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THE INFLUENCE OF BODY COMPOSITION AND PHYSICAL ACTIVITY ON
INFLAMM-AGING, FATIGUE AND FUNCTION IN OLDER ADULTS

BY

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DISSERTATION

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ABSTRACT

Persistent feelings of fatigue are a widespread complaint reported by older adults, and are associated with detriments in health and quality of life. Aging is also accompanied by gains in adiposity, reductions in physical activity, and loss of lean mass and physical function. This study assessed the influences of body composition [adiposity (%Fat) and mineral-free lean mass (MFLM)] and physical activity (total and moderate-to-vigorous; MVPA) on fatigue and function in older adults. Furthermore, we sought to determine the mediating role of systemic inflammation on these health outcomes. One-hundred eighty-two community-dwelling older adults were recruited to participate in this study (age = 69.2±6.7 years, 98 men, 84 women) Body composition [adiposity (%Fat) and relative muscle mass (Skeletal Muscle Index (SMI); appendicular MFLM/ht²] was quantified via dual-energy X-ray absorptiometry (DXA). Physical activity (PA) was assessed by the Physical Activity Scale for the Elderly (PASE), and accelerometers were worn to determine total and MVPA. Fasting blood samples were obtained for measurement of serum C-reactive protein (CRP), Interleukin-6 (IL-6), the soluble IL-6 receptor (sIL-6R) and WBC count. Fatigue was assessed by the Multidimensional Fatigue Inventory (MFI), to determine levels of general, physical and mental fatigue as well as reduced activity and motivation. Lower-extremity physical function (LEPF) was evaluated by 7-m walk tests, a Timed Up and Go (Up&Go), a 30-second chair stand test (30-Chair), a 6-min walk, the Short Physical Performance Battery (SPPB) and the Star-Excursion Balance Test (STAR). It was hypothesized that 1) women would report higher levels of fatigue and have poorer performance of physical function than men, 2) adiposity would be an independent predictor of fatigue and LEPF, 3) PA would be inversely related to fatigue and positively with LEPF, and 4) inflammation would be positively associated with fatigue. Understanding the biological and behavioral influences on fatigue and function is imperative for combating health detriments in older adults.

Men and women reported similar levels of fatigue in all dimensions ($p > 0.05$) with the exception of women reporting higher levels of mental fatigue than men ($p = 0.05$). Adiposity was positively correlated with several measures of fatigue (r range = 0.20 to 0.42), whereas PA was inversely associated with the same measures of fatigue (r range = 0.18 to 0.37), both of which were not related to mental fatigue. CRP, IL-6 and WBC were also related to several dimensions of fatigue (r range = 0.15 to 0.26). Compared across PA-adiposity groups, in the absence of an interaction, there was a main effect of PA and adiposity on general and physical fatigue ($p < 0.05$). Regression analyses revealed that the psychosocial variables depression and sleep quality and adiposity independently explained variance in general and physical fatigue. Adiposity and inflammation are positively related to general and physical fatigue, with adiposity remaining a predictor of both dimensions, independent of other associated factors. In addition, PA is inversely associated with these same dimensions of fatigue, and is an independent predictor of

mental fatigue. Adiposity, physical activity and inflammation are identified as potential targets for reducing fatigue in older adults.

Men performed better on all LEPF tests than women (all $p < 0.05$). Unlike all other independent variables, MFLM and SMI were not related to any LEPF outcomes. In the absence of a significant interaction, main effects for adiposity were found for mobility tests of LEPF, including WALK, Up&Go, 30-Chair and 6-min walk. There was a main effect of PA on 6-min walk only with greater PA corresponding to better performance. On STAR balance tests, an interaction existed for medial, posterior and composite reaches ($p < 0.05$). After accounting for influences of sex, age and number of co-morbidities, %Fat remained a significant predictor of all mobility measures and the STAR composite, as did PA for Up&Go and 6-min walk (all $p < 0.05$).

Our results suggest that adiposity is a major determinant of fatigue and both balance and gait-related physical function in relatively healthy older adults. Physical activity may help to prevent age-associated fatigue and loss of mobility; however there does not seem to be an added benefit of MVPA.

Given the high prevalence and associated health detriments of fatigue in older adults, longitudinal studies involving reductions in adiposity and increasing physical activity as possible prevention and treatment strategies for both fatigue and mobility impairments are warranted. Due to the complexity of these relationships, future work should simultaneously assess body composition components, physical activity and inflammation to further our understanding the disablement process. Uncovering the key influential factors contributing to fatigue and disability is essential for development and implementation of effective prevention and treatment strategies.

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CHAPTER 1

Introduction

1.1 Significance

According to the National Institute of Aging (NIA), ~35 million Americans are over the age of 65, with estimates suggesting this population will double within 20 years (NIA). Epidemiological data indicate that as much as 1/3 of this population, or more than 10 million elderly Americans, have disordered body composition, including excess adiposity and inadequate levels of muscle mass which directly or indirectly contribute to astronomical health care costs estimated at more than 18 billion dollars annually (1). With these changes in the aging demographics, age-related reductions in physical function are a primary public health concern. Detriments in physical function are predictive of falls, fractures, hospitalizations, cognitive decline, loss of independence and even mortality (2). A more comprehensive understanding of factors influencing physical function is imperative for successful aging and maintenance of independence in older adults.

Fatigue can be categorized as both a performance decrement and a subjective perception. The NIH (3) defines fatigue as a perceived lack of physical or mental energy and fatigability as the degree of fatigue associated with activity in any dimension (i.e. physical, mental, emotional, and/or social). Approximately 50% of older adults report fatigue (4). Notably, among otherwise healthy individuals, fatigue has been associated with disability and loss of independence (5), and is reported as the most common cause for restricting activity of all types (6).

Recent evidence suggests a relationship between obesity, as measured by body mass index (BMI), and fatigue (7), which may be potentially mediated by chronic systemic inflammation (8). This relation may be augmented in older adults (9) due to relative increases in a) adiposity (10) and b) pro-inflammatory cytokines (11). Furthermore, higher levels of adiposity have also been linked to reductions in lower-extremity physical function (LEPF) and elevated risk for physical disability in the elderly (12). Limited evidence suggests that systemic inflammation accelerates loss of muscle mass and is associated with frailty (13). Our own data (14) and others (15;16) indicate that older women report greater fatigue than their male counterparts. This sex disparity in fatigue aligns with other reports of elevated health risk in older women compared to men including obesity, chronic systemic inflammation, and physical disability (17).

