirement Survey, which determines a participants' frequency and intensity of activity in a typical week. These authors used the continuous score in their study.

MACCE

Outcomes within the definition of MACCE were evaluated in four studies (Table 6.2) by Nery et al.,[127] Martini et al.,[129] Rengo et al.,[131] and van Laar et al.[136] The follow-up periods were one (Nery et al.[127]) two (Martini et al.,[129] and van Laar et al.[136]) and five years (Rengo et al.[131]) postoperatively. Unadjusted differences between active versus inactive patients and MACCE (defined as atrial fibrillation, hospital admission, reoperation and MI) were found one-year postoperatively in the Nery et al.[127] study. The Martini et al.[129] study found no differences (defined as mortality, re-hospitalization, cerebrovascular accident and MI) at two years postoperatively The unadjusted rates of mortality within two years post-surgery was significantly higher in the active versus inactive group were found in the study by van Laar and colleagues.[136] The study by Rengo and associates found a significant and dose-response relationship between physical activity and postoperative cardiac and all-cause mortality after controlling for preoperative demographics, medical history, medications, and clinical characteristics.[131]

Table 6.2. Major adverse and cerebrovascular events and postoperative events within 30 days

Reference	Outcome definition	Adjustment variables	Number of events per group	OR or HR and 95% CI
Major adverse cerebrovascular and cardiac events				
Nery, 2007[127]	One year postoperative AF, hospital readmission, new CABG, PCI, MI	None	Active: 8/25 (31%); Inactive: 17/30 (57%)[a]	NR
Martini, 2010[129]	Two year postoperative death, re-hospitalization, cerebrovascular accident, MI	None	Active: 9/66 (14%); Inactive: 31/119 (26%)	NR
Rengo, 2010[131]	Five-year postoperative cardiac and all-cause mortality	Demographics, medical history, medications, and clinical findings.	NR	Adjusted proportional hazard models: *All-cause mortality:* Exp(B) 0.248 (95% CI 0.141-0.434) [a] *Cardiac mortality:* Exp(B) 0.272 (0.133-0.555) [a]
van Laar 2015[136]	Two-year mortality	None	Active: 5/65 (13%); Inactive: 11/50 (22%)[a]	NR
Postoperative events within 30 days				
Markou, 2007[126]	Perioperative MI, Re-intervention, postoperative complications (wound, renal, neurological, pulmonary, gastrointestinal)	None	MI: Active: 4/226 (2%); Inactive: 11/202 (5%) [a] Reoperation: Active: 15/226 (7%); Inactive: 9/202 (5%), Wound infection: Active: 3/226 (1%); Inactive: 7/202 (3%), Renal: Active: 3/226; Inactive: 7/202	NR
Nery, 2010[130]	Mortality, MI, reoperation	Age, smoking, PVD, COPD, Cleveland Risk Score.	Mortality: Active: 0/66 (0%); Inactive: 7/136 (5%) MI: Active: 1/66 (2%); Inactive: 6/136 (4%) Reoperation: Active: 0/66 (0%); Inactive: 1/136 (0.5%)	Multivariate OR for being active: 0.22 (95% CI 0.09-0.51, p=0.001)

Rengo, 2010[131]	Low-output syndromes, MI, cardiac support, stroke, bleedings, mediastinitis, pneumonia, dialysis	None	Any surgical complication: Active: 53/267 (19.7%); Inactive: 60/320 (18.6%)	NR
Giaccardi, 2011[132]	Atrial fibrillation	Age, episodes of AF one year preop, episodes of AF in the first week, β-blockers, amiodarone, left ventricular volume, left atrial emptying fraction	Postoperative atrial fibrillation: Active: 6/74 (8.1%); Inactive: 27/84 (32.1%)[a]	Multivariate OR for being inactive: 4.04 (95% CI 1.16-14.14, p=0.029)
Noyez, 2013[134]	Mortality, reoperation, stroke, renal insufficiency, sternal wound, ventilation	≥75 years, valve surgery, female, high operative risk, renal disease, obesity, NYHA IV, Insulin, vascular pathology, poor LVEF, lung disease, MI, neurological event	Hospital mortality: Active: 7/1815 (0.4%); Inactive: 15/1335 (1.1%)[a] 30 day mortality: Active: 10/1815 (0.6%); Inactive: 20/1335 (1.5%)[a] Reoperation: Active: 105/1815 (5.8%); Inactive: 68/1335 (5%) Stroke: Active: 9/1815 (0.5%); Inactive: 12/1335 (0.9%) Renal insufficiency: Active: 32/1815 (1.8%); Inactive: 39/1335 (2.9%)[a] Sternal wound: Active: 10/1815 (0.6%); Inactive: 17/1335 (1.3%)[a] Ventilation >2 days: Active: 31/1815 (1.7%); Inactive: 54/1335 (4.0%)[a]	Hospital mortality multivariate OR for being inactive: 1.20 (95% CI 0.4-3.5, p=0.617) 30 day mortality multivariate OR for being inactive: 1.10 (95% CI 0.5-2.7, p=0.70)

[a] indicates statistical significance (P<0.05). CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MI, myocardial infarction; NR, not reported; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio; AF, atrial fibrillation; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

30-day events

Five studies (Markou et al.,[126] Nery et al.,[130] Rengo et al.,[131] Giaccardi et al.,[132] and Noyez et al.[134]) evaluated postoperative events within 30 days of surgery (Table 6.2). The postoperative events measured varied significantly between the studies. Three studies (Nery et al.,[130] Giaccardi et al.,[132] and Noyez et al.[134]) examined if physical activity was an independent protective factor against postoperative events. Physical activity was an independent protective factor against the combined outcome of mortality, MI, and reoperation in the study by Nery et al.;[130] as well as postoperative atrial fibrillation in the Giaccardi and associates study;[132] but was not significant for in-hospital or 30-day mortality in the Noyez et al.[134] study.

Postoperative health-related QOL

No studies evaluated postoperative health-related QOL.

Hospital and ICU length of stay

Three studies by Markou et al.[126] and Nery et al.[127,130] compared hospital length of stay between active vs. inactive cardiac surgery patients (Table 6.3). Hospital length of stay was longer in the inactive group in two of three studies (both by Nery et al.[127,130]). One of the studies by Nery et al.[130] did not report hospital length of stay summary statistics between the active vs. inactive groups. However that study reported an independent association between the preoperative active vs. inactive group and a reduced likelihood of prolonged hospital length of stay, though "prolonged" was not defined in the study.

Table 6.3. Hospital length of stay, ICU length of stay, and postoperative activities of daily living and physical activity.

First author, year	Adjustment variables	Length of stay/number of events per group	Odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI)
Hospital length of stay			
Markou, 2007[126]	None	Active: 6.9 ± 8.2 days; Inactive: 7.3 ± 7.1 days	NR
Nery, 2007[127]	None	Active: 12 ± 5 days, median 9 days (IQR 8-15); Inactive: 15 ± 8 days, median 12 (IQR 9-19)[a]	NR
Nery, 2010[130]	Age, sex, Cleveland Risk Score, smoking, systemic arterial hypertension, stroke, MI, and PVD.	NR	HR: 0.67 (95% CI 0.49-0.93) [a]
ICU length of stay			
Markou, 2007[126]	None	Active: 2.2 ± 5.3 days; Inactive: 2.1 ± 3.5 days	NR
Cacciatore, 2012[133]	For ICU LOS >3 days: age, off-pump CABG, stroke, renal failure.	Active: 2.58 ± 1.09 days; Inactive: 3.33 ± 1.68 days[a,b]	For ICU length of stay >3 days Univariate OR: 0.984 (95% CI 0.977-0.992) [a] Multivariate OR: 0.992 (95% CI 0.983-1.000) [a]
Noyez, 2013[134]	None	Active: 1.3 ± 1.9 days; Inactive 3.0 ± 41.8 days [a] ICU > 5 days: Active: 19/1815 (1.0%); Inactive: 46/1335 (3.4%) [a]	NR
Postoperative ADLs			

Cacciatore, 2012[133]	Age, gender, CABG, NYHA ≥3, ICU LOS ≥3 days, Off-pump CABG, diabetes, renal failure, stroke, PVD, COPD, Cumulative Illness Rating Scale.	NR	Beta: 0.099
Postoperative Physical activity			
Markou, 2007[127]	Age ≥75 years, gender, neurological disease, vascular disease, diabetes, and preoperative physical activity.	Better PA post-operatively: Active: 48/226 (21.2 %), Inactive: 129/202 (64%) [a] Equal PA post-operatively: Active: 112/226 (49.6%), Inactive: 59/202 (29.2%) [a] Worse PA postoperatively: Active: 66/226 (29.2%), Inactive: 14/202 (6.9%) [a]	Decreased postoperative PA OR (inactive group as reference): 8.1 (95% CI 3.5-13.5) [a]
Markou, 2008[128]	Diabetes, vascular disease, neurological disease, renal disease, MI, preoperative activity level.	NR	For becoming physically inactive postoperatively Male OR (inactive group as reference): 7.11 (95% CI 3.6-13.9) [a] Female OR (inactive group as reference): 11.0 (95% CI 2.2-55) [a]
Min, 2015[135]	None	NR	Each weekly preoperative activity point was associated with a loss of 0.78 points at 6 weeks, p<0.001, and 0.65 points at 6 months) [a]

[a] indicates statistical significance (P<0.05). [b]Unpublished data obtained from Cacciatore et al, [19]. ICU, Intensive Care Unit; ADL; activities of daily living; IQR, interquartile range; NR, not reported; MI, myocardial infarction; PVD, peripheral vascular disease; HR, hazard ratio; OR, odds ratio; CABG, coronary artery bypass graft; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; PA, physical activity.

Three studies compared ICU length of stay between the preoperative physical activity groups (Table 6.3) (Markou et al.,[126] Cacciatore et al.,[133] and Noyez et al.[134]). Two studies (Markou et al.[126] and Noyez et al.[134]) found that the inactive group had a significantly longer ICU length of stay compared to the active group. In the study by Cacciatore and colleagues,[133] they found in their multivariate analysis that the active group was less likely to have a prolonged ICU length of stay >3 days compared to the inactive group after controlling for age, off-pump CABG, stroke, and renal failure.

Postoperative ADLs

One study by Min et al.[21] examined the impact of preoperative physical activity and postoperative ADLs at the time of hospital discharge and revealed no statistically significant ($p= 0.079$) association between the two after adjusting for preoperative demographics and clinical variables.

Cardiac rehabilitation attendance

No studies evaluated cardiac rehabilitation attendance postoperatively.

Postoperative physical activity behavior

The impact of preoperative physical activity on postoperative physical activity levels was examined in the two studies by Markou et al.[126,128] and in the other study by Min et al.[21] (Table 6.3).These studies found that the active group preoperatively was more likely to be physically inactive postoperatively. In both of the Markou et al.[126,128] studies, they completed a multivariate analyses and found that this association remained statistically significant after controlling for age, gender, and preoperative clinical characteristics.

Risk of bias

The risk of bias assessment via the Newcastle-Ottawa Scale can be viewed in Table 6.4. Since some studies assessed multiple outcomes, the risk of bias assessments were based on their highest possible score (e.g., some outcomes were assessed with a multivariable analysis, while others were not in the same study). All studies scored at least 3 out of 4 for the selection of study groups. There was variability across studies for the ascertainment of exposure or outcome of interest. Total risk of bias scores ranged from 5 to 9, suggesting the studies were of moderate to high quality, respectively.

