Examining the Relationship of Physical Activity, Inflammation & Adiposity on Physical Function with Gender Differences

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EXAMINING THE RELATIONSHIP OF PHYSICAL ACTIVITY, INFLAMMATION & ADIPOSITY ON PHYSICAL FUNCTION WITH GENDER DIFFERENCES

By

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ABSTRACT
EXAMINING THE RELATIONSHIP OF PHYSICAL ACTIVITY, INFLAMMATION & ADIPOSITY ON PHYSICAL FUNCTION WITH GENDER DIFFERENCES

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Older adults are a rapidly growing segment of the population in the United States. The ability to maintain physical function declines with age and is a critical factor that contributes to living independently. Physical activity has been shown to slow declines in physical function and decrease chronic inflammation. Increases in adipose tissue and decreases in muscle mass are associated with aging. The increase in adipose tissue produces inflammatory markers that can negatively impact older adults' health. Males and females' biological changes with aging have been hypothesized to differ. The purposes of this study were to :1) examine the relationship between physical activity, inflammation, with physical function 2) determine if adiposity was a predictor and moderator of physical function and 3) determine if there were gender differences in these relationships for community dwelling older adults.

This study was a cross-sectional secondary data analysis of the Health and Retirement Study (HRS)Wave 13 (2016) core biennial data and Venous Blood Study (n=4042). The mean age of study participants was 68.38 years old (*SD* = 9.64) and included 57.7% females (n=2332) and 42.3% males (n= 1710). Physical function, the outcome variable, included semi-tandem balance test and 3 self-report items addressing balance, grip strength, and walking endurance. Physical activity was measured using five self-report items assessing frequency of walking, sports or activity and mild, moderate, and vigorous activity. Chronic low-level inflammation was measured with the pro-inflammatory markers interleukin-6 and high sensitive c-reactive protein and anti-inflammatory biomarker interleukin-10. BMI was used to measure of adiposity. Using confirmatory factor analysis, latent factors were created for physical function, physical activity, and inflammation. Factor loadings and acceptable model fit (CFI scaled 0.871, CFI robust 0.879, SRMR 0.050, and gamma hat scaled 0.964) supported the indicators represented the measurement model. Latent regressions were significant ($p<.001$) and showed physical activity is positively associated with physical function and inflammation negatively impacts physical function. Correlations showed inflammation is negatively correlated with both physical activity and function. Adiposity was not a significant predictor and further moderation testing was not indicated. Model comparison between genders supported using the overall model versus gender specific models.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1: Introduction

Physical function is an integral part of older adult health and their ability to live and function independently. The World Health Organization (WHO, 1948) defines "health" as encompassing the physical, psychological and social well-being of individuals, not merely the absence of disease. Each of these aspects of health also play a role in physical function. Older adults are at risk for declines in physical function due to age, biological changes in body composition, decreasing performance and cognitive decline (Seals et al., 2016). Recent literature highlights a male-female health survival paradox, where women have higher survival rates, but worse health and lower functioning compared to male counterparts (Crimmins et al., 2019). Overall, both genders with decreased function face health and psychosocial challenges that require additional resources.

In contrast to age related declines, successful aging, healthy aging and active aging are terms utilized to define an older adult's ability to maintain physical function, prevent cognitive decline, decrease probability of disease and reduce associated chronic disease adverse outcomes. Healthy aging focuses on preventative health strategies that allow older adults to remain physically and socially involved in their communities and lives. The ability to maintain healthy or successful aging has been associated with participation in regular exercise, abstinence from smoking, and maintaining proper weight (Ferdows et al., 2018). Further, the ability and adherence to participation in physical activity improves objective measures of performance associated with physical activity and physical function that are correlated with maintaining independence (Anton et al., 2015). Physical activity and physical function have been shown to have a longitudinal bidirectional relationship where initial physical activity and function levels predict later levels of both (Metti et al., 2018). Thus, a person with poor initial physical function will participate in less physical activity and over time their physical function will worsen.

The American Association of Retired Persons (AARP, 2018) reports that 3 out of 4 older adults prefer to remain in their homes and communities, even when that requires living alone. In order for older adults to live safely and independently, additional focus needs to be placed on maintaining and improving physical function. Today an estimated 46 million older adults living in the United States and by 2030, it is expected to increase by 18 million and double to 90 million by 2050 (Rural Health Information Hub, 2019). Advances in science, healthcare, and technology have extended the lifespan for older adults. With increases in life span and population size, it is imperative to address ways to foster maintaining independence. To address older adults' physical function and independence, it is essential to build pathways to connect social and biological measures. Linking preventive health strategies such as physical activity, weight control and screening for low level inflammation to physical function during the aging process can aid in earlier identification or potential for decline and development of additional interventions.

Physical Activity

Physical activity, as defined by the American College of Sports Medicine, is "bodily movement that is produced by the contraction of skeletal muscles that increases energy expenditure" (American College of Sports et al., 2009). Participation in moderate to vigorous physical activity decreases with age and correspondingly sedentary time increases as a result of health status, employment changes and retirement (Jones et al,, 2018; Van Dyck et al., 2016). The Department of Health and Human Services Physical Activity Guidelines recommends 150 minutes of multicomponent exercise for older adults, even those with chronic conditions, due to the physical and psychological benefits that have been consistently proven. Evidence suggests that regular exercise can minimize the physiological effects of a sedentary lifestyle and increase active life expectancy through limiting the development and progression of chronic diseases and disabling conditions (American College of Sports et al., 2009). Physical activity has a dose dependent relationship with health outcomes (Hupin et al., 2015) in which participating in physical activity has been shown to increase life expectancy, improve quality of life and reduce all-cause mortality (Reimers et al., 2012). Even lower doses of physical activity below the 150-minute recommendations show improvements in health outcomes (Hupin et al., 2015). Evidence supports that increasing minutes spent participating in physical activity correspond with greater improvement in health outcomes (American College of Sports et al., 2009; Hupin et al., 2015). Thus, physical activity is key for preventative health across the lifespan.

Inflammation

Inflammation is part of the biological process of aging and the systematic affects it can have on older adult's health are not fully known. Acute inflammation is related to injury or infection, whereas chronic low-level inflammation is a basal response to aging and is hypothesized to be maladaptive (Kennedy et al., 2014). Low grade or chronic inflammation differs from acute inflammation in magnitude, underlying causes, purpose, and molecular triggering (Kushner et al., 2010). Chronic inflammation is the body's physiological response to maintain homeostasis (Rodriguez-Hernandez et al., 2013). Chronic inflammation associated with aging often referred to as "inflamm-aging" can last weeks, months, or even years and although itself is not a specific disease, it increases an individual's risks for multiple chronic conditions, morbidity, and mortality (Dagdeviren et al., 2017) (Pahwa et al., 2020). The body's pro-inflammatory response that causes increased production of inflammatory cytokines has been shown to increase risk for metabolic syndromes, cardiac disease and diabetes (Rodriguez-Hernandez et al., 2013).

A primary source for inflammatory cytokines is adipose tissue. Pro-inflammatory biomarkers such as interleukin-6 (IL-6), c-reactive protein (CRP), and anti-inflammatory interleukin-10 (IL-10) are objective measures of potential exposure to disease processes, as well as testing effectiveness of interventions (Wirth et al., 2017). IL-6 is an inflammatory mediator produced by the cells of the immune system, vascular endothelial cells, adipocytes and skeletal muscle (Singh & Newman, 2011). CRP is a systemic acute phase protein produced in response to inflammatory mediators, injury, infection and malignancy (Kuczmarski et al., 2013; Singh & Newman, 2011). IL-10 is an anti-inflammatory cytokine produced primarily by marcrophages and causes suppressed production of pro-inflammatory cytokines (Dagdeviren et al., 2017; Ribeiro et al., 2019; Rong et al., 2018). Further research is needed to differentiate between chronic inflammatory biomarkers, metabolism, and aging to aid in understanding systemic effects that chronic inflammation can have on older adults' physical function.

Adiposity

During the aging process, there is a shift in body composition. For older adults the amount of muscle mass and associated strength decreases which can result in significant muscle deterioration, increase in adipose tissue and potentially sarcopenia (K.Kim et al., 2016). Muscle mass and strength are critical for older adults maintaining physical function and independence (Studenski et al., 2014). Body Mass Index (BMI) is frequently used as a measure of adiposity.

According to the Centers for Disease Control and Prevention (CDC, 2017), BMI is categorized as underweight (<18.5), normal (18.5-25), overweight (25-30), and obese (>30). There are three classes of obesity based on BMI: class I (30-34.9), class II (35-39.9), and class III (>40) (CDC, 2017). Obesity has been recognized by the CDC and WHO as an epidemic, with nearly 34% of adults in the United States affected by obesity (Mitchell et al., 2011). Obese older adults are at increased risk for adverse health outcomes, decreased cognitive performance and declines in physical function (Batsis, 2019).

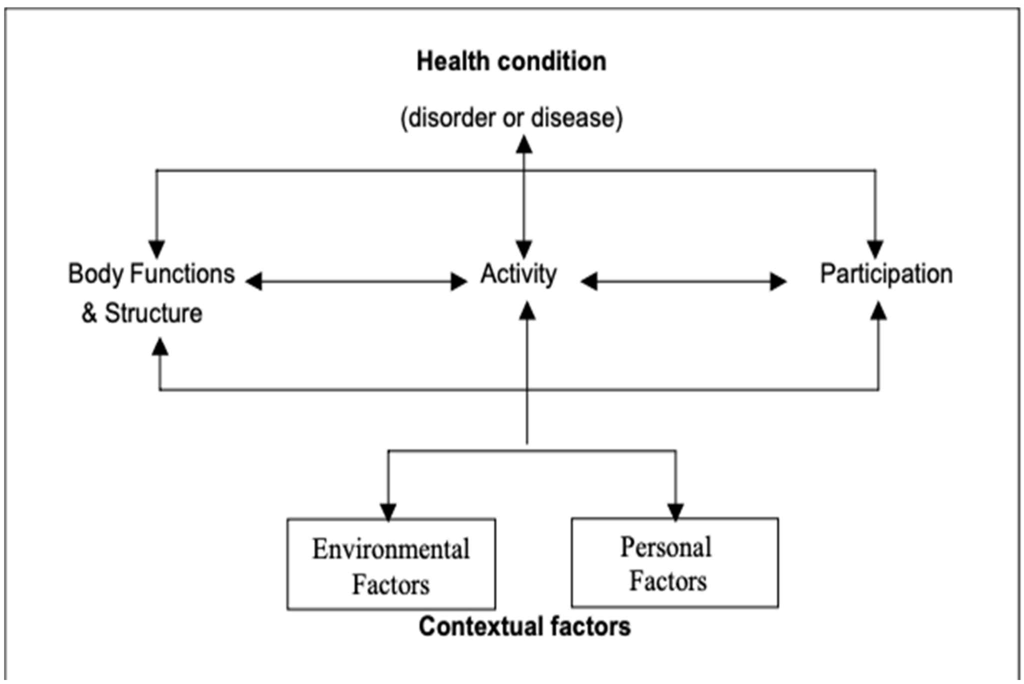
Additionally, the literature suggests obesity impacts health and physical capacity to a greater extent in women due to shifts in hormones following menopause, making this group particularly vulnerable to physical impairment (Wanigatunga et al., 2016). The Women's Health Initiative Study found over three years that increased fat mass and multimorbidity are associated with lower physical function (Bea et al., 2018; Rillamas-Sun et al., 2016). Adiposity is a modifiable personal risk factor for older adults that influences both physical function and physical activity.

Theoretical Framework

The International Classification of Functioning, Disability and Health (ICF) underpins this research (WHO, 2001). The model, as depicted in Figure 1, classifies an individual's functioning as a dynamic state along a continuum.

Figure 1

World Health Organization International Classification of Functioning, Disability & Health https://www.who.int/classifications/icf/icfbeginnersguide.pdf



The initial version of the ICF was published in 1980 and was called the International Classification of Impairments, Disabilities and Handicaps (WHO, 1980). However, in 1993, efforts began to revise the model to include elements of the social and physical environment. A revised version focusing on health and functioning versus disability was endorsed at the World Health Assembly in May 2001 (WHO, 2001). It is intended to provide information worldwide to differentiate between levels of functioning and disability with a common language and operational definitions. The model is to be used at the individual, institutional, and social levels by classifying health and health-related domains. Despite the multidimensional use of the framework, the field of nursing does not use this model often.

The ICF integrates both the medical and social models of health to form a biopsychosocial model that ensures all aspects of a health condition are considered (WHO, 2001). Function or disability is viewed as the interaction between the health condition or disease and the contextual factors of either environment and/or personal which in turn influences the three potential levels of human functioning: 1) body or body part 2) whole person 3) whole person in the social context (WHO, 2001). This multi-purpose framework is intended to be used in research, policy development, and clinical care, focusing on comprehensive population health (WHO, 2001).

Vulnerability and Significance to Nursing

Older adults living in the community are a vulnerable population due to their higher prevalence of chronic disease and disability. According to the CDC, 80% of older adults report having at least one chronic illness (CDC, 2016). Chronic conditions require additional healthcare resources that can affect an individual's daily life and ability to physically function. With aging and increased disease and disability, cognitive and functional decline increases put these individuals at higher risk for adverse health outcomes (CDC, 2016). Additional external and internal factors that make an older adult more vulnerable include sensory impairment, living alone, adverse life events, mental illness, lack of a social network, dependence on a caregiver, and lack of community resources (CDC, 2016).

Healthcare providers, in particular nurses, need to address and find ways to improve care related to vulnerable populations. Healthy People 2030, the CDC, and National Institute of Aging, all highlight the importance of preventative health care, physical activity, and empowering older adults to maintain independence and care for chronic conditions as national objectives. All of these objectives explore relationships among multiple facets of physical function that affect daily life for community dwelling older adults. The proposed research addresses these national objectives, which is important for the field of nursing by potentially aiding in preventative care strategies and future interventions to improve or maintain physical function in community dwelling older adults. Additionally, the proposed research can advance knowledge by examining the association between biological markers (inflammation and adiposity) to objective and self-report performance measures (physical function) which is critical in older adults' ability to function on a daily basis. Potential results will guide further longitudinal or experimental research to explore causality and impact future intervention development.

Study Purposes

The purposes of this study were to: examine the relationship between physical activity, inflammation, with physical function, determine if adiposity was a predictor and moderator of physical function, and determine if there were gender differences in these relationships for community dwelling older adults. The first aim of the study is to explore the relationships between self-report physical activity, inflammation (IL-6, hsCRP, and IL-10) and physical function (semi-tandem balance, hand grip strength, and gait speed) in a community dwelling older adult population from the Health and Retirement Study Data set. The second aim is to examine gender differences in the relationships between physical activity, inflammation and physical function. The third aim addresses the moderating effect adiposity has on the relationship between physical activity and physical function and inflammation and physical function. The results of the aims of this study will lay the groundwork for a program of research that focuses on the biological, physical, and social factors of physical function.

For this dissertation, the research study will be presented in three chapters including Introduction, Review of the Literature, Research Design and Methods, and two manuscripts. The first manuscript will report results of aims one and three, the relationships between self-report physical activity and inflammation (IL-6, hsCRP, and IL-10) and physical function (usual gait speed, balance, and grip strength) and how adiposity moderates these relationships. The second manuscript will report the results for aim two examining gender differences in the relationships between physical activity, inflammation and physical function.

Chapter 2: Review of the Literature

The following is a comprehensive review of the literature focusing on the main concepts introduced and defined in Chapter 1: physical function, physical activity, inflammation, and adiposity. Each of these concepts is discussed individually and in relation to the other key concepts, with the addition of gender specific considerations.

Physical Function

Physical function is a health status concept that has shifted from impairment assessment at the individual level of disability to a focus on measurement of function for all ability levels of the population (Fries et al., 2014). For older adults, their overall health impacts how they physically function each day to maintain their independence. Physical function has been shown to decrease with advancing age, due to biological changes in body composition, decreasing performance and cognitive decline (Seals et al., 2016). Older adults throughout the aging process are at risk for multiple physical and psychological issues that can potentially impair function, some of which can be mitigated or delayed through preventive care and health promotion interventions.

Physical function is multidimensional and typically encompasses gait or mobility, grip strength and balance. A systematic review by Berquist et al. (2019) identified 120 different objective performance measures utilized in research to assess functional decline and fitness in older adults. Of the different objective performance measures used, 69 addressed balance, 51 muscle strength, and 96 used multi-component performance measures that included gait, strength and balance.

Mobility

Mobility is the ability to move independently with or without assistive devices for ambulation, exercise, and function on a daily basis. Mobility is frequently measured using usual gait speed. This measure assesses an individuals' walking velocity on a straight path assessment test and provides information about functional capacity (Soubra et al., 2019). Gait speed has been hypothesized to be the "functional" sixth vital sign due to its predictive relationship and association with balance, functional ability, health status, and hospitalization (Fritz & Lusardi, 2009). Gait speed can be used as a sole predictor or can be combined with other physical objective measures to assess physical function (Fritz & Lusardi, 2009). Walking tests to evaluate usual gait speed can range from 3-10 meters long with an additional 5 meters for anticipated acceleration and deceleration (Soubra et al., 2019). Usual gait speed and other walking tests can be performed in an individual's home, outside, or within the healthcare setting and are a cost-effective objective performance measure that captures physical function (Fritz & Lusardi, 2009).

A usual gait speed of less than 1.0 meter/second (m/s) is associated with a faster rate of decline in older adults (White et al., 2013), as well as a risk factor for death (Studenski et al., 2011). Normal usual gait speed for women and men between 80–99 years old has been found to be 0.94 m/s and 0.97 m/s respectively (Bohannon & Williams Andrews, 2011). In a systematic review by Abellan van Kan et al., (2009) gait speed at usual pace as a single item assessment tool was found to be risk factor for disability, cognitive impairment, institutionalization, fall and mortality. In a pooled analysis of 9 cohort studies Studenski et al. (2011) found survival for older adults increased across all gait speeds with each 0.1 m/s increments. However, evidence exists that women and men have different gait patterns that can potentially affect function and mobility throughout aging. Specifically, women having greater ankle range of motion than men who generally have greater hip range of motion (Ko et al., 2011).

The Lifestyle Interventions and Independence for Elders (LIFE) is a study that began as a pilot in 2005 and now is a phase 3 multi-site randomized control trial aimed at lifestyle interventions to maintain mobility and independence for older adults (Rejeski et al., 2005). Layne et al. (2017) in a secondary analysis of the LIFE intervention data found that older adults with higher step counts by accelerometry had greater increases in gait speed. Other factors found to positively influence mobility and function were higher levels of self-reported physical activity, lower BMI, and younger age (Layne et al., 2017).

The covariates of age, gender and socioeconomic status have all been studied related to gait speed and are factors to consider when assessing mobility. Older adults with a lower socioeconomic status, measured by income, education level, and occupation classification, have environmental and community resource limitations, such as living situations and surrounding environment, that negatively impact their mobility (Stringhini et al., 2018; Xu et al., 2019). As individuals age their mobility decreases, even for healthy older adults. Multiple studies have shown that age is a predictor of mobility and functional mobility as measured by gait speed (De Breucker et al., 2019; de Sá Brandão et al., 2019; Xu et al., 2019). As age increases, there is a negative correlation or decrease in older adults' gait speed (De Breucker et al., 2019). Overall, usual gait speed provides insight into the current health status of older adults and the ability to function and accomplish activities of daily living.

Despite consistent findings with higher gait speed and improved physical and psychological health outcomes, gender differences in gait speed have inconsistent results.

Aranda-García et al. (2015) found females demonstrated slower gait speeds when compared to male counterparts, due to decreased muscle strength and balance. Other results indicated older women have slower walking speeds and fewer step counts than males (Higueras-Fresnillo et al., 2018; Izawa et al., 2015; Xu et al., 2019). Alternatively, De Breucker et al.(2019) and Ko et al.(2011) found no gait speed differences by gender, but rather attributed differences to cadence, stride, and range of motion. Gender is often controlled or held constant as a covariate in physical function research. However, a gap in gender differences in mobility exists due to inconsistent research findings related to physical function that necessitates further exploration.

Grip Strength

Muscle strength and associated muscle mass decline with age, resulting in overall decreased body strength (Forrest et al., 2018; Gale et al., 2007). Grip strength is an objective performance measure of body strength and muscle power (Reid & Fielding, 2012). Grip strength has been shown to be an indicator of all-cause mortality in the United States (Forrest et al., 2018; Gale et al,, 2007) and worldwide (Leong et al., 2015; Oksuzyan et al., 2017; Sasaki et al., 2007). Decreased grip strength is associated with cardiovascular mortality, cardiovascular disease and increased hospitalizations (Gale et al., 2007; Leong et al., 2015; Sasaki et al., 2007). Additionally, some research supports that older men have greater declines in grip strength and thus overall muscle strength compared to their female counterparts (Wearing et al., 2018).

Grip strength can be measured in the field or clinical setting with a hand dynamometer. The hand dynamometer has been shown to be an effective tool for assessing strength (Guerra & Amaral, 2009). No meaningful cutoffs of grip strength associated with physical function and health outcomes across the older adult population have been reported, however, grip strength needed by older adults to manage heavy tasks is reported as 18.5 kg for women and 28.5kg for men (Wang & Chen, 2010). Grip strength is independently associated with mobility status, general health status, physical function, and weight status (Forrest et al., 2018; Wearing et al., 2018).

Longitudinal studies and cross-sectional secondary data analyses with large non heterogenous samples have explored the association between grip strength and health outcomes, physical activity, function and all-cause mortality in adults and older adults. Strand et al. (2016) in a 17-year longitudinal population cohort study in Norway found weaker grip strength over time from middle age to older adult was associated with an increased all-cause mortality for cardiac and pulmonary chronic illnesses, but not cancer related diagnoses. The investigators proposed that hand grip strength is a biomarker of aging over the lifespan (Strand et al., 2016). Similar to gait speed, hand grip strength decreases with age (Forrest et al., 2018). Leong et al (2015) found similar results longitudinally across seventeen countries and added that grip strength was a stronger predictor of all-cause mortality and cardiovascular mortality than systolic blood pressure.

Participation in physical activity prevents age associated muscle loss and aids in maintaining independence. Grip strength is used to assess muscle maintenance and sarcopenia in older adults and is commonly used in physical activity intervention research. Bann et al. (2015) found that greater time in higher light intensity physical activity increased grip strength in men not women. Despite not being able to engage in traditional exercise, older adult grip strength differed by level of activity, with more active individuals having higher grip strengths (Germain et al., 2016). Hand grip has been identified as a valuable current measure of physical function and having potential for identifying future decline (WHO, 2017). The use of grip strength in older adults is essential to assess the shift in body composition that occurs throughout the aging process. Further work needs to be done on the relationship of hand grip with additional health outcomes and relationships to biological processes of aging.