Notably, physical activity is an effective treatment for reducing systemic inflammation in older adults (18) and attenuating fatigue in younger adults and cancer patients (19;20); however, the impact of physical activity on fatigue in relatively healthy older individuals is unknown. Moreover, the relations among weight status, physical activity, inflammation and physical function, fatigability and perceptions

of fatigue are unclear. Interdisciplinary research is needed to develop optimal strategies to reduce fatigue, preserve function and enhance quality of life in older individuals. In this context, the overarching objective of the proposed research is to evaluate the impact of weight status and habitual physical activity on fatigue in relatively healthy older men and women. To achieve this objective, older men and women (n=200; 60-85 y) will be recruited stratified on weight status (normal, overweight or obese) and physical activity level (sedentary, active) and evaluated for body composition, physical activity, LEPF, systemic inflammation and fatigue. In this context, the specific aims are as follows:

1.2 Specific Aims

Specific Aim 1: To determine the relative impact of weight status and habitual physical activity on perceptions of fatigue and objectively measured physical function (LEPF, muscle strength and endurance), in age- and BMI matched relatively healthy older men and women. We hypothesized that: 1) increased BMI would negatively impact both fatigue and physical function in both sexes but to a greater degree in women compared to men, 2) habitual physical activity would be associated with reductions in perceived fatigue and improved physical function and would attenuate negative effects of adiposity on fatigue and function in both sexes, 3) higher perceptions of fatigue would relate inversely to physical function.

Specific Aim 2: To determine the mediating role of systemic inflammation on the relations among weight status, habitual physical activity, fatigue and physical function in older men and women. We hypothesized that: 1) the favorable impact of habitual physical activity and negative impact of adiposity on fatigue would be mediated in part by systemic inflammation, and, 2) the relation between inflammation and fatigue would be stronger in women compared to men.

Secondary Aim 1: To determine the relative influences of disordered body composition (increased adiposity with reduced muscle mass) and reduced muscle quality on physical function in older men and women. We hypothesized that: 1) increased adiposity would negatively influence physical function, 2) low levels of skeletal muscle mass would not directly influence physical function, and 3) habitual physical activity would be positively associated with physical function performance.

Summary: Identification of both physiological and behavioral influences on fatigue, defined multi-dimensionally, as a means of reducing fatigue and subsequent detriments in function and threats to independence will require interdisciplinary scholarship. Given the sex disparity in fatigue and risk of

disability, approaches may need to differ in older women and men. Given the increasing prevalence of obesity and changing aging demographics, this research agenda has high public health importance.

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CHAPTER 2

Literature Review

2.1 Public Health Significance of Fatigue in Older Adults

Fatigue is a widespread complaint reported clinically. Although prevalence estimates vary widely, there is a general consensus that 10 - 25% of the general population perceives they are fatigued (1;2). Fatigue appears to be much more prevalent in older adults, with some estimates suggesting as many as 50% of elderly individuals experience fatigue (3). Importantly, this age group is likely most susceptible to the deleterious consequences of fatigue including reductions in physical activity, muscle weakness, and cognitive impairments. Among otherwise healthy individuals, fatigue has been associated with depression (4), disability and loss of independence (5) and mortality (6). Unlike the fatigue symptoms that typically accompany other underlying medical conditions such as cancer, chronic heart failure, or hypothyroidism, general fatigue complaints in the elderly often remain unexplained. Older individuals have the added challenge of combating this fatigue to complete their activities of daily living to remain independently living. As discussed below, body composition, habitual physical activity and chronic systemic inflammation are all implicated in the etiology of fatigue in older adults.

2.2 Body Composition Changes with Age

Normal aging is accompanied by a progressive reduction in lean mass, increases in total adipose tissue, increased abdominal adipose tissue accumulation especially in women after menopause, and lipid infiltration into the muscle (7;8). However, these alterations in body composition and fat distribution are often masked when assessed by BMI as often no substantial change, if any, in BMI appears, due to a reduction in muscle mass that accompanies the increase in fat mass (9). A number of studies, including those from our lab, have demonstrated an increased discrepancy between BMI and %Fat in the aging population (10).

The public health significance of the detrimental changes in body composition with age is both metabolic and functional, with the latter being of increased research and clinical focus. As previously explained, identification of the primary determinant of body composition and strength in relation to physical function is challenging, and not well understood. With respect to body composition, it is intuitive that the interaction between reduced skeletal muscle mass and increased adiposity may have the most impact on physical function. That is to say, lower levels of muscle mass may not be problematic if the load being carried (i.e., total body mass) is relatively low as well. On the other end of the spectrum, an individual with a high level of muscle mass, but a disproportionately elevated total body mass will likely

have detriments in function. The somatotype at greatest risk for disability is a frail obese individual (relatively low levels of muscle mass in combination with elevated fat mass), which unfortunately represents a rapidly growing portion of the population (11). This disordered body composition profile has been coined ‘sarcopenic obesity’. Recently, the definitions of sarcopenia and sarcopenic obesity have been topics of debate as the definition method selected not only alters the prevalence estimates, but also the relation to physical function and risk of disability. The term sarcopenic obesity in particular is a relatively new concept (within the last ~5 years). It has recently been suggested that sarcopenia, particularly as it relates to classification of SO, should be determined based on strength rather than muscle mass *per se*.

A number of potential underlying mechanisms have been suggested for the progressive loss of muscle mass and strength with aging, including changes in hormonal status, neuronal changes, phenotypic shifts in fiber type, and malnourishment (12). Two factors that have also been speculated, and may provide a more direct link between elevated adiposity and reduced muscle mass are physical inactivity (13) and chronic inflammation (14;15) (both systemic and in muscle). Thus, these two conditions may be pathogenically related. In this regard, there may be a cyclic relation between sarcopenia and obesity. Both conditions lead to reductions in physical capacity and function and subsequently higher levels of physical inactivity. It is clear, at least theoretically, to see how these alterations in body composition may potentiate each other and facilitate detriments in physical function and quality of life in older adults.

Recently, evidence has suggested that simply assessing changes in muscle mass with age does not provide an adequate representation of the detriments in physical ability. Perhaps equally important in relation to declines in physical functional ability is a reduction in muscle strength and muscle quality. The age-related loss of muscle strength was recently termed ‘dynapenia’ from the translation of ‘poverty of strength’. This new term was proposed by Clark and Manini in order to differentiate changes in body composition, i.e., muscle mass loss, from alterations in muscle strength (12). The aging process is often accompanied by a reduction in the association between muscle mass and muscle strength driven in part by changes in muscle quality, quantified as leg strength normalized by leg mineral-free lean mass, which has been determined to be the most important factor for physical function in obese frail elderly individuals (16). Not only are older adults experiencing reductions in muscle mass, but the muscle mass they retain has less contractile ability. This reduction in muscle quality is likely multi-faceted and remain incompletely characterized. However, there appears to be an inverse relationship between obesity and muscle quality (17). Ideal measurements of muscle quality incorporate the measurement of muscle physiological cross-sectional area (PCSA), which is directly proportional to maximal force production (18). PCSA is influenced substantially by muscle pennation angle. Some evidence suggests that pennation

angle is reduced in older adults, thereby effectively decreasing the PCSA and partially accounting for reductions in muscle quality (18). This shift in pennation angle and reduction in PCSA is theorized as one possible explanation for changes in muscle quality in obesity. Unfortunately, methods to assess these parameters are not widely available, are burdensome for participants, and expensive.