Table 6.4. Newcastle-Ottawa scale risk of bias scores

Reference	Selection	Comparability	Outcome	Total
Markou, 2007[126]	3	2	3	8
Nery, 2007[127]	3	0	2	5
Markou, 2008[128]	3	2	2	7
Martini, 2010[129]	3	0	2	5
Nery, 2010[130]	3	2	2	7
Rengo, 2010[131]	4	2	3	9
Giaccardi, 2011[132]	3	2	2	7
Cacciatore, 2012[133]	3	2	2	7
Noyez, 2013[134]	3	2	3	8
Min, 2015[135]	4	2	1	7
van Laar[136]	3	0	3	6
Average scores ± SD	3.18±0.40	1.45±0.93	2.27±0.65	6.91±1.22

Maximum scores are 4, 2, and 3 for selection, comparability, and outcome, respectively. Maximum total score is 9. A lower score within each category and for a total score indicates a higher risk of bias.

Discussion

The purpose of this systematic review was to determine if physical activity before cardiac surgery was associated with postoperative health outcomes. Given the different self-reported physical activity tools used that prevented comparison across studies, the inconsistent use of adjustment for potential confounders, and the varying outcomes evaluated for MACCE and 30 day postoperative events, it cannot be concluded that preoperative physical activity is associated with postoperative outcomes in adult cardiac surgery patients. This systematic review highlights important gaps within the literature on this topic. Therefore, key recommendations for examining the impact of preoperative physical activity behavior on post-surgical outcomes of cardiac patients are provided (Table 6.5).

Table 6.5. Guidelines for physical activity measurement and outcome assessment in cardiac surgery patients: limitations and opportunities for future research

<table>
<tr><th>Drawbacks</th><th>Opportunity</th></tr>
<tr><td colspan="2">Physical activity</td></tr>
<tr><td>1. Heterogeneity in tools used across studies</td><td rowspan="3">-use of objectively measured tools (e.g., pedometers, accelerometers) accompanied by a questionnaire which can produce data that can be compared across studies, such as step counts, intensity, and duration of physical activity.
-Capture physical activity behavior as soon as a patient is placed on a wait list, or in non-elective cases, as soon as possible prior to surgery.
-Physical activity should be assessed ideally over a 7 day period.
-Physical activity should be assessed by intensity and duration per week, and in steps per day.</td></tr>
<tr><td>2. Only subjective measures were used</td></tr>
<tr><td>3. Time of preoperative physical activity assessment was unclear in most studies</td></tr>
<tr><td colspan="2">Outcomes</td></tr>
</table>

4. Heterogeneity in MACCE and postoperative events within 30 days definitions	-MACCE should be evaluated as a long-term outcome and defined as death, stroke, myocardial infarction, and the need for re-do cardiac surgery. Each outcome should be evaluated individually. -30-day postoperative events should be evaluated using the STS checklist:[10] along with reasons, evaluate unexpected return to the operating room, complications due to pulmonary, cardiovascular, gastrointestinal, hematological, urologic, infection, neurological, and other important miscellaneous outcomes (e.g., unexpected admission to ICU, or other events requiring admission to operating room requiring anesthesia. -re-hospitalization for any cause after cardiac surgery should also be added to outcomes.
5. No patient-oriented outcomes were assessed	-Capture postoperative health-related quality of life, mental health, pain, and cardiac symptoms using validated tools within the first 30 days and at least one-year postoperatively.
Statistical procedures	
6. Shortage of studies addressing confounders	-use multivariate analysis, including logistic or linear regression, or analysis of variance statistical procedures. Ensure that a power analysis is conducted prior to conducting the study.
MACCE, major adverse cerebrovascular and cardiac events. STS, Society of Thoracic Surgeons. ICU, intensive care unit.	

The different self-reported physical activity tools used across the studies makes it difficult to compare the preoperative physical activity levels of patients prior to cardiac surgery. Even so, it is important to note that in the studies included in this systematic review, most of the studies identified a sub-sample of cardiac surgery patients who were more vulnerable to poor health outcomes by categorizing patients as active or inactive prior to surgery using their self-reported physical activity measures. However, the way the physical activity tools measured physical activity (e.g., over the past year or in the past week; see the Methods section) could have influenced the outcomes of the study. There seems to be no universally accepted tool to measure self-reported physical activity levels, and it is unclear if any of the physical activity tools identified by this review have been validated in the cardiac surgery patient.[137] One advantage of using self-reported physical activity measures in studies is their ease of administration compared to other objectively measured physical activity tools. Furthermore, self-reported physical activity tools appear to provide some value when assessing the independent association between activity levels and poor outcomes. In fact, most physical activity guideline recommendations for health benefits, including those in North America, are based on self-reported measures.[138,139] Another strength of using a subjective physical activity tool in the preoperative cardiac surgery patient is that it would capture a patient's physical activity behavior before they are placed on a waiting list, when they might refrain from being physically active in fear of making their condition worse. However, cardiac surgery patients and other patient populations tend to misreport their physical activity levels compared to objectively measured physical activity.[120,140] Nevertheless, this systematic review found no studies that evaluated objectively measured physical activity before cardiac surgery and its link to postoperative health outcomes. Evidence suggests there is a stronger association between objective measures of physical activity and various cardiovascular and metabolic biomarkers as compared to subjective measures of physical activity.[141,142] While it is unclear which objective measures of physical activity are most appropriate in the complex cardiac surgical patients, future studies should use a physical activity tools such as accelerometers or pedometers.

There were inconsistent findings across studies assessing the same outcomes, and many studies did not adjust for clinically relevant variables that could influence the health outcomes of cardiac surgery patients. It is possible that most of the included studies were not statistically powered to detect changes between inactive and active groups. The study by Rengo et al.[131] had the largest sample size of the four studies that assessed MACCE outcomes, which found a significant protective association between preoperative physical activity and cardiac and all-cause mortality five years postoperatively after controlling for clinically relevant variables (Table 6.2). In contrast, the largest study examined in this systematic review by Noyez and colleagues[134] found no association between preoperative activity and hospital and 30-day mortality after controlling for covariates (Table 6.2). It is difficult to determine if patient-level factors influence outcomes (e.g., elective or acute patients, surgery type, older versus younger, females vs. males) as the samples were somewhat heterogeneous. Even so, some of the results of this systematic review are promising. Specifically, of the studies which controlled for confounding variables, five studies found a protective, independent association, between higher preoperative physical activity levels when assessing clinical outcomes, including MACCE,[17] 30 day postoperative events,[130,132] hospital length of stay,[130] and ICU length of stay;[133] whereas, only two studies found no protective association for 30 day postoperative events[134] and postoperative ADLs.[135] Yet, more studies are needed to elucidate the impact of preoperative physical activity on post-cardiac surgical outcomes that control for clinically relevant variables. Clinical variables included in the cardiac surgical risk models (e.g., EuroSCORE, STS score) could attenuate or mitigate the relationship between preoperative physical activity behavior and postoperative outcomes. Collectively, future studies are needed to determine if preoperative physical activity is a protective factor for health outcomes after cardiac surgery which control for clinically relevant variables known to impact cardiac surgery outcomes.

An unanticipated finding was that patients who were active before surgery had a higher likelihood of being physically inactive postoperatively, after controlling for co-morbidities.[126,128,135] Healthcare providers may have advised patients with more severe symptomology prior to surgery to refrain from physical activity. Also, the relief of cardiac symptoms after surgery among inactive patients could have led them to become more active postoperatively. However, these possibilities were not explored in the included studies.

While outside the scope of this systematic review, future studies should investigate if changes to physical activity levels prior to cardiac surgery impact long-term patient health-outcomes. Cardiac rehabilitation programs are intended to support cardiac patients in becoming more physically active postoperatively and it has been shown that patients who attend such programs reduce their risk for cardiac-related mortality and hospitalization rates.[118] Evidence suggests that among those referred to cardiac rehabilitation after cardiac surgery, only 40% attend.[120] However, the literature is less clear on whether patients who attend cardiac rehabilitation are more physically active compared to those who do not attend. It is possible that patients who adopt and sustain a more physically active lifestyle on their own after cardiac surgery could yield similar health benefits compared to those who attend an exercise-based rehabilitation program, but this hypothesis requires further investigation.

Previous randomized controlled trials comparing an exercise program to standard care prior to elective cardiac surgery (i.e., "Prehab") demonstrate reductions in hospital length of stay and improvements in walking ability postoperatively.[121-123] However, there were mixed findings from this systematic review when comparing preoperative physical activity behavior and hospital stay.[126,130] These divergent findings suggest either that a medically supervised and individualized physical activity program is needed to derive the health benefits of physical activity prior to cardiac surgery, or that patients are misreporting their physical activity behaviors. Future cohort studies in this area should address the drawbacks of the included studies in this systematic review included in Table 6.5, while randomized trials should focus on whether preoperative exercise therapy programs are feasible and efficacious in clinical practice.

The findings of this systematic review suggest that the literature would benefit from standardization of the definition of measures such as MACCE and postoperative events within 30 days. The heterogeneity in reporting of outcomes can lead to considerably different conclusions across studies.[143] Attempts should also be made to ensure other clinically important outcomes are captured, such as the addition of 30-day events. Only one study in this review compared physically active versus inactive patients preoperatively and reported on the individual postoperative events within 30 days.[134] Collectively, uniform outcome reporting and appropriate outcome definitions are recommended when examining the outcomes of cardiac surgery.[143]

Patient-oriented outcomes should also be captured to ensure that cardiac surgery is improving other outcomes that patients value. No studies in this review determined if there was a link between preoperative physical activity behavior and postoperative health-related QOL, and only one study evaluated postoperative ADLs.[135] QOL postoperatively tends to improve in some older patients, while others tend to decline.[144] Importantly, the preoperatively physical activity and overall functional status of cardiac surgery patients could play a role in the postoperative trajectory of these outcomes such as QOL. Other patient-oriented outcomes, including postoperative pain and cardiac symptoms, could also be investigated.

If physical activity is to be assessed in the preoperative period, the extent of missing data may also be a concern, especially with objective physical activity measures. The possibility of missing data from individual studies included in this systematic review was outside the objectives of the present study, but is a salient point that should be considered for future investigations. It is also important to understand patient-level factors associated with missing data. The use of statistical techniques that address missing data, such as multiple imputation, is one approach to address missing physical activity data. Importantly, it has been shown that multiple imputation leads to precise estimates of predicting 30-day mortality risk in cardiac surgery patients when important clinical variables are missing, as compared to estimating risk with a complete case analysis.[145]

Limitations

One limitation to consider is that the patients included across the studies evaluated in this systematic review may have been different, as the recruitment criteria were not always clearly stated. A small sample of studies explicitly stated that they excluded those with physical limitations and healthcare providers may have advised higher risk patients to not participate in physical activity. There is also a limitation associated with the methodology of this systematic review: only studies written in English were included, raising the possibility that some studies were missed.

Conclusion

Due to the mixed findings in this systematic review, it cannot be concluded that self-reported physical activity behavior before cardiac surgery is associated with health outcomes after surgery. The mixed findings could be due to the heterogeneity in physical activity tools used, definitions of outcomes, and the few studies adjusting for other potentially confounding variables. These findings highlight the need for more research in this area.

CHAPTER 7: GENERAL DISCUSSION

The aging population is growing at a rapid rate, and it is estimated that almost one fourth of individuals will be over the age of 60 by 2050 globally.[40] By extension, it is expected that the healthcare and public health systems will need to respond to a higher burden of chronic conditions and disabilities. However, every older person is different and the complexities of aging are affected by a milieu of individual and environmental factors. Frailty is a concept that describes this heterogeneity in aging and is linked to increased vulnerability to poor health outcomes.[43,146] In turn, this has led to efforts in identifying and implementing potential strategies to treat and prevent frailty.

This thesis determined if alternative approaches to the accumulation of physical activity and sedentary behaviors were associated with frailty. In addition, it was determined if there were sex and CVD-specific differences in the relationship between bouts of MVPA and patterns of sedentary behaviors with frailty. Lastly, this thesis determined if preoperative physical activity influenced post-cardiac surgical outcomes.