Balance

Balance is the final component of physical function that is an influential factor in older adults' ability to live independently and remain free of injury. Balance can be static or dynamic and involves multiple systems and joints to maintain control and movement which aid in determining whether an older adult can complete activities of daily living (Dunsky et al., 2017). It is influenced by sensory inputs such as vision or hearing and how the body processes inputs and reacts. Changes in balance are part of the aging process, due to decreases in spatiotemporal gait parameters, vision, and hearing (Osoba et al., 2019). For older adults, balance and gait disorders have been associated with increased risk of falls, decline in physical function, and injury (Salzman, 2010).

Fear of falling, injury and previous experiences play a role in an older adults' physical function and balance (Roaldsen et al., 2014). Multimodal exercise interventions focused on balance training and exercise for older adults with osteoporosis have shown positive improvements in gait speed, fall self-efficacy, balance performance and self-rated physical function (Halvarsson et al., 2015). Further, the self-perceived functional limitations older adults' experience and their ability to adapt influence balance and adverse outcomes (Roaldsen et al., 2014).

Exercise interventions aimed at improving balance for older adults have presented opportunities for success. Pilates has been utilized in two different studies addressing postural balance for stroke survivors and community dwelling elders (Campos de Oliveira et al., 2015; Lim et al., 2016). Both studies showed improvements in postural balance. In another study, high intensity functional exercise consisting of lower limb strength and balance exercises, slowed the decline of balance and assistance required for activities of daily living for adults with dementia not attributed to Alzheimers (Toots et al., 2016). In summary, balance is related to an individuals' ability to walk, move and function on a daily basis and is influenced by physical activity, but opportunties to examine other factors that contribute to function still exist.

Disability

Physical function has been shown to be linked with levels of disability and the ability to complete activities of daily living (Cavanaugh et al., 2018). A spiral of deconditioning has been hypothesized to exist when individuals become inactive; concurrent deterioration occurs that results in negative health conditions and overall worsening of health (Painter & Johansen, 1999). Decreases in gait speed with age have been shown to be associated with higher levels of disability and a reduced ability to complete activities of daily living (Albert et al., 2015). Alternately, optimal longevity can be extended with lifestyle and behavioral interventions that focus on physiological function (Seals et al., 2016). Disability and physical function have also been linked to older adults' level of adiposity or BMI. Higher levels of disability and lower physical function have been shown to be more prevalent for obese when compared to non-obese older adults (Lisko et al., 2015)

To date, many longitudinal cohort studies have addressed disability and physical function but have not included precision medicine variables and techniques including genetic biomarkers, metabolomics and biological measures. Gaps and further research in this relationship need to be conducted to determine gender differences in objective measures of physical function and the influence of inflammation on this relationship.

Health Implications

Psychological Health. Improvements in or maintenance of physical function for older adults not only aids in delaying disability and preservation of independence, but also has been shown to positively impact self-rated health, quality of life and depression. Older adult's mental health is impacted by their physical functional status (Ohrnberger et al., 2017). Multiple studies have shown that quality of life, health related quality of life and vitality scores are positively correlated with objective measures of physical function (Kim, 2016; Noradechanunt et al., 2017; Sales et al., 2017; Vale et al., 2018). Further, Pederson et al., (2017) found that team training, when compared to a control group with no intervention, for older adults improved psychological well-being, general quality of life, and health-related quality of life, as well as decreased anxiety and depression levels. Additionally, self-reported depression scores decreased with participation in physical activity and improved physical function (Bauman et al., 2016; Thralls et al., 2019), except in low impact exercise interventions studies in which depression scores did not change (Noradechanunt et al., 2017).

Multimorbidity. Declines in physical function can have negative consequences for overall health in older adults and has been linked to multimorbidity. Multimorbidity is the coexistence of more than one chronic condition and is common in older adults with more than two-thirds of Medicare beneficiaries being classified as having multimorbidity (Lochner et al., 2013). Jindai et al. (2016) found cross-sectionally that the number of chronic conditions influence an individual's physical function status and odds of multimorbidity increase for individuals who are obese (Rao et al., 2018). Cross sectional analyses from four separate waves of the National Health and Nutrition Examination Survey (NHANES) indicated a positive association between multimorbidity and the number of functional limitations with a stronger association in women than men (Jindai et al., 2016). Kriegsman et al. (2004), found longitudinally that older adults in Amsterdam with three or more chronic conditions had a fourfold risk of decline in physical function. In addition, the association between multimorbidity and functional limitations is stronger in older adults over 75 years old (Jindai et al., 2016). Thus, as individuals age and are diagnosed with more chronic conditions, they are more at risk for functional decline. Moreover, multimorbidity has an indirect effect on mortality through its association with long-term physical functioning (Wei et al., 2019).

Research supports that there are associations between multimorbidity, physical function and gender. Women over eighty years of age with multimorbidity have an inverse relationship with physical function scores (Rillamas-Sun et al., 2016). Other factors that influenced multimorbidity and physical function were cognitive impairment, obesity, smoking status, participation in physical activity, age, hypertension and hyperlipidemia (Rillamas-Sun et al., 2016). Jindai et al. (2016) found the association between physical function and multimorbidity is stronger for women than in men with each additional diagnosed chronic illness increasing their functional limitations.

As highlighted, multiple cross sectional, longitudinal, and experimental studies have examined the relationship between physical function, physical activity and other health related outcomes. However, many of the studies do not differentiate whether the improvements in health-related outcomes could be attributed to physical function or physical activity or the interaction of both. This study aims to fill this gap.

Based on the well documented physical and psychological benefits, the Department of Health and Human Services Physical Activity Guidelines recommend 150 minutes of multicomponent exercise per week for older adults, even those with chronic conditions. Improvements in functional limitations from physical activity can deteriorate over time without continued adherence. For individuals who do not continue long term physical activity adherence, there are still reported benefits of interventions or participation. Participation in physical activity results in higher reported function or at minimum return to baseline, versus those who did not do any physical activity and result in physical function below baseline or a loss of abilities or independence (Henderson et al., 2018). Thus, physical activity is integral to maintaining mobility and independence.

Physical Activity and Physical Function

Many physical activity interventions have objective performance outcome measures, such as gait speed, grip strength, and balance tests, that relate to older adults functioning. Chase et al. (2017) in a meta-analysis review found the effect size of the relation between physical function and physical activity to be moderate (delta = 0.45) with physical, mental and cognitive activities improving objective performance outcome measures (Chase et al., 2017; Dipietro et al., 2019). Maintenance of physical function through various types of physical activity has shown positive results and has been hypothesized to impact an older adults' ability to live independently. Multiple physical activity types, including walking (Dondzila et al., 2015), yoga (Wang et al., 2016), aerobic and resistance (Sousa et al., 2014), multimodal (Shahtahmassebi et al., 2019) and multimodal with a behavioral or health education component (Gretebeck et al., 2019; Henderson et al., 2018) have shown to be successful at improving outcome measures of physical function that address mobility, balance, strength and endurance.

Cross sectional study results indicate that regular participation in physical activity (Edholm et al., 2019; Yorston et al., 2012) and, specifically, meeting physical activity guidelines (Thralls & Levy, 2018), positively impacts older adults' objective performance measures of physical function. Other studies have found that age-related declines in physical function can be offset by exercise (Bauman et al., 2016; Bouaziz et al., 2016; Brooks et al., 2018; Shah et al., 2017). Further, the Physical Activity Guidelines Advisory Committee Scientific Report highlighted for the general aging population, physical activity improved physical function and reduced age-related loss of physical function in an inverse graded manner (Dipietro et al., 2019). Longer duration, or minutes spent participating in physical activity, is associated with an increased effect size for improved physical function (Chase et al., 2017). Two quasi experimental studies utilized multiple time point measures to show the positive long-term effects physical activity can have on strength, mobility, and balance measures of physical function (Thralls et al., 2019; Wang et al., 2016). Lastly, randomized control trials comparing exercise with and without trunk exercises (Shahtahmassebi et al., 2019), aerobic exercise with and without resistance training (Sousa et al., 2014) and physical activity versus an education intervention (Henderson et al., 2018) showed improvements in physical function outcome measures.

Low intensity exercise. Participation in low intensity exercise that does not meet the physical activity guidelines has the potential to improve physical function for previously sedentary older adults and those with chronic conditions. Self-report of light intensity physical activity has been linked with improvement in the cardiometabolic risk factors of high-density lipoprotein cholesterol and total cholesterol (Y.Li, et al., 2019). Further, a systematic review of low to moderate intensity physical activity interventions for rural older adults showed tailoring interventions to the older adult population, check-ins at multiple time points, and personal contact improve effectiveness (Moore et al., 2016). Hupin et al. (2015), found physical activity below the 150 minutes of moderate to vigorous intensity is beneficial and reduces mortality, but further differentiation is needed with multiple chronic conditions. Participation in physical activity, even if it is low intensity has also been associated with chronic disease prevention and psychological benefits.

Chronic Disease Prevention

The 2018 Physical Activity Guidelines Report reflects the evidence of epidemiological studies between 2006-2017, indicating that participation in physical activity has an inverse dose dependent relationship with all-cause mortality and cardiovascular disease mortality. The dose response relationship suggests that risk reduction has no lower limit, meaning any physical activity is beneficial and risk of mortality and disease decrease with increased physical activity. Further, the dose response relationship does not vary by age, sex, race or weight (U.S. Department of

Health and Human Services, 2018). A meta-analysis of dose specific exercise interventions found that even low doses of moderate to vigorous physical activity reduced mortality risk by 22% and risk reduction was positively correlated with dose of physical activity (Hupin et al., 2015). Participation in physical activity also can decrease risk factors for other chronic conditions and adverse health outcomes such as diabetes, stroke, coronary heart disease, peripheral vascular disease, fractures, falls, weight, and elevated cholesterol (U.S. Department of Health and Human Services, 2018). A meta-analysis by Li & Siegrist (2012) of 21 cohort studies found that physical activity decreased cardiovascular disease risk for incident coronary heart disease and stroke for men by 20-30 percent and women by 10 to 20 percent.

Psychological Benefits

Physical activity also plays a role in an older adults' psychological health. Exercise produces endorphins, that can reduce perceptions of pain and trigger positive feelings. Results of three studies indicate that participation in physical activity increased the quality of life of older community dwelling adults (Chou et al., 2012; Vale et al., 2018; Yorston et al., 2012). Further that older adults who participate in physical activity decrease depressive symptoms (Thralls et al., 2019). The positive impact that physical activity has on depressive symptoms, anxiety and mental health is further supported with evidence from an integrative and systematic review that highlights participation in physical activity improves age related functional decline and mental health symptoms (Bauman et al., 2016; Bouaziz et al., 2016). In addition, it was found that an increase in psychological stress can also negatively affect functional status (Yorston et al., 2012).

Both the physical and psychological benefits of physical activity are supported in the literature, with a need to further explore biological relationships.

The literature supports that the aging process and associated decline in physical function can be slowed through participation in physical activity. The results from a wide array of types of studies, cross sectional, quasi-experimental, and randomized control trials all highlight the positive effect physical activity can have on physical function whether measured longitudinally, at one point in time, or following the manipulation of an intervention.

Inflammation

The trans-National Institutes of Health Geroscience interest group identified inflammation as one of seven pillars of aging that are interrelated and need further investigation (Kennedy et al., 2014). Inflammation is part of the biological process of aging and the systematic affects it can have on older adult's individual health is not fully known. Aging research results are inconsistent where one study has shown that as age increases inflammatory cytokines increase whereas others show decreases or no change. Elevated levels of cytokines have been found to be predictive of cardiovascular disease, type II diabetes, Parkinson's and Alzheimer's disease (Luan & Yao, 2018). For chronic inflammation associated with the aging process it is valuable to assess baseline chronic inflammation values and potential for tissue damage from excess inflammation or a failed inflammatory response (Luan & Yao, 2018). Acute inflammation is related to injury or infection, whereas chronic low-level inflammation is the basal response to aging (Kennedy et al., 2014). Inflammatory markers have been shown to be predictors of morbidity and mortality, but it is unclear how they influence other age-related changes

(Fabbri et al., 2015; Franceschi & Campisi, 2014; Varadhan et al., 2014). Aging research results are inconsistent where one study has shown that as age increases IL-6 increases, while CRP does not (Piber et al., 2019) and another study found that both IL-6 and CRP increased with age over a ten-year time span (Nash et al., 2013). Previous research has shown that IL-6 and CRP are decreased by aerobic exercise and strength training, while IL-10 increased (Ryan, 2004). Inconsistences are present in the literature for the relationship of inflammation with aerobic and resistance physical activities, highlighting a gap and need for further research.

Inflammation and Physical Activity

Multiple studies have highlighted the inverse relationship between inflammation and physical activity, or a positive correlation with its counterpart sedentary behavior. The literature is not consistent in number or type of inflammatory markers studied when investigating physical activity or sedentary behavior. Two quasi experimental studies indicated that increased physical activity decreased inflammation, measured solely by CRP and by CRP and IL-6 (Adams et al., 2015; Marques et al., 2018). Further one of the studies differentiated between self report from participants who met the recommended 150 minute physical activity recommendation versus those who did not and found lower levels of CRP (Adams et al., 2015). Comparison of the highest quaritle of active energy with the lowest quartile of active energy revealed the highest quartile had lower CRP measured by Bodymedia's SenseWear® armband (Adams et al., 2015). In comparison, a randomized control trial, by Hebert et al. (2013) with the intervention focused on diet and physical activity, resulted with decreased CRP at one year, but no change in IL-6 for the intervention group. Nicklas et al. (2016) found in a randomized control trial with data measured at baseline and 18 months an inverse relationship between IL-6 concentrations and physical activity; those with higher plasma IL-6 were less active across four measures of physical activity, whereas CRP was only correlated with one measure.

Nash et al. (2013) found that over ten years an elevated IL-6 profile was independently associated with age, physical activity, obesity, smoking status and lower levels of high-density lipoprotein cholesterol, whereas higher levels of CRP were only associated with obesity and smoking status. Yet both of the biomarkers from population cohort data increased over time with age (Nash et al., 2013). A confirmatory factor analysis utilizing the biomarkers of IL-6, CRP and fibrinogen showed good fit of inflammation. In the model the factor loading of physical activity was associated with lower levels of inflammation, supporting that these biomarkers are representative of inflammation and physical activity can lower these inflammatory markers (Friedman et al., 2015).

Two cross sectional studies took the reverse approach and showed that sitting or sedentary time increased levels of inflammatory markers (Howard et al., 2016; Pryzbek et al., 2019). Pryzbek et al. (2019) found a positive association between sedentary time and CRP for stroke survivors, but no association between survivors self-reported participation in physical activity and CRP. A third cross sectional study by Gennuso et al. (2013) found that more time spent sedentary measured by accelerometer was related to weight gain, BMI, waist circumference, and elevated CRP. With another cross-sectional study highlighting that moderate or low physical activity was associated with higher levels of CRP versus high physical activity (Howard et al., 2016). Finally, Nicklas et al. (2016)

found the inflammatory markers of IL-6 decreased with increased steps per day and physical activity expenditure, while CRP did not significantly change.

Inflammation and Physical Function

Similar to physical activity, physical function has been shown to be inversely associated with inflammatory markers, but results are inconsistent in inflammatory markers studies. In particular the biomarker of CRP has shown a strong association with physical function decline independent of social and biological variables (Sousa et al., 2016). Sousa et al. (2016) in a cross-sectional analysis found increased CRP with decreased objective measures of physical function that included hand grip strength, gait speed and the short physical performance battery. The author hypothesized that CRP as a biomarker of inflammation, could be predictive of physical decline independent of other biological and social variables (Sousa et al., 2016). Other objective measures of physical function that have been cross sectionally positively correlated with IL-6 were knee extensors and knee flexors (Felicio et al., 2014). Latent class modeling examining healthy aging indicated that walking speed, balance and activities of daily living to decrease with increases in CRP, moreover the modeling showed elevated CRP levels had increased risk of adverse aging (Lassale et al., 2019).

In addition, linear regression models showed associations between BMI, IL-6, and physical fatigability with minor differences between genders (Cooper et al., 2019). One study examined baseline data from a randomized control trial and found an association between poor physical function, especially strength, with chronic inflammation, for participants who were obese and had cardiometabolic risk (Tay et al., 2019). Lastly, logistic regression modeling showed grip strength, inflammation and muscle mass to explain 42% of the variance in physical performance for females and 37% for males (Legrand et al., 2013). To the contrary the same modeling showed that low physical performance, muscle mass and the inflammatory profile were not significant (Legrand et al., 2013). Generally, inflammatory biomarkers provide insight into biological changes in health conditions and physical functioning, with opportunities for furthering knowledge related to the role and presence in these processes.

Adiposity

Adiposity is the amount of fat present that is frequently quantified by BMI (CDC, 2014). BMI is an objective measure of body fat based on height and weight. Within the older adult population, adiposity needs to be viewed from different perspectives due to age related changes in body composition. Muscle mass and associated strength often decreases with age, which can result in significant muscle deterioration, increase in adipose tissue and potentially sarcopenia (K. Kim et al., 2016). Muscle mass and strength are critical pieces of older adults maintaining physical function and independence (Studenski et al., 2014). According to the CDC, BMI is categorized as underweight (<18.5), normal (18.5-25), overweight (25-30), and obese (>30) (CDC, 2017). Older adults in the underweight and obese BMI categories are at increased risk of adverse health outcomes due to malnutrition and impairments. Physical inactivity is related to obesity as well as mobility impairments (Asp et al., 2017).

Adiposity and Physical Function

Increased adiposity, or greater amounts of fat, is a defining characteristic of obesity and is associated with impairment in physical function (Lohman et al., 2019). An older adult's BMI has been shown to be positively correlated with mobility limitations

(Murphy et al., 2014). Investigators conducting multiple cross-sectional observational studies found BMI to have significant effects on functional performance (Chen et al., 2015; Gretebeck et al., 2017; Sertel et al., 2017). A longitudinal cohort study further differentiated between metabolically healthy obese and unhealthy obese and found over two decades the unhealthy obese have twice the rate of functional decline (Bell et al., 2017). In this particular study metabolically healthy was defined as participants with 0 or 1 of the following 5 metabolic risk factors: elevated high-density lipoprotein (HDL) cholesterol, or use of lipid lowering medication, blood pressure > 130/85 mm Hg or use of anti-hypertension medication, elevated fasting plasma glucose or use of anti-diabetic medication; triacylglycerol or homeostatic model assessment (HOMA) of insulin-resistance (Bell et al., 2017). Differences between metabolically healthy versus unhealthy are still evolving but highlight that there is contradictory evidence which supports an obesity paradox.

The contradictory research that has shown no association between obesity and physical function (Bell et al., 2017; Ferreira et al., 2013; Skinner et al., 2017). The contradictory results have introduced the term “obesity paradox”, in which the obese individual experiences a protective benefit from the excess adipose tissue rather than negative outcomes (Jahangir et al., 2014; Skinner et al., 2017). In the obesity paradox it is proposed that higher BMI status leads to increased metabolic reserve, lower sympathetic response to stress, and superior survival (Jahangir et al., 2014). Further work differentiating between different levels of BMI, potential moderating effect of BMI and physical function is a gap that will be explored in this study.

The weight at which an individual enters older adulthood has been linked to the trajectory of their health throughout this time (Reinders et al., 2015). The Health, Aging and Body Composition Study examines risk factors for functional decline and changes in body composition that occur with aging (Simonsick et al., 2001). Results from this study indicate that BMI trajectories over time for obese men had the highest risk of decline in physical function, whereas obese women lose more lean mass (Baker et al., 2019; Reinders et al., 2015). Further, the weight an individual enters old age can be a predictor for loss in lean muscle mass and physical function (Baker et al., 2019; Reinders et al., 2015). Results from the Women's Health Initiative study indicate that increased fat mass and multimorbidity is associated with lower physical function over three years (Bea et al., 2018; Rillamas-Sun et al., 2016). Additionally, the authors suggest adiposity and lean mass should be examined for prediction of physical function in postmenopausal women over time (Bea et al., 2018).

The underweight older adult population is also at risk because they have shown weaker grip strength (Hardy et al., 2013) and lower overall physical function (Ferreira et al., 2013; Jahangir et al., 2014). Underweight individuals are potentially at risk for adverse outcomes, requiring further research. The underweight and obese have decreased physical function, significant adverse health outcomes, and an increased risk for mortality (Batsis & Zagaria, 2018). Further, individuals from both BMI categories report low levels of self-rated health (Lorem et al., 2017).

Obese. As individuals age, there is a greater propensity to become obese due to physiological changes that occur as part of the aging process. Previous studies have shown that body weight increases gradually over the lifespan and then plateaus at about

60 years of age, which gives older adults increased risk for obesity and sustained adverse effects of excess weight (Wanigatunga et al., 2016). BMI has been shown in multiple studies to be a predictor of physical functioning level (Chen et al., 2015; Ghachem et al., 2019; Leigh et al., 2016; Wanigatunga et al., 2016)with greater levels of obesity being more indicative of a higher disability risk (Lisko et al., 2015). Obesity is associated with an increased risk of developing chronic diseases such as diabetes, osteoporosis, disability and hip fractures, all-cause mortality in older adults 65-74 years old and decreases in physical function (Batsis, 2019).

Low levels of physical function and sedentary behavior increase obese older adults' risk for incident disability, mortality, falls, hypertension, metabolic syndrome, depression, and mobility limitations (Batsis & Zagaria, 2018; Murphy et al., 2014). Recent studies focus on the effects physical activity interventions have on physical function in an obese population. Physical activity interventions, regardless of the type of exercise improved varying objective physical performance measures of physical function (Boukabous et al., 2019; Fritz et al., 2018; Liquan et al., 2019; Straight et al., 2018). While intervention studies that also measured body, composition found a decrease in fat mass following the exercise intervention (Fritz et al., 2018; Liquan et al., 2019; Straight et al., 2018), with one reported no change in fat mass (Boukabous et al., 2019). Highlighting the positive impact physical activity can have on physical function and adiposity, specifically for obese populations.