Some evidence also suggests that muscle power, the ability to produce force quickly, may be a more important predictor of gait speed than muscle strength (19). Muscle power appears to decline earlier in life than does muscle strength, likely due to phenotypic shifts in muscle fiber type and reduced contractile properties of the muscle. In terms of fatigue resistance, studies comparing older adults to their young counterparts are equivocal. Interestingly, obese individuals experience greater muscle fatigue (or reductions in power) with repeated knee extension repetitions when completed voluntarily, with no difference when induced via electrical stimulation (17). The possibility exists that there is a reduction in central activation in obese individuals, independent of changes in physiologic muscle function. Whether this deficit is neural or psychological has not been determined. This paradox between true physiological fatigue and psychological perceived effort/fatigue highlights the interplay between different domains of fatigue and the difficulty that exists in assessing these components. Several possibilities exist for a connection between reduced muscle mass and perceptions of fatigue/energy, including reductions in energy availability, reduced capacity to perform work, and an increase in relative workload of a given task.

2.3 Causes of Fatigue in Elderly: Role of Obesity and Systemic Inflammation

Causes of fatigue are likely multi-faceted, however, several recent studies have identified a higher prevalence and severity of reported fatigue in obese individuals (20). This issue is particularly relevant given the recent obesity epidemic in the United States (21) and the well established link with several chronic diseases including cardiovascular disease, type 2 diabetes mellitus and cancer. Notably, older adults are not protected from this epidemic, as the aging process is associated with disordered body composition (i.e. greater adiposity and reductions in lean mass) (22) as described in the previous section. Obesity is now recognized as a contributing factor to reductions in physical function and frailty in older adults (23). Indeed, the most common elderly phenotype in the near future may be a frail obese person at high risk for physical disability (11). This disordered body composition in the elderly is intuitively linked to fatigue, although this is not well established. Moreover, the link between perceptions of fatigue and objectively measured physical functional abilities and muscle fatigability is unstudied and of high importance for successful aging.

It has been suggested that the association between obesity and fatigue may be mediated by inflammation (24). The relationship between adiposity, particularly central adiposity, and elevated levels

of inflammation is established; however, whether inflammation is the mediator between obesity and fatigue remains to be determined. High levels of inflammatory cytokines are known to induce sickness behaviors, including lethargy, by directly or indirectly interacting with the central nervous system (25). Although recent reports have identified a relationship between inflammation and fatigue in chronic disease populations (26), this association remains to be determined in relatively healthy elderly individuals. Evidence to the contrary exists in younger adults, demonstrating adiposity as a predictor of fatigue, with no association between inflammation and fatigue (27). Because aging is associated with chronic low level systemic inflammation (28), it has been speculated that both adiposity and pro-inflammatory cytokines may contribute to the increased prevalence of fatigue in older individuals compared to younger cohorts (29). This theory is partially supported by our recent data that suggests inflammation, assessed solely by C-reactive protein (CRP), is a mediator relating obesity to fatigue in this population (30). It should be noted that two factors that require consideration when investigating fatigue are sleep quality and depression. It is well-established that sleep quality is linked to fatigue (31). Depression is also related to reported fatigue (4;32). Moreover, the link between depression and sleep disturbance is well established (20). However, the independent contributions of obesity and habitual physical activity, sleep disturbance, and depression to fatigue are largely unknown in the elderly.

2.4 Physical Activity: An Important Health Behavior to Reduce Fatigue in Older Adults?

The importance of habitual physical activity for optimal health status across the lifespan is well established. Insufficient levels of physical activity have also been associated with reported fatigue in both men and women (33). Recent literature suggests that increasing physical activity may attenuate perceptions of fatigue, at least in younger adults and cancer patients (34;35). Little data exist regarding the influence of varying levels of habitual physical activity, both activities of daily living and structured purposeful exercise, on fatigue, particularly in the elderly. From a mechanistic perspective, accumulating evidence has identified an anti-inflammatory effect of exercise (36), which may in turn result in subsequent reductions in perceptions of fatigue. Furthermore, regular physical activity has been proven effective in counteracting the adverse effects of adiposity on health status (37); however, whether habitual physical activity can attenuate fatigue in obese individuals has not been determined.

2.4a Fatigue as a Barrier to Physical Activity

The detrimental effects of fatigue on quality of life are well established. There are intuitive relationships between perceptions of fatigue and psychological well-being. However, what is less understood is the degree to which these links are driven by changes in behavior. Lack of energy and feeling “too tired” are among the leading reasons/excuses people give as barriers to exercise. A recent

survey by Reichert et al. 2007, demonstrated that ~ 38% of the 3000 individuals surveyed reported “feeling too tired” was their biggest barrier to exercising. In individuals ≥ 70 years of age, ~43% reported this barrier to habitual physical activity (38). Although many benefits to exercise are well established and accepted by the general public, physical inactivity remains a major public health concern. Gaining a better understanding of the ‘risk factors’ for physical inactivity is critical to determine strategies to elicit behavior change.

The difficulty arises in discerning the interaction between fatigue and physical activity because this relationship is likely bi-directional. A substantial quantity of research has demonstrated a causal link between physical activity and mood, at least acutely. Exercise appears to produce a bodily state of arousal, which creates a feeling of vigor (at least in light to moderate exercise). This acute change in perceptions of energy remains for up to several hours following the exercise bout. Theoretically, when an individual engages in physical activity they will potentially have a greater perception of energy, which may allow them to complete both physical and mental tasks of daily living, including running errands, yard-work, cleaning house, balancing the checkbook, etc. Unfortunately, similar to other beneficial health parameters influenced acutely and chronically by exercise, this outcome of enhanced energy is insufficient in stimulating individuals to exercise in the first place, particularly those having difficulty overcoming their feelings of fatigue and tiredness to initiate exercise.

2.4b Importance of Physical Activity for Function and Fatigue

Physical activity has been consistently associated with improvements in physical function in older adults. These benefits manifest as both a prolonged time until mobility disability occurs in the lifespan as well as improvements in functional testing scores. For example, physical activity has been shown to improve status [assessed via the short physical performance battery (SPPB)] scores by >1 point which has been supported as a clinically meaningful improvement in function (39). A study by Nosek and colleagues highlights the interactive effects of disability, fatigue, and psychosocial correlates with physical activity. In older women living with disabilities, those experiencing disability for a longer period of time report less physical activity. Women with higher levels of self-efficacy for physical activity engage in more physical activity, across durations of disability. Additionally, individuals perceiving a greater degree of vigor tend to partake in better health related activities, including having better nutritional habits (40).

2.5 Sex Disparity, Fatigue, Obesity, Inflammation and Physical Disability

It has also been suggested that women may exhibit a greater degree of fatigue and/or perceptions of fatigue, particularly as they age (1;41); however, this finding is equivocal (2;27). Our own data suggest that older women have greater perceptions of fatigue (30) and reduced LEPF (42) compared to their male counterparts; however, sex differences in fatigue severity and in differing functional domains of fatigue (i.e., physical, mental, etc.) in older adults has not been well characterized. There are known sex differences in adiposity, habitual physical activity and cardiorespiratory fitness, and systemic inflammation that may influence fatigue. Additionally, women report greater levels of depression and sleep disturbance in late life (43). The mediating effects of weight status and physical activity on the relation between systemic inflammation and reported fatigue and how these relations differ in older men and women is inadequately characterized.