Overview of findings

The data generated from this thesis could inform additional recommendations to current physical activity and sedentary behavior guidelines for adults and provides a stepping stone to shape how we think about targeting reductions in sedentary behaviors and supporting a more physically active lifestyle in middle-aged to older adults. Table 7.1 provides a summary of the findings across the NHANES studies. Data in the table describe the associated increase or decrease in the number of FI variables from the β-coefficients in the multivariable linear regression models which controlled for the most covariates across the three NHANES studies.

Table 7.1. Relationship between bouts of MVPA and patterns of sedentary behaviors with the differences in the number of frailty index deficits across the NHANES studies.

Parameter	Study 1 (NHANES initial model)	Study 2 (NHANES sex-differences)		Study 3 (NHANES CVD-differences)	
		Females	***Males***	***No CVD***	***CVD***
Bouted MVPA[a]					
≥100 guidelines	↓1.03	↓2.08*	↓1.42*	↔	↓1.61**
50-99% guidelines	↓1.29	↓2.70*	↓1.29*	↔	↓2.29**
1-49% guidelines	↓0.84	↓1.53*	↓0.99*	↔	↓1.39**
Sporadic MVPA[a]					
≥100 guidelines	↓2.24	↓3.38*	↓4.30*	↓2.76	↓2.25
50-99% guidelines	↓2.25	↓2.74*	↓3.69*	↓2.72	↓1.72
1-49% guidelines	↓1.57	↓1.64*	↓2.26*	↓2.18	↓1.06
Prolonged sedentary bouts	↑0.52	↑0.97**	↔	↔	↑0.65
Total breaks in sedentary time (per 10 breaks)	↔	↔	↔	↔	↔
Avg break intensity (per 100 counts/min)	↓0.81	↓0.97	↓0.84	↓0.72	↓0.79
Avg break duration (per min)	↓0.61	↔	↓0.70	↔	↓0.73

Table shows data from the most adjusted statistical models. Down arrow (↓) indicates a lower frailty score. Up arrow (↑) indicates a higher frailty score. Left-right arrow (↔) indicates a non-significant relationship
[a]Reference group is participants meeting 0% of physical activity guidelines
*Relationship between sporadic MVPA and frailty for females was found after removal of total sedentary time as a covariate.
**Statistically significant interaction effect was found.

This thesis demonstrated that MVPA accumulated in at least 10 minute bouts was associated with a lower FI. This finding supports current physical activity guidelines. However, an interesting finding was that bouted MVPA was generally associated with a clinically meaningful protective association with frailty across the NHANES studies among individuals meeting as low as 1-49% of the physical activity guidelines. Furthermore, those who met 50-99% of physical activity guidelines had a similar protective association with frailty compared to those who met ≥100% of the guidelines. These data suggest current physical activity guidelines should not be silent about the health benefits of lower MVPA accumulation.

Sporadic MVPA accumulated in less than 10 minute bouts was generally more strongly associated with a lower FI than bouted MVPA across the NHANES studies. Furthermore, meeting less than the recommended 150 minutes per week of MVPA through sporadic MVPA resulted in significant associated lower FI scores. Collectively, these findings suggest that sporadic MVPA should be included as a way to meet physical activity guideline recommendations.[34-36]

This thesis could inform additional recommendations to adult sedentary behavior guidelines. For example, this thesis demonstrated that prolonged, uninterrupted periods of sedentary time lasting at least 30 minutes were detrimentally associated with frailty. Furthermore, when breaking up sedentary time, this thesis provides data to suggest that it is not the frequency at which breaks are performed, but the duration and intensity of those breaks that lead to associated higher FI scores.

The second NHANES study provides data to suggest that there are sex differences in the association between patterns of sedentary behaviors with frailty. Specifically, prolonged bouts of sedentary behavior were more detrimentally associated with frailty in women versus men. This finding suggests that more emphasis should be placed on limiting women's time spent in sedentary pursuits.

A salient finding from the third NHANES study was that bouted MVPA was associated with lower FI scores among those with CVD compared to those without CVD. This finding suggests that bouted MVPA should be recommended to people with CVD in conjunction with sporadic MVPA. In fact, these data support the cardiac rehabilitation-specific guidelines delivered by the Canadian Association of Cardiovascular Prevention and Rehabilitation, which recommend that 150 minutes of MVPA per week be accumulated in at least 10 minute bouts.[147]

The overall findings generated from the systematic review investigating the impact of preoperative physical activity on post-cardiac surgical outcomes were mixed and currently do not support that physical activity before cardiac surgery is linked to better health outcomes after a patients' surgical intervention (Table 7.2). The relatively small number of studies (n=11 with a total of 5733 participants) relied on self-reported physical activity measures, few studies adjusted for confounders, and there was heterogeneity in the definition of postoperative MACCE and adverse events within 30 days. As such, it was identified that there is a need to conduct research that uses objective assessments of physical activity and sedentary prior to cardiac surgery, clearly define outcomes, and adjust for clinically relevant variables.

Table 7.2. Summary of findings from the systematic review on the impact of preoperative physical activity on post-cardiac surgical outcomes.

Outcome	No. of studies	No. of studies adjusting for covariates	Sample size across studies	Main finding
Frailty	0/11	-	-	-
MACCE	4/11	1/4	942	3/4 studies found a significant association between physical inactivity and increased risk of MACCE
Postoperative events within 30 days	5/11	3/5	4525	The largest study (n=3150) found no independent association between physical activity and postoperative events[134]
Hospital length of stay	3/11	1/3	685	2/3 studies found hospital length of stay was longer in the inactive group vs. active group
ICU length of stay	3/11	1/3	3828	1/3 studies found an independent protective association between physical activity and longer ICU length of stay
Postoperative activities of daily living	1/11	1/1	250	Non-significant relationship found.
Postoperative cardiac rehabilitation attendance	0/11	-	-	-
Postoperative quality of life	0/11	-	-	-
Postoperative physical activity	3/11	1/3	1058	High preoperative physical activity was associated with lower postoperative physical activity

Table describing main outcomes revealed from the systematic review on preoperative physical activity and post cardiac-surgical outcomes.
MACCE, major adverse cerebrovascular and cardiac events. ICU, intensive care unit.

Conceptual model of thesis findings: Take a Break from Sitting and get Moving!

A conceptual model (Figure 7.1) was developed to integrate the findings generated in this thesis with existing physical activity and sedentary behaviour guidelines. The "Take a Break from Sitting and get Moving" model (which will be referred to as "the Model") is informed by the adult North American and World Health Organization physical activity guidelines,[34-36] which recommend 150 minutes per week of MVPA in at least 10 minute bouts to derive health benefits. The Model also incorporates adult sedentary behavior guidelines from Australia and the United Kingdom, which suggest limiting extended periods of sitting time and to break up sitting time as often as possible.[87,88] Lastly, recommendations from the Canadian 24-hour Movement Guidelines for limiting sedentary behaviors in children and youth were incorporated into the Model.[150] These guidelines provide the recommendation to limit extended periods of sitting and to limit recreational screen time to 2 hours per day.

While there is some overlap between the physical activity and sedentary behavior pattern variables measured in the NHANES studies, it was felt that individually determining their relationship with frailty might shed light into informing new recommendations to public health delivered guidelines for physical activity and sedentary behavior. Overall, the Model is intended to provide new ways of thinking into how middle-aged to older adults can achieve the recommendations within the physical activity and sedentary behavior guidelines. Throughout the description of the Model, the term "health benefits" will be used interchangeably with reductions in frailty to align the recommendations provided by the physical activity and sedentary behavior guidelines with the NHANES studies.

Figure 7.1. Conceptual model of thesis findings.

This conceptual model has adopted a "Take a break from sitting and get moving!" approach, which combines recommendations to reduce sedentary behaviors, and to increase physical activity levels intense enough to provide additional health benefits beyond that of breaking up sedentary time.

Break Up Sedentary Time

The "Break Up Sedentary Time" component of the Model focuses on limiting time spent in extended periods of sedentary behaviors through movement breaks. The recommended approach in the Model is to focus on the intensity of movement during those breaks in relatively short amounts of time, rather than the total number of breaks. In general, this recommendation is supported by the NHANES studies (chapters 3-5), which demonstrated that every two prolonged bouts of sedentary time lasting at least 30 minutes per day were detrimentally associated with one frailty deficit score increase.

Whereas, every additional 100 counts/min (which measures increasing intensity of physical activity) and every two minutes in average break duration registered by accelerometer was associated with an approximate one lower FI deficit score. These data are considered clinically relevant given that adults accumulate approximately one deficit every year.[148]

To break up sedentary time, low intensity movement behaviors may only be needed to influence health outcomes. For example, household chores such as cooking, ironing, or washing dishes are shown to register approximately 200-300 counts/min on a uniaxial accelerometer, which is two and three times above the sedentary behavior counts/min threshold, respectively.[149] Overall, these recommendations align with the adult sedentary behavior guidelines in Australia and the United Kingdom, as well as the 24-hour Movement Guidelines for children and youth.[87,88,150] However, the Model is unique to current sedentary behavior guidelines by including a movement intensity and duration component when breaking up sedentary time.

The Break Up Sedentary Time facet of the Model provides a measurable recommendation to limit sedentary time. The first suggestion is to limit time spent in uninterrupted sitting to less than 30 minutes as much as possible. This recommendation is supported, in general, by the NHANES studies (see <u>Table 7.1</u>). Previous studies have also identified that prolonged bouts of sedentary time are linked to poor cardio-metabolic health,[54,77] and all-cause mortality.[151] In fact, Honda et al.[54] demonstrated that adult office workers in the highest quartile of sedentary time lasting at least 30 minutes had the greatest increased risk for developing the metabolic syndrome over 3 years compared to the lowest quartile (hazard ratio: 2.85 [95% CI, 1.31-6.18]). Overall, the recommendation to limit prolonged sedentary behaviors is supported by previous literature, and adds to the adult sedentary behavior guidelines.

A second measureable recommendation within the Model is to limit recreational screen time to two hours per day. Longitudinal studies that were identified in Chapter 2 of this thesis indicated that higher amounts of television viewing were associated with a higher risk for becoming frail.[3,10,16] In fact, Garcia-Esquinas et al.[16] reported a higher odds of frailty (OR: 1.47 [95% CI, 1.09-1.97]) in people watching television at least 3 hours per day over a 3.5 year follow up compared to those watching less than 2 hours per day.[16] This advice is supported by the 24-hour Movement Guidelines for children and youth recommendation to limit screen time to two hours per day.[150] However, recommending to limit television viewing time to less than 2 hours per day would add to the adult sedentary behavior guidelines.

Being Active for Health

The "Being Active for Health" component of the Model (Figure 7.1) provides a guideline to participate in physical activity intense enough to derive additional health benefits to that of limiting extended periods of sedentary time. This component of the Model focuses on the importance of the intensity of movement at a moderate to vigorous intensity, rather than the duration of physical activity bouts. This recommendation was mostly supported by the first three NHANES studies, which found that sporadic MVPA was more consistently associated with a lower FI, as compared to physical activity accumulated in 10 minute bouts or longer (see Table 7.1).

Recommending intensity of movement in the Model over physical activity bout length aligns with the growing body of evidence reporting similar associations between bouted and sporadic MVPA with better cardio-metabolic health scores.[48,81,152] However, this advice is in contrast to current North American and World Health Organization physical activity guidelines, which suggest that MVPA be accumulated in at least 10 minute bouts for health benfits.[34-36] Possibly the first recommendation to accumulate physical activity in bouts of at least 10 minutes was from Hardman in 2001 based on evidence from three randomized controlled trials comparing the health outcomes derived from one long bout of physical activity versus multiple 10 minute bouts of activity.[153] There were likely challenges with the measurement of sporadic MVPA when Hardman made the recommendation in 2001 that MVPA should be accumulated in at least 10 minute bouts, as many studies relied on self-report at that time. With modern physical activity assessment tools, such as accelerometers, it has become feasible to compare the health benefits of objectively measured bouted and sporadic physical activity.