Underweight. Older adults are at risk for lower body weight and underweight BMI due to potential for malnutrition (Jahangir et al., 2014). The poor nutritional status can contribute to declines in physical function and independence. Lower BMI is beneficial at younger ages, however with age and transition to older adulthood, low BMI poses increased risks (Lorem et al., 2017). Previous results have found low body weight to be associated with osteoporosis and traumatic events, such as falls, which lead to fractures and increased morbidity and mortality (Jahangir et al., 2014; Reinders et al., 2015). Secondly, underweight individuals experience higher chronic disease burden, decreased immune function, malnutrition, falls, frailty and increased mortality (K. Kim et al., 2016; Roh et al., 2014).

A few cross-sectional studies have investigated the association between underweight BMI and physical function. One study found that individuals who were underweight had worse lower extremity physical performance compared to normal weight counterparts and concluded that being underweight was more detrimental to physical function than being overweight (Ferreira et al., 2013). A second study found that participants who classified as normal body weight, (BMI 18.5-24.9) on the low end of BMI had decreased mobility and balance compared to obese and overweight BMI (Sertel et al., 2017). Lastly, Wei et al (2019), found that underweight and overweight participants had a ten-point lower physical function score when compared to normal weight individuals. Further research needs to aid in finding differences between all BMI values, separate from the imposed categories and potential contributing factors. Thus, this study will examine the hypothesized moderating effect of both high and low BMI values with physical function.

Adiposity and Physical Activity

Physical activity is associated with decreases in BMI, but the ability to show causality between these two concepts is difficult due to many cofounding variables. A systematic review focusing on whether physical activity prevents weight gain found that activities that increase energy expenditure or calories burned to 1500-2000 calories per week are successful for weight maintenance (Fogelholm & Kukkonen-Harjula, 2000). The incorporation of physical activity and increased energy expenditure for older adults has shown positive health implications and decreases in BMI and fat mass (Elhakeem et al., 2018). Not only has physical activity shown an inverse relationship with BMI, but also leisure time and low intensity physical activity as well.

Leisure time physical activity is common for older adults due to retirement and the desire for activities with decreased intensity as a more feasible option for this population (Cardenas Fuentes et al., 2018). Physical activity has been found to be inversely associated with BMI, waist circumference and abdominal obesity (Cardenas Fuentes et al., 2018). Despite older adults engaging in leisure time physical activity, longitudinal research has shown increases in BMI at the population level (Droyvold et al., 2004). Pandey et al. (2017), examined data from three different cohort studies and found a strong dose dependent association between leisure time physical activity, BMI and the additional variable of risk for overall heart failure. Greater exposure to low impact physical activity has been shown to lower BMI in older adults (Elhakeem et al., 2018). Other recent findings support low intensity physical activity as an intervention to replace sedentary or standing time as a means to improve body composition in older adults (Powell et al., 2020). Light physical activity has also been shown to partially mediate the relationship between environment walkability and BMI (Koohsari et al., 2019). The inverse relationship between type and dose of physical activity, light physical activity or low intensity and BMI has been shown. Yet the health outcomes and factors associated with this relationship will be further explored with the proposed study.

Adiposity and Inflammation

Fat or adipose tissue that is associated with higher BMI is also a source of systemic pro-inflammatory cytokines in obesity (Cooper et al., 2019; Rodriguez-Hernandez et al., 2013). Weight gain and the accompanying rise in inflammatory markers are associated with metabolic syndrome (Pearson et al., 2003). Alternately, it has been shown that with weight loss blood concentrations of pro-inflammatory cytokines lowers (Rodriguez-Hernandez et al., 2013). One study showed an increase in BMI and body fat with increased IL-6 (Cooper et al., 2019), while a second study found regional fat loss reduced CRP (Beavers et al., 2015). Normal BMI compared to overweight or obese BMI is associated with higher CRP levels (Clark et al., 2016). Higher BMI or obesity across the lifespan is associated with greater amounts of chronic low-grade inflammation.

Obesity is associated with low level inflammation caused by activated macrophages, mast cells and T lymphocytes, leading to insulin resistance, increased fat mass, and decreased in muscle mass (Batsis & Villareal, 2018). Findings from a cross sectional study indicated that increased plasma IL-6 and CRP concentrations in older adults was associated with the development of insulin resistance and concurrent decline of muscle mass and strength (Clendenen et al., 2011). Ribeiro et. al (2019) found in a cross-sectional study of older women, the anti-inflammatory marker cytokine, IL-10, had a strong relationship with BMI. Results showed older healthy weight females IL-10 levels had a positive correlation with waist circumference, hip circumference and the waist height ratio, whereas for overweight older females there was no correlation (Ribeiro et al., 2019).

The knowledge about the role of inflammation and associated biomarkers has evolved over time. Initial cross-sectional studies found correlations between BMI and IL-6 but not TNF-alpha (Mohamed-Ali et al., 1997). Longitudinally Visser et al. (1999) found that over six years increases in BMI are associated with increased CRP for both men and women, with women having three times the likelihood of elevated CRP levels (Visser et al., 1999). Over time the inclusion of multiple markers and differentiation between biomarkers has evolved but the evidence continues to support pro-inflammatory biomarkers increase with elevated BMI in an individual, while with weight loss inflammatory markers decrease. A cross sectional comparison of normal weight to overweight and obese participants found higher CRP values for the overweight and obese groups (Clark et al., 2016). In agreement with these findings, another cross-sectional study found decreased CRP with body fat mass reduction and the loss of abdominal fat volume (Beavers et al., 2015). A meta-analysis of 51 cross sectional studies addressing the topic of obesity and inflammation found elevated CRP with obese individuals, and a stronger association for women (Choi et al., 2013). Whereas anti-inflammatory IL-10 has been shown to decrease with age and increased BMI in mice and it is hypothesized a similar relationship exists with humans (Dagdeviren et al., 2017). Recent literature, mainly all of cross-sectional design, highlight the relationship multiple inflammatory biomarkers have with BMI, but further work is warranted to gain more insight into the role of biomarkers in aging health.

Gender Specific Differences

Physical Activity Gender Differences

Participation in moderate to vigorous physical activity decreases with age and differs between genders (Keadle et al., 2016). In general males participate in more exercise that is of greater intensity then females. Keadle et al. (2016) found across three national surveys that men consistently self-reported higher levels of physical activity compared to female counterparts. While Li et al. (2017) compared accelerometry data between genders and found that males had higher step counts, greater physical activity frequency and more moderate to vigorous physical activity then females. Yet it was found that women have higher levels of low intensity physical activity in the house than males (Li et al., 2017). Similarly, Amagasa et al. (2017) found via accelerometer comparison that women had lower moderate to vigorous physical activity, but higher low intensity physical activity minutes which resulted in greater total time spent in physical activity. Underscoring that gender differences in physical activity type, frequency and time are present and influence other factors of health, in particular physical function.

Physical Function Gender Differences

Body composition differences, hormonal shifts and post-menopausal symptoms in women are foundational to why older men and women differ in levels of physical function and objective performance (Bea et al., 2018). For women, menopause typically increases body weight and fat mass, especially in visceral areas but decreases in fat-free mass, whereas with men, testosterone decreases by 1% per year which negatively impacts muscle mass and fat distribution (Batsis & Villareal, 2018). Multiple researchers have found gender differences between physical function and body composition that highlight older women more often have higher adiposity and decreased muscle strength that result in lower overall physical performance (Batsis & Villareal, 2018; Landi et al., 2017; Tseng et al., 2014). While men reported higher levels of physical activity, had lower adiposity, greater muscle strength and greater lean mass than female counterparts (Straight et al., 2015).

Gender differences related to physical function go beyond the objective measures and include rates of decline and location. Gender differences in rates of physical functional decline vary with country of residence. Rates of decline have been shown to be slower in females (Botoseneanu et al., 2016) and faster in the United States for both males and females when compared with English counterparts (Bendayan et al., 2017). Numerous large cohort, cross sectional and experimental studies have included measures of physical function with other health and social variables that have data and results to provide foundational knowledge and guide future work**.** Gaps in the literature exist when determining gender differences beyond anthropometric measures and multimorbidity. Thus, gender differences in physical function need to be further differentiated by varying levels of adiposity, the role of adiposity as a moderator and the influence of inflammatory marker variables. This study will fill this gap by contributing to the knowledge regarding varying levels and moderating role of BMI.

Adiposity and Gender differences

The aging process causes biological changes in body composition, where fat mass increases and muscle mass decreases but this may differ by gender. A review on the epidemic of obesity throughout the lifespan found the peak of prevalence of obesity to be between 50-60 years of age (Low et al., 2009). A seminal longitudinal study compared body composition of young and older males by computerized tomography found that with aging weight decreased due to loss of lean tissue and distinct differences in fat distribution between age groups (Borkan et al., 1983). Despite this study not including the comparison to the female gender, it provides foundational knowledge of changes in body composition with aging.

Typically, men have more lean mass and accumulate adipose tissue in the trunk and abdomen compared to females who have more fat mass and adipose tissue around the hips and thighs (Bredella, 2017). In addition, differences exist due to hormone shifts, in which women are post-menopausal with an increased risk for weight gain and increased mass, especially in visceral areas (Batsis & Zagaria, 2018). Whereas for men with aging the amount of testosterone decreases, which subsequently can decrease muscle mass and increase fat (Batsis & Zagaria, 2018). Due to these gender specific variances, women generally have a higher incidence of obesity and BMI in developed countries worldwide (Low et al., 2009). Although the BMI differences between genders is not necessarily always the primary aim of a research study, often times this data is still collected and reported with demographics or controlled for with covariates. For example, a cross sectional study of NHANES data investigating sarcopenia, obesity and mortality, reported an obesity prevalence of 60.8% in women and 54.4% in males in a large cohort sample demonstrating the difference (Batsis et al., 2014). The differences in gender, body composition, and adiposity also influence the biomarkers of inflammation present in the aging process.

Inflammation and Gender Differences

Gender differences between inflammatory biomarkers have been inconsistent and inconclusive in the older adult literature. One population cohort study found that gender specific differences in inflammation are larger at younger ages and decrease over time (Mitchell & Aneshensel, 2017). Females with a reported higher incidence of obesity, decreased physical activity and thus increased adipose tissue, hypothetically should have higher levels of inflammatory markers. However, two studies found no difference between systemic inflammatory markers and gender (Z. Li et al., 2019; Piber et al., 2019), equivalent inflammatory profiles (Legrand et al., 2013), and one study's baseline comparison of gender and inflammation did not show significant differences (Marques et al., 2013). But the study with no baseline inflammation differences between genders, implemented a 32-week exercise intervention and found a decrease in IL-6 and CRP with the treatment that differed between males and females, such that males had a greater decrease in inflammation (Marques et al., 2013).

Contradictory to these findings, two other studies (Clark et al., 2016; Kuczmarski et al., 2013) and a review (Woloshin & Schwartz, 2005) report that female gender has a significant association with inflammation, and more specifically black females have the highest risk of inflammation. A confirmatory factor analysis of three biomarkers: IL-6, CRP, and fibrinogen found females to have higher levels of inflammation compared to men, with increased age and being non-white as additional increased risks (Friedman et al., 2015). Lastly one study found IL-6 and CRP increased with age and were higher for males, while TNF-alpha did not change (Ferrucci et al., 2005). In addition, the age gender interaction was significant and suggested that age related inflammation may have different causes between genders (Ferrucci et al., 2005). The inconsistencies underscore the need for future research on inflammation, its role in the aging process, and potential for gender differences.

Gaps in the literature

Despite extensive literature supporting the positive affect physical activity has on physical function for older adults, further research still is needed to investigate the inflammatory marker links, moderating effect of BMI and influence of gender specific differences. There are several gaps in the literature that this study addresses and will add further knowledge and support to existing evidence. First, the use of the ICF framework has only been utilized a few times in the nursing literature and further testing of the framework and application of the findings adds to nursing knowledge. Second, few studies have used structural equation modeling to examine the relationships of physical function, physical activity and inflammation. One study specifically examined the relationship of these concepts with a small sample, a composite inflammation score, and did not distinguish between genders (Tay et al., 2019), underscoring the need to further investigate the relationship with a larger sample and advanced statistical testing to limit measurement error. The use of advanced statistical testing and modeling with these constructs is warranted, due to most of the prior research utilized single or multiple measures for comparison. The benefit of using utilizing structural equation modeling (SEM), in this study was that the factors consisted of multiple indicator variables and tested between multiple factors.

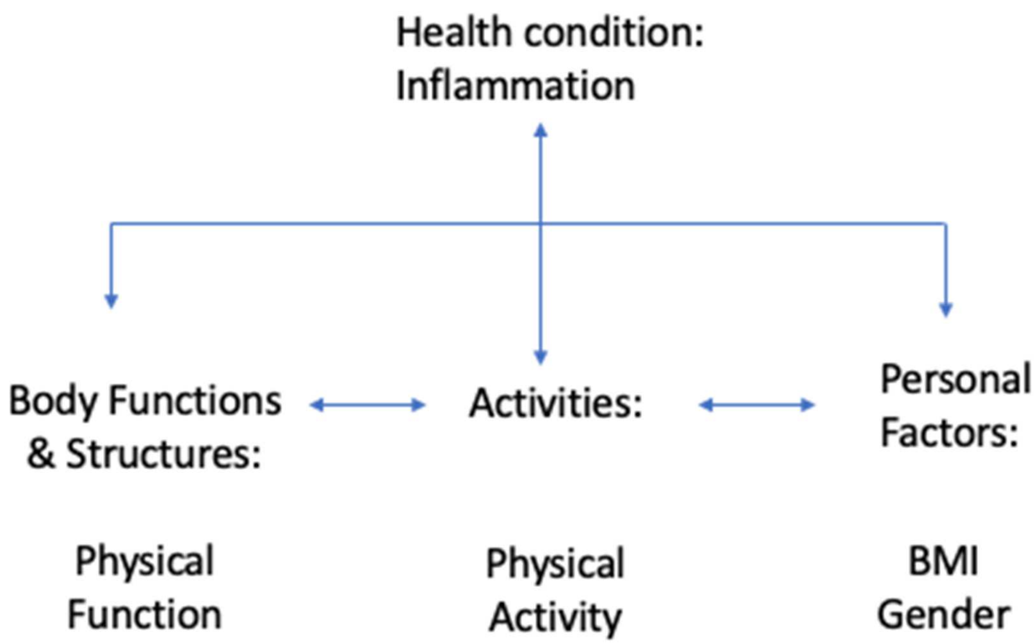
Utilizing this analytical approach allowed multiple indicator variables to be tested together, to confirm their representation of an “unmeasurable” construct and then compared between genders to further the knowledge about the multiple constructs and association of all three concepts. Further, the relationship between these variables has been examined with exercise as a moderating effect, but no studies to date have utilized the same approach with exploration of the role of BMI moderating these relationships. BMI will also be utilized as a continuous measure versus grouped according to categories, which will provide a greater understanding of the role BMI has within these relationships along the continuum. Lastly, gender differences in physical activity and physical function are present in the literature, however more research is needed to determine causes and what influences the role gender plays in the construct's relationships. This study provided additional insights that prompts further research or interventions.

Theoretical Framework

The framework underpinning this research was the World Health Organization's International Classification of Functioning, Disability and Health (ICF) (WHO, 2001). Within the ICF, an individual's functioning is considered to be a dynamic state along a continuum influenced by multiple factors. Double sided arrows within the framework highlight that the relationship between the concepts are continuous and bidirectional. The overarching aim of this research was to examine the relationships between inflammation (health condition), physical activity (activities), adiposity (personal factor), and physical function (body structure and function). Figure 2 depicts the relationships of the biopsychosocial concepts from the ICF framework.

Figure 2

Theoretical Framework for Proposed Study



In the ICF, body functions and structures are described as the individual body movements and potential impairments with functions defined as physiological and psychological functions of body systems, while structures are defined as anatomical parts of the body such as organs, limbs and their components (WHO, 2001). The components of physical function are included in the definition of body functions and structure by providing information at the individual and objective level of how a body part or system of parts moves or is impaired. Operationalized strength is the "ability to generate maximal muscle force" (Reid & Fielding, 2012) and balance is the "ability to maintain posture, respond to voluntary movements and react to external perturbations (Osoba et al., 2019). Mobility within the ICF Framework is defined as movement in indoor and outdoor environments including use of assistive devices or transportation (WHO, 2001).

Each of these concepts is reliant on the body's internal biologic and external physiologic abilities and therefore conceptually aligns with body functions and structures.

Within the ICF framework, activities are defined as "functioning at the level of the individual and the activity limitations they experience" (WHO, 2001). With activity being the execution of a task or action by an individual, therefore, actions and tasks encompass physical activity. The individual ability of an older adult to engage in activities can be interconnected to physical activity. The operational definition of physical activity for this study has been established by the American College of Sports Medicine as the "body movement that is produced by the contraction of skeletal muscles and that increases energy expenditure" (American College of Sports et al., 2009). Thus, the concept of activities from the framework encompasses level of participation in activities or tasks which are physical activity for the proposed research.

Personal factors are described as an internal and contextual which "influence how disability is experienced by the individual" (WHO, 2001). Personal factors can include gender, age, coping styles, social background, education, profession, past and current experience, overall behavior patterns, character and other factors that influence how disability is experienced by the individual (WHO, 2001). The facet of individual adiposity is a personal factor of interest due to the role it plays in experiencing overall health. This is calculated by dividing a person's weight in kilograms by square of height in meters (CDC, 2017). It is used to determine the amount of body fat and is specific to the individual. For the proposed study the personal factors or demographic data of interest will be gender and adiposity.

Philosophical Underpinnings

Scientific inquiry is a blend of philosophical viewpoints and research approaches that congruently support the purpose and objectives of the researcher (Racher & Robinson, 2003). A researcher's approach to inquiry usually consists of the three components of a paradigm. The three components of a philosophical paradigm a researcher utilizes consists of their beliefs about reality (ontology), their relationship with what can be known (epistemology), and how the research is conducted in relation to the question and context (methodology) (Houghton et al., 2012). Multiple paradigms exist with similarities and differences; however, the researcher's selection of the paradigm influence the objectives and the research process (Houghton et al., 2012). For the purposes of the proposed research study the philosophical paradigm of post-positivism will guide and support the researcher and study.

Post-positivism evolved out of the positivism paradigm in the twentieth century, by critical thinkers, in particular Karl Popper and Jacob Bronowski, who challenged positivists in regard to objectivity (Clark, 1998). Post-positivists embrace that knowledge is our best understanding of a phenomenon resulting from hypothesis testing, theory generation and falsification (Young & Ryan, 2019). In this paradigm, obtaining knowledge is an iterative process focusing on advancing science through inquiry.

Within nursing and health care professions the use of the post-positivism is common due to its focus on seeking causation, predication and explanation in complex aspects of human lives (Clark, 1998). The ontology of the post-positivist philosophy research and the associated outcomes are an estimation of truth, not the truth itself and there is acknowledgement that complete objectivity is impossible (Houghton et al., 2012). Typically, the research is based on a theory or framework that has concepts and variables with empirical measures. Theories consist of already established knowledge with the ability to generate new hypotheses for further knowledge development or falsification of previous knowledge (Young & Ryan, 2019). Multiple measures are viewed as an asset within this paradigm to aid the researcher in supporting aims and identifying limitations. The epistemology of post-positivism focuses on iterative knowledge development and the inability to ever fully understand a concept. There is acknowledgment that some variables are unobservable within this realm and that humans created the knowledge, thus objectivity at some level is unavoidable (Houghton et al., 2012). Methodology within the paradigm focuses on building knowledge through existing theories and frameworks with hypothesis testing (Young & Ryan, 2019). Different methods such as quantitative, qualitative, or mixed methods are acceptable and encouraged to obtain multiple perspectives. Results support understanding a phenomenon in the specified context with the ability for reproducibility (Young & Ryan, 2019). Hence the proposed study aligns with the post-positivism paradigm by testing the ICF framework and proposed hypotheses variables and relationships of physical activity, physical function, inflammation, adiposity and gender. As highlighted in the literature review these concepts have been shown to be related with the proposed study iteratively testing some of the relationships and exploring new additions.

Study Aims and Research Hypotheses

Aim 1: Determine the relationship between self-report physical activity and inflammation and physical function in community dwelling older adult population.

> *Hypothesis 1:* Increased self-report of walking and playing sports or exercise are associated with increased physical function in community dwelling older adults controlling for age, gender and comorbidities.

Hypothesis 2: Higher levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines of chronic low-level inflammation will be associated with lower physical functioning in the community dwelling older adult population controlling for age, gender and comorbidities.

Hypothesis 3: The interaction of decreased physical activity and increased pro-inflammatory cytokines will be negatively associated with physical function controlling for age, gender, and comorbidities.

Hypothesis 4: Increased self-reported physical activity will be associated with decreased chronic low-level inflammation (IL-6, hsCRP) controlling for age, gender, and comorbidities.

Aim 2: Examine the relationship between self-report physical activity and inflammation on physical function between genders in a community dwelling older adult population.

Hypothesis 1: Female gender will be associated with decreased physical activity and increased pro inflammatory cytokines (IL-6, hsCRP) and decreased anti-inflammatory cytokine (IL-10) that will negatively impact physical function.

Hypothesis 2: Male gender will be associated with increased physical activity and decreased pro-inflammatory cytokines (IL-6, hsCRP) and increased anti-inflammatory cytokines (IL-10) that will positively impact physical function.

Aim 3: Examine how the relationship between physical activity and inflammation on physical function is moderated by BMI.

Hypothesis 1: BMI will moderate the relationship between physical activity and inflammation on physical function. Such that as BMI increases, physical activity will decrease, inflammation increases, and physical function decrease for community dwelling older adults.

Study Assumptions

This study contained several assumptions. First, with the use of the HRS secondary data set, the researcher assumes that the field workers and third-party laboratory technicians and facilities collected data and processed specimens in accordance with protocols and procedures. Next, for objective measures of physical function (gait speed, balance, and grip strength) and BMI, the field researchers performed the objective performance measure testing and height and weight data collection as described in the protocols and procedures for the HRS study. Lastly, the assumption that the indicator or measured variables are representative of the latent constructs for physical function, physical activity and inflammation is present, despite the proposed confirmatory factor analysis.

Chapter 3: Methodology

Research Design

A descriptive cross-sectional design that utilizes secondary data analyses of the Health & Retirement Study (HRS) was conducted to examine the associations between inflammation, physical activity and physical function of older adults. Older adults living in the community were selected for this study due to the importance of preventive health and the ability to maintain physical function and independent living despite confounding chronic diseases. The data set is part of a nationwide longitudinal survey conducted in the United States that began in 1992 targeted at understanding aging at the population level for community dwelling, noninstitutionalized older adults (HRS, 1995). The HRS is a joint effort between the National Institute of Aging and University of Michigan, with additional funding provided by the U.S. Social Security Administration (Fisher & Ryan, 2018). Data collection began in 1992 with wave one of individuals between 51-61 years of age, born between 1931-1941 and spouse or partner (HRS, 1995). The study merged with the Asset and Health Dynamics Among the Oldest Old in 1998, which captured data from participants born between 1890-1923 (Sonnega et al., 2014). In order to have a representative sample, two additional cohorts were added; individuals born during the Great Depression between 1924-1930 and during World War II born between 1942-1947 (Sonnega et al., 2014). Proxy respondents are allowed for individuals unable to complete the interview themselves, which is approximately 9% for each wave of the study (Sonnega et al., 2014).