2.6 Interactions Among Inflammation, Strength, Fatigue and Physical Function

2.6a Inflammation and Fatigue

In young adults, individuals categorized as having insufficient fatigue, that is fatigue not severe or persistent enough to be diagnosed with chronic fatigue syndrome, have elevated levels of inflammation compared to their non-fatigued counterparts (26). In addition, these individuals report worse physical component (PCS) and mental component (MCS) summary scores based on the SF-36. When collapsed across fatigue groups, scores on the PCS were higher in subjects with CRP levels above the clinical cut-off (>3 mg/L) when compared to subjects with CRP <3 mg/L. We aim to determine if these relationships exist in an aging population.

2.6b Fatigue and Physical Function

Although intuitively there is an inverse relationship between fatigue and function, this has not been well studied. In a recent study, Hardy and Studenski (2008) assessed ~500 older men and women (44% female, 74 yrs) for tiredness (fatigue) (44). Participants were asked if, during the past month, they had been “feeling tired most of the time.” Subjects reporting tiredness also rated the degree to which this fatigue affected their function. Function was assessed subjectively using the SF-36 physical component index and National Health Interview Survey Activities of Daily Living (NHIS) scale and objectively using usual gait speed over 4-meters. BMI, GDS, & chronic conditions served as covariates. Tired individuals included a higher proportion of females, and reported more chronic conditions, higher depression scores, worse subjective function (SF-36 PCS of 50 vs. 74), and had slower usual gait speed (0.82 m/s vs 0.92 m/s), but had similar levels of cognitive function. Participants were then followed up for

3 years. For all 3 outcomes of function tiredness at baseline was associated with poorer function through the follow-up period, but followed similar rates of decline to participants not reporting tiredness at baseline. The relation among fatigue and physical function, and the directionality of the relations, remains an important public health topic.

2.6c Inflammation, Fatigue and Physical Function

Due to the detrimental effects fatigue has on function and mobility, there has been increasing focus on identifying mediators of this disablement process. Very recently interest has emerged in identifying a relationship between chronic inflammation and impairments in physical function. Recently, a group at Wake Forest University published a study combining data from four clinical trials, in which over 500 older men and women (≥ 55 years) were assessed for grip strength, physical function using the SPPB, inflammation (IL-6, TNF- α and CRP), and body composition via DXA (45). Elevated levels of IL-6 and CRP related to poorer grip strength and SPPB performance scores, independent of disease status. These results were not impacted by controlling for lean mass, but were attenuated after controlling for adiposity.

The inverse relationship between adiposity and mobility is well established, as discussed previously. Although there is a clear biomechanical component involved in this relationship, it appears this is not solely responsible. The possibility exists that inflammation could be mediating this reduction in function. Stenholm et al., recently shed light on this mediation (46). This group assessed the risk of walking limitation based on self-reported walking difficulty in completing 500 meters and slow maximal walking speed (<1.2 m/s). There was an increased risk of walking limitations based on all measures of adiposity (BMI, waist circumference and %Fat). In a separate analysis individuals with high CRP levels and those with low handgrip strength had more prevalence of walking limitations, but no interaction existed between these variables and %Fat. Using logistic regression, CRP was found to be a significant explanatory factor in the association between high %Fat and walking limitation.

Bautmans and colleagues recently sought to examine relations between objectively measured strength and muscular endurance in relation to perceptions of fatigue (47). Using a prolonged isometric handgrip to identify resistance to fatigue, the researchers identified that better fatigue resistance was related to: less self-perceived tiredness, less fatigue during ADLs, and being bothered less by fatigue. Furthermore, fatigue resistance was associated with both balance and basic mobility. Fatigue resistance was also moderately associated with circulating TNF- α in both males and females ($r = -0.45$). Interestingly, when stratified by high or low inflammatory status, individuals with high IL-6 and high Hsp70 had the least fatigue resistance. Findings from this study support both poor muscle endurance and elevations in inflammation leading to detriments in function.

The most comprehensive analysis to date regarding the influence of fatigue on strength and function came from the InCHIANTI study. Vestergaard and colleagues performed a cross-sectional analysis on ~1000 older Italian men and women, age 65 and over. In this study they defined fatigue based on 2 questions: whether participants felt that “everything was an effort” and/or they “could not get going” on three or more days in the past week (48). These items were selected from the Center for Epidemiologic Studies-Depression scale (CES-D). Physical function was objectively measured via handgrip strength, the SPPB and walking speed during a 400-m walk. Disability was defined as the inability to complete the 400-m walk or self-reported difficulty in ADL and/or IADL, assessed as any difficulty on any 1 ADL or IADL item. Biomarkers were assessed as well, including CRP, IL-6, TNF- α for inflammation, and TSH, fT4 and fT3 for thyroid function. Adjusting for age, fatigued men and women had higher prevalence of disability in IADL, and poorer performance on all measures of physical function, including the SPPB, 400-meter walk, and had weaker handgrip strength. Fatigued individuals also reported poorer health, sleep quality, and more depressive symptoms. Importantly, fatigue was associated with an increased risk of being sedentary in men, and had a tendency to increase risk in women ($p = 0.07$). Also notable, fatigued men and women had higher CRP levels than non-fatigued, which partially explained the relationship between fatigue and function. Of note, the inflammatory status of the participants in this study are quite high, with means of both fatigued and non-fatigued men and women well above the clinical cut-off in terms of metabolic outcomes ($>3\text{mg/L}$).

2.7 Influence of Fatigue and Inflammation and Cognition

2.7a Fatigue and Cognition

It is estimated that somewhere between 50-75% of patients with chronic fatigue syndrome (CFS) report cognitive impairments, many of which are severe enough to interfere with daily function (49). Common cognitive complaints in this population include inability to concentrate, problems with memory, slower thought processing, and mental fatigue. However, studies objectively assessing cognitive dysfunction in CFS as compared to controls have been equivocal (49;50). Capuron et al. suggest the presence of mental fatigue in patients with CFS may explain the heterogeneity of objectively measured cognitive dysfunction (49). Along this line, we speculate that increased mental fatigue in an otherwise health population will relate to poorer cognitive function.

The vast majority of studies assessing ‘fatigue’ and cognition has been performed in disease populations, such as (CFS), or in response to severely fatiguing stimuli such as INF- γ treatment and acute sleep deprivation. As stated previously, studies objectively assessing cognition have provided mixed results. However, some evidence exists in support of the measurements of choice reaction time, rapid

visual information processing, and aspects of spatial working, spatial recognition, and pattern recognition memory (49-51). These tests encompass a variety of different cognitive processes and their use provides a comprehensive assessment of the construct of cognition. A review by Lieberman summarized the relationship between self-reported mood states and objectively measured ‘mental energy’ via cognitive tasks. The literature supports the efficacy of reaction time tasks, choice reaction time tasks in particular, and vigilance tasks as measures sensitive to detect differences in mental energy (52). In addition to these tasks, rapid visual information processing tasks are recommended as a way to evaluate sustained attention, which have also been proven effective in detecting differences in CFS as compared to controls.