The Being Active for Health component of the Model indicates that low amounts of MVPA will lead to health benefits, and recommends that individuals start by moving and then build up to 150 minutes of MVPA per week.[34-36] These suggestions align with the findings in the NHANES studies, and provide the addition to physical activity guidelines that low quantities of physical activity lead to health benefits. Previous studies have shown that accumulating lower than the recommended weekly 150 minutes of MVPA is associated with better health.[52,53] O'Donovan and colleagues demonstrated that adults (n= 63,591) who reported accumulating 1-149 minutes per week of MVPA had a lower risk for all-cause (hazard ratio: 0.61 [95% CI, 0.57-0.65]) and cardiovascular mortality (hazard ratio: 0.56 [95% CI, 0.49-0.64]) similar to those who reported accumulating at least 150 minutes per week of MVPA (all-cause mortality hazard ratio: 0.56 [95% CI, 0.50-0.62]; CVD mortality hazard ratio: 0.51 [95% CI, 0.41-0.63]).[53]

Tailored recommendations

Tailored recommendations are provided within the Model that add to current physical activity and sedentary behavior guidelines for adults. Specifically, customized recommendations are provided for females and those with CVD based on the findings from the second and third NHANES studies, respectively. The first tailored recommendation in the Model indicates that females may benefit more from limiting their time spent in extended periods of sedentary behaviors than males. This suggestion is not meant to indicate that males will not benefit from limiting extended periods of sitting. In fact, more time spent in sedentary behaviors increases the risk of type 2 diabetes,[154] some cancers,[155] cardiovascular disease,[100,154] and mortality[108] in both men and women. Rather, the advice that women may benefit more from men in limiting their sedentary time is meant to suggest that females may be at a greater risk than men for adverse health outcomes. There is some evidence to support this recommendation, which demonstrated that total time spent in sedentary behaviors has been demonstrated to increase the cardio-metabolic risk of females to a greater extent than males.[82,83]

The second tailored recommendation in the Model advises that individuals with CVD may derive additional health benefits from participating in bouted MVPA as a part of their total physical activity accumulation. This was a unique finding and it is unclear why non-CVD participants did not have a protective association with frailty from bouted MVPA. One study demonstrated a greater magnitude of benefit in physical function if participants with CVD were defined as active compared to those without CVD but also defined as physically active.[156] However, that study did not examine sporadic and bouted MVPA separately. The mechanistic relationship between sporadic and bouted MVPA with frailty by the presence of CVD is unclear. It is possible that sporadic MVPA was a sufficient stimulus that resulted in an associated lower FI among non-CVD NHANES participants. Whereas, there could have been a protective association with chronic low grade inflammation, which is a shared abnormality in frailty and CVD,[63] occurred as a result of bouted MVPA in CVD patients.

The finding that people without CVD did not have a significant protective association with frailty from bouted MVPA does not align with current physical activity recommendations in adults. However, amongst participants with CVD, these data align with the general and cardiac rehabilitation-specific physical activity guidelines. For example, the Canadian Association of Cardiovascular Prevention and Rehabilitation indicates that patients attending cardiac rehabilitation should accumulate 150 minutes per week of bouted MVPA.[104] However, these guidelines should also recognize the importance of the total accumulation of MVPA, as sporadic MVPA also resulted in associated reductions in MVPA amongst the NHANES participants with CVD.

Are the conceptual model recommendations appropriate for cardiac surgery patients?

The Model indicates that it is unclear if more specific populations, such as cardiac surgery patients, would derive health benefits (or reductions in frailty) from following its recommendations given the inconsistent findings in study 4. Before initiating this review, the intention was to synthesize evidence determining the link between preoperative physical activity and sedentary behaviors on post-cardiac surgical outcomes (see Table 7.2), including frailty. However, no studies determined if sedentary behaviors were linked to cardiac surgery outcomes, and no studies measured frailty as an outcome. Even so, the following discussion provides suggestions for implementing recommendations from the Model into the standard of care for cardiac surgery patients before their operation.

The Break Up Sedentary Time component of the model could be delivered to elective cardiac surgery patients who are usually placed on a waiting list for their operation. Healthcare providers could recommend to their patients that they limit their time spent in extended periods of sitting during their preoperative cardiac assessment. This approach may be feasible and safe to implement outside of a medically supervised environment (i.e., centre-based cardiac rehabilitation). For example, a cardiac tele-rehabilitation (or tele-prehab) service could be implemented in isolation or as an adjunct to centre-based cardiac rehabilitation. Tele-rehabilitation uses communication technologies such as the internet and mobile technology to provide rehabilitation services at a distance.[157] Healthcare providers could deliver tele-prehab and would allow them to more closely monitor their progress in limiting their sedentary behaviors and other health behavior promotion and risk factor modification.

Focusing on limiting time spent in sedentary behaviors may receive more support from patients undergoing cardiac surgery, as well as from their families, caregivers, as compared to one that advises participating in MVPA. It would also be a first step to get a population who tend to be highly sedentary preoperatively to break up their sedentary time. In turn, reducing time spent in sedentary behaviors would enable them to engage in more physical activity than before. This approach could lead to improved surgical outcomes and the possibility of maintaining these health behaviors postoperatively.

The Being Active For Health Model component could be implemented within a medically supervised fitness facility (i.e., cardiac rehabilitation). A concern with using a physical activity-based strategy prior to surgery is the possibility of increasing a patients' risk for having an adverse event. However, previous studies have demonstrated that engaging in a preoperative physical activity-based intervention is safe and can improve functional outcomes preoperatively and reduce patients' hospital length of stay.[121-123] One key element to ensuring that such a program is feasible and safe is to reassure the patient and their care providers that physical activities have previously been shown to be safe and will be supervised and overseen by medical professionals. Furthermore, cardiac rehabilitation healthcare providers can deliver additional mental health support and strategies to promote health behavior change in addition to the implementation of exercise training. This multi-faceted approach may provide an optimal intervention to cardiac surgery patients who may be overwhelmed and find it difficult to cope with the fact that they require surgery to manage their CVD.

Limitations of the Model and future research

There are limitations to the Model presented. Overall, given the cross-sectional nature of the NHANES findings and the non-significant findings in the systematic review in Chapter 6, the Model recommendations should be interpreted with caution and require more evidence. The NHANES studies only looked at frailty as an outcome and did not examine other health outcomes, which limits the generalizability of the thesis findings to physical activity and sedentary behavior guideline recommendations. Furthermore, the recommendations in the Model refer only to the aerobic component of current physical activity guidelines and no advice is provided for resistance-based physical activities. This is a limitation of most observation cohort studies that examine physical activity through the use of accelerometry.

In terms of the Break Up Sedentary Time component, it is unclear if there is an optimal break in sedentary time intensity and duration threshold needed to confer a protective association with frailty. Furthermore, it is unclear if the 100 accelerometer counts/min threshold is an appropriate threshold to distinguish between sedentary time and light intensity physical activities in middle-aged to older adults.[34] This cut-point was chosen as it was specifically used in the original NHANES study that analyzed the 2003-04 and 2005-06 accelerometer data.[76] Collectively, additional research is needed to identify optimal break in sedentary time intensity and durations that are needed to derive a clinically meaningful protective association with frailty.

Within the Being Active For Health facet of the Model, it is unclear if higher intensity physical activities beyond MVPA confer an additional protective association with frailty as no participants in the NHANES studies performed activities beyond that of vigorous intensity. Further research should investigate if high intensity interval training, which includes short bursts of high intensity activity close to maximal intensity, interspersed by periods of low intensity activity, are associated with frailty. This type of training is likely to confer an additional protective association with frailty compared to MVPA and is shown to be safe in higher risk populations such as those with heart failure and stable coronary artery disease.[158,159]

It is also unknown from the NHANES studies if meeting significantly more (e.g., 300 min/week) than the recommended physical activity guidelines is associated greater protective association with frailty. Only 32/2317 individuals accumulated 300 min/week of bouted MVPA and 21/2317 through sporadic MVPA thus limiting the statistical power to test this possibility. A greater reduction in the risk of developing heart disease and diabetes occurs in those meeting double the physical activity guidelines compared to people meeting the recommended activity levels.[98,160,161] As such, future research is needed to determine if meeting more than the weekly 150 minutes of MVPA results in a greater protective association with frailty.

Barriers to implementing the Model in cardiac surgery patients preoperatively, particularly the Being Active For Health component, include trying to fast track patients into a physical activity-based program who may have short surgery wait times, transportation to a medical fitness facility, and the endorsement from patient families, caregivers, and healthcare providers. More evidence is needed regarding the efficacy and safety limiting prolonged bouts of sedentary time and increasing physical activity behaviors prior to cardiac surgery.

Conclusion

The results from this thesis inform new recommendations to current physical activity and sedentary behavior guidelines for middle-aged and older adults, providing the basis for a “Take a Break from Sitting and Get Moving” Model. In particular, breaking up time spent in uninterrupted periods sedentary behaviors may be as essential as engaging in MVPA for a protective association with frailty. Furthermore, the total accumulation of MVPA appears to be more important than bout duration. Females may derive greater protective association with frailty than males from limiting sedentary behaviors. Patients with CVD had beneficial associated reductions from bouted MVPA while people with CVD did not. Implementing the proposed Model before cardiac surgery could lead to improved patient outcomes postoperatively, but needs to be tested. Collectively, the data generated in this thesis provide novel contributions to how we think about the treatment and prevention of frailty through physical activity promotion and sedentary behavior reduction.

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APPENDICES

Appendix 1. List of frailty index variables used.

Appendix 2. Permission to use the list of frailty index variables table.

Appendix 3. Permission to re-use published material for Chapter 6.

Appendix 4. Curriculum Vitae

Appendix 1. Frailty index variables used in the study.

Deficit:	**Coding (0=no deficit, 1= deficit)**
Stroke	0= No; 1= Yes
Thyroid condition	
Cancer	
Heart attack	
Heart disease	
Angina/angina pectoris	
Osteoporosis	
Arthritis	
High blood pressure	
Cough regularly	
Broken hip	
Confusion or inability to remember things	
Weak/failing kidneys	
Leaked/ lost control of urine	
Diabetes	0= No; 1= Yes or borderline
Cataract operation	0= No; 0.5= One eye; 1= Both eyes
Difficulty managing money	0= No difficulty; 1= Some or much difficulty, unable to do
Difficulty standing up from armless chair	
Difficulty getting in and out of bed	
Difficulty standing for long periods of time	
Difficulty stooping, crouching, kneeling	
Difficulty grasping/holding small objects	
Difficulty lifting or carrying	
Difficulty preparing meals	
Difficulty using fork and knife	
Difficulty dressing yourself difficulty	
Difficult attending social event	
Difficulty pushing or pulling large objects	
Difficulty seeing steps/curbs in dim light	
Health compared to 1 year ago	0= Better or same; 1= Worse
Self-reported health	0 = Excellent; 0.25= Very good; 0.5= Good; 0.75= Fair; 1= Poor
General vision	0 = Excellent; 0.25= Good; 0.5= Fair; 0.75= Poor; 1= Very poor
General hearing	0= Good or excellent; 0.5= Little or moderate trouble; 1= Lot of trouble or deaf

Frequency of healthcare use	0= 0-3 times; 0.5= 4-9 times; 1= 10+ times
Overnight hospital stays	0= 0 times; 0.5= 1-2 times; 1= 3+ times
Medications	0= 0-3; 0.5= 4-7; 1= 8+
Laboratory values	
Heart rate at rest (bpm)	0= 60-99; 1= < 60 or 100+
Resting Systolic blood pressure (mmHg)	0= <120; 0.5= 120-139; 1= 140+
Resting Diastolic blood pressure (mmHg)	0=
Homocysteine (umol/L)	0= <8; 0.5= 8-15; 1= 15+
Folate, serum (nmol/L)	0= 4.5-29.5; 0.5= 29.6-45.3; 1= <4.5 or 45.3+
Glycohemoglobin (%)	0= < 5.7; 0.5= 5.7-6.4; 1= 6.5+
Red blood cell count (million cells/uL)	0= 3.93-5.69; 1= <3.93 or 5.69+
Mean cell hemoglobin (pg)	0= 27-32; 1= <27 or 32+
Red cell distribution width (%)	0=11.5-14.5; 1= <11.5 or 14.5+
Lymphocyte percent (%)	0=20-45; 1= <20 or 40+
Segmented neutrophils percent (%)	0=40-60; 1= <40 or 60+
Albumin (g/L)	0= 32-44; 1= <32 or 45+
Aspartate aminotransferase (IU/L)	0= 8-33; 1= <8 or 34+
Fasting glucose (mmol/L)	0= 3.9-6.1; 1= <3.9 or 6.2+

Appendix 2. Permission to use the list of frailty index variables table.