Sample and Setting

The initial samples were selected using a multi-stage probability design that included four selection stages (HRS, 1995). Eligible participants were identified by household financial units which required at least one household member to be from the 1931-1941 birth years (HRS, 1995). The first stage consisted of probability proportionate to size sampling of Metropolitan Statistical Areas and non-Metropolitan Statistical Areas (HRS, 1995). Second, sampling of area segments in the primary stage units occurred. Systematic selection was conducted from the list of eligible housing within the selection area. Lastly, a household financial unit within the sample housing unit was selected (HRS, 1995). The sample obtained from the described procedures is referred to as the core sample. Subsequent steady state sampling is used to replenish and add to the core sample every six years with younger cohorts (HRS, 2008).

In addition to the core sample, supplementary oversampling was done with Hispanic, Black populations and residents of the state of Florida (HRS, 1995). Florida was oversampled for supplemental analysis at the state level and was funded separately (HRS, 1995). Sampling weights are used to counterweigh the oversampling populations and allow for the core and supplemental data to be combined for analysis (HRS, 1995). Institutionalized individuals in prisons, long term care facilities and other care facilities are excluded. However, if an individual has entered the study and subsequently moves to a long-term care facility, their data and interviews continue.

The sample is re-interviewed biennially, with steady state sampling occurring every six years to add newly aged individuals between 51-56 years of age (Fisher & Ryan, 2018). This has led to the addition of the early baby boomers (1948-1953) and mid baby boomers (1954-1959) (HRS, 1995). To date, there are 13 waves of data with 43,478 participants (HRS, 1995). The setting for interviews and surveys is mixed mode with the sample divided in half and data collection for surveys either taking place at the participants' place of residence or over the telephone (Sonnega et al., 2014). Performance measures are conducted in the individuals' place of residence. Response rates range from 47.4 to 81.3% across waves and cohorts with an average response of 73% (Sonnega et al., 2014). The study used data from Wave 13, with data collection field dates from February 2016 to September 2017. In this wave, the core biennial data had a sample of n=35,935 (HRS, n.d.). Participants from the core sample were requested to participate in the additional venous blood study on a voluntary basis. The venous blood study (n=9934) was conducted concurrently with core biennial data from wave 13 and had an 82.9% completion rate (HRS, 2017). The core biennial data was merged with the venous blood study sample and matched according to the person and household identifying number to obtain a complete dataset.

Inclusion and exclusion criteria

The inclusion criteria were to be a participant in the HRS study that included community-dwelling adults aged 51-61 years or older, and willingness of participants from the core biennial sample to voluntarily complete the venous blood study. Exclusion criteria included participants with incomplete physical function data, since this is the primary outcome variable. Secondly, the participants who did not respond to the gender question were excluded due to the hypothesized statistical model based on sex. Thus, the final sample for this study n=4042 consisted of the merged core biennial and venous blood study, excluding participants with incomplete information for gender and physical function measures.

Protection of human subjects

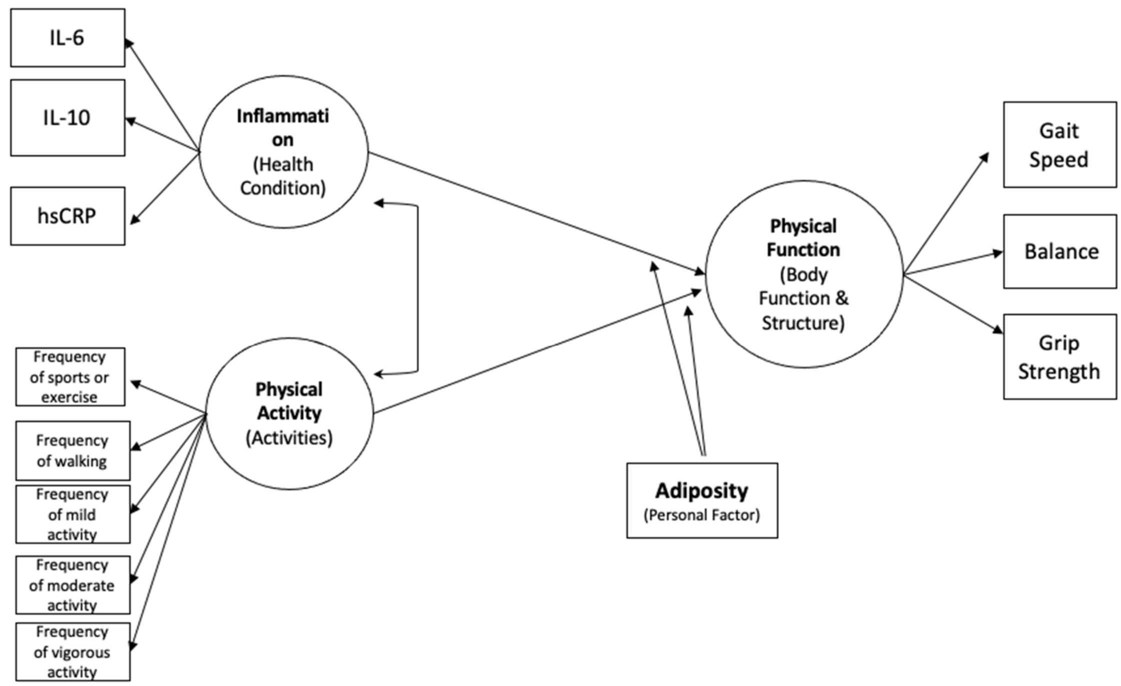
The parent HRS study obtained Institutional Review Board approval through the University of Michigan Health and Behavioral Sciences through December 31, 2023 (HRS, 2018). This study was submitted to the Marquette Institutional Review Board and it was determined review was not required prior to study initiation, since participant information was deidentified prior to obtainment, and there was no risk of harm.

Measures

The variables of interest in this study theoretically aligned within the four different factors of the model: physical function (outcome variable), and the predictor variables that include physical activity, inflammation, and personal factors. Measures for each factor are described below and depicted in the model, Figure 3.

Figure 3

Model with Factors & Indicators



Outcome Factor: Physical Function

Physical function is defined by usual gait speed, hand grip strength, and three sequential performance-based balance tests side by side, semi-tandem, and full tandem.

Usual Gait Speed. Usual gait speed is an objective performance measure aimed at evaluating an individual's mobility status. It is an objective performance measure conducted by the trained interviewer in the participants' home. Participants watch a video demonstration of the test. If needed, the participant is able to use any assistive device which is noted during the data collection. The interviewer sets up with masking tape in a straight and clear area of participants home (HRS, 2016a). The participant is instructed to walk a five-meter walking course at his/her usual pace. The test is repeated with results of both tests recorded in seconds. These values were converted to meters/second (m/s) and an average of the two tests quantify usual gait speed.

Reliability for usual gait speed has been found to be acceptable across several studies. In a study of older community dwelling females, intraclass correlation coefficients were high for usual gait speed performed at four meters (.715), six meters (0. 861), and ten meters (0.902), highlighting all are acceptable measures for usual gait speed with greater distances having greater reliability (H. Kim et al., 2016). Similarly, results of two studies that evaluated gait speed at 5, 8 and 10 meters of community elders and those with stroke found results were comparable between distances, meaning each distance could be used equally to assess usual gait speed (Ng et al., 2012; Ng et al., 2013). For older adults' usual gait speed, no matter what the testing distance, has shown to be a reliable and valid measure for assessing physical function, quality of life, and general health (H. Kim et al., 2016)

Grip Strength. Grip strength was measured using a hand dynamometer, made by Smedley (Denmark). Explicit instructions were given to participants by interviewers as well as physical demonstration. Participants' hand grip strength was measured in both hands twice with results recorded by the interviewer to the nearest 0.5 kilograms with the average of each side used for analysis (HRS, 2016a).

Test-retest reliability of grip strength by dynamometer in older adults has been established with intraclass correlation coefficients >.80 (Bohannon, 2017) and equal to or greater than .75 when using the mean score, best score and the first two readings within a sequence (Wang & Chen, 2010). Wang and Chen (2010) also reported a 75% sensitivity of 35kg for men and 22kg for women. Validity of the hand dynamometer has been established through comparison of strength measurement with a sphygmomanometer. Spearman Rho correlation coefficient test measuring within-instrument reliability showed a high correlation for each instrument at .85 for the sphygmomanometer and .82 for the Jamar dynamometer (Hamilton et al., 1992). Construct validity has been evaluated by comparing the sphygmomanometer with the Jamar dynamometer which resulted in a .75 correlation (Hamilton et al., 1992).

Balance. The three sequential performance-based balance tests utilized in this study, side by side, semi-tandem, and full tandem are all static steady state balance tests (Bergquist et al., 2019). Each of these balance tests can be done in the field or clinical setting with minimal equipment and cost. The objective performance measure of balance was an outcome indicator of physical function with a progressive series of balance tests starting with the semi-tandem balance test. The interviewer described and demonstrated the test to the participant as well as showing them a card with a visual representation of each of the tests. For the semi-tandem balance test, the participant stands with the side of the heel of one foot touching the big toe of the opposite foot, with either foot being in front. If the participant successfully holds the position for ten seconds with the semi-tandem balance, then they advance to the full tandem balance where they stand with the back of the heel of one foot touching the toe of the opposite foot. Alternatively, if they are unable to complete the semi-tandem test then the side-by-side balance test is given, where participants stand with feet together and use other parts of their body to maintain balance but are unable to move their feet. Each balance test is performed in sequential order with a maximum of two balance tests performed with results recorded to two decimal places (HRS, 2016a).

A study examining the reliability and validity of field tests for assessing physical function in 55-70-year old's reported reliability for the balance test during 3 stances: parallel (94.7% agreement), semi-tandem (73.7%), and tandem (52.6%) (Ritchie et al., 2005). Additionally, the three sequential balance tests were utilized in two other studies that had balance as a predictor for mobility. (Cesari et al., 2009; Ostir et al., 1998). While the test-rest reliability of tandem balance test being reported as 0.91 (Franchignoni et al., 1998), the three sequential balance measures do not have additional reported reliability or validity measures.

Overall, one of the initial research studies, The Successful Aging Field Study conducted by the MacArthur Research Network (Guralnik et al., 1994) established that objective performance measures were valid instruments for assessment of function in the community dwelling older adult population. Subsequent studies have been conducted further supporting the validity and reliability of objective performance measures to quantify the factor of physical function (Beninato & Ludlow, 2016; H. Kim et al., 2016; Ritchie et al., 2005; Seeman et al., 1994; Weber et al., 2018). Self-report surveys or questionnaires are also in the literature to quantify physical function. Many of these have shown convergent validity with the objective physical performance measures (Latham et al., 2008).

Predictor Factors

Physical Activity. Self-report of participation in physical activity was assessed via two self-report questions from the Everyday Life and Well-being questionnaire and three questions from the health section in the core biennial HRS (HRS, 2016c; HRS2016e). Participants indicated how often they participated in specific activities using a seven-point Likert response scale, with seven possible Likert response options ranging from daily (1), several times a week (2), once a week (3) , several times a month (4), at least once a month (5), not in the last month (6) , never/not relevant (7) for the following questions: how often do you "walk for twenty minutes or more" and "how often do you play sports or exercise" (HRS, 2016c). A sum score for all the social participation items is available, but since only the two items specific to physical activity are being utilized in this study, each item or question will be evaluated independently. The other three self-report questions asked participant how frequently they participated in mild, moderate, and vigorous physical activity with five point-Likert response options of greater than one time per week (1), one time per week (2), one to three times per month (3), hardly ever (4), and every day (7) (HRS, 2016d). In consultation with the statistician, the decision to treat the physical activity indicators as continuous was made.

For older adults, the most frequently reported exercise is walking and gardening or yard work (CDC, 1999). Thus, responses that include walking or taking part in sports or exercise daily or several times a week and once a week will represent participation in regular exercise where the remaining categories do not. Psychometric properties are reported for some of the subscales within the HRS but not for the physical activity individual items (HRS, 2016c).

Participant self-report for assessing physical activity is often utilized in research due to cost and feasibility but has shown to be valid with varying studies and populations (Martins et al., 2017; Resnick et al., 2008; Yuko et al., 2017). A systematic review comparing self-report of physical activity versus directly measured found correlations (-0.71 to 0.96) dependent on the type of activity and gender (Prince et al., 2008). The use of self-report of physical activity participation can be presented with yes/no questions, open response or Likert items to obtain frequency, intensity and duration data. A systematic review of self-reported physical activity and double labeled water found reliability of mean percentage difference increased with recall time and were lowest among self-report diaries (Dowd et al., 2018). Further, responsiveness and reliability of self-reported physical activity items decrease with time (Dowd et al., 2018). Physical activity frequency will be assessed for the proposed study with Likert responses that do not have reliability or validity information available.

Inflammation. The continuous variables representing inflammation were the biomarkers of c-reactive protein (CRP), interleukin-6 (IL-6), and interleukin-10 (IL-10). The proinflammatory cytokines of CRP and IL-6 and anti-inflammatory cytokine IL-10 were used to quantify inflammation. Biomarkers were collected via blood sample on a voluntary basis from HRS participants, with recruitment following core biennial interviewing in 2016. Blood specimens were collected by a third-party partner, Hooper Holmes Health & Wellness in the participants home within four days of agreement to participate (HRS, 2016b). Six separate vials of blood were collected with hsCRP, IL-6, and IL-10 being from the same serum separator tube assay. All laboratory assays were analyzed at the University of Minnesota Advanced Research and Diagnostic Laboratory.

The amount of high sensitivity (hsCRP) circulating in the blood was used as a measure of CRP. It was measured in serum using a latex-particle enhanced immunoturbidimetric assay kit and read on the Roche COBAS 6000 Chemistry analyzer (Roche Diagnostics) (HRS, 2016b). The reference range is 0.5 to 10 mg/L, with high sensitivity measuring chronic low-level inflammation compared to the regular laboratory value of CRP. The laboratory inter-assay CV is 5.1% at a concentration of 1.05 mg/L and 6.7% at a concentration of 3.12 mg/L (HRS, 2016b). No reported sensitivity and specificity for hsCRP is available.

Serum IL-6 and IL-10 are measured by a laboratory technique that links enzymes immunosorbent assay (ELISA) on a system called ELLA made by Protein Simple (San Jose, CA). The manufacturer of ELLA reports the assay of the laboratory kit is correlated to a comparable, Quantikine ELISA Kit, with a slope of 0.9-1.1 and an R^2 greater than .9 (HRS, 2016b). IL-6 and IL-10 are continuous numerical measurements that quantifies the amount of the protein in the blood. Serum IL-6 has a possible range of .42 pg/ml-784.50 pg/ml with a sensitivity of 1.5 pg/ml with a mean value of 6.95 and standard deviation of 20.44 (Crimmins et al., 2020). IL-10 has a range of .33pg/ml-179.60pg/ml with a mean of 3.98 and standard deviation of 3.88 (Crimmins et al., 2020). A quality control sample of 102 pairs of cytokines for the VBS was conducted and found reliability between IL-6 (.9810) and IL-10 (.9879) cytokines (Crimmins et al., 2020).

Sensitivity, specificity, and normal ranges for inflammatory cytokines as a biological tool vary based on the diagnosis or condition of interest and are generally low. Further many diagnoses and conditions do not have established cytokine reference ranges. Laboratory methods, as well as policies and procedures utilized for the Venous Blood Study were described in detail and tested prior to study initiation (HRS, 2016b). Despite these measurements lacking specificity, they still can provide insight into underlying disease processes (Bray et al., 2016).

Personal Factors

Adiposity. An individual's BMI is a proxy measure for individual adiposity. The measures of height and weight were used to calculate BMI, [weight (pounds) /height (inches)]^2 x 703. BMI is a continuous predictor variable that aligns with personal factors. An interviewer visited participants home or place of residence and measured each individual's height and weight. Height is measured by asking participant to remove shoes and stand against a wall, where a marking is placed on the wall and the height is measured using a tape measure in inches and recorded. Weight was measured with shoes off on a scale brought in by the interviewer and recorded in pounds (HRS, 2016a). With the height and weight from the data set BMI was calculated using the above prescribed formula for eligible participants.

BMI reliability and validity are inconsistent across studies. The correlation of BMI classification based on measured height and weight has shown that diagnostic performance for BMI weakened with increases in age (Romero-Corral et al., 2008). Further that BMI had a correlation with body fat percentage in men of (.65) and in women (.87), and also with lean mass (0.73, 0.74) (Romero-Corral et al., 2008). Whereas the correlation between self-reported clinical measures and recorded clinical measures of BMI has a correlation of r=0.96 (Thomas et al., 2016). Lastly, web based reported height and weight validated anthropometrics with an in-person measurement found ICC of 0.94 for height and 0.99 for weight with BMI classification correct in 93% of cases and a kappa value of 0.89 (Lassale et al., 2013). Despite the limitations and individual differences associated with BMI, it is an appropriate measure to use for assessing adiposity in the proposed study at the population and cohort level, especially since there will be differentiation between genders and advanced technologies are not available.

Gender. The gender variable was a categorical variable that was used to determine gender differences in the measurement model, factor means, variances, and correlations between males and females for the predictor and outcome variables. Gender was measured using a single item in which an interviewer asks the participant "Is respondent's first name male or female" with response options of (1) male or (2) female. The selected gender was then assigned to a participant profile.

Data Collection and Management

Biennial core data from Wave 13 that was collected in 2016, which is available free to the public was downloaded from the HRS site located at https://hrs.isr.umich.edu/data-products/access-to-public-data, by creating a doctoral student user account. Physical function, physical activity and personal factors were in the biennial core file, which is available via a registered user account (HRS, n.d.). Inflammatory markers were part of the sensitive health data and supplemental file that the researcher requested through the registered user account with a sensitive data form access user agreement and sensitive data order form. Upon approval, the files were downloaded by the researcher on the HRS data download system. The sensitive data was stored in a double verification password protected data file on the researcher's One Drive cloud storage system to ensure security and meet HRS study requirements. The data files were merged based on household identifier and person number per the Health and Retirement Study's recommendations and cleaned for use in analysis (HRS, 2017).

Data Analysis Procedures

The data was analyzed using R 3.5.0, (R Core Team, 2018), SAS (Version 9.4) and STATA (Version 16). Data from the sensitive files and the core biennial data was merged by household identity number and person number. Data was merged, cleaned and recoded in IBM SPSS (Version 26). Descriptive statistics were run in SPSS for each of the indicators and covariates to show mean, standard deviation and range of items. The demographics of the sample were analyzed for gender breakdown and self-identified race categories. The data was analyzed utilizing Structural Equation Modeling (SEM). A proposed model consisting of the latent constructs and indicators, based on previously conducted research and theory, was tested for relationships (Brown, 2015; Kline, 2016). The hypothesized theoretical model was tested to see if it is supported by the data. Figure 2 is the hypothesized model.

There were three ordered steps that will address the aims of the study. Prior to Aim 1, a confirmatory factor analysis was conducted to establish the relationship between self-report physical activity and inflammation (IL-6, hsCRP, and IL-10) with physical function (gait speed, balance, and grip strength) in community dwelling older adult population from the HRS set. Gender model comparisons was performed to address Aim 2 to determine if there are gender differences in the relationship between physical activity and inflammation on physical function. Data analysis for Aim 3 examined how the relationship between physical activity and inflammation on physical function is moderated by BMI with latent regressions and tested the moderating effect of BMI. Each of these proposed SEM statistical approaches is described below with the associated aim.

Confirmatory Factor Analysis

Prior to addressing Aim 1 to determine the relationship between self-report physical activity and inflammation (IL-6, hsCRP, and IL-10) on physical function (gait speed, balance, and grip strength) in community dwelling older adult population from the

Health and Retirement Data set, a measurement model was established with a Confirmatory Factor Analysis (CFA). A CFA tested the latent factors of physical activity (predictor), inflammation (predictor), and physical function (outcome) with the hypothesized model. The goal of CFA is to obtain estimates for each parameter in the measurement model. The parameters consisted of factor loadings, factor variances, covariances, and indicator error variances that produced a predicted variance-covariance matrix. The first step was model specification which was driven by theory and prior research evidence (Brown, 2015). The latent factors are unobserved or unmeasured constructs that are indirectly measured by indicator observed variables (Kline, 2016). The indicators of each of latent factors has been described under measurement instruments, where physical function has indicators of gait speed, balance, and grip strength, physical activity has indicators of whether participant walks or engages in physical activity and inflammation has indicators of hsCRP, IL-6 and IL-10.

Next the model was over identified based on the number of free parameters. The hypothesized model is over identified due to the number of variances and covariances being greater than the number of parameters to be estimated. With over identified models, the variance-covariance matrix for the hypothesized model that most closely resembles the sample covariance matrix is determined through an iterative process. This process entailed analyzing and determining the factor loadings from the variance-covariance matrix with the estimation procedure of maximum likelihood (ML). In CFA, ML is based on the fundamental principle to find model parameter estimates that maximize the probability of the observing the same results if the data was collected again from the same sample population (Brown, 2015). Convergence of the model occurred when the statistical programming and the researcher concludes that the parameter estimates cannot be improved any further (Brown, 2015).

Then model fit was evaluated by observed covariances and implied covariances. Model fit was assessed by exact fit (chi-square), approximate absolute fit (RMSEA, gamma-hat) and approximate relative fit (CFI). The exact fit, chi-square utilizes model comparison with the goal being to test the null hypothesis that the implied and sample matrices are equal. Chi-square is sensitive to sample size, which can lead to rejection of models that have too large or too small of sample sizes (Van de Schoot, 2012). The model fit was assessed with gamma hat and CFI values, for both of these higher values will indicate better fit. Next the absolute fit RMSEA compared model fit to a saturated model with results of zero indicating exact fit and values better (Van de Schoot, 2012). And SRMR to evaluate the average bias from the predicted item correlation, where lower number indicated lower bias and better overall model fit.