2.7b Inflammation and Cognition

Inflammation has been implicated as a potential contributor to cognitive decline, possibly linking with fatigue. Use of a paper-pencil version of the Stroop test in older adults to assess cognition demonstrated a moderate association between inflammation and cognitive decline (53). Using more sophisticated cognitive testing techniques, Gimeno et al. (2008) also identified a relationship between low-grade inflammation and performance in specific domains of cognition (54). When followed up however, baseline inflammatory status did not relate to cognitive decline. In a sample of older women, CRP was associated with a decline in memory, but not in cognitive speed (55). Taken together, there is a growing body of evidence, all of which is very recent, supporting a relationship between inflammation and cognition. This area is in its infancy and can benefit from more comprehensive assessments of cognition, inflammation and fatigue status.

2.8 Limitations in the Literature: Fatigue, Inflammation and Physical Function in Older Adults

2.8a Conceptualizing Fatigue

Assessing the construct of fatigue is challenging as it is a multi-dimensional. There are several different domains of fatigue, including physical, mental, emotional, etc. Measurement of the prevalence and severity of fatigue often require different instruments. Selection of a measurement tool is equally challenging, as there are more than 30 questionnaires developed to measure ‘fatigue’. Unfortunately, each scale or set of questionnaires differs slightly. For example, one scale may assess ‘exhaustion’ whereas another may attempt to assess ‘lack of energy’. Adding to this complexity is the subjectivity of an individual’s perception of fatigue. Each individual’s responses may differ based upon a multitude of factors, including the adjectives used in the question, the phrasing of the question, personality traits, etc. Even more influential are the external factors that both acutely and chronically impact one’s feelings of

energy/fatigue, including work/life stress, family concerns, sleep quality, recent activity, etc. This latter idea, also contributes to the measurement of fatigability, or the fatigue created by a given stimulus.

2.8b Comparison of Objective and Subject Measures of Fatigue & Function

Self-reported fatigue and function is often used as single measures of each construct. What hasn't been well characterized is the relationship between these assessments and objectively measured physical function. It is expected that an increase in perceptions of fatigue would relate to poorer performance. However, the extent to which perceptual fatigue influences physical function has not been established. For example, does a reduction of 2 points on the MFI general fatigue subscale correspond with a meaningful improvement in physical activity and function? Mallinson and colleagues performed this type of analysis in cancer patients receiving chemotherapy treatment (56). This group assessed motor and cognitive functions using both self-report and objective measures. Self-reported and observed data were moderately correlated ($r = 0.30$ to 0.71). Reported fatigue correlated moderately with functional performance as well ($r = 0.30$ to 0.45). The researchers concluded that self-report measures of fatigue and function are valuable indicators of objectively measured function. They provide evidence that SF-36 physical function sub-scores <50 are associated with greater difficulty performing activities of daily living.

From a methodological standpoint, it is important to capture the fatigability of individuals after both practical tasks encountered in daily life, as well as to more vigorous stimuli. Furthermore, incorporating both types of tasks allows the researcher to assess fatigue relative to an absolute task and to tasks equal in relative intensity across individuals. It is theorized that more physically active and 'fit' individuals will be less susceptible to fatigue, even at equivalent relative intensities, and that any fatigue that is experienced will be to a lesser severity. In contrast, it is speculated that obese individuals may experience greater perceptions of fatigue from the same relative stimuli.

Fatigue following a particular activity is very difficult to quantify. Specifically, in terms of performing tasks of daily living and or 'basic' functional tasks, less 'fit' individuals are working at a greater (substantially greater in some instances) relative intensity than their more robust counterparts (57). Hypothetically, climbing a flight of stairs has an estimated energy cost of ~ 3 METS. Converting this to a VO_2 value this is 10 ml/kg/min. For individuals with a VO_{2max} of 15 ml/kg/min they are working at 67% of their maximal aerobic capacity (and likely above their lactate threshold). Conversely, if the individual's VO_{2max} was 25 ml/kg/min, they would only be working at $\sim 40\%$ of the maximal capacity. Furthermore, dynamic tasks, such as ascending or descending a flight of stairs rely substantially on muscle strength and/or muscle power (of the lower body). Obese individuals must have more strength to move their greater load, or will have the inability to perform these types of tasks. From a practical

standpoint this is extremely relevant, in terms of one's ability to carry out activities of daily living, however it does pose some methodological concerns. Designing a study that assesses several domains of fatigue, including: self-perceptions, muscle fatigue and mental fatigue, as well as in multiple contexts: 'normal' morning levels and following both physical and mental tasks, may provide a better understanding of factors influencing fatigue as it relates to changes in behavior. Furthermore, this approach may aid in the identification of factors pre-disposing or underlying fatigue in older adults.

2.8c Limitations in the Literature Regarding Body Composition, Function and Fatigue

Importantly, previous studies that have used this method to categorize "impaired muscle strength" have stratified by tertiles of hand grip strength within gender. It is acknowledged that hand grip strength is a useful indicator of muscle strength and has been associated with physical function. However, leg strength has a stronger association with physical function and is more predictive of disability (7). Future studies would benefit from the use of this type of strength assessment in combination with body composition methods that accurately assess adiposity (rather than BMI) to categorize sarcopenic-obesity. Furthermore, these studies should include a composite of functional tasks to evaluate the individual and interactive influences of both impaired muscle strength and obesity on function in older adults.

In addition to these limitations identified above, according to the NIH focus group regarding fatigue in the elderly (58), several questions still exist with regard to body composition and fatigue. These "future questions" include: What is the relationship between muscle mass (sarcopenia) and fatigue? What is the relationship between adiposity and fatigue? To what extent is the effect of adiposity on fatigue mediated by fat mass alone vs. metabolic mediators; for example, adipokines? What is the relationship between muscle function and the symptom of fatigue? Can older pre-frail adults serve as a model to examine the sequence of events leading to fatigue? What is the role of the central nervous system in altered muscle function and symptomatic fatigue?

Along these lines we propose an additional question that remains to be answered: What is the relationship between muscle strength ("dynapenia") and/or muscle quality (particularly in the lower body) and fatigue?

2.8d Summary and Call for Interdisciplinary Approaches to the Study of Fatigue, Inflammation and Function in Older Adults

As stated above, the NIH focus group on fatigue in the elderly identified several unanswered questions remaining in this understudied area. In addition to those mentioned previously, those of particular interest and relevance to the present study include those related to:

Inflammation and the central nervous system:

- Are there “best markers” for fatigue?
- Can we develop aggregate inflammatory and HPA axis markers that are most predictive of symptoms and adverse outcomes?
- Can we more appropriately and directly target specific components of inflammatory pathways?
- Can we identify genotypes/phenotypes “at risk” for fatigue and target individuals for intervention?

In the psychosocial domain unanswered questions are:

- Is it more useful for studies to focus on the presence of fatigue or the absence of energy?
- Can interventions be developed that increase positive affect without costly energy; for example, meditation or relaxation?

Finally, in the functional status domain, the following questions remain:

- Which social, psychological, physiological, or health factors explain the association between tiredness and functional decline?
- Is tiredness related to other indicators of aging, such as biological indicators? Is tiredness in midlife related to functional decline in old age?
- Is the predictive power of measures of function and fatigue the same among different ages or between sexes?