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Licensed Content Author	Joanna Blodgett,Olga Theou,Susan Kirkland,Pantelis Andreou,Kenneth Rockwood
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Appendix 3. Permission to re-use published material for Chapter 6.

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> Sincerely,
>
> Scott Kehler

Appendix 4. Curriculum Vitae

D. Scott Kehler: PhD (C)
Email: [redacted]

Affiliations

University Affiliation

Faculty of Kinesiology and
Recreation Management
123 Active Living Centre
University of Manitoba

Research Affiliation

Institute of Cardiovascular Sciences
St. Boniface Hospital Research Centre
R4012-351 Tache Ave.
Winnipeg, MB, Canada, R2H 2A6

Education

2013-Current **Doctor of Philosophy: Applied Health Sciences**
University of Manitoba
Thesis: *Investigating the impact of physical activity and sedentary behavior on frailty in middle-aged and older adults*
Supervisor: Dr. Todd A. Duhamel
GPA: 4.3 out of 4.5.
Expected time to completion: December 2017

2010-2012 **Masters of Science: Kinesiology**
University of Manitoba
Thesis: *Pre-habilitation Program for Elective Coronary Artery Bypass Graft Surgery Patients: A Pilot Randomized Controlled Trial*
Supervisor: Dr. Todd A. Duhamel
GPA: 4.25 out of 4.5

2008-2010 **Bachelor of Kinesiology (*Honors*)**
University of Manitoba
GPA: 4.10 out of 4.5

2003-2007 **Bachelor of Physical Education (*Honors*)**
University of Manitoba
GPA: 3.76 out of 4.5

Awards and Distinctions

Postdoctoral Fellowships and Awards (4)

2018-2020 **Canadian Institutes of Health Research Fellowship Award** $135,000

	The CIHR Fellowship award is one of the most competitive postdoctoral fellowships in Canada. Only the top 15% of 1052 applicants received this award.	
2018-2019	**Maritime Strategy for Patient Oriented Research SUPPORT Unit Postdoctoral Fellowship (declined)** This two-year fellowship is granted to post-graduates working in patient-oriented research within Nova Scotia. Since the award was declined, I am considered an honorary recipient.	$100,000
2018-2019	**Izaak Walton Killam Postdoctoral Fellowship (top-up)** This two-year fellowship is granted to post-graduates at Dalhousie University with superior research ability. Only 4-8 applicants receive a fellowship annually. The original amount was $99,000.	$9,000
2018	**University Internal Medicine Research Foundation Internal Research Fellowship (top-up)** The one-year fellowship is intended to foster the development of promising individuals as researchers. Fellowship will be used as a top-up to the Killam Postdoctoral Fellowship. The original non top-up amount was $55,000.	$10,000

Graduate Scholarships and Studentships (12)

2015-2018	**Sir Gordon Wu Scholarship** This studentship is awarded in recognition of intellectual ability and academic accomplishments of graduate students at the University of Manitoba.	$55,000
2015-2016	**Research Manitoba Graduate Studentship (declined)** This studentship is awarded in recognition of academic research excellence among graduate students pursuing health research and is the highest provincial-level scholarship awarded in Manitoba	$35,000
2015-2018	**Canadian Institutes of Health Research Frederick Banting and Charles Best Canada Graduate Scholarship** This award is among the highest Canadian doctoral research awards. Only the top 12% of 1212 applicants received this scholarship in the 2014-2015 competition year.	$105,000
2014	**Canadian Institutes of Health Research Population Intervention for Chronic Disease Prevention Strategic**	$2,000

	Training Initiative in Health Research Graduate Fellowship (top-up) This national training program recognizes outstanding graduate trainees who are involved in population health research by awarding them with a fellowship.	
2014-2016	**Canadian Institutes of Health Research Knowledge Translation Canada Strategic Training Initiative in Health Research Graduate Fellowship** This national training program recognizes outstanding graduate trainees who are involved in population health research by awarding them with a fellowship.	$23,000
2013-2014	**Manitoba Health Research Council Graduate Studentship** This studentship is awarded in recognition of academic research excellence among graduate students pursuing health research and is the highest provincial-level scholarship awarded in Manitoba.	$35,000
2013-2016	**University of Manitoba Graduate Fellowship (declined)** This fellowship is given to the top students entering their graduate program in recognition of outstanding academic performance and research excellence.	$64,000
2011-2012	**Manitoba Health Research Council Graduate Studentship** This studentship is awarded in recognition of academic research excellence among graduate students pursuing health research and is the highest provincial-level scholarship awarded in Manitoba.	$35,000
2011	**Institute of Cardiovascular Science Graduate Studentship (declined)** This studentship is awarded in recognition of excellent among trainees conducting their training program at the St. Boniface Hospital Research Centre.	$10,000
2011	**Ruth Asper Scholarship in Physical Education and Kinesiology** This scholarship is awarded to the top trainee in the Kinesiology and Recreation Management graduate program who focus on the physical and psychosocial aspects of fitness and physical activity through research.	$6,000
2010	**Institute of Cardiovascular Science Graduate Studentship**	$16,200

This studentship is awarded in recognition of excellent among trainees conducting their training program at the St. Boniface Hospital Research Centre.

2009	**University of Manitoba Student Union Scholarship** This scholarship is presented to the top 4% of students enrolled in the final year of their undergraduate degree program	$750

Awards and Achievements (19)

2017	**Dean of Graduate Studies Student Achievement Award** I was one of the three selected out of 23 applicants to receive this award in recognition of my overall academic excellence, leadership, teaching ability, volunteerism, and service to others as a mentor to fellow students	$1000
2017	**Honorable mention: Dr. Naranjan Dhalla Cardiovascular Awards Day Poster Competition** I received an honorable mention for presenting data on "*The link between patterns of sedentary behaviors and frailty: does the presence of cardiovascular disease have an influence?*"	$50
2017	**First prize, doctoral category: Canadian Institutes of Health Research Institute of Aging poster competition** This prize was awarded to only one of the selected 13 doctoral students who underwent a preliminary screening process prior to the Canadian Association of Gerontology Annual Symposium. The poster was entitled "*Can the Clinical Frailty Scale Improve the Prediction of In-hospital Mortality and Morbidity in Elective Cardiac Surgery Patients?*"	$500
2016	**Novo Nordisk Foundation Saltin Symposium on Exercise and Integrative Physiology (Invited)** This symposium is a training opportunity for PhD students to engage in learning opportunities that focus on genes, proteomics, metabolomics, and their interaction with the environment that predict health and human performance. I was one of only 12 PhD trainees to be invited to attend.	$1075
2016	**Canadian Institutes of Health Research Institute of Aging – Summer Program on Aging Travel Award** This travel award provides graduate students with a training opportunity to learn more about frailty and improving the care of this high risk population.	$700
2016	**Canadian Institutes of Health Research IMPACT Doctoral Salary Award**	$5,000

	This award recognizes graduate students at the University of Manitoba who excel in cardiovascular or pulmonary research.	
2016	**Second Place: University of Manitoba Applied Health Sciences Oral Presentation Competition** I was ranked second in the oral presentation competition among my cohort of trainees in the Applied Health Sciences PhD program.	$100
2015	**University of Manitoba Tri-Council Top-up Award** This award is given to students in recognition of being awarded Tri-Council funding.	$5,000
2015	**First Place: University of Manitoba Applied Health Sciences Three Minute Thesis Competition** I was awarded the top three minute thesis competitor among my cohort of trainees in the Applied Health Sciences PhD program.	$350
2015	**Three Minute Thesis Finalist** I was selected as one of the top 9 out of 139 applicants at the University of Manitoba's Three Minute Thesis competition. The title of my presentation was "*Is exercise healthy for older adults before heart surgery? The exercise PREHAB study"*.	No dollar amount
2014	**Canadian Institutes for Health Research Young Investigators Forum Travel Award** This travel award is recognizes outstanding young investigators and gives them an opportunity to present their research at this annual forum. I presented findings from research group's study entitled, "*Impact of Physical Activity on Depression After Cardiac Surgery*"	$1,000
2014	**Heart and Stroke Foundation Manitoba Dr. Dexter Harvey Award in Primary Prevention** This award gives the successful applicant the opportunity to participate in research-related activities in chronic disease prevention to help further their careers as researchers.	$5,000
2013	**Canadian Cardiovascular Society Have a Heart Bursary** This travel award recognizes promising medical students, graduate and post-doctorate trainees in training and provides free attendance and lodging for the Canadian Cardiovascular Congress. I presented our findings on a	$1,250

project entitled "*Pre-habilitation program for elective coronary artery bypass graft patients*".

2013	**Canadian Institutes for Health Research Young Investigators Forum Travel Award** This travel award is recognizes outstanding young investigators and gives them an opportunity to present their research at this annual forum. Received an <u>*Outstanding Oral Presentation*</u> award for my presentation on the "*Enhancing primary care counseling and referrals to community-based physical activity opportunities for sustained lifestyle change (ENCOURAGE) project*."	$1,000
2013	**First Place: PhD Student Poster Presentation, Health, Leisure, and Human Performance Research Institute Research Day: University of Manitoba** This award is presented to the top PhD level student poster presentation, which described the overall findings for a project entitled "*Pre-habilitation program for elective coronary artery bypass graft patients*".	$500
2012	**First Place: Masters Student Poster Presentation, Applied Health Sciences Research Day, University of Manitoba** This award is presented to the top master's level student poster presentation which described the overall findings for a project entitled "*The Impact of Physical Activity on Depression after Cardiac Surgery (IPAD-CS)*".	$500
2012	**Canadian Institutes for Health Research Young Investigators Forum Travel Award** This travel award is recognizes outstanding young investigators and gives them an opportunity to present their research at this annual forum. My presentation was titled: *"Examining the efficacy of a rolling admissions cardiac rehab program delivery model: preliminary data"*.	$1,000
2011	**Canadian Association of Cardiac Rehabilitation Graduate Student Award** This award is received by the top four applicants in Canada for their outstanding contributions to research in the field of cardiac rehabilitation.	$3,000
2011	**Best Clinical Poster Presentation, Cardiac Sciences Research Symposium St. Boniface General Hospital Cardiac Sciences Program** This award is presented in recognition of an outstanding poster presentation which described the clinical rationale,	$500

research design and baseline data for a project entitled "*The Impact of Physical Activity on Depression after Cardiac Surgery (IPAD-CS)*".