Correlations between factors and residual correlations were examined. The factor of physical function and physical activity were expected to be positively correlated with each other due to previous literature and research. Local fit was evaluated with residual correlations >.1 assessed and determined if modification was needed. Modifications were only added if they improved the model fit, have medium to large effect size, and were theoretically relevant. Reliability measures for each factor was provided with maximal reliability (MR), alpha, average variance extracted, and omega. Following the establishment of the measurement model through the CFA, to address Aim one regressions between the latent factors of physical activity and inflammation on physical function were tested. Missing data was handled with full information maximum likelihood.

Gender Model Comparisons

Aim 2 was explored with gender model comparison to examine the relationship between self-report physical activity and inflammation (IL-6, hsCRP, and IL-10) with physical function (gait speed, balance, and grip strength) between genders in a community dwelling older adult population. Each of the genders had their own theoretical model as displayed in Figure 1, and sex specific CFA models were established for males (n=1710) and females (n=2332). The indicators for each factor and gender were determined from the CFA. With the latent constructs of physical activity, physical function and inflammation validated through the CFA, exploration of the how the constructs measured across genders was explored through model fit and latent parameter comparisons. Thus, the indicators of physical function, physical activity and inflammation were evaluated between males and females, with the parameters of factor loadings and intercepts. Prior to comparison the group data was screened for outliers to ensure any bias will not affect factor loadings and intercepts (Van de Schoot, 2012).

The factorial structure, and latent parameters of means, variances and correlations were be compared between gender models. First, the factor loading estimates and significance, followed by R^2 values for indicators, correlations between factors, and overall model fit measures were compared between the male and female measurement models. Next regressions were done for each gender model between all the factors and results compared. The individual gender specific model's estimates and model fit measures were then compared with the total sample model.

Latent Regression with Moderation

To address Aim 3, examining the relationship between physical activity and inflammation on physical function with moderation by BMI, a latent regression with moderation was tested. Once the latent parameters were established, the latent regression model was tested including the predictors of physical activity, inflammation and the outcome of physical function with the moderator of BMI.

The moderation process consisted of two steps. First, the main effects model was estimated, which was the total sample model CFA. This evaluated the effects of physical activity and inflammation on physical function. This was used as the baseline model to evaluate the effect of the moderation. Second, the moderation effect model was estimated. This included the regressions being moderated by BMI. The moderation will be evaluated by the p-value of the interaction terms, and the change in $R^{2,}$ by adding BMI to the model as a predictor. The increase in explained variance (R^2) determined the magnitude of the effect for the moderation. These two steps addressed the overall issue if there is a moderation effect with what magnitude of effect. Next, if needed it was tried to identify how does BMI moderated these relations. This was done by probing and plotting. Probing evaluated each regression at different levels of the moderator, to identify how much the regression slopes changed in function of BMI. Finally, plotting was used to visualize how these regressions change in function of BMI (Darlington & Hayes, 2017).

Limitations

As with any cross-sectional epidemiological study, there were limitations of the study. Since the data used in this secondary data analysis is limited to one point in time, causality cannot be inferred. Physical activity was measured via self-report questions that can be influenced by social desirability. Tools and instruments used in the secondary data set do not have psychometric properties available, which is a known weakness with secondary data analysis. Next the use of measured height and weight to calculate BMI is more reliable than self-report of height and weight, due to the influence of social desirability and bias in self reporting, where weight is generally underestimated and height overestimated (Gildner et al., 2015). However, the measure of BMI does not differentiate between location of fat or amount or take into consideration age or gender; however, it can still provide insight into screening for health conditions and population health trends. Utilizing advanced technology to measure adiposity may provide more reliable data for the amount of adipose tissue. Lastly, with a large secondary data set there is missing data, that even when handled appropriately, can be a weakness.

All research conducted using human participants poses the risk of measurement and human error. The HRS researchers increased internal validity through the development of the policies and procedures developed by the researchers, training of researchers and field representatives to assure consistency, quality and assurance checks with external laboratory facilities, and changes were vetted and tested prior to implementation. As a result of these actions, there is strong methodological rigor (HRS, n.d.). With the diverse nationally representative sample as described above, the study has external validity, that allows results to be generalizable to the community dwelling older population.

Chapter 4: Results

This chapter includes the preliminary confirmatory factor analysis model, modifications made to the model, and statistical methods. Following the preliminary analyses, two manuscripts are included in the chapter. The first manuscript addresses aims one and three which determined the relationship between self-report physical activity and inflammation with physical function and moderating effect of BMI in community dwelling older adult population from the Health and Retirement Data set. The second manuscript addresses aim two which examined the relationship between self-report physical activity and inflammation on physical function between genders.

Statistical methods

Wave 13 of the Health and Retirement Core 2016 biennial data was obtained from an SPSS zip file downloaded and then merged with Venous Blood Study data based on household identifying number and person number. The data was cleaned and recoded in SPSS prior to uploading in R for analysis. Prior to addressing Aim 1, a Confirmatory Factor Analysis (CFA)was conducted to test and establish the hypothesized measurement model as described previously and displayed in Figure 3. For the CFA, the lavaan package was utilized for analysis (Rosseel, 2012). In the hypothesized model the outcome factor of physical function consisted of the biophysical indicators of balance (semi-tandem, full-tandem, side-by-side), grip strength, and gait speed. Any participants with missing data on any of the primary outcome biophysical physical function measures was removed. Further in looking at descriptive statistics, the full tandem (n=2042) and side by side (n=192) sequential balance measures did not have enough participants due to the increase in testing complexity and it was determined that only the semi-tandem balance should be included. With this inclusion/exclusion criteria, the result was a sample of n= 2307. The sample consisted of males (n=989) and females (n=1318) with a mean age of 75 years old (*SD* =6.97, range 65-100).

The predictor factor of physical activity with indicators of frequency of participation in mild, moderate, and vigorous physical activity (5 point Likert questions), frequency of walking and sports/exercise (7 point Likert questions) and the predictor factor of inflammation having the indicators of Interleukin- 6 (IL-6) (picograms per milliliter), Interleukin-10 (IL-10) (picograms per milliliter), and high sensitivity c-reactive protein (hsCRP)(milligrams/liter), which are continuous numerical venous blood counts of markers. The results of the hypothesized CFA measurement model did not support the biophysical measures as indicators of the physical function factor. Results as depicted in Table 1 highlight that physical function did not hold together as a factor with all the indicators of physical function having low factor loading estimates, p values >.001, and low correlations between indicators suggesting the items did not define a construct. The only physical function indicators that had correlations was left and right-hand grip strength, despite model fit being acceptable (gamma hat 0.971, SRMR 0.048, CFI 0.724), indicating that physical function was not the factor as hypothesized from the literature.

Table 1

Preliminary Latent Factor Estimates

Latent Variables	Estimate	Std. Error	P	CI Lower	CI Upper	Std. all	R^2
Physical Activity							
Sport	0.365	0.140	0.00	0.338	0.391	0.774	0.600
Walking	0.311	0.013	0.00	0.285	0.336	0.602	0.363
Vigorous	0.192	0.010	0.00	0.172	0.213	0.483	0.233
Moderate	0.152	0.016	0.00	0.121	0.183	0.267	0.071
Mild	0.093	0.016	0.00	0.060	0.125	0.153	0.024
Inflammation							
CRP	0.390	0.082	0.00	0.229	0.551	0.423	0.179
IL-10	0.116	0.037	0.01	0.045	0.188	0.124	0.015
IL-6	0.399	0.084	0.00	0.235	0.563	0.424	0.180
Physical Function							
Mean Gait Speed	0.051	0.052	0.327	-0.051	0.153	0.052	0.003
Mean Grip Strength L	-0.278	0.112	0.013	-0.498	-0.058	-0.292	0.085
Mean Grip Strength R	-0.281	0.115	0.014	-0.506	-0.056	-0.297	0.088
Semi-Tandem	0.007	0.015	0.666	-0.024	0.037	0.026	0.001

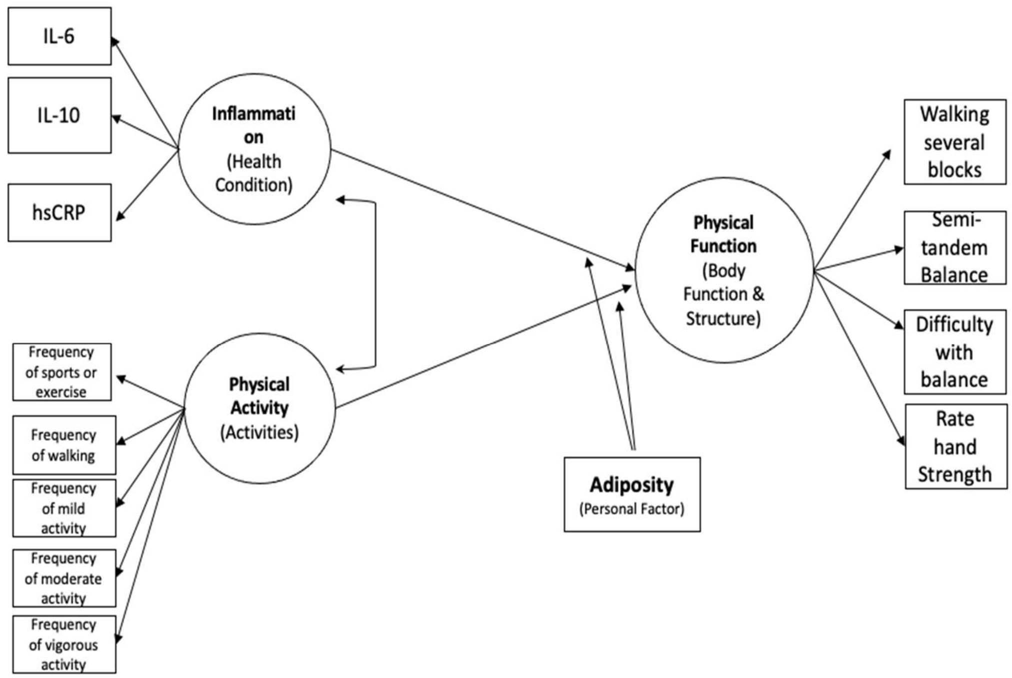
The hypothesized model and data were from a secondary data source thus the physical function construct indicators not holding together could be due to artifact of the sample, how the measures were collected, or which participants in the sample completed these items. The literature related to physical function and available secondary data core items was revisited to identify additional Likert items associated with the components of physical function: walking or endurance, balance, and strength. Within the core biennial survey, subsection functional limitations and helpers, there are Likert self-report items to assess respondent hand strength, balance, and difficulty walking that conceptually aligned with the previous indicators of physical function (HRS, 2016d). The item to represent hand grip strength or strength is: How would you rate your hand strength? With four Likert responses of very strong, somewhat strong, somewhat weak, or very weak. The item that aligns with balance is: How often do you have difficulty with balance? With four Likert responses of often, sometimes, rarely, or never. To address walking or endurance, only binary questions were available with limited responses, thus the question: “Because of a health problem do you have any difficulty with walking several blocks” was included with responses of “yes” or “no” (HRS, 2016d). The model was revised to include these three Likert physical function indicators and the biophysical semi-tandem balance. Each of the individual physical function Likert questions are part of the core biennial survey and thus do not have a total score or individual reliability available.

Revised Model

In the revised model (Figure 4) the outcome factor of physical functions consisted of the indicators: semi-tandem balance (time in seconds), self-report of balance (4-point Likert item), self-report of hand grip strength (4-point Likert item) and self-report of difficulty walking several blocks (binary question). The predictor factor of physical activity with indicators of frequency of participation in mild, moderate, and vigorous physical activity (5 point Likert item), frequency of walking and sports/exercise (7 point Likert item) and the predictor factor of inflammation having the indicators of Interleukin-6 (IL-6) (picograms per milliliter), Interleukin-10 (IL-10) (picograms per milliliter), and high sensitivity c-reactive protein (hsCRP)(milligrams/liter), which are continuous numerical venous blood count of markers.

Figure 4

Revised Hypothesized Structural Equation Model



With the revised model, the sample from the Health and Retirement Data set consisted of the merged core biennial data from 2016 and Venous Blood Study with any participant with missing data for any of the outcome physical function indicators excluded, and any participant less than fifty years of age (n=78) resulting in a final sample of n= 4042.

The subsequent embedded two manuscripts will further describe the statistical analysis and results. The first manuscript will address aims one and three which determined the relationship between self-report physical activity and inflammation with physical function and moderating effect of BMI in the community dwelling older adult population. The second embedded manuscript addresses aim two which examined the relationship between self-report physical activity and inflammation on physical function between genders.

Manuscript 1

Relationship between physical activity, inflammation and physical function in older adults: Results from the Health & Retirement Study

Abstract

Functional decline is part of the process of aging that can be influenced by physical activity in older adults. Aging is also associated with increased levels of pro-inflammatory and decreased levels of anti-inflammatory cytokines that are hypothesized to increase older adults' risk for chronic conditions or "inflammaging". These biomarkers of inflammation are associated with increased adiposity. The purpose of this study was to examine relationships between physical activity, inflammation, and physical function and the potential moderating effect of adiposity (BMI) in community dwelling older adults. This cross-sectional study used core biennial data from Wave 13 of the HRS and Venous Blood Study (VBS) merged. The final sample (n=4042) included individuals who participated in the VBS and had complete data for the outcome of physical function. Structural equation modeling was used to establish the model and test the relationships between the factors. The results show that physical activity positively impacts physical function ($p < .001$) while inflammation negatively influences physical function ($p < .001$), and adiposity was not a predictor in the model ($p=0.055$). Results highlight the importance of physical activity for older adults to maintain physical function and decrease chronic inflammation.

Keywords: older adults, physical function, exercise, body mass index, inflammation

Physical function naturally declines during aging due to biological changes in body composition, decreasing physical performance and cognitive decline (Seals et al., 2016). For community dwelling older adults, physical function levels can affect their ability to care for themselves and live independently. With the drastic demographic shift, or “grey tsunami”, the older adult population has increased from 52 million in 2018 to 72 million in 2020, with further increases anticipated until 2030 (U.S. Census Bureau, 2019). Furthermore, older adults prefer to remain in their homes and communities, even when that requires living alone, underscoring the importance of maintaining physical function and independence (AARP, 2018).

Age related changes in physical function have shown a bi-directional relationship with participation in physical activity. Declines in physical function are associated with decreased physical activity and interventions have shown that improvement in physical function increases physical activity engagement (Metti et al., 2018). However, for older adults, participation in moderate to vigorous physical activity decreases with age and correspondingly, sedentary time increases as a result of change in health status, employment changes and retirement (Jones et al., 2018). For older adults, even those with chronic conditions, the current physical activity guidelines recommend 150 minutes of multicomponent physical activity per week. (U.S. Department of Health and Human Services, 2019). Participation in physical activity, including low intensity physical activity, has shown to improve health, increase life expectancy, improve quality of life and reduce all-cause mortality for older adults (American College of Sports et al., 2009; Hupin et al., 2015). Evidence suggests participation in physical activity can also decrease chronic low-level inflammation that poses an increased risk for chronic conditions (Howard et al., 2016).

During the aging process, a shift in body composition occurs where muscle mass and associated strength decrease, which results in significant muscle deterioration and increases in adipose tissue (K. Kim et al., 2016). An increase in fat or adipose tissue is a source of systemic pro-inflammatory cytokines that is associated with higher body mass index (BMI) and obesity (Cooper et al., 2019; Rodriguez-Hernandez et al., 2013). Obesity is related to negative health outcomes, however the strength of the relationship or potential moderating effect has yet to be determined. Chronic low-level inflammation, associated with elevated BMI, is caused by activated macrophages, mast cells and T lymphocytes. Elevated BMI and chronic low-level inflammation lead to insulin resistance, increases in fat mass, and decreases in muscle mass (Batsis & Villareal, 2018). Skeletal muscle mass has been shown to be a marker of physical performance, influenced by muscle size, physiological stimuli, and pathological conditions (Costamagna et al., 2015). Physiologically as muscle ages it is susceptible to wasting due to fat infiltration and damage to muscle fibers causing inefficiency and greater weakness unrelated to the total mass of the muscle (Costamagna et al., 2015). Muscle mass and strength are critical for older adults to maintain physical function and independence (Studenski et al., 2014).

Chronic low-level inflammation increases during the aging process and has been hypothesized to adversely impact physical function and physical activity (Pahwa et al., 2020). Pro-inflammatory cytokines have been shown to decrease with physical activity (Adams et al., 2015; Marques et al., 2013) and increase with sedentary time (Gennuso et al., 2013; Pryzbek et al., 2019). Inflammation negatively effects physical function and activity through catabolic effects on muscle and increased risk for chronic conditions (Sousa et al., 2016). Due to results in mice, it has been hypothesized that in human's chronic low-level inflammation depends on pro-inflammatory cytokine expression and anti-inflammatory reduction which both are associated with weakness and increased muscle loss (Costamagna et al., 2015). Previous research has focused on one inflammatory biomarker at a time with the results of single indicators being mixed. Pro-inflammatory (IL-6, hsCRP) and anti-inflammatory (IL-10) cytokines have been linked to chronic conditions, but further research is needed to determine their role in preventative health (Monastero & Pentyala, 2017).

The relationships between physical activity, inflammation, adiposity and physical function are associated with older adult health outcomes and independence and need further exploration. The framework for this study is the International Classification of Functioning, Disability and Health framework (ICF) (World Health Organization [WHO], 2001). The ICF biopsychosocial model ensures all aspects of function or disability are considered (WHO, 2001). Function or disability is viewed as a bidirectional relationship between the health condition (e.g., inflammation), activity (e.g., physical activity), and environment and/or personal (e.g., gender, adiposity) contextual factors which in turn influences human functioning (physical function). In this study, adiposity or BMI was hypothesized to be a moderator based on literature supporting the concept that BMI can alter the strength or direction of the relationship between physical activity and inflammation with physical function. Therefore, the purpose of this study was to examine the relationships between physical activity, inflammation, and physical function and the potential moderating effect of adiposity (BMI) in community dwelling older adults.

Methods

Design

This study was a cross sectional secondary data analysis using the Health and Retirement Study (HRS) 2016 core biennial data, Wave 13, and the Venous Blood Study, and supplemental data (HRS, 2016, HRS, 2020). The HRS (Health and Retirement Study) is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. The data set is a nationwide longitudinal survey that began in 1992 with individuals 51-61 years old, targeted at understanding aging at the population level for community dwelling, noninstitutionalized older adults. Initial samples were selected using a multi-stage probability design with subsequent steady state sampling used to replenish and add to the core sample every six years with younger cohorts (HRS, 2008). For the core biennial interviews and surveys, the sample was divided in half with data collection for surveys either taking place at the participants' place of residence or over the telephone (Sonnega et al., 2014).

Sample

The sample included participants from the core biennial data (n=35,935), Wave 13 who also participated in the Venous Blood Study (n=9934) (HRS, 2016b; HRS 2016d; HRS, 2020). The VBS was a supplemental voluntary study offered to HRS participants, following the core 2016 biennial data collection for 2016 with data collection dates from February 2016 to September 2017 (HRS, 2016a). In order to be included in this study, participants had to participate in the VBS and be over the age of 50. Participant data was excluded if data was missing for any physical function outcome measures since these were the primary outcomes and aim of this study, resulting in a final sample of n=4042.

Measures

Physical Function

The biophysical measure of semi-tandem balance and three Likert items from the core biennial survey subsection “functional limitations and helpers” that address balance, strength, and difficulty walking were used to assess physical function. Balance was measured via the semi-tandem balance test and a single self-report item. For the semi-tandem balance test, the time (in seconds) the participant successfully held the side of the heel of one foot touching the big toe of the opposite foot was recorded with a maximum time of ten seconds. Participants also indicated how often they had difficulty with balance: often (1), sometimes (2), rarely (3), or never (4). For hand strength, participants rated it as either very strong (4), somewhat strong (3), somewhat weak (2), or very weak (1). To assess difficulty walking, participants responded yes or no to the following question, “Because of a health problem do you have any difficulty with walking several blocks”? (HRS, 2016d).

Physical Activity

Two self-report questions from the Everyday Life and Well-being questionnaire and three questions from the health section in the core biennial survey (HRS, 2016c; HRS, 2016d) were used to measure physical activity. For the Everyday Life and Well-being questionnaire, participants indicated how often they “walk for twenty minutes or more” and “play sports or exercise”, with seven response options ranging from daily (7), several times a week (6), once a week (5), several times a month (4), at least once a month (3), not in the last month (2), and never (1) (HRS, 2016c; HRS, 2016d). Additionally, three questions from the health section of the core biennial survey were used to assess physical activity. Participants responded to how frequently they participated in mild, moderate, and vigorous physical activity with five response options: every day (5), greater than one time per week (4), one time per week (3), one to three times per month (2), hardly ever or never (1) (HRS, 2016d).

Inflammation

Three biomarkers from the Venous Blood Study were used to measure chronic low-level inflammation: high sensitivity c-reactive protein (hsCRP), interleukin-6 (IL-6), and interleukin-10 (IL-10). The hsCRP and IL-6 biomarkers are proinflammatory cytokines that increase with aging and IL-10 is an anti-inflammatory cytokine that decreases with the aging process (Dagdeviren et al., 2017; Singh & Newman, 2011). All biomarkers were from the same serum separator tube assay and analyzed at the University of Minnesota Advanced Research and Diagnostic Laboratory (HRS, 2016b). Blood specimens were collected by a third-party partner, Hooper Holmes Health & Wellness in the participants' home within four days of agreement to participate and it was recommended but not required for participants to fast prior to obtaining blood sample (HRS, 2016b).

The hsCRP was measured in serum using a latex-particle enhanced immunoturbidimetric assay kit and read on the Roche COBAS 6000 Chemistry analyzer (Roche Diagnostics) (HRS, 2016b). It has a reference range of 0.5 to 10 mg/L, with high sensitivity measuring chronic low-level inflammation compared to the regular laboratory value of CRP. Serum IL-6 and IL-10 were measured by a laboratory technique that links enzymes immunosorbent assay (ELISA) on a system called ELLA made by Protein Simple (San Jose, CA). For quality control, the HRS Venous Blood Study analyzed a sample of 102 pairs of cytokines and found reliability between IL-6 (.9810) and IL-10 (.9879) cytokines (Crimmins et al., 2020).

Adiposity

Adiposity was quantified by body mass index calculated from measured height and weight using the formula [weight (pounds) /height (inches)]^2 x 703 (CDC, 2014, HRS, 2016a).

Covariates

Age (years) at time of the interview was included as a continuous variable. Gender was recoded to indicate male (0) and female (1). For chronic conditions, a sum score was created in which participants reported the presence of chronic conditions (yes =1 or no = 0) from a list that included hypertension, diabetes, cancer, lung disease, heart condition, stroke, emotional psychological, depression, Alzheimer's, dementia, arthritis, high cholesterol, osteoporosis, incontinence, sleep disorder, and pain (HRS, 2016d).