Importantly, to date no study has assessed these interacting relationships of strength, fatigue, body composition and inflammation using a multi-dimensional fatigue analysis. Furthermore, strength has been demonstrated to be an important determinant of functional ability, but has been based solely on handgrip strength in these analyses. Inclusion of more direct measures of lower-body strength may provide better insight regarding the influence of strength in the context of both fatigue and function. Only the study by Vestergaard stratified their analyses by sex. Additionally, although sedentary status was controlled for in one study, the effect of physical activity (quantity or intensity), on these outcomes has not been evaluated. Given what we now know regarding the anti-inflammatory effect of exercise, including physical activity into these models may have important health implications.

2.9 Summary

The interactive relations among body composition, physical activity, inflammation, physical function and fatigue remains to be determined in older adults. Identification of both physiological and behavioral influences on fatigue, defined multi-dimensionally, as a means of reducing fatigue and subsequent detriments in function and threats to independence will require interdisciplinary scholarship. Given the sex disparity in fatigue and risk of disability, approaches may need to differ in older women and men. Given the increasing prevalence of obesity and changing aging demographics, this research agenda has high public health importance.

2.10 Preliminary Studies

The brief summaries below provide evidence of: 1) the scientific rationale for the proposed work in this application; 2) the proposed study being a logical extension of our previous work; 3) our ability to recruit elderly men and women; 4) our expertise with the methodologies to be utilized; and 5) our well-rounded and established environment, which allows us to view these issues from an interdisciplinary perspective.

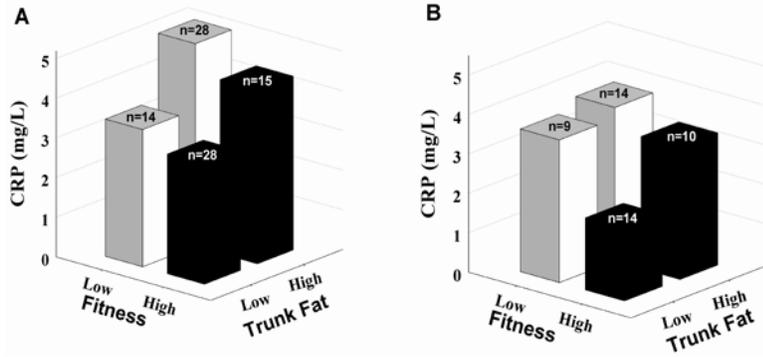
2.10a Sex, Adiposity and Inflammation

Stronger relationship between central adiposity and C-reactive protein in older women than men.

Valentine RJ, Vieira VJ, Woods JA, Evans EM. Menopause:2009; 16(1):84-9.(59)

Objective and Methods: The purpose of this study was to determine the sex-specific independent relationships between physical activity, fitness, central and whole body adiposity and CRP in sedentary older adults (70.0±5.4 years; N=132, 47 men, 85 women). Results and Conclusions: CRP tended to be higher in women than men (4.0±2.9 vs. 3.1±2.3 mg/L, p=0.07). All measures of adiposity were positively associated with CRP in women (r range=0.22 to 0.28, all p<0.05), whereas neither physical activity nor fitness were related. In contrast, %Fat was the only measure of adiposity associated with CRP in men (r=0.36, p=0.01) and VO_{2peak} was inversely correlated to CRP (r=-0.31, p=0.04). Trunk fat was the only independent predictor of CRP in women, while %Fat and anti-inflammatory medication use were independent predictors of CRP in men. In sedentary healthy older adults the relation between regional body fatness, aerobic fitness and CRP differs between sexes such that a) central adiposity was most strongly associated with CRP in women, whereas %Fat was the strongest predictor of systemic inflammation in men and b) the negative association between fitness and CRP was stronger in men.

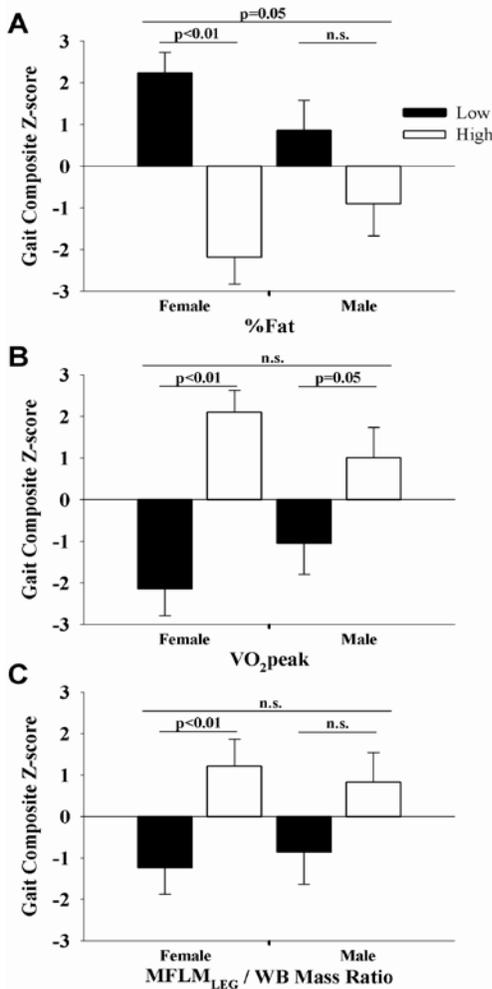
Figure 2.1



2.10b Physical Activity, Strength, Body Composition and Physical Function

Sex impacts the relation between body composition and physical function in older adults. Valentine RJ, Mistic MM, Rosengren KS, Woods JA, Evans EM. Menopause:2009; 16(3):518-23. (42)

Figure 2.2



Objective and Methods: To determine the sex-specific relationships between physical activity, aerobic fitness, adiposity (%Fat), mineral-free lean mass (MFLM) and balance and gait in older adults. Eighty-five female and 49 male sedentary, healthy, community-dwelling older adults (69.6±5.4 and 70.3±4.7 years, respectively) were evaluated on habitual physical, aerobic fitness, whole and regional body composition, and lower-extremity physical function (LEPF) using gait tasks and computerized dynamic posturography. **Results and Conclusions:** Males tended to perform better on all LEPF tasks than women (all p≤0.1). Physical activity was not related to gait; however, fitness was in both sexes (r>0.50, all p<0.05). Body fat was related to gait in women (r=-0.38, p<0.05) but not men. In women only leg MFLM was positively associated with balance (r=0.27, p<0.05). There was an interaction with sex for %Fat on gait (p=0.05), and for MFLM_{LEG} on balance (p<0.05). In sedentary healthy older adults women are more strongly impacted by alterations in body composition. Lower %Fat and preservation of lower body lean mass have important

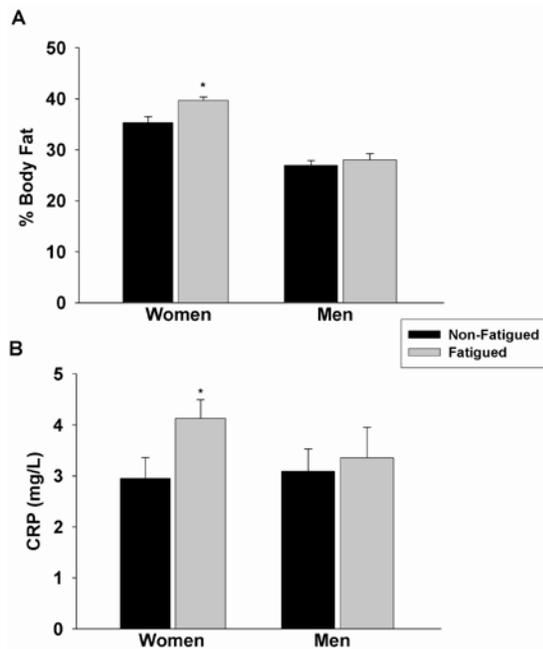
implications for reducing the risk of physical disability, especially in older women.