Publications

Underline indicates junior trainees who I mentored as a graduate student

Published and accepted manuscripts in refereed journals (12)

1. Boreskie K, **Kehler DS,** Costa EC, Cortez PC, Berkowitz I, Hamm NC, Moffat TL, Stammers AN, 1Kimber DE, Hiebert BM, Kent D, Cornish D, Blewett H, Nguyen TN, Arora RC, Duhamel TA. Protocol for the HAPPY Hearts Study – Cardiovascular Screening for the Early Detection of Future Adverse Cardiovascular Outcomes in Middle-Aged and Older Women: A prospective, observational cohort study. Accepted to *BMJ Open*.

2. Lytwyn J, Stammers AN, **Kehler DS**, Jung P, Alexander B, Hiebert BM, Dubiel C, Kimber D, Hamm N, Clarke M, Fraser C, Pedreira B, Duhamel TA, Arora RC. The impact of frailty on functional survival in patients one-year post cardiac surgery. Submitted to the *Journal of Thoracic and Cardiovascular Surgery (impact factor: 4.45)*. Jun 24. pii: S0022-5223(17)31359-4. doi: 10.1016/j.jtcvs.2017.06.040.

3. **Kehler DS,** Stammers AN, Tangri N, Hiebert B, Fransoo R, Schultz AS, Macdonald KM, Giacomontonio N, Hassan A, Légaré JF, Arora RC†, Duhamel TA†. Systematic Review of preoperative physical activity and its impact on post-cardiac surgical outcomes. *BMJ Open (impact factor: 2.37)*. †contributed equally as senior authors. Aug 11;7(8):e015712. doi: 10.1136/bmjopen-2016-015712.

4. **Kehler DS,** Kent D, Beaulac J, Strachan L, Wangasekara N, Chapman S, Lamont D, Lerner N, Boreskie S, Avery L, Duhamel TA. Examining Patient Outcome Quality Indicators Based on Wait Times From Referral To Entry Into Cardiac Rehabilitation: A Pilot Observational Study. *Journal of Cardiopulmonary Rehabilitation and Prevention (impact factor: 1.82)*. 2017. Feb 6. doi: 10.1097/HCR.0000000000000232. [Epub ahead of print].

5. **Kehler DS,** Ferguson T, Stammers AN, Bohm C, Duhamel TA, Arora RC, Tangri N. Prevalence of frailty in Canadians 18-79 years old in the Canadian Health Measures Survey. *BMC Geriatrics (impact factor: 2.61)*. 2017. Jan 21;17(1):28. doi: 10.1186/s12877-017-0423-6.

6. Stammers AN, **Kehler DS**, Afilalo J, Avery LJ, Bagshaw SM, Grocott HP, Legare JF, Logsetty S, Metge C, Nguyen T, Rockwood K, Sareen J, Sawatzky JA, Tangri N, Giacomontonio N, Hassan A, Duhamel TA, Arora RC. Protocol for The Prehab Study - Pre-operative Rehabilitation for reduction of Hospitalization After coronary

Bypass and valvular surgery: A Randomized Controlled Trial. *BMJ Open (impact factor: 2.37)*. 2015. Mar 9;5(3):e007250.

7. Stammers AN, Susser SE, Hamm NC, Hlynsky MW, Kimber DE, **Kehler DS**, Duhamel TA. The regulation of sarco(endo)plasmic reticulum calcium-ATPases (SERCA). *Canadian Journal of Physiology and Pharmacology (impact factor: 1.82)*. 2015. Jan 19: 1-12.
8. **Kehler DS**, Stammers AN, Susser SE, Hamm NC, Kimber DE, Hlynsky MW, Duhamel TA. Cardiovascular complications of type 2 diabetes in youth. *Biochemistry and Cell Biology (impact factor: 1.90)*. 2014. Dec 7: 1-15.
9. Sawatzky J†, **Kehler DS†**, Ready AE, Lerner N, Boreskie S, Lamont D, Luchik D, Arora RC, Duhamel TA. Pre-habilitation program for elective coronary artery bypass graft surgery patients: a pilot randomized controlled study. *Clinical Rehabilitation (impact factor: 2.82).* 2014. † indiates an equal contribution to the project that warrants co-first authorship.
10. Horne D†, **Kehler DS†**, Kaoukis G, Hiebert B, Garcia E, Chapman S, Duhamel TA, Arora RC. Impact of Physical Activity on Depression after Cardiac Surgery – (IPAD-CS). *Canadian Journal of Cardiology (impact factor: 4.40)*. 2013; 29(12):1649-1656. † indiates an equal contribution to the project that warrants co-first authorship.
11. Horne D†, **Kehler DS†**, Kaoukis G, Hiebert B, Garcia E, Duhamel TA, Arora RC. Depression before and after cardiac surgery: do all patients respond the same? *Journal of Thoracic and Cardiovascular Surgery (impact factor: 4.45)*. 2013; 145(5):1400-6. † indiates an equal contribution to the project that warrants co-first authorship.
12. Epp RA, Susser SE, Morissette MP, **Kehler DS**, Jassal DS, Duhamel TA. Exercise training prevents the development of cardiac dysfunction in the high fat diet-fed, low-dose streptozotocin diabetic rat. *Canadian Journal of Physiology and Pharmacology (impact factor: 1.82)*. 2013; 91(1):80-9.

Submitted manuscripts for peer-review (3)

1. Costa EC, Hay JL, **Kehler DS**, Boreskie KF, Arora RC, Umpierre D, Szwajcer A, Duhamel TA. Effects of high-intensity interval training versus moderate-intensity continuous training on blood pressure in prehypertensive and hypertensive individuals: a systematic review and head-to-head meta-analysis of randomized trials. Submitted to *Sports Medicine* August 10, 2017. Revision requested
2. Kehler DS, Clara I, Hiebert B, Stammers AN, Hay JL, Schultz ASH, Arora RC, Tangri N, Duhamel TA. The association between bouts of moderate to vigorous physical activity and patterns sedentary behavior with frailty. Submitted to *Experimental Gerontology*. September 28, 2017. Revision requested.
3. Kent DE, **Kehler DS,** Garcia E, Chapman S, McGavock J, Katz A, Metge C, Betteridge D, Bouchard D, Strachan S, Duhamel TA. The ENCOURAGE project:

ENhancing Primary Care COUnseling and Referrals to Community-based Physical Activity Opportunities for Sustained Lifestyle ChanGE. To be submitted to *Applied Physiology, Nutrition and Metabolism* October 28, 2017.

Manuscripts in preparation (6)

1. Guillemette L, **Kehler DS**, Hamm N, McGavock JM, Duhamel TA. Impact of Exercise in Pregnancy on Children's Cardiometabolic Risk Factors: A systematic review and meta-analysis. To be submitted to the *American Journal of Preventive Medicine* December 2017.
2. **Kehler DS,** Stammers AN, Meade L, Mazowita AE, Strachan S†, Duhamel TA†. A mobile health application to support Employees to reduce sedentary behavior in the workplace with behavior change techniques: A protocol for the ENCOURAGE App. To be submitted to the *Journal of Medical Internet Research Protocols* October 2017.
3. Guindi MN, Davies JL, **Kehler DS**, Tangri N, Duhamel TA, Logsetty S, Arora RC. The outcomes of delirium in the multi-trauma patient population: a systematic review. To be submitted to the *Journal of Critical Care* November 2017.
4. **Kehler DS**, Clara I, Hiebert B, Stammers AN, Hay JL, Schultz ASH, Arora RC, Tangri N, Duhamel TA. Sex-differences in the association between bouts of physical activity and patterns of sedentary behavior with frailty. To be submitted to *Experimental Gerontology* December 2017.
5. **Kehler DS**, Clara I, Hiebert B, Stammers AN, Hay JL, Schultz ASH, Arora RC, Tangri N, Duhamel TA. Does the presence of cardiovascular disease impact the association between bouts of moderate to vigorous physical activity and patterns of sedentary behaviors with frailty? To be submitted to *Maturitas.* December 2017.
6. **Kehler DS**, Hay JL, Stammers AN, Clara I, Schultz ASH, Arora RC, Tangri N, Duhamel TA. The association between sedentary behaviors and frailty: a systematic review of cross-sectional and longitudinal studies. To be submitted to the *Age and Aging.* December 2017.

Published theses (1)

1. **Kehler DS**. Pre-habilitation Program for Elective Coronary Artery Bypass Graft Surgery Patients: A Pilot Project. MSc Thesis. 2012. My role was to manage the overall project and to collect and analyze primary and secondary research data (100% contribution). Link: http://mspace.lib.umanitoba.ca/handle/1993/13238

Research reports (1)

1. Duhamel TA, McDonald G, Garcia E, Chapman S, **Kehler DS**, Petherick L, Norman M, Buchanan P, Glazebrook C, Gysel A, Brown K, Dunn N. AFTER THE SCHOOL BELL RINGS: A Manitoba After School Recreation Project. 2013. A

Recreation Connections Research Report. URL: http://www.afterschoolmanitoba.ca/assets/after%20the%20bell_july24_final.pdf.

Published chapters in edited books (2)

1. Hamm NC, Stammers AN, Susser SE, Hlynsky MW, Kimber DE, **Kehler DS**, and Duhamel TA. The regulation of cardiac sarco (endo)plasmic reticulum calcium-ATPases (SERCA2a) in response to exercise. In: Regulation of CA^{2+}-ATPases, V-ATPases, and F-ATPases. Springer Science+Business Media, LLC, New York. 2015.

2. **Kehler DS,** Dhalla NS and Duhamel TA. Biochemical Mechanisms of Exercise-Induced Angiogenesis. In: Biochemical Basis and Therapeutic Implications of Angiogenesis (pp 181-206). Ed. By JL Mehta and NS Dhalla, Springer Science+Business Media, LLC, New York. 2013.

Knowledge translation articles (4)

1. **Kehler DS**. Want to live longer and feel better? Get off your butt. *Winnipeg Free Press*. November 22, 2013. URL: http://www.winnipegfreepress.com/local/want-to-live-longer-and-feel-better-get-off-your-butt-232964891.html.
2. Kent D, **Kehler DS,** Duhamel TA. Got a minute? That's all it takes to improve your health and well-being. *WAVE Magazine.* 2013. URL: http://www.wrha.mb.ca/wave/2013/09/got-a-minute.php.
3. Kent D, **Kehler DS,** Duhamel TA. A prescription for exercise? *Inspire Magazine*. Published July 2013. URL: http://www.wrha.mb.ca/extranet/inspire/2013/130612-a-prescription-for-exercise.php.
4. Hayward K, **Kehler DS.** Stand up for your health. *WAVE Magazine.* 2013. URL: http://www.winnipeginmotion.ca/winnipeg/common/uploads/files/LG_PA_StandUp_W14.pdf.

Published abstracts in refereed journals (10)

†indicates I did a podium presentation; *indicates I did a poster presentation.

Podium presentations: 4 **Poster presentations:** 2

1. **†Kehler DS,** Clara I, Hiebert B, Schultz ASH, Arora RC, Duhamel TA. Intensity and duration of breaks from sedentary time is associated with frailty independent of total sedentary time and moderate to vigorous activity. *Applied Physiology, Nutrition, and Metabolism*. 2017.