The parent HRS study obtained Institutional Review Board approval through the University of Michigan Health and Behavioral Sciences through December 31, 2023 (HRS, 2018). Since participant information was deidentified prior to receiving the data and there was no risk of harm, additional approval was not required.

Data Analysis

The data was downloaded, merged and cleaned in IBM SPSS (Version 26) prior to uploading to R (Version 3.5.1) for analysis. The data was from multiple HRS data files and was merged using the variables of person identifying number and household identifying number as instructed in HRS codebooks (HRS, 2016d). All indicators for each factor had different scales, thus all were standardized to change the location (mean) and scale (standard deviation) of the variables but not change the form of the distribution prior to data analysis. Descriptive statistics showed that all three of the biomarkers were positively skewed, which was consistent with previous literature, thus the biomarkers were log transformed for analysis.

All physical activity and physical function items were treated as independent indicators for their respective factor. Physical activity and physical function Likert items had questions with 4, 5, and 7 response choices. All items were recoded in the opposite direction so low values reflect less physical activity or lower physical function and higher values indicate more frequent participation in physical activity and greater physical function. All Likert items were treated as continuous. Full information maximum likelihood (FIML) was used to handle missing data. A p-value of .001 was set for significance.

Confirmatory Factor Analysis (CFA) was conducted to test and establish the hypothesized measurement model (Figure 1). Utilizing this analytical approach allows multiple indicator variables to be tested together, to confirm their representation of an “unmeasurable” construct and limits measurement error. The fixed variance method of identification was used for the initial measurement CFA. Analyses were run with the lavaan package from R and the MLR estimator and scaled fit measures were utilized to correct for non-normality and robustify the model (Rosseel, 2012).

A confirmatory factor model was fit with the outcome factor of physical function and predictor factors of physical activity and inflammation. Model specification was driven by theory and prior research evidence (Brown, 2015). Figure 1 shows the confirmatory factor measurement model with indicators and results.

Results

The mean age of study participants was 68.38 years (*SD* = 9.64, range = 50-100). The samples self-reported racial/ethnic groups were 14.5% Hispanic, 73.9% White, 17.3% Black/African American, and Other 8.2% and included 57.7% females (n=2332) and 42.3% males (n= 1710). Many participants were obese or overweight with the sample having a mean BMI of 30.04 (*SD* =6.09). Multimorbidity was present in the sample with a mean of 3.85 (*SD* =2.35) chronic conditions reported out of 14. Inflammatory biomarkers were elevated across the sample: hsCRP 4.61 (*SD=10.36*), IL-6 7.19 (*SD= 44.23*), IL-10 4.06 (*SD= 9.54*). Participants on average reported mild or moderate intensity of physical activity participation several times per month. Physical function indicators showed participants self-reported a mean of difficulty with balance sometimes, semi-tandem balance time 9.68 (*SD=1.46*), somewhat weak hand grip strength, and more than half did not have difficulty walking several blocks. Table 1 shows descriptive statistics for each factor indicator item.

Measurement CFA results showed degrees of freedom scaled = 48, chi-square scaled = 371, p<.001 and overall model fit of CFI scaled (0.950), CFI robust (0.954), SRMR (0.026), and gamma Hat scaled (0.9861), root mean square error of approximation (RMSEA) scaled (.041, [CI] = [0.037,0.047]) indicating acceptable overall fit. Figure 1 shows the initial measurement model, unstandardized factor loading estimates, and R^2

values. All of the null hypotheses that the factor loadings are equal to zero would be rejected with all $p<.001$. The standardized factor loadings were greater than 0.2 representing shared variance and commonality between the indicators to form a latent factor. R^2 for physical activity indicators range from 17-48%, inflammation 17-59%, and physical function 9-45%. The correlations between the factors were all significant ($p<.001$) and showed that inflammation was negatively correlated with physical activity (-0.326) and physical function (-0.367), while physical activity and physical function were positively correlated (0.664).

Local model fit shows residual correlations were low with no values above 0.1, indicative of low differences between observed and predicated covariances recommended by Kline (2016). The total maximal reliability for the model was 0.82 with each of the factor maximal reliability measures listed in the Table 2. Based on the factor loadings, overall and local fit estimates and R^2 estimates, the established model was used as the measurement model and for subsequent statistical analyses.

Next, latent regressions between the predictor factors, physical activity and inflammation on physical function was conducted to examine hypothesized relationships. The latent regression results between inflammation and physical function and between physical activity and physical function support rejecting the null hypothesis ($p<.001$) and no further model trimming were needed. In this model, inflammation and physical activity accounted for 47% of the variance in older adults' physical function.

The covariates of age, gender, and number of chronic conditions were added to the model with the full partial method that tested covariate effects from both predictor and outcome variables. The explained variance in physical function increased from 0.47

in the model without covariates to 0.61 with covariates, thus covariates accounted for 14% change in the explained variance in physical function. The covariates of age and chronic conditions were significant ($p<.001$) as displayed in Table 3. However, no mean differences between males and females ($p =.209$) were noted for inflammation and gender, and thus were removed from the model resulting in a better fit model (scaled chi square difference test, $p =0.215$). Results of the model with unstandardized estimate regressions and R^2 for each factor is displayed in Figure 2.

The model with the selected indicators predicts 61% of the explained variance in older adults' physical function. For the predictor factors, the model accounts for 7.4% of explained variance for inflammation and 13% of explained variance for physical activity. The model was overidentified with 77 degrees of freedom. Overall model fit for the final model was CFI scaled (0.871), CFI robust (0.879), SRMR (0.050), and gamma hat scaled (.964) indicating good fit of the model to the data. The chi-square model fit $\chi^2(77) = 1288$; $p <.001$ indicated non-significance with a p value close to zero indicating this data did not follow a chi-square distribution. Large sample sizes, such as in this study, support that chi-square tests for model fit are not reflective of differences that exist between sample and estimated population covariance due to these fit indices being sensitive to larger sample sizes. Finally, a predictive effect of BMI was not found (unstandardized estimate = 0.00, $p=.055$) between physical activity, inflammation and physical function, indicating no need to test a moderating effect.

Discussion

This study investigated the relationships between physical activity, inflammation and physical function for community dwelling older adults and found physical activity positively influences physical function, while inflammation negatively influences physical function. Secondly, study results indicated physical activity and physical function were negatively correlated with inflammation, while BMI was not a predictor or moderator of physical function in this sample. These results align with previous research that investigated the impact physical activity can have on physical function (Chase et al., 2017; Dipietro et al., 2019) and the negative influence of chronic low-level inflammation on physical activity (Sadjapong et al., 2020) and physical function (Sousa et al., 2016; Tay et al., 2019).

In this study, the model included the predictors of physical activity, inflammation and covariates of chronic conditions, age, and gender accounted for 61% of the variance in physical function. These results align with previous research that found grip strength, inflammation and muscle mass to explain 42% of the variance in physical performance for females and 37% for males (Legrand et al., 2013). Suggesting that even though this study with physical activiy, inflammation, and covariates predicted 61% of the variance in physical function, there are additional domains or indicators which could be added to the model and increase the ability to predict variance in physical function.

In this study, balance, strength, and walking endurance were used as measures of physical function which aligns with previous research supporting the multiple dimensions of physical function. The multicomponent measures of function selected in this study align with a literature review by Beaton et al. (2015) that found 195 different pyschometric measures of functional decline in community dwelling elders. Further, this review found the measures were clustered across six health domains: medical status, performance capacity, participation, demographics, anthropometry and relationships with health providers (Beaton et al., 2015). Similarly, a systematic review by Berquist et al. (2019) identified 120 different objective performance measures to assess functional decline and fitness in older adults. The measures used addressed balance, muscle strength, and multi-component performance (Bergquist et al., 2019). In agreement with Berquist et al. (2019) physical function in this study, included multiple variables that addressed balance, strength and walking endurance with each indicator's explained variance highlighting their contribution to its multi-dimensionality with walking endurance having the highest factor loading. The results of this study align with previous work and re-emphasize that physical function is multi-dimensional consisting of balance, strength, and walking endurance.

Physical activity and physical function were negatively correlated with inflammation suggesting the adverse impact cytokines can have on older adults' physical health. These findings are consistent with previous research that chronic low- level inflammation has a negative impact on older adults' physical activity (Adams et al., 2015; Marques et al., 2018; Sadjapong et al., 2020) and ability to maintain physical function (Lassale et al., 2019; Sousa et al., 2016). Inflammatory cytokines through the processes of aging have been shown to decrease immune function and reduce cellular immune response (Moldoveanu et al., 2001). Pro-inflammatory cytokines impede muscle protein metabolism by triggering catabolic pathways and downregulating anabolic pathways (Costamagna et al., 2015). Both mechanisms can result in lower muscle mass which influences an older adult's physical function and activity. Further it has been hypothesized that inflammation contributes to age related muscle depletion through protein breakdown and impaired muscle tissue formation (Costamagna et al., 2015).

Regular physical activity can slow age-related changes in cytokine production which in turn can improve an older adult's physical function (Moldoveanu et al., 2001). Systemic low- level inflammation decreases with regular exercise due to reductions in fat mass and adipose tissue inflammation (Woods et al., 2012). This suggests that older adults who participate in a regular exercise regimen will have less adipose tissue which results in decreased production of pro-inflammatory and increased anti-inflammatory cytokines, resulting in better physical function. Hence, it is imperative for older adults to participate in regular physical activity to reduce systemic low-level inflammation which in turn affects their functional ability as well as risk reduction for chronic conditions. The negative affect inflammatory cytokines have on older adult's physical health indicates a need for preventative health screening of these biomarkers to proactively identify older adults at risk for functional decline and cardiometabolic health.

This study included multiple indicators of inflammation with both pro and anti-inflammatory properties thus providing greater evidence that both biomarkers influence an older adults' ability to physically function. Much of the previous research only utilized one pro-inflammatory cytokine, mainly CRP or IL-6, to assess the relationship between inflammation and physical function (Felicio et al., 2014; Lassale et al., 2019; Sousa et al., 2016). The use of one biomarker may not address individual or biological differences. For example, Custodero et al. (2020) found an inverse correlation between IL-6 and knee extensor strength, but no other objective performance measures of physical function were significantly associated with IL-6 (Custodero et al., 2020). Chronic low-level inflammation is the result of the expression of pro-inflammatory mediators as well as a reduction in anti-inflammatory cytokines, hence both should be investigated for relation to physical function.

This study utilized two pro-inflammatory cytokines, IL-6 and hsCRP, and one anti-inflammatory cytokine, IL-10, and the results highlight the need to include more expansive panels of biomarkers. Another similar study with multiple inflammatory biomarkers found a partial mediating effect of inflammation on multimorbidity and functional limitations, suggesting inflammation has both direct and indirect effects on physical function (Friedman et al., 2015). Friedman et al. (2015) included three pro-inflammatory cytokines (IL-6, CRP, TNF-alpha) in a study examining inflammation in mediating the relationship between multimorbidity and functional limitations and found multimorbidity was positively associated with increased inflammation and functional limitations (Friedman et al., 2015). In this study, results show that the proinflammatory cytokines had higher factor loading estimates than the anti-inflammatory cytokine, suggesting that pro-inflammatory cytokines may be more indicative of physical functional decline than anti-inflammatory cytokines. Previous research indicates that participating in physical activity lowers pro-inflammatory biomarkers (Moldoveanu et al., 2001), but IL-10 and other anti-inflammatory cytokines have not been studied extensively in relation to physical activity or physical function. The results of this study show that IL-10 negatively impacts both physical activity and physical function for both men and women. However, IL-10 had the lowest factor loading estimate compared to the pro-inflammatory cytokines, suggesting anti-inflammatory and pro-inflammatory cytokines should be treated as individual factors due to different biological mechanisms. In this study, both pro-inflammatory and anti-inflammatory cytokines showed an inverse relationship with physical function and physical activity; further research should include both cytokines with larger panels of biomarkers and differentiation between pro and anti-inflammatory cytokines to establish relationships.

Chronic low-level inflammation has also been linked to the development of chronic diseases. Approximately 85% of older adults have at least one chronic condition and 60% report having two chronic conditions (NIA, 2017). Higher levels of inflammation have been associated with increased odds of developing cardiac disease and metabolic disorders (Rodriguez-Hernandez et al., 2013). Pro-inflammatory biomarkers, such as interleukin-6 (IL-6), c-reactive protein (CRP), and anti-inflammatory interleukin-10 (IL-10) measure potential exposure to disease processes, as well as are used to test effectiveness of physical activity interventions (Wirth et al., 2017). Chronic conditions were included in this present model as a covariate due to the negative impact multimorbidtiy can have on physical function (Jindai et al., 2016; Rillamas-Sun et al., 2016; Wei & Mukamal, 2018). Multimorbidity increases older adult mortality rates and can cause functional decline in this population due to side effects of various conditions (Wei et al., 2019). The results of this study support that the covariates of multimorbidity and age negatively influence physical function because when they were added to the model, the explained variance in physical funciton increased by 14%. These results are congruent with previous evidence that multimorbidity can negatively impact physical function (Jindai et al., 2016; Rillamas-Sun et al., 2016; Wei & Mukamal, 2018). The addition of the covariate chronic conditions was significant ($p<.001$) and demonstrates they play a role in aging, physical function, physical activity, and inflammation.

In this study, BMI was not a significant predictor and thus no testing for moderation was indicated. Previous research supports BMI as a predictor of physical function (Chen et al., 2015; Ghachem et al., 2019; Gretebeck et al., 2017; Leigh et al., 2016; Wanigatunga et al., 2016) with greater levels of obesity being more indicative of highter disability risk (Lisko et al., 2015). Tay et al. (2019) found that chronic low-level inflammation is associated with poor physical function and strength in obese older adults and this relationship is strongest with multiple elevated pro-inflammatory cytokines (Tay et al., 2019). BMI has been found to be associated with poor physical performance and mobility limitations but measurement of adipose tissue in the abdomen and thighs may provide additional information (Reinders et al., 2015). BMI was not a significant predictor of physical function in this study which may be due to the sample consisting of overweight and obese participants (mean BMI = 30.04, SD= 6.09). The use of BMI may not be a good marker of obesity in an aging population as it does not have the ability to quantify muscle mass and adipose tissue. Since muscle mass and strength are critical components in maintaining physical function and independence in older adults, this distinction may be necessary (Studenski et al., 2014). Advanced technology and measures of BMI may provide more accurate and representative measures of body composition in the older adult population. Previous research by Bea et al (2018) utilized dual-energy X-ray absorptiometry scans and found that fat mass >5%, but not lean muscle mass, was associated with lower physical function for women (Bea et al., 2018) suggesting that the use of advanced technology may provide more accurate and diagnostic screening data for adiposity. The need for advanced technology measures of BMI is also perpetuated by increases nationwide in sarcopenic obesity (Batsis & Villareal, 2018). This health phenomenon is characterized by age related loss in muscle, function and strength as well obesity which reinforces the need for advanced measures of adiposity and physical activity to maintain muscle mass and prevent decline.

However, there is contradictory research that has shown no association between obesity and physical function (Bell et al., 2017; Ferreira et al., 2013; Skinner et al., 2017). From these contrary results, the theory of the "obesity paradox" has evolved where the obese individual experiences a protective benefit from the excess adipose tissue rather than negative outcomes (Jahangir et al., 2014; Skinner et al., 2017). This "protective benefit" effects both bone and muscle and stems from the need to move a heavier mass compared to individuals with less adipose tissue. In this study, the mean BMI of participants was 30 which is classified as obese (>30) and just slightly over the overweight (25-30) category according to CDC guidelines (CDC, 2017). This suggests that in this sample, the participants may fall into the obesity paradox and have a protective effect from adipose tissue. The results of this study did not show BMI as a predictor but still contribute to the body of literature that obese older adults can positively influence their physical function by participating in physical activity. The obesity paradox has been found in population and clinical observational studies that investigate cardiovascular and metabolic conditions, but the need to examine this paradox related to physical function still exists (Wang & Ren, 2018). Recently, Nicholson et al. (2021) found in a sample of 56% obese older adults that for those with moderate or high fitness levels, there was a protective effect of adiposity on leptin production which is indicative of health indices (Nicholson et al., 2021). Results suggest advanced measures of adiposity may be a more sensitive indicator of health than using BMI (Nicholson et al., 2021). Further research is needed with BMI high risk categories with advanced measures of adiposity to aid in identifying additional factors that influence physical function.

Limitations

While this study has a number of strengths, there are some limitations to consider. Although the data is from a large longitudinal national study, the data for this study was from wave 13, and thus cross sectional, which precludes inferring causality. Additionally, some key outcome variable data was missing and, thus, a small number of cases were eliminated, but all predictors missing data were handled with full information maximum likelihood. Another consideration is that the measures for physical function and physical activity were self-report questions which can be influenced by social desirability. Additionally, Likert scale items were all treated as continuous indicators which assumes equal distance between responses. BMI was calculated with measured height and weight, which does not take into account the biological body composition changes older adults typically experience. Additionally, BMI was used as a continuous variable, versus categories of BMI which does not allow for focus on high-risk groups. Despite the limitations, the findings are generalizable since the study had a large nationally representative sample from a well-established longitudinal secondary data set of community dwelling older adults.

Conclusion

The results of this study support the evidence that physical activity has a positive effect on physical function for older adults, while chronic low-level inflammation negatively influences both physical activity and physical function. These results demonstrate the importance of considering these factors as well as others that may explain additional variance in physical function for community dwelling older adults. Future research should focus on additional factors that contribute to physical function. Specific analyses focused on the higher risk BMI categories of obese and underweight as they relate to inflammation, physical activity and physical function of older adults are areas of opportunity. Further research should also focus on expansive panels of pro and anti-inflammatory markers along with studies of longitudinal design to determine long term effects and change over time.

Table 1

Descriptive statistics for Sample (N=4042)

Variable	n	Mean	SD	Range
Physical Activity				
Play Sport/Exercise (1=never, 2=not in last month, 3=1x/month, 4=several times per month 5= 1x/week, 6=several times/week, 7=daily)	3330	3.73	2.25	1-7
Walk for 20 minutes (1=never, 2=not in last month, 3=1x/month, 4=several times per month 5= 1x/week, 6=several times/week, 7=daily)	3349	4.50	2.16	1-7
Vigorous Activity (1=hardly ever or never, 2= 1-3x/month, 3=once a week, 4=more than once a week, 5= daily)	4022	2.10	1.33	1-5
Moderate Activity 1=hardly ever or never, 2= 1-3x/month, 3=once a week, 4=more than once a week, 5= daily)	4034	3.09	1.27	1-5
Mild Activity 1=hardly ever or never, 2= 1-3x/month, 3=once a week, 4=more than once a week, 5= daily)	4039	3.43	1.02	1-5
Adiposity (BMI)	3901	30.04	6.09	10.49-64.61
Inflammation				
hsCRP (mg/L)	4042	4.62	10.36	0 - 234
IL10(pg/ml)	4042	4.06	9.54	0.33-561
IL-6 (pg/ml)	4042	7.19	44.23	0.67-2605
Physical Function				

Difficulty with Balance (1=often,2=sometimes,3=rarely,4 =never)	4042	2.97	0.94	1-4
Difficulty walking several blocks (0=yes 1=no)	4042	0.72	0.45	0-11-4
Rate hand strength (4=very strong,3=somewhat strong,2=somewhat weak, 1=very weak)	4042	2.92	0.69	
Semi-tandem Balance (seconds)	4037	9.68	1.46	0 -10

Table 2

Reliability Estimates for Initial Measurement Model

Factor	Maximal Reliability	Alpha	Omega	Average Variance Extracted
Physical Activity	0.77	0.74	0.76	0.41
Inflammation	0.70	0.55	0.61	0.38
Physical Function	0.63	0.51	0.53	0.35

Table 3

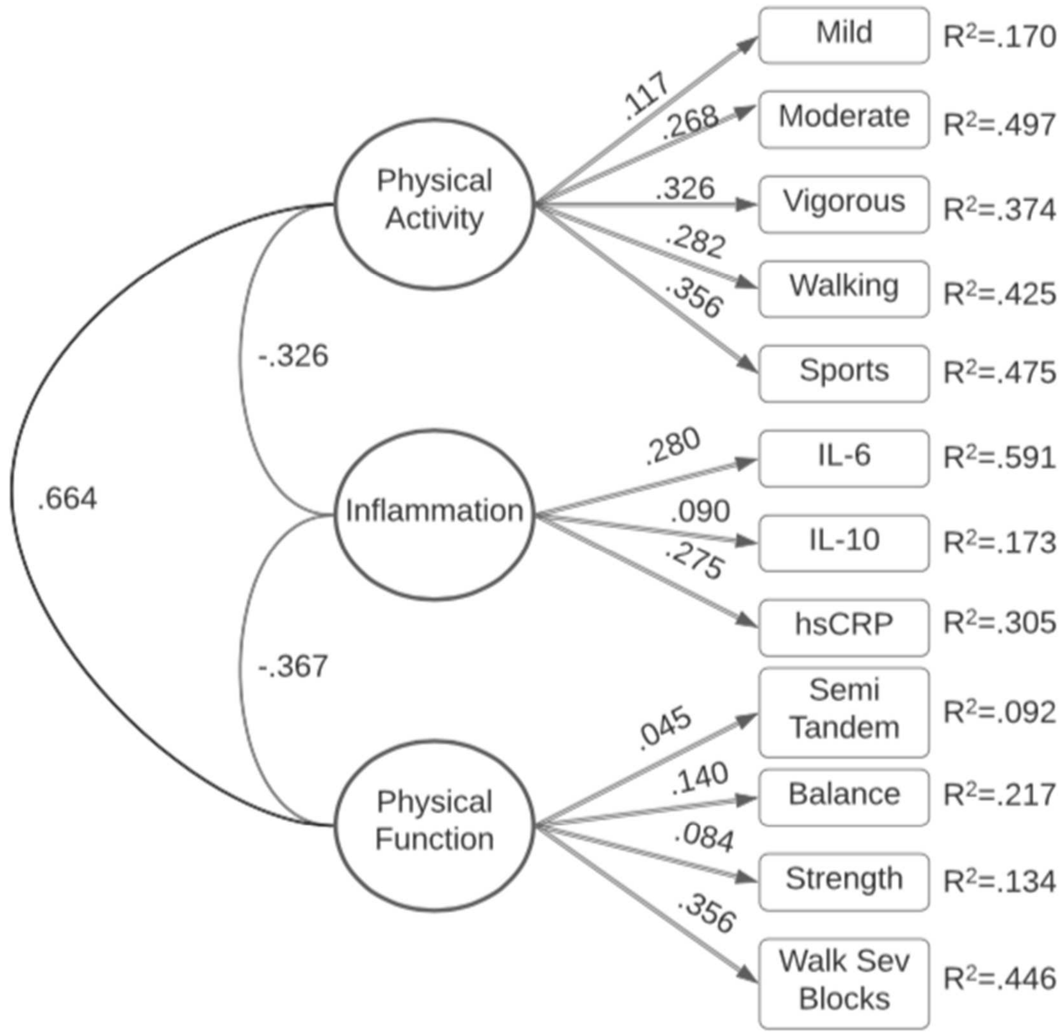
Regressions between Factors and Covariates

Factor & Covariates	Estimate	Std Error	P value	Std all
Physical Activity~				
Gender	-0.148	0.040	<.001	-0.068
Age	-0.013	0.002	<.001	-0.012
Sum Chronic Conditions	-0.143	0.008	<.001	-0.313
Inflammation~				
Gender	0	-	-	-
Age	0.015	0.002	<.001	0.135
Sum Chronic Conditions	0.097	0.010	<.001	0.219
Physical Function~				
Gender	-0.309	0.088	<.001	-0.096
Age	-0.022	0.004	<.001	-0.131
Sum Chronic Conditions	-0.311	0.030	<.001	-0.457

Note. Each factor and regression with the covariate effects is displayed. All results were <.001 excluding the inflammation and gender regression which was trimmed to remove effects from the model as described in results.