2.10c Adiposity, Physical Activity, Inflammation and Fatigue

Sex differences in the relationship between obesity, C-reactive protein, physical activity, depression, sleep quality and fatigue in older adults. Valentine RJ, McAuley E, Vieira VJ, Baynard T, Hu L, Evans EM, Woods JA. Brain Behav Immunol: 2009; 23(5):643-8. (30)

Objective and Methods: The aim of this study was to assess sex differences in fatigue and the extent to which adiposity, physical activity and inflammation relate to fatigue (as assessed by 2 items taken from the Chohen-Hoberman Inventory of Physical Symptoms (CHIPS) questionnaire) in sedentary older adults. **Results and Conclusions:** Although similar in age (70 y) and BMI (28.0 kg/m²) women (n = 80) reported 63% greater fatigue than men (n = 47). Adiposity (r = 0.44), CRP (r = 0.29), physical activity (r = -0.26) and fitness (r = -0.41) were related to fatigue in women (all p < 0.05), but not in men. Depression was also related to fatigue in women (r = 0.37), and was the only variable related to fatigue in men (r = 0.42). In women, fatigue was independently explained (all p < 0.05) by CRP (6.6%), depression (6.3%),

Figure 2.3



physical activity (5.8%), and adiposity (3.9%); however, in men, only depression explained variance in fatigue (12.0%). CRP was 40% higher and adiposity 12% higher in women reporting fatigue compared to those with no fatigue; no such differences existed in men. Obese women perceived a greater degree of fatigue than non-obese women, but this was not the case in men. Women report more fatigue than men which was independently associated with inflammation, depression, physical activity and adiposity, whereas in men the only independent predictor was depression. Strategies to prevent fatigue may differ in older women and men, especially with regard to inflammation, physical activity and adiposity.

2.10d Fatigue and Physical Function

Objective and Methods: To complete a preliminary analysis of an on-going study of 49 older adults (70.5 ± 6.2 y, 30 females, 19 males) in which we have been able to collect body composition, physical function, physical activity, and fatigue [assessed by the Multidimensional Fatigue Inventory (MFI)] measures. **Results and Conclusions:** Relative body fatness (%Fat) was correlated to general and mental fatigue in women (r = 0.39 and 0.44, respectively), and although the association between adiposity

and physical fatigue was non-significant in men the strength of the relationship was similar, but likely underpowered ($r = 0.35$, $p = 0.15$). Overweight and obese individuals reported higher levels of general fatigue (9.7 vs. 6.8) and physical fatigue (11.3 vs. 9.9) than those in the normal-weight category ($p < 0.05$), however the sample size limited breakdown by obesity class within sex. In contrast to adiposity, physical activity was inversely associated with all aspects of fatigue (r range = -0.29 to -0.47). In the whole group, the reduced activity subscale was inversely related to normal gait speed ($r = -0.33$). In women, general fatigue, reduced activity, and reduced motivation all corresponded to slower gait and worse performance on the timed up-and-go (r range = 0.38 to 0.47), whereas no relationship was apparent in men. Thus, these cross-sectional data appear to be supportive of our position that both physical activity and body composition are implicated in fatigue, and severity of fatigue and may have relevance for physical function. Moreover, these relationships may differ in older men and women.

Adiposity and Physical Activity Influence Physical Function and Fatigue in Older Women. Valentine RJ, Guest DD, McAuley E, Evans EM. Med Sci Sports Exer: 2010; 42(5):565. (60)

Objective and Methods: Both physical activity and adiposity have been associated with functional performance and fatigue in the elderly; however, the relative impact of each is not established. The aim of this study was to examine the independent contributions of physical activity and adiposity on physical function and fatigue in older community-dwelling women ($N = 43$; 69.7 ± 6.1 yr). Assessments included physical performance via 7-m obstacle walk (7-OB), chair stand (CHAIR) and 6 min walk (WALK); general, physical and mental fatigue via the Multidimensional Fatigue Inventory (MFI); physical activity by weekly pedometer count (STEPS); and adiposity (%Fat) by DEXA. **Results and Conclusions:** As expected, an inverse relationship existed between STEPS and %Fat ($r = -0.38$, $p = 0.01$) and greater STEPS improved 7-OB, CHAIR and WALK performance (r range = 0.42 to 0.51, $p < 0.01$). Greater adiposity was associated with poorer 7-OB ($r = 0.43$, $p = 0.004$) and WALK ($r = 0.52$, $p < 0.001$) performance. Similarly, greater %Fat was associated with higher general fatigue ($r = 0.30$, $p = 0.049$) and mental fatigue ($r = 0.31$, $p = 0.045$) but not physical fatigue ($p = 0.43$). STEPS were related to general fatigue ($r = -0.32$, $p = 0.04$) but not physical or mental fatigue ($p > 0.05$). Hierarchical multiple regression analyses were conducted to determine the independent contribution of %Fat and STEPS to 7-OB, WALK and general fatigue. Greater adiposity ($\beta = 0.32$) and fewer STEPS ($\beta = -0.31$) were associated with poorer 7-OB ($R^2 = 0.27$, $p = 0.002$) and WALK performance ($R^2 = 0.37$, $p < 0.001$; $\beta = -0.36$ and 0.38 , respectively). However, only %Fat ($\beta = 0.30$) was an independent positive predictor of fatigue ($p = 0.049$, $R^2 = 0.09$). Physical function performance is influenced by adiposity and habitual physical activity; however, adiposity is the primary predictor of general fatigue in older women.

2.10e Summary: The preliminary data that the PI and research team has assembled to date is well aligned with the research questions in the proposed project. Indeed, the specific aims of the proposed project are the next step in this line of inquiry. Whereas each of these pieces has been investigated, no single study has captured these variables, along with lean body mass, muscle strength and quality in an attempt to identify the physiological and behavior mediators of fatigue as well as the translational consequences fatigue places on function and independence.