2. ***Kehler DS,** Stammers AN, Horne D, Hiebert B, Kaoukis G, Arora RC, Duhamel TA. Does preoperative physical activity and depression impact postoperative outcomes in adult cardiac surgery patients? A secondary analysis. *Applied Physiology, Nutrition, and Metabolism*. Oct 2015.
3. †**Kehler DS,** Stammers AN, Horne D, Hiebert B, Kaoukis G, Arora RC, and Duhamel TA. The impact of preoperative physical activity and depression on postoperative hospitalization and mortality in adult cardiac surgery patients. *Journal of Cardiopulmonary Rehabilitation and Prevention*. Oct 2015.
4. ***Kehler DS,** Sawatzky JA, Ready AE, Arora RC, and Duhamel TA. Pre-habilitation Program for Elective Coronary Artery Bypass Graft Patients: A Pilot Project. *Applied Physiology, Nutrition, and Metabolism.* Oct 2014.
5. †**Kehler DS**, Sawatzky J, Arora RC, and Duhamel TA. Exercise Pre-habilitation Program for Elective Coronary Artery Bypass Graft Surgery Patients. *Journal of Cardiopulmonary Rehabilitation and Prevention.* Oct 2013.
6. Ready AE, Norman M, Metge C, **Kehler DS**, Bernosky M, Duhamel TA, and the ENCOURAGE TEAM. Health Care Providers Promoting Physical Activity in Primary Care: Disconnect Between Knowledge, Attitudes and Practice. *Journal of Science and Medicine in Sport*. 15(6):384. 2012.
7. †**Kehler DS**, Horne D, Hiebert B, Kaoukis G. Garcia E, Chapman S, Arora RC, Duhamel TA. The association between physical activity and depression after cardiac surgery. *Journal of Cardiopulmonary Rehabilitation and Prevention.* Oct 2012.
8. Kent D, Wangasekara N, Chapman S, **Kehler DS**, Luchik D, Lamont D, Boreskie S, Duhamel TA. Sustaining cardiac rehabilitation outcomes over the long term: can program entry models have influence? *Journal of Cardiopulmonary Rehabilitation and Prevention.* Oct 2012.
9. Horne D, **Kehler DS**, Kaoukis G, Hiebert B, Garcia E, Duhamel TA, Arora RC. Depression and cardiac surgery: predictors and the impact of physical activity. *Canadian Journal of Cardiology.* Oct 2012.
10. †**Kehler DS,** Horne D, Hiebert B, Kaoukis G, Garcia E, Babiak I, Arora RC, Duhamel TA. Impact of physical activity on depression after cardiac surgery (IPAD-CS*). Journal of Cardiopulmonary Rehabilitation*. Oct 2011.

Abstracts from conference proceedings (26)

†indicates I did a podium presentation; *indicates I did a poster presentation.

Podium presentations: 5 **Poster presentations**: 9

1. ***Kehler DS,** Hiebert B, Stammers AN, Arora RC, Duhamel TA. Can the Clinical Frailty Scale Improve the Prediction of In-hospital Mortality and Morbidity in Elective Cardiac Surgery Patients? Canadian Association of Geriatrics Annual

Meeting. Winnipeg, MB. 2017.

2. ***Kehler DS,** Stammers AN, Horne D, Hiebert B, Kaoukis G, Arora RC, Duhamel TA. Is preoperative physical activity behavior and depressive symptoms linked to postoperative health-outcomes and estimated costs due to cardiac surgery and re-hospitalization? Institute of Cardiovascular Sciences Poster Day. Winnipeg, MB. October 2016. *Awarded Best Clinical Research Poster.*

3. ***Kehler DS,** Stammers AN, Horne D, Hiebert B, Kaoukis G, Arora RC, Duhamel TA. Preoperative Physical Activity Behavior, But Not Depressive Symptoms, Impacts One-Year Health Outcomes After Cardiac Surgery. The Saltin Symposium on Exercise and Integrative Physiology. Copenhagen, Denmark. September 2016.

4. ***Kehler DS,** Stammers AN, Horne D, Hiebert B, Kaoukis G, Arora RC, Duhamel TA. Is preoperative physical activity behavior and depressive symptoms linked to postoperative health-outcomes and estimated costs due to cardiac surgery and re-hospitalization? 33rd Annual Spring Research Symposium – Dialogue on Aging. Winnipeg, MB. April 2016.

5. Stammers AN, **Kehler DS,** Hiebert BM, Giacomontonio N, Hassan A, Duhamel TA, Arora RC. Optimizing the Pre-Operative Risk Profile of Older Adults Undergoing Elective Cardiac Surgery: Preliminary Results from a Multi-Centre, Randomized Controlled Trial. 33rd Annual Spring Research Symposium – Dialogue on Aging. Winnipeg, MB. April 2016.

6. ***Kehler DS,** Kent D, Garcia E, Chapman S, Strachan S, Bouchard D, Norman M, Ready E, Katz A, Edwards J, Harlos S, Betteridge D, Edye-Mazowita A, Boreskie S, McGavock J, Vanance D, Botting I, Metge C, Beck K, Schmalenberg J, Duhamel TA. Enhancing primary care counseling and referrals to community-based physical activity opportunities for sustained lifestyle change: the ENCOURAGE project. Knowledge Translation Canada Summer Institute. Quebec City, QC. 2014.

7. ***Kehler DS,** Horne D, Kaoukis G, Hiebert B, Garcia E, Chapman S, Arora RC, Duhamel TA. Impact of Physical Activity on Depression after Cardiac Surgery. Canadian Institutes of Health Research Young Investigators Forum Proceedings. Edmonton, AB. 2014.

8. Meade L, Strachan SM, **Kehler DS**, Kent D, Garcia E, Duhamel TA, and the ENCOURAGE project researchers. Physical activity self-definition and the ENCOURAGE project: an intervention outcome and a physical activity correlate. Canadian Society for Psychomotor Learning and Sport Psychology Conference Proceedings. Kelowna, BC. 2013.

9. ***Kehler DS**, Sawatzky J, Arora RC, Duhamel TA. Pre-habilitation Program for Elective Coronary Artery Bypass Graft Surgery Patients. Cardiac Sciences Research Day, Winnipeg, MB. 2013.

10. ***Kehler DS**, Sawatzky J, Arora RC, Duhamel TA. Pre-habilitation Program for Elective Coronary Artery Bypass Graft Surgery Patients. Health, Leisure, and

Human Performance Research Institute Research Day, Winnipeg, MB. 2013. *Awarded 1st place for best poster presentation.*

11. †**Kehler DS**, Kent D, Garcia E, Chapman S, Strachan S, Bouchard D, Norman M, Ready AE, Katz A, Edwards J, Harlos S, Bettridge D, Edye-Mazowita A, Boreskie S, McGavock J, Vanance D, Botting I, Metge C, Beck K, Schmalenberg J, Duhamel TA. Enhancing primary care counseling and referrals to community-based physical activity opportunities for sustained lifestyle change: The ENCOURAGE project – preliminary data. Canadian Institutes of Health Research Young Investigators Forum Proceedings, Toronto, ON. 2013. *Awarded Outstanding Oral Presentation.*

12. ***Kehler DS,** Kent D, Chapman S, Babiak K, Garcia E, Luchik D, Lamont D, Boreskie S, Duhamel TA. Examining the effects of two cardiac rehabilitation program delivery models: preliminary data. Canadian Institutes of Health Research Young Investigators Forum Proceedings, Montreal, QC. 2012.

13. †**Kehler DS**, Horne D, Hiebert B, Kaoukis G. Garcia E, Chapman S, Arora RC, Duhamel TA. Physical activity is a predictor of depression after cardiac surgery. Cardiac Sciences Research Day Proceedings, Winnipeg, MB. 2012.

14. Horne D, **Kehler DS**, Kaoukis G, Hiebert B, Garcia E, Duhamel TA, Arora RC. The natural history of depression before and after cardiac surgery. Cardiac Sciences Research Day Proceedings, Winnipeg, MB. 2012.

15. Kent D, Wangasekara N, Chapman S, **Kehler DS**, Luchik D, Lamont D, Boreskie S, Duhamel TA. Examining the efficacy of a rolling admissions cardiac rehab program delivery model: preliminary data. Cardiac Sciences Research Day Proceedings, Winnipeg, MB. 2012.

16. ***Kehler DS**, Horne D, Hiebert B, Kaoukis G. Garcia E, Chapman S, Arora RC, Duhamel TA. The association between physical activity and depression after cardiac surgery. University of Manitoba Applied Health Sciences Research Day Proceedings, Winnipeg, MB. 2012. *Awarded 1st place for best poster presentation.*

17. †**Kehler DS**, Sawatzky J., Arora RC, Duhamel TA. Pre-surgery exercise therapy for patients waiting for Coronary Artery Bypass Graft (CABG) Surgery: A Pilot Project. Exercise Physiologists of Western Canada Conference Proceedings, Edmonton, AB. 2011.

18. Garcia E, **Kehler DS**, Kent D, Luchik D, Lamont D, Boreskie S, Duhamel TA. Examining the longitudinal effects of two different cardiac rehabilitation delivery models on physical activity. Exercise Physiologists of Western Canada Conference Proceedings, Edmonton, AB. 2011.

19. †**Kehler DS,** Horne D, Hiebert B, Kaoukis G, Garcia E, Babiak I, Arora RC, Duhamel TA. Impact of physical activity on depression after cardiac surgery (IPAD-CS): preliminary results. Cardiac Sciences Research Day Conference Proceedings,

Winnipeg, MB. 2011. *Awarded best clinical research poster.*

20. Morissette MP, Epp RA, Susser SE, **Kehler DS**, Xu, YJ, and Duhamel TA. AMPK regulates sarcoplasmic reticulum calcium pump activity in muscle. Exercise Physiologists of Western Canada Conference Proceedings, Edmonton, AB. 2011.
21. Susser, SE, Epp RA, Morissette MP, **Kehler DS,** Smith DR, Fernyhough P, Duhamel TA. Resveratrol prevents the inhibition of SERCA2a in the diabetic heart. Exercise Physiologists of Western Canada Conference Proceedings. 2011, Edmonton, AB.
22. Duhamel TA, Epp RA, Morissette M, **Kehler DS,** Susser SE, and Long YJ. Exercise training prevents diastolic dysfunction and the pathological remodeling of sarcoplasmic reticulum proteins in the diabetic heart. 2nd Canada-Cuba International Heart Symposium Conference Proceedings, Cuba. 2011.
23. Epp RA, Morissette M, **Kehler DS,** Susser SE, Long YJ, Duhamel TA. A cellular energy sensing protein, which is called adenosine monophosphate-activated protein kinase, (AMPK) appears to regulate the functional characteristics of calcium-transport proteins in the heart. 1st Annual Undergraduate Life Sciences Conference Proceedings, Winnipeg, MB. 2010.
24. Epp RA, Morrissette M, **Kehler DS,** Susser SE, Long YJ and Duhamel TA. The role of AMPK for regulating SERCA2a function in cardiac tissue. Exercise Physiologists of Western Canada Conference Proceedings, Regina, SK. 2010.
25. **†Kehler DS**, Horne D, Arora RC, Kaoukis G, Duhamel TA. Impact of physical activity on depression after cardiac surgery (IPAD-CS). Exercise Physiologists of Western Canada Conference Proceedings, Regina, SK. 2010.
26. Susser SE, Epp RA, Morissette M, **Kehler DS**, Long YJ, Jassal DS, Duhamel TA. Exercise therapy prevents the development of diabetes-induced diastolic heart failure. Exercise Physiologists of Western Canada Conference Proceedings, Regina, SK. 2010.

Research Experience

02/2015- **06/2017**	**Knowledge Synthesis Research Coordinator** Department of Applied Health Sciences, University of Manitoba Project title: preoperative physical activity behavior and peri-operative health outcomes of cardiac surgery patients. Job description: Conception of systematic review idea; coordinate electronic search strategy; screen studies for inclusion; data extraction; draft, revise, and submit manuscript from study results.