Figure 1

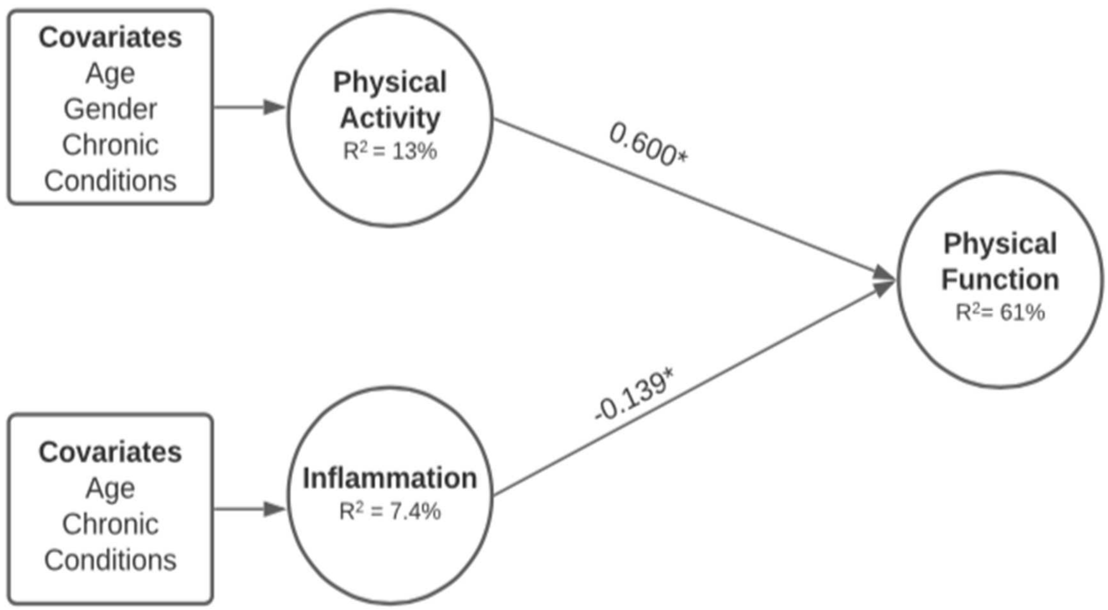
Confirmatory Factor Measurement Model with Correlations, Unstandardized Estimates and R^2 for Indicators



Note. IL-6 = interleukin-6; IL-10 = interleukin-10; hsCRP= high sensitivity c-reactive protein. All modeled correlations between factors and unstandardized factor loading estimates are significant (p<.001) with R^2value next to each indicator.

Figure 2

Latent Regression Model with Covariate Effects



Note. Latent factor regression unstandardized estimate * indicates p<.001. R^2 for each factor's variance in model indicated in circle with factor. Regression estimates for each covariate in Table 2. Inflammation and gender regression which was trimmed to remove effects from the model as described in results.

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Manuscript 2:

Gender differences in the relationship between physical activity, inflammation and physical function in older adults: Results from the Health & Retirement Study

Abstract

Physical function is a key health indicator associated with older adults' ability to maintain independent living. This study examined gender differences in the relationships between physical activity, chronic low-level inflammation, and adiposity with physical function. A cross sectional secondary data analysis of core biennial data from Wave 13 of the Health and Retirement Study (HRS) and the Venous Blood Study (VBS) was conducted. The sample (n=4042, males n=1710, females n=2332) included individuals who participated in the VBS and had complete data for the outcome of physical function. Structural equation modeling established gender specific measurement models with Confirmatory Factor Analysis. Both the female (CFI=0.94, SRMR=0.03, R^2 =0.91) and male (CFI=0.95, SRMR=0.03, R^2 =0.93) models showed acceptable model fit. Results highlight that for both genders, physical function was positively correlated with physical activity, while inflammation was negatively correlated with physical function and physical activity. Male and female regressions were significant ($p<.001$) for all predictors and covariates. Regression estimate differences were not greater than (.018), with the highest difference between genders being inflammation. Results highlight that physical function for men and women is influenced by the indicators representative of physical activity and inflammation.
Keywords: physical function, physical activity, inflammation, older adults, adiposity

Older adults are rapidly increasing in number and it is projected that by 2030, one in five Americans will be 65 years or older (Colby & Ortman, 2014). This increase will place additional pressure on healthcare, thus increasing the need for health care providers and systems to focus on prevention and early identification of risk factors to aid in optimizing their health. For this population, preventive health such as physical activity, screening for biomarkers of inflammation and maintaining independence and physical function are essential.

Participation in physical activity impacts physical function and can prevent declines in aging (Manini & Pahor, 2009). However, participation in physical activity decreases with age and differs between genders (Keadle et al., 2016). Males participate in more exercise that is of greater intensity and frequency(Keadle et al., 2016; Li et al., 2017). While females have increased levels of low intensity physical activity, especially activities in the house and total time spent performing low intensity exercises (Amagasa et al., 2017; Li et al., 2017). Gender differences in physical activity type, frequency and time are evident and influence other factors of health. Studies that have examined gender differences between physical function and body composition have shown that older women often have higher adiposity and decreased muscle strength which results in lower overall physical performance, while men have higher levels of physical activity, lower adiposity, greater muscle strength and more lean mass (Batsis & Villareal, 2018; Landi et al., 2017; Tseng et al., 2014). Additionally, rates of functional decline between genders have also been shown to vary based on country of residence (Bendayan et al., 2017). The trajectory of functional decline is slower in females than males (Botoseneanu et al., 2016). Further, when compared with English counterparts, both genders have faster decline in the United States (Bendayan et al., 2017).

Gender differences in body composition may contribute to level of participation in physical activity and ability to physically function. Aging causes biological changes in body composition, where fat mass increases and muscle mass decreases but this differs by gender. Typically, men have more lean mass and accumulate adipose tissue in the trunk or abdomen and females have more fat mass and adipose tissue around the hips and thighs (Bredella, 2017). Differences may exist due to hormone shifts, such as women experiencing menopause. Aging men experience a decrease in testosterone, which consequently can decrease muscle mass and increase fat (Batsis & Zagaria, 2018).Post-menopausal woman with decreased estrogen and progesterone have an increased risk for weight gain, especially in visceral areas (Batsis & Zagaria, 2018). Further it has been shown worldwide, that women in developed countries have a higher incidence of obesity and elevated BMI compared to male counterparts (Low et al., 2009).

For both genders, obesity is associated with chronic low-level inflammation. Higher BMI or obesity across the lifespan is associated with greater amounts of chronic low-grade inflammation. Physiologically, inflammation is caused by activated macrophages, mast cells and T lymphocytes, that leads to insulin resistance, increases in fat mass and decreases in muscle mass (Batsis & Villareal, 2018). Limited evidence suggests that inflammation impairs muscle homeostasis and the formation of muscular tissue (Costamagna et al., 2015). Physiologically this occurs as a result of inflammatory cytokines inhibiting anabolic and stimulating catabolic pathways (Costamagna et al., 2015). Thus, chronic low-level inflammation can decrease muscle mass and potentially decrease both physical activity and function.

In cross-sectional studies, pro-inflammatory cytokine levels have been found to increase with BMI and decrease with weight loss for multiple biomarkers (Beavers et al., 2015; Clark et al., 2016; Tay et al., 2019). Recent studies suggest gender differences exist with regard to inflammatory cytokines, with females having increased risk for elevation and associated with negative outcomes (Choi et al., 2013; Friedman et al., 2015). However, there is also contradictory evidence that shows no difference in low level inflammation between genders (Legrand et al., 2013; Piber et al., 2019) highlighting the need to further examine gender differences in the relationships between, inflammation and physical function. Therefore, the purpose of this study was to examine gender differences in the relationships between physical activity, inflammation, physical function and adiposity (body mass index) in community dwelling older adults.

Methods

The framework for this study is from by the World Health Organizations International Classification of Functioning, Disability and Health framework (ICF), model of disability or functioning (WHO, 2001). The ICF provides a biopsychosocial model where functioning is considered to be a dynamic state along a continuum influenced by multiple factors (WHO, 2001). In this framework, function or disability, is viewed as the interaction between the health condition, body functions or structures, activity and either environment and or personal contextual factors. In this study physical function as a body function or structure was the primary outcome, with the health condition of inflammation interacting with the activity concept of physical activity and personal factors of gender and adiposity.

Design

This study was a cross sectional secondary data analysis of the Health and Retirement Study (HRS) 2016 core biennial data (n=35,935) Wave 13, and the Venous Blood Study (VBS) and supplemental file (n=9934) (HRS, 2016; HRS, 2020). The HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. The HRS is a national longitudinal study aimed at understanding aging at the population level for community dwelling, noninstitutionalized older adults. The study utilizes multi-stage probability design with steady state sampling every six years to add younger cohorts to the core sample (HRS, 2008). Core biennial interviews and surveys were mixed modes with the sample divided and data collection taking place at the participants' place of residence or over the telephone (Sonnega et al., 2014).

Sample

The sample included core biennial data from Wave 13, merged with the VBS. Participants were offered an incentive of fifty dollars to complete the VBS following completion of the 2016 core biennial survey, with data collection field dates from February 2016 to September 2017 (HRS, 2016a). Participants with missing data for gender designation or any of the physical function Likert item outcome measures or gender designation were excluded since these were the aim of the study and primary outcomes, resulting in a final sample of n=4042.

Measures

Physical Function

Physical function was measured by semi-tandem balance and three self-report items that address strength, balance, and walking from the core biennial survey subsection “functional limitations and helpers”. In the semi-tandem balance test, participants stand with the side of the heel of one foot touching the big toe of the opposite foot, with either foot being in front, and the time in seconds (0-10), the participant successfully holds the position is recorded. Grip strength was assessed with the question: “How would you rate your hand strength?” The four response options were: “very strong”, “somewhat strong”, “somewhat weak”, or “very weak”. Participants rated their level of difficulty (often, sometimes, rarely, or never) in balance with the question: “How often do you have difficulty with balance?” For walking or endurance, the question: “Because of a health problem do you have any difficulty with walking several blocks?” was included with response options of “yes” or “no” (HRS, 2016d).

Physical Activity

Physical activity was measured with five self-report questions (HRS, 2016c, HRS, 2016d). Two individual questions were from the Everyday Life and Well-being questionnaire that include how often participants “walk for twenty minutes or more” and “play sports or exercise”, with seven response options ranging from “daily”, “several times a week”, “once a week”, “several times a month”, “at least once a month”, “not in the last month”, and “never” (HRS, 2016c, HRS, 2016d). In addition, three questions from the health section in the core biennial survey were used and asked participants how frequently they participate in mild, moderate, and vigorous physical activity with five response options of: “every day”, “greater than one time per week”, “one time per week”, “one to three times per month”, “hardly ever or never” (HRS, 2016d).

Inflammation

From the cross-sectional VBS, three biomarkers of inflammation: high sensitivity c-reactive protein (hsCRP), interleukin-6 (IL-6), and interleukin-10 (IL-10), were utilized. Two of the biomarkers, hsCRP and IL-6, are proinflammatory cytokines that theoretically increase with aging and IL-10 is an anti-inflammatory cytokine that decreases with the aging process (Dagdeviren et al., 2017; Singh & Newman, 2011). Biomarkers were from the same serum separator tube assay and analyzed at the University of Minnesota Advanced Research and Diagnostic Laboratory (Health and Retirement Study, 2016b). Hooper Holmes Health & Wellness was a third-party partner who collected blood specimens in the participants home within four days of agreement of participation. It was recommended for participants to fast, but not a requirement (HRS, 2016b).

HsCRP had a reference range of 0.5 to 10 mg/L, with high sensitivity measuring chronic low-level inflammation. It was measured in serum using a latex-particle enhanced immunoturbidimetric assay kit and read on the Roche COBAS 6000 Chemistry analyzer (Roche Diagnostics) (HRS, 2016b). Serum IL-6 and IL-10 were measured by immunosorbent assays (ELISA) on a system called ELLA made by Protein Simple (San Jose, CA). For quality control, the HRS Venous Blood Study did a quality control analysis of 102 pairs of cytokines and found reliability between IL-6 (.9810) and IL-10 (.9879) cytokines (Crimmins et al., 2020).

Adiposity

Body mass index (BMI) was used as a measure of adiposity. An interviewer visited each participant's home or place of residence and measured height and weight with established procedures (HRS, 2016a). BMI was calculated from height and weight using the formula [weight (pounds) /height (inches)]^2 x 703, for eligible participants (CDC, 2014).

Covariates

The covariates of age, gender and sum count of chronic conditions were included. Participants age was measured in number of years old at time of interview. Gender was coded to indicate male (0) and female (1). The participant self-reported presence of chronic conditions as yes (1) or no (0) and a count of conditions was created. The chronic conditions included were hypertension, diabetes, cancer, lung disease, heart condition, stroke, emotional psychological, depression, Alzheimer's, dementia, arthritis, high cholesterol, osteoporosis, incontinence, sleep disorder, and pain (HRS, 2016d).

The HRS study obtained Institutional Review Board approval through the University of Michigan Health and Behavioral Sciences through December 31, 2023 (HRS, 2018). Participant information was deidentified thus there was no risk of harm and an additional review was not necessary.

Statistical Analysis

Secondary data was obtained through a registered user account and sensitive data health request. The data was merged from multiple HRS files using the variables of person identifying number and household identifying number as instructed in HRS codebooks (HRS, 2016d). The data was downloaded, merged and cleaned in IBM SPSS (Version 26). Subsequent analysis was conducted in SAS (Version 9.4) and STATA

(Version 16). Indicators were standardized prior to data analysis, to change the location (mean) and scale (standard deviation) of the variables but the form of the distribution was not changed. Likert items were analyzed independently and treated as continuous variables. All response options were recoded to have all lower number responses represent lower physical activity or poorer physical function and higher responses indicate more frequent participation in physical activity and greater physical function. All the biomarkers were positively skewed, which was consistent with previous literature, thus the biomarkers were log transformed prior to analysis. Full information maximum likelihood (FIML) was used to handle missing data due to less restrictive assumptions about patterns of missing information, reduction of bias, and the ability to retain larger samples. An alpha of .001 was used in this study to indicate significance.

Results

The sample consisted of females (n=2332, 57.7%) and males (n= 1710, 42.3%) with a mean age of 68.38 years old (*SD* = 9.64, range = 50-100). Participant's self-reported racial/ethnic groups were 14.5% Hispanic, 73.9% White, 17.3% Black/African American, and Other 8.2%. The sample had a mean of 3.85 (*SD* =2.35) chronic conditions reported out of 14, indicating presence of multimorbidity. The means of inflammatory biomarkers were: hsCRP 4.61 (*SD=10.36*), IL-6 7.19 (*SD= 44.23*), IL-10 4.06 (*SD= 9.54*), showing elevated levels of chronic low-level inflammation. On average participants reported mild or moderate intensity physical activity participation several times per month. Participants self-reported a mean of difficulty with balance sometimes, a semi-tandem balance mean time of 9.68 seconds (*SD=1.46*), somewhat weak hand grip strength, and more than half did not have difficulty walking several blocks. Table 1 displays descriptive statistics for each indicator by gender.

Independent sample t-tests were conducted between genders for all of the indicators (see Table 1). Unequal variance was assumed as a result of Levene's test for the indicators of BMI, vigorous, moderate, mild, difficulty with balance, hand strength, difficulty walking several blocks, and semi-tandem balance. The independent sample t-test results indicated that group means were statistically different ($p<.001$) between males and females for all indicators with the exception of walk for twenty minutes, sports/exercise, semi-tandem balance, BMI and all inflammatory markers (hsCRP, IL-6, IL-10).

A total sample confirmatory factor model was previously established with the same factors and indicators (Citation of manuscript 1). A confirmatory factor analysis was conducted for each gender followed by separate regression analyses for males and females. Figure 1 shows the female Confirmatory Factor Analysis measurement model. In this model, all factor loadings and correlations were significant ($p<.001$) and R^2 for physical activity indicators ranged from 18-49%, inflammation 3-63%, and physical function 7-49%. Correlations between factors showed inflammation was negatively correlated with physical activity (-0.320) and physical function (-0.140), while physical activity was positively correlated with physical function (.585). Figure 2 shows the male Confirmatory Factor Analysis measurement mode. For males, all factor loadings and correlations were significant ($p<.001$) with R^2 for physical activity indicators ranging from 13-50%, inflammation 3-57%, and physical function 10-46%. The negative correlations between the factor of inflammation and physical activity (-0.365) and physical function (-0.154) were higher for males than females. While the positive correlation between physical activity and physical function (0.522) was lower in males than females.

Model fit measures for the gender specific models and the total sample model are in presented in Table 2. Each model had a non-significant chi-square with a p value near to zero indicating this data did not follow a chi-square distribution which is common in large data sets. Across the fit measures, all models had acceptable fit with the total model sample having the highest (CFI 0.95, R^2 0.93) and lowest (SRMR 0.03, RMSEA 0.04 [0.04, 0.05]) fit measures when compared with the gender specific models.

Gender specific regressions between the factors of physical activity and inflammation on physical function with the covariates of BMI and sum of chronic conditions was conducted. Results are in Table 3. For both males and females, the regressions between all factors were $p<.001$. Each of the factor loading estimates showed no greater difference than .018 between genders with the largest estimate difference for inflammation. The regression estimates show that for each one unit increase in physical activity, an older adult's physical function increases by 0.541 units for males and 0.554 units for females. For each one unit increase in inflammation, an older adult's physical function decreases by 0.142 for males and .162 units for females. In these models, inflammation and physical activity account for 62% of the variance in older males' adults' physical function and 64% for females. Table 3 highlights the additional regression results.

Discussion

This study compared gender differences in the relationship between physical function, physical activity, inflammation and adiposity. By utilizing structural equation modeling, this study used multiple indicators for each factor to determine the presence of relationships. Results from independent sample t-tests showed no mean difference between genders for the indicators of walk for twenty minutes, sports/exercise, semi-tandem balance, BMI and all inflammatory markers (hsCRP, IL-6, IL-10). Model fit results support using an overall sample model versus gender specific models. Overall, the confirmatory factor analysis models by gender showed small differences in correlations between physical activity, inflammation and physical function. With males having higher correlations between inflammation and physical function and physical activity. While for females the correlation was higher between physical function and physical activity. Each of the models had significant factor loadings for all of the indicators and acceptable fit measures, with the total sample model having the best fit. The covariates of BMI and chronic conditions showed small changes in the variance of physical function.

In a study that used similar methods and indicators by Freidman et al. (2015) found contradictory results with females having higher levels of inflammation compared to men, with increased age and being non-white as additional increased risk factors. However, Freidman et al (2015) utilized three pro-inflammatory cytokines (IL-6, CRP, and fibrinogen) while this study used two pro-inflammatory (IL-6, hsCRP) and one anti-inflammatory (IL-10). A notable difference with this study is the use of high sensitivity CRP, was used in this study which is more sensitive and indicative of chronic low-level inflammation, while Friedman et al. (2015) used CRP. The differing results bring into question whether additional pro-inflammatory markers or a panel with more indicators of pro-inflammatory markers would provide greater insights.

In this study the pro and anti-inflammatory cytokines had enough shared variance to hold the indicators together as a factor of inflammation, indicating both biomarkers play a role in chronic low-level inflammation. There has been limited research conducted that includes both pro and inflammatory cytokines and physical function. One study, by Rong et al. (2018) examined the relationship between sarcopenia and the inflammatory markers of IL-6, IL-10 and the IL-6/IL-10 ratio for older adults. Results showed that sarcopenia was higher in older individuals and those with higher visceral fat as well as elevated IL-6, IL-10, and IL-6/IL-10 ratio levels (Rong et al., 2018). This study contributes to the literature by using both pro and anti-inflammatory cytokines highlighting their negative influence on physical function and physical activity for both genders.

The t-test results by gender showed mean differences for physical function and physical activity, but no mean differences among inflammatory markers. Bea et al. (2018) suggested that declines in physical function objective measures was a result of body composition differences, hormonal shifts and post-menopausal symptoms in women. It was also suggested that adiposity and lean mass should also be considered in the prediction of physical function among postmenopausal women over time (Bea et al., 2018). Other research and literature support that older adults' body composition and hormonal gender differences contribute to physical function (Batsis & Villareal, 2018; Brady et al., 2014; Landi et al., 2017; Tseng et al., 2014). The absence of difference in inflammatory markers between genders agrees with previous work that showed the hormonal milieu of both females and males changes (Gubbels Bupp et al., 2018). Thus, research suggests that genders are more physiologically similar with advanced age due to declines in estrogens and progesterone in females and testosterone in males.

The factor loading showed small estimate differences between males and females and all regressions were significant for both genders ($p<.001$). In the model the addition of BMI showed a 1% increase for males and 2.5% increase for females for the variance in physical function. The large sample size may have influenced the results of the regressions. The mean BMI for the sample was 29 for males and 30 for females, which falls in the overweight (25-30) and obese (30-35) categories, but on the lower threshold of classification for obesity (CDC, 2014). With the sample mainly being classified as overweight, the potential negative impacts of obesity or underweight BMI's with physical function was not apparent. Further the differences between males and females, especially with BMI, may not have been as evident in this sample.