02/2013-
ongoing

Research Assistant
Asper Clinical Research Institute, St. Boniface General Cardiac Sciences Program

Project title: The PREHAB study: Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery: a randomized controlled trial

Job description: Recruit and obtain consent from cardiac patients undergoing cardiac surgery; collect and analyze data from questionnaires and physical tests; draft and revise manuscripts from study results.

01/2012-
05/2017

Research Assistant
Asper Clinical Research Institute, St. Boniface Hospital Cardiac Sciences Program.

Project title: Early Detection of Cardiovascular Disease: The Cardiovascular Screening Project

Job description: Complete the ethics submissions, revisions, and amendments for the project; obtain consent from research participants; collect and analyze physical activity, quality of life, and a series of physical tests, such as the 6 Minute Walking Test, 5 Meter Gait Speed Test, and blood pressure response to exercise.

08/2011-
07/2013

Project Coordinator
Asper Clinical Research Institute, St. Boniface Hospital Cardiac Sciences Program

Project title: Enhancing primary care counseling and referrals to community-based physical activity opportunities for sustained lifestyle change (ENCOURAGE).

Job description: Recruit and obtain consent from patients receiving care at two primary care sites and served as a liaison between the principal investigator and the Winnipeg Regional Health Authority; collect and analyze physical activity, quality of life, and depression data; draft, revise and submit manuscripts from study results.

01/2011-
01/2013

Project Coordinator
Asper Clinical Research Institute, St. Boniface Hospital Cardiac Sciences Program.

Project title: Pre-habilitation program for elective coronary artery bypass graft surgery patients: a pilot randomized controlled trial.

Job description: Recruit and obtain consent from pre-operative elective coronary artery bypass graft surgery patients; collect and analyze physical activity, quality of life, physical activity self-efficacy, and anxiety and depression data; draft, revise and submit manuscripts from study results.

12/2010-12/2012 **Project Coordinator**
Reh-Fit Centre, Winnipeg, MB.

Project title: Examining the longitudinal effects of two different cardiac rehabilitation delivery models on daily physical activity.

Job description: Recruit and obtain consent from cardiac rehabilitation clients, collect and analyze physical activity, quality of life, depression and anxiety, and 6-Minute Walk Test data, and manage junior research assistants who recruit and consent patients for the study; draft, revise and submit manuscripts from study results.

12/2010-08/2012 **Research Coordinator**
Asper Clinical Research Institute, St. Boniface Hospital Cardiac Sciences Program.

Project title: Impact of Physical Activity on Depression after Cardiac Surgery (IPAD-CS).

Job description: Recruit and obtain consent from cardiac surgery patients, collect and analyze physical activity and depression data, and manage junior research assistants who recruit and consent patients for the study; draft, revise and submit manuscripts from study results.

06/2010-09/2010 **Research Assistant**
Winnipeg *in-motion*
Job description: completed a literature review on pre-school physical activity interventions.

Teaching Credentials and Experience

Credentials (1)

03/2017 **Certification in Higher Education Teaching**

This three year program is offered to graduate students to build their skills in teaching undergraduate students. Students are required to complete coursework, take 20 hours of workshops, complete a teaching practicum, and develop a teaching dossier.

Full courses (1)

05/2015-06/2015 **Instructor Level I**
Faculty of Kinesiology and Recreation Management, University of Manitoba
Course: KIN 3470: Exercise Physiology (3 credit hours)
Number of students: 33

Keynote speaker (1)

04/2017 **Presentation for the Manitoba Association of Cardiology Technologists Annual General Meeting**
Presentation title: The PREHAB Study

Invited Presentations (3)

10/2016 **Café Scientifique: Family Caregiving: How can we improve the experience?**
Location: McNally and Robinson, Winnipeg, MB
Audience: General public

04/2015 Presentation title: Is exercise healthy for older adults before heart surgery? (15 minute presentation)
University of Manitoba
Audience: The "Leaders of Tomorrow" high school students

02/2013 Presentation title: Physical activity and health (30 minute presentation)
École River Heights School
Audience: Grade 7/8 student science class

Guest Presenter (10)

03/2017 Presentation title: Introduction to systematic reviews and meta-analyses (75 minute presentation)
Faculty of Kinesiology and Recreation Management, University of Manitoba
Course: PERS 7130: Quantitative Methods in Kinesiology.

02/2016 Presentation title: The metabolic systems: control of ATP production and use in skeletal muscle (180 minute presentation)
Faculty of Kinesiology and Recreation Management, University of Manitoba
Course: KIN 4470: Advanced Exercise Physiology

02/2016 Presentation title: Carbohydrate and lipid metabolism (180 minute presentation)
Faculty of Kinesiology and Recreation Management, University of Manitoba
Course: KIN 4470: Advanced Exercise Physiology

10/2015 Presentation title: Introduction to systematic reviews and meta-analyses (75 minute presentation)
Faculty of Kinesiology and Recreation Management, University of Manitoba
Course: PERS 7130: Quantitative Methods in Kinesiology.

10/2014 Presentation title: Introduction to the Research Process (75 minute presentation)
Faculty of Kinesiology and Recreation Management, University of Manitoba
Course: PERS 3350: Introduction to Research Methods

07/2014 Presentation title: The Role of Physical Activity and Fitness in Cardiovascular Medicine (180 minute presentation)
Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre
Course: N/A: University of Manitoba Medical Student Lecture

11/2014 Presentation title: Functional Capacity of the Cardiovascular System (50 minute presentation)
Faculty of Kinesiology and Recreation Management, University of Manitoba
Course: KIN 3470: Exercise Physiology

11/2014 Presentation title: Physical Activity, Fitness, and Cardiovascular Disease Prevention and Management (180 minute presentation)
Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre
Course: N/A: University of Manitoba Medical Student Lecture

06/2012 Presentation title: Physical Activity, Fitness, and Cardiovascular Disease Prevention and Management (180 minute presentation)
Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre
Course: N/A: University of Manitoba Medical Student Lecture

01/2012 Presentation title: Exercise as a treatment for depressive symptoms and disorders (180 minute presentation)

Faculty of Kinesiology and Recreation Management, University of Manitoba
Course: KIN 4160: Advanced Pathology and Sports Medicine

Teaching Assistant and Grader/Marker Positions (13)

Fall 2016, 2015, 2014 & 2013 — **Grader/Marker.**
Course: PERS 3350: Introduction to Research Methods.
Job description: Marked and provided feedback to over 100 student's assignments, mid-terms, and final examinations.

Spring 2014 & 2013; Fall 2011 & 2010 — **Teaching Assistant.** Head Laboratory Demonstrator
Course: KIN 3470: Exercise Physiology.
Job description: 10-15 minute presentations on instructions for laboratory exercises; guided student hands-on experience in the laboratory.

Winter 2014 & 2013 — **Grader/Marker.**
Course: PERS 1500: Foundations of Physical Education and Kinesiology.
Job description: Marked and provided feedback to over 100 student's assignments, mid-terms, and final examinations.

Winter 2011 & 2010 — **Teaching Assistant.** Head Laboratory Demonstrator
Course: KIN 3450: Motor Control and Learning
Job description: Demonstrated and guided over 100 students in completing the laboratory experiments; marked and provided feedback to student's assignments and final examination.

Winter 2011 — **Grader/Marker.**
Course: KIN 3512: Principles of Fitness Training
Job description: Graded and provided feedback to over 50 student's assignments and final examination.

Membership in Professional Associations

2013-ongoing — Canadian Society for Exercise Physiology

2013-2016 — University of Manitoba Graduate Student Association

2013-2016 — University of Manitoba Centre for the Advancement of Teaching and Learning

2010-ongoing — Canadian Association of Cardiovascular Prevention and Rehabilitation

2006-2010 — Manitoba Fitness Council

Academic service

<u>Manuscript reviewer (3)</u>

2016 **JACC Heart Failure (1 manuscript)**

2015 & 2016 **Clinical Rehabilitation (2 manuscripts)**

<u>Service to professional organizations (1)</u>

2015-2016 **Secretary, Canadian Cardiac Rehabilitation Registry Research Sub-Committee**
Canadian Association of Cardiovascular Prevention and Rehabilitation
<u>Description:</u> Take the minutes during bi-monthly committee meetings. Also provided input on strategic directions of the registry.

<u>Service to the undergraduate and graduate student community (4)</u>

2017 **Speaker, Tips for being a Successful Research Assistant workshop at the Summer Research Training Institute**
University of Manitoba
<u>Description:</u> I drew from my experiences as a Research Assistant to provide tips on being successful in such a position. I also provided advice on how to use those experiences when applying for other positions.

2015-2016 **Voting member, Graduate Student Association Internal Development Review Committee**
University of Manitoba
<u>Description:</u> Review whether major members (e.g., President, Vice-President) of the Graduate Student Association are fulfilling their roles.

2013-2016 **Voting member, Graduate Student Association Awards Committee**
University of Manitoba
<u>Description:</u> Review graduate student and teaching award applications; voting rights on who should be selected for the awards.

2013-2016 **Co-Councillor, Graduate Student Association**
University of Manitoba
<u>Description:</u> Represent the Applied Health Science students and act as a voice for any concerns of graduate trainees; voting rights on

changing policies affecting graduate students; host graduate student events (social and academic)

<u>Student mentorship (14)</u>

I manage the daily research activities of junior trainees during their undergraduate and graduate level education. Specifically, my role is to train students to recruit and obtain informed consent from research participants, ensure that trainees follow research protocol guidelines and collect quality data from participants. Furthermore, I teach trainees in using surveys, objective measures of physical activity, and complete medical chart reviews for research purposes.

<u>Master's students (9)</u>

9/2015-ongoing **Kevin Boreskie**. Masters of Science, Kinesiology and Recreation Management student, University of Manitoba.

09/2014-12/2016 **Dustin Kimber.** Masters of Science, Kinesiology and Recreation Management student, University of Manitoba.

09/2014-ongoing **Michael Hlysnky.** Masters of Science, Kinesiology and Recreation Management student, University of Manitoba.

09/2014-07/2016 **Naomi Hamm.** Masters of Science, Kinesiology and Recreation Management student, University of Manitoba.

05/2014-07/2016 **Andrew Stammers.** Masters of Science, Kinesiology and Recreation Management student, University of Manitoba.

09/2011-08/2013 **Eric Garcia.** Masters of Science, Kinesiology and Recreation Management student, University of Manitoba.

09/2011-08/2013 **David Kent.** Masters of Science, Kinesiology and Recreation Management student, University of Manitoba.

09/2011-ongoing **Soyun Chapman.** Masters of Science, Kinesiology and Recreation Management student, University of Manitoba.

5/2011-08/2012 **Nilu Wangasekara.** Medical student (Master's equivalent), Faculty of Medicine, University of Manitoba.

<u>Undergraduate students (5)</u>

06/2015-08/2015 **Braden Cruise.** Bachelor of Kinesiology, Faculty of Kinesiology and Recreation Management, University of Manitoba.

01/2015-05/2015 **Courtney Addison.** Bachelor of Kinesiology, Faculty of Kinesiology and Recreation Management, University of Manitoba.

01/2013-04/2013 **Meghan Rempel.** Bachelor of Kinesiology, Faculty of Kinesiology and Recreation Management, University of Manitoba.

05/2011-08/2011

09/2010-12/2010	**Kyle Babiuk.** Bachelor of Kinesiology, Faculty of Kinesiology and Recreation Management, University of Manitoba.
	Ihor Babiak. Bachelor of Kinesiology, Faculty of Kinesiology and Recreation Management, University of Manitoba.

Media Relations

Featured in the media (2)

01/2017 **UM Today News**
Title of feature: Rising Star: Applied Health Sciences PhD candidate's physical activity research is setting him apart from the pack
URL: http://news.umanitoba.ca/rising-star/

01/2017 **Research LIFE Magazine**
Title of feature: Rising Star
URL: http://umanitoba.ca/research/research_life.html