In this study, self-reported chronic conditions were reported as an average of 3.5 for males and 4.0 for females. The total model r-squared increased by 4% for males and 3% for females with the addition of the covariate of chronic conditions. The factor loading estimates of chronic conditions for both genders were negative, consistent with the literature that increases in number of chronic conditions, negatively influences physical function(Rillamas-Sun et al., 2016; Wei & Mukamal, 2018; Yorke et al., 2017). In addition, women generally have higher numbers of chronic conditions that influence their physical health. These results are in agreement with a study by Jindai et al. (2016), that utilized another secondary data source, NHANES, and found the association between physical function and multimorbidity was stronger for women than in men with each additional diagnosed chronic illness increasing their functional limitations (Jindai et al., 2016). The physiological mechanisms of chronic conditions may influence physical activity, physical function, and inflammatory cytokines differently.

The results of this study highlight that individual indicators can have gender differences, while the model comparison results support using the total sample model versus individual gender models. Gender differences in physical activity and physical function are present in the literature, however more work needs to be done to determine causes and what influences the role gender plays in these relationships.

Limitations

Despite this study being from a large national data set with objective measures of biomarkers, there are limitations to consider. The study was a cross-sectional design which precludes interpretation to include any causality. Within the model, indicators of physical function and physical activity were self-report which can be influenced by social desirability especially for items regarding personal characteristics such as physical activity and health practices. Further the self-report items were treated as continuous variables, assuming equal distances between responses. Another consideration is that the gender comparison of model and regression results were not statistically compared. Rather regressions, overall model fit, and estimates measures between genders were compared, and the samples did not have equal sample sizes. The semi-tandem balance test had a time limit of 10 seconds with the mean times (males=9.76, females=9.62) near the upper end suggesting possible ceiling effects. This study was limited by inflammatory markers available from a secondary data source, further longitudinal work needs to be done with more biomarkers. Lastly adiposity was quantified by BMI, calculated by measured height and weight. The use of height and weight to calculate BMI does not discriminate, especially in an aging population, between muscle mass and adipose tissue. Advanced technology would provide greater information about body composition breakdown.

Conclusion

The results of this study support that even though individual indicators of physical function and physical activity had mean differences between genders, the overall model with the total sample model had better fit. The results by gender contribute to the evidence and reinforce that for both males and females' physical activity is positively correlated with physical function while inflammation is negatively correlated with both physical function and physical activity. Chronic low-level inflammation negatively influences an older adults' physical function and participation in physical activity. Preventive health that focuses on physical activity interventions for maintenance of physical function is key for older adults to maintain independence. Inflammatory markers did not have mean differences between genders, but there is a need for further work with both pro and anti-inflammatory cytokines and the role they play in physical function, disease progression and physical activity over time.

BMI did not add variance to the model, but it showed mean differences for males and females suggesting further work should investigate this indicator with advanced technology such as dual energy x-ray absorptiometry. The subtle changes in estimates and r-squared values prompts further research to be conducted with BMI that is categorical that focuses on the higher risk categories of obese and underweight. Future research should focus on gender differences longitudinally with multiple time points to provide more insight into changes. Lastly, the addition of the covariate of chronic conditions negatively influenced physical function for both genders, highlighting the importance of prevention and management of chronic conditions for all older adults.

Table 1

Descriptive Statistics of Indicators and Independent Sample T-tests Comparing Genders

Indicators	Gender	n	Mean (SD)	Std. Error Mean	T-test significance (2-tailed)
Physical Activity					
Sports/Exercise	M	1379	3.87 (2.25)	0.06	0.003
	F	1951	3.63 (2.25)	0.05	
Walk for 20	M	1394	4.58 (2.14)	0.06	0.069
	F	1955	4.45 (2.16)	0.05	
Vigorous Activity	M	1706	2.34 (1.36)	0.03	<.001*
	F	2316	1.93 (1.28)	0.03	
Moderate Activity	M	1707	3.21 (1.22)	0.03	<.001*
	F	2327	3.01 (1.30)	0.03	
Mild Activity	M	1708	3.24 (1.08)	0.03	<.001*
	F	2331	3.57 (0.94)	0.02	
Inflammation					
hsCRP (mg/L)	M	1710	4.44 (11.74)	0.28	0.344
	F	2332	4.75 (9.21)	0.19	
IL-10	M	1710	3.95 (2.22)	0.05	0.506
	F	2332	4.15 (12.41)	0.26	
IL-6	M	1710	6.77 (19.24)	0.47	0.602
	F	2332	2.81 (0.72)	0.02	
Physical Function					
Difficulty with balance	M	1710	3.03 (0.92)	0.02	<.001*
	F	2332	2.91 (0.95)	0.02	
Rate hand strength	M	1710	3.07 (0.62)	0.02	<.001*
	F	2332	2.81 (0.72)	0.02	
Difficulty walking several blocks	M	1710	0.76 (0.43)	0.01	<.001*
	F	2332	0.68 (0.47)	0.01	
Semi-Tandem	M	1707	9.76 (1.24)	0.03	0.003
	F	2330	9.62 (1.61)	0.03	
BMI (Adiposity)	M	1649	29.82 (5.08)	0.13	0.038
	F	2252	30.21 (6.73)	0.14	
Sum Chronic Conditions	M	1710	3.64 (2.30)	0.06	<.001*
	F	2332	4.00 (2.37)	0.05	

Note. M = males and F = females. T-test significance with * indicate p<.001 and mean differences between genders for those indicators.

Table 2

Comparison of Model by Gender and Total Sample

Model	CFI	SRMR	R^2	RMSEA		χ^2		
				Value	90% CI, (LL, UL)	Value	df	p
Male	0.95	0.03	0.91	0.04	(0.03, 0.04)	180.07	51	<.0001
Female	0.94	0.03	0.93	0.05	(0.04, 0.05)	316.53	51	<.0001
Total Sample	0.95	0.03	0.93	0.04	(0.04,0.05)	436.36	51	<.0001

Note. Structural equation modeling was used for the analysis. CFI= comparative fit index; SRMR = standardized root mean square residual; RMSEA= root mean square error of approximation; CI= confidence interval; LL=lower limit; UL=upper limit.

Table 3

Summary of Gender Regression with Physical Function

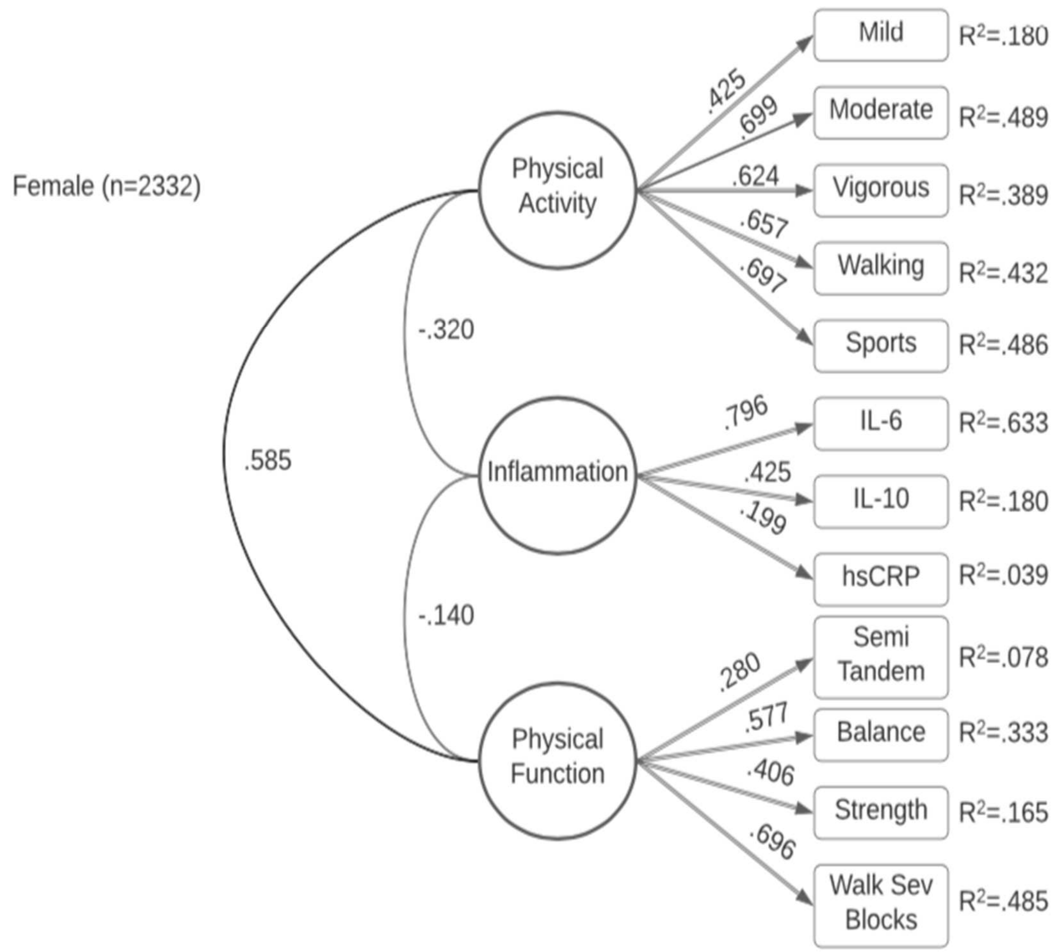
	Male (n=1710)					Female (n=2332)				
Factors	Estimate	Standard Error	P	Partial R square	Model R square	Estimate	Standard Error	P	Partial R square	Model R square
Physical Activity	0.541	0.018	<.001	0.545	0.545	0.554	0.016	<.001	0.555	0.555
Inflammation	-0.143	0.018	<.001	0.022	0.567	-0.161	0.015	<.001	0.026	0.580
BMI	0.012	0.001	<.001	0.007	0.574	0.007	0.001	<.001	0.025	0.606
Chronic conditions	-0.079	0.006	<.001	0.045	0.619	-0.090	0.006	<.001	0.029	0.635

Note. All regressions between physical function and factors and covariates were significant at $p<.001$

Figures

Figure 1

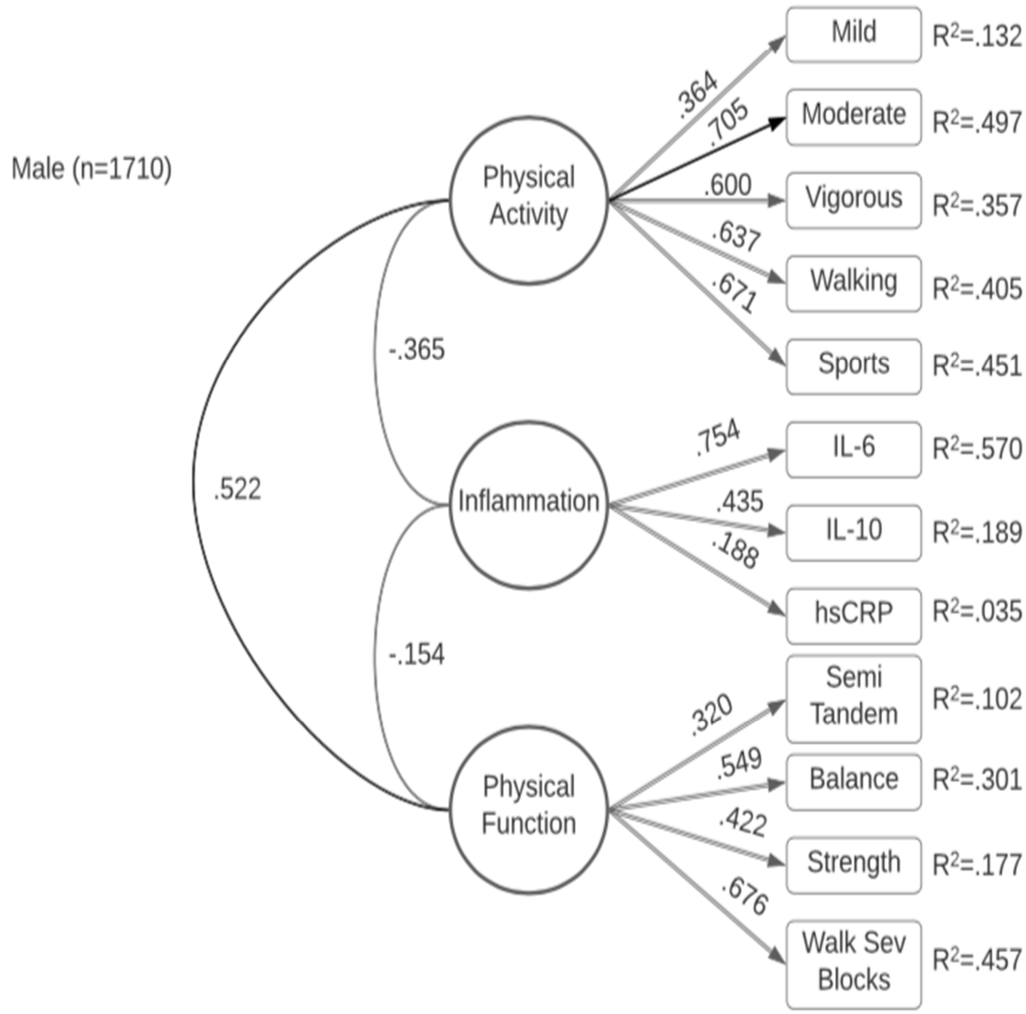
Female Confirmatory Factor Measurement Model with Correlations, Estimates and R^2 for Indicators



Note. IL-6 = interleukin-6; IL-10 = interleukin-10; hsCRP= high sensitivity c-reactive protein. All modeled correlations between factors and unstandardized factor loading estimates are significant ($p<.001$) with R^2value next to each indicator.

Figure 2

Male Confirmatory Factor Measurement Model with Correlations, Estimates and R^2 for Indicators



Note. IL-6 = interleukin-6; IL-10 = interleukin-10; hsCRP= high sensitivity c-reactive protein. All modeled correlations between factors and unstandardized factor loading estimates are significant ($p<.001$) with R^2value next to each indicator.

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Conclusion

In conclusion, the HRS sample and indicator items supported the proposed confirmatory factor analysis model with the factors of physical function, physical activity, inflammation, and adiposity. The results of the first manuscript underscore the role physical activity and inflammation have on physical function, with no predictive or moderating effect of BMI. The second manuscript indicates that the total sample model should be used over gender specific models, despite independent mean differences in indicator variables between genders. Additional discussion, summary of findings, and recommendations for future research will be discussed in the following chapter.

Chapter 5: Conclusions, Discussion & Future Considerations

Physical function is a critical factor in an older adult's overall health and ability to maintain living independently. The ability to maintain physical function throughout the process of aging can be enhanced by participation in physical activity. The older adult population is also at risk for development of chronic low-level inflammation due to biological changes in the aging process. The aging process and increases in adiposity that biologically occur with age can increase chronic low-level inflammation. This low-level inflammation can affect the ability to physically function and participate in physical activity, as well as increasing the risk for chronic health conditions. Males and females differ in survival statistics and chromosomes. The female gender with two X chromosomes has been hypothesized to have an immunological advantage over males with an X and Y chromosome (Libert et al., 2010).

This study examined the relationships between physical activity, inflammation, and adiposity with physical function for community dwelling older adults. Further it also explored whether there were gender differences present in these factors. This chapter will discuss summary of the study's findings, conclusions organized by aim, discussion, implications for future research, and end with a conclusion.

Summary of Findings

The purpose of this cross-sectional study was to examine the relationships between physical activity, inflammation, and potential moderating effect of adiposity, with physical function in an older adult population and compare relationships between genders. Structural equation modeling was used to quantify the unmeasurable factors with multiple indicators and limit measurement error. The first step in establishing the measurement model was a confirmatory factor analysis that resulted in the outcome factor of physical function not holding together with the biophysical measures of gait speed, grip strength, and balance. As a result, these indicators were removed, excluding semi-tandem balance and Likert items addressing the same theoretical physical function constructs (walking endurance, grip strength, and balance) were added to the model. The measurement model was established with good overall and local model fit.

After establishment of the measurement model the covariates of age, chronic conditions and gender were added to the model. The covariate of gender with the factor of inflammation was not significant and was removed from the model resulting in a better fit model. Regressions between the factors resulted with physical activity positively influencing physical function and inflammatory markers negatively impacting physical function. Correlations between factors showed negative correlations between physical activity and physical function with inflammation. The addition of adiposity as measured by BMI as a predictor and a potential moderator resulted with an insignificant interaction and therefore further analyses with moderation was not necessary. The overall model was split by gender and indicator estimates as well as overall model fit were compared. Factor loading estimates between genders were similar with inflammation and chronic conditions both having negative factor loadings, meaning that they negatively impact the outcome of physical function. Total model fit was compared with gender specific model fit and the results supported utilizing the total sample model.

Conclusions

The first aim of the study was to determine the relationship between self-report physical activity and inflammation with physical function in community dwelling older adult population from the Health and Retirement Data set. The results support the hypotheses that walking, sports or exercise, and all levels of physical activity (mild, moderate, vigorous) positively impact and improve physical function. Second that higher levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines had a negative effect on both physical function and physical activity. The third aim was to examine how the relationship between the factors of physical activity and inflammation on physical function is moderated by BMI. The hypothesis that BMI would moderate this relationship was not supported by the results and rejected. In this sample, BMI did not prove to be a significant predictor and therefore moderation was not present. The second aim was to examine the relationship between self-report physical activity and inflammation on physical function between genders in a community dwelling older adult population. Model comparison between total sample and gender specific models supported use of the total sample, despite mean differences in individual indicators from independent sample t-tests.

Discussion

Discussion related to the results of aims one and three are included in the first manuscript and those pertinent to aim two are in the second manuscript in Chapter 4. Additional discussion beyond the manuscripts is addressed here. The results of this study support previous research that physical activity positively impacts physical function for older adults (Edholm et al., 2019; Gretebeck et al., 2019; Shahtahmassebi et al., 2019; Sousa et al., 2014). The indicator variables of the factor of physical activity resulted in unstandardized factor loadings for sports (.356), vigorous activity (.326), and walking (.282) with moderate (.268) and mild (.117) having lower values. Findings of this study suggest the highest ranking of the factor loading estimates indicates greater intensity of activity better fit with the construct, which is consistent with the literature and recommendation for 150 minutes of moderate to vigorous physical activity per week (U.S. Department of Health & Human Services, 2018). Lower intensities of physical activity have proven to still be beneficial (Noradechanunt et al., 2017) with the relationship between physical activity and physical function dependent on the dose (Dipietro et al., 2019). This suggests that for the community dwelling aging population aerobic, muscle-strengthening, and multicomponent physical activity with greater intensity and duration had the greatest improvements in physical function.

Secondly, the ICF framework was tested with the application of the concepts of health condition (inflammation), body functions and structures (physical function), activities (physical activity), and personal factors (adiposity, gender). The application of these concepts to the framework and within a confirmatory factor analysis measurement model were well supported with the data from the HRS data set. This model did not include the concepts of participation and environmental factors which could be added in the future. Painter and Marcus (2013) successfully applied the framework to evaluate the factors of physical function and physical activity for the chronic kidney disease population (Painter & Marcus, 2013). A systematic review and meta-analysis, by Hoski et al. (2021) applied the participation concept from ICF framework to determine the effectiveness of lifestyle interventions (Hoski et al., 2021). The review showed low effects of behavioral or lifestyle interventions on the participation in later life, with the evidence being of low quality.

A second article used the framework in a literature review to identify early indicators of functional decline in community dwelling older adults. In the review, Beaton et al. (2015), found 195 measurement tools representing 107 constructs that align under the ICF framework. Despite the measurement tools and constructs not necessarily being defined and used consistently across the articles in the review, the synthesized results highlight how functional decline can be applied in ICF framework and the community setting (Beaton et al., 2015). Previous use of this framework within the nursing literature has been limited, but this study contributes to the evidence which supports its use within the profession of nursing and other healthcare disciplines.

Lastly, the gender comparison in this study did not statistically compare the models but evaluated overall fit and individual indicators. Previous research has been mixed whether there are gender differences in physical function, physical activity, and inflammation. The proposed hypotheses suggested that females would have lower physical activity and physical function with higher inflammatory cytokines levels and higher adiposity. This study showed significant regressions results between all the factors in the model for both genders but supported using the total sample model rather than the gender specific models. However independent sample t-tests did show mean gender differences with the indicators of physical function and physical activity, but not inflammatory cytokines or BMI. The mean differences between genders are congruent with the literature that males and females differ in physical function levels which is influenced by types of physical activity (Gallagher et al., 2014; Landi et al., 2017). No mean differences in inflammatory cytokines between genders was found but inflammation did negatively impact physical function and physical activity for both genders which aligns with previous research (Friedman et al., 2015; Nash et al., 2013). The inconsistent results for gender differences and inflammatory markers brings more questions to the forefront, necessitating further research to be conducted with these factors.

Suggestions for Future Research

Future research with the same concepts should focus on studies of longitudinal and experimental design. Additional recommendations by aims are included in the manuscripts in Chapter 4. As previously stated, the concepts of participation and environmental factors from the ICF framework were not included in this study. The opportunity to add these factors to the model and test both the concepts and framework is needed. Other considerations include inflammatory cytokines being explored across longer periods of time with greater panels of pro- and anti-inflammatory cytokines. Further the specific role inflammatory markers play in disease specific chronic condition development should be addressed. Even though the evidence is mixed on gender differences in health conditions, further research is warranted to add evidence and further develop precision medicine. Adiposity should be further explored with variations in composition over time, gender specific changes, and focusing on the high-risk categories of underweight and obese. Another consideration is to utilize advanced measures of adiposity, to discriminate between muscle and adipose tissue in the older adult population.

Conclusion

In summary, physical function is a key component of an older adult's overall health. Preserving physical function by participation in physical activity is a preventative health strategy that should be encouraged for the older adult population due to the positive impact physical activity and function have on each other. Elevated pro-inflammatory and decreased anti-inflammatory cytokines can negatively impact an older adults daily physical functioning and ability to participate in regular physical activity. Screening for chronic low level inflammatory cytokines should be investigated as a way to proactively address chronic conditions and risk for physical functional decline. Chronic health conditions can negatively influence an older adult's ability to function. Mean differences between genders exist in physical functioning and physical activity and should be considered when addressing preventive health strategies. Physical decline associated with aging and maintaining independence are complex health issues that should be proactively addressed with preventive health measures and screening throughout the aging process.

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