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CHAPTER 3

The Associations of Adiposity, Physical Activity and Inflammation

With Fatigue in Older Adults

Abstract

Persistent feelings of fatigue are a widespread complaint reported by older adults, and are associated with detriments in health and quality of life. **Purpose:** The aim of this study was to determine the influence of weight status, habitual physical activity and inflammation on perceptions of fatigue in relatively healthy older adults. **Methods:** One-hundred eighty-two older men and women (age = 69.2±6.7 years, 98 men, 84 women) were assessed for adiposity (body mass index (BMI) and percent fat via dual-energy X-ray absorptiometry, physical activity (PA) using accelerometers, systemic inflammation via serum C-reactive protein (CRP), Interleukin-6 (IL-6), sIL-6R and WBC count, and fatigue according to the Multidimensional Fatigue Inventory (MFI). **Results:** Men and women reported similar levels of fatigue in all dimensions ($p > 0.05$) with the exception of women reporting higher levels of mental fatigue than men ($p = 0.049$). Adiposity was positively correlated with fatigue (r range = 0.20 to 0.42), whereas PA was inversely associated with fatigue (r range = 0.18 to 0.37), both of which were not related to mental fatigue. CRP, IL-6 and WBC were also related to several dimensions of fatigue (r range = 0.15 to 0.26). Compared across PA-adiposity groups, there was a main effect of PA and adiposity on general and physical fatigue ($p < 0.05$). Regression analyses revealed that the psychosocial variables depression and sleep quality and adiposity independently explained variance in general and physical fatigue. **Conclusion:** Adiposity and inflammation are positively related to general and physical fatigue, with adiposity remaining, independent of other associated factors. In addition, PA is inversely associated with these same dimensions of fatigue, and is an independent predictor of mental fatigue. Adiposity, physical activity and inflammation are identified as potential targets for reducing fatigue in older adults.

Key Words: fatigue, adiposity, inflammation, depression, physical activity

3.1 Introduction

Persistent feelings of fatigue are a widespread complaint reported by older adults. Prevalence estimates for fatigue range from 10% to upwards of 50% in the elderly population (1;2)). Detriments associated with fatigue include, but are not limited to, cardiovascular disease (3), depression (4), and mortality (5). Furthermore, among otherwise healthy individuals, fatigue has been associated with disability and loss of independence (6), and is reported as the most common cause for restricting activity of all types (7).

Recent evidence suggests a relationship between obesity, as measured by body mass index (BMI), and fatigue (8), which may be potentially mediated by chronic systemic inflammation (9). This relation may be augmented in older adults (10) due to age-related increases in a) adiposity (11), b) pro-inflammatory cytokines (12) and c) reductions in physical activity.

The importance of habitual physical activity for optimal health status across the lifespan is well established. Notably, physical activity is an effective treatment for reducing systemic inflammation in older adults (13). Insufficient levels of physical activity have also been associated with reported fatigue in both men and women (14). Recent literature suggests that increasing physical activity may attenuate perceptions of fatigue, at least in younger adults and cancer patients (15;16). Little data exist regarding the influence of varying levels of habitual physical activity on fatigue in the elderly. Regular physical activity has been proven effective in attenuating the adverse effects of adiposity on health status (17); however, whether habitual physical activity can alleviate fatigue in obese individuals has not been determined.

Moreover, the relations among weight status, physical activity, inflammation and perceptions of fatigue are unclear. Interdisciplinary research is needed to develop optimal strategies to reduce fatigue, preserve function and enhance quality of life in older individuals. In this context, the primary objective of the present study was to evaluate the influence of adiposity, habitual physical activity and systemic inflammation on fatigue in relatively healthy older men and women. It was hypothesized that 1) women would report higher levels of fatigue than men, 2) adiposity would be a predictor of fatigue, 3) PA would be inversely related to fatigue, and 4) inflammation would be positively associated with fatigue. Understanding the biological and behavioral influences on fatigue is imperative for combating these detriments in older adults.

3.2 Materials and Methods

Participants

One hundred eighty-two community-dwelling older adults between the ages of 60 and 85 (84 women, 98 men; 69.2±6.7 years) participated in this study. Exclusion criteria included the presence of

severe arthritis, human immunodeficiency virus, smoking, current diagnoses of inflammatory disease or cancer, uncontrolled metabolic or cardiovascular disease, and current use of medications that could influence immune measurements (e.g., corticosteroids). All women were post-menopausal. Participants taking anti-inflammatory medications, medications for depression and statins were included in the study and use was controlled for statistically (see Table 3.2 for medication usage). Following eligibility screening all participants completed a university Institutional Review Board approved informed consent prior to enrollment in the study.

Physical Activity

Physical activity was determined using the Physical Activity Scale for the Elderly (PASE) (18), which estimates the total level of household, occupational and leisure-time physical activities over the past month. Accelerometers (ActiGraph single-axis model, Health One Technology) were used to provide an objective measure of physical activity over 1 week. Participants were instructed to wear the monitor on the non-dominant hip, under clothing, and fastened to a belt worn around the waist. Valid days for accelerometer data were determined by 10 hours of wear time during the waking hours (19), defined as the moment upon getting out of bed in the morning through the moment of getting into bed in the evening. We considered the data to be spurious when counts exceed 20,000 per minute (19), and required that participants had five valid days of data for a reliable estimate of weekly physical activity.

Body Composition

Standing height and weight measurements were completed with subjects wearing light-weight clothing and no shoes. Height was obtained using a stadiometer (Seca, Model 242) with measures obtained to the nearest 0.1 cm. Weight was measured on a calibrated digital scale (Tanita, Model BWB-627A). Whole-body and regional soft tissue composition was measured by dual-energy X-ray absorptiometry (DXA) using a Hologic Discovery A bone densitometer (software version 12.7.3). This software allows isolation of specific regions of interest (ROI), and abdominal fat mass was quantified as a region from L1-L4 to provide a proxy for central adiposity. Precision for DXA measurements of interest are ~ 1-1.5% in our laboratory. Body Mass Index (BMI) was calculated by dividing body mass (kg) by height (m) squared [(kg)/ht(m)²].

Fatigue

Fatigue was measured by completion of the Multidimensional Fatigue Inventory (MFI; (20)). The MFI is used to capture five distinct dimensions of fatigue experienced “lately”, including: general fatigue, physical fatigue, mental fatigue, and perceptions of reduced motivation and reduced activity. In each of

the five subscales, scores range from 4-20, with higher scores indicating greater fatigue. In order to minimize confounding factors imposed by diurnal variation, this questionnaire was completed on the morning of the blood draw. Internal consistency for the MFI subscales was good ($\alpha = .82$), suggesting the five domains adequately reflect a single construct.

Sleep, Depression and Stress

Participants also completed the Pittsburgh Sleep Quality Index (PSQI) (21). The PSQI is a 19-item instrument reflecting overall sleep quantity and quality over the past month, with higher scores reflecting poorer sleep quality. Depression was assessed by the Geriatric Depression Scale (GDS; (22), a 30-item mood scale, assessing how an individual has felt over the past week. Scores on this scale range from 0 to 30, with higher scores corresponding to greater levels of depression. Finally, the Perceived Stress Scale (PSS; (23)) was completed to assess perceived stress. The PSS ranges from 0-40, with higher scores representing a higher level of stress. Each scale had good internal consistencies (all Cronbach $\alpha > .80$). The GDS, PSQI and PSS all have well-established psychometric properties.

Systemic Inflammation

Following an overnight fast, venous blood samples were drawn from an antecubital vein into EDTA or serum separator tubes for plasma and serum, respectively. Serum tubes were allowed to clot for 20-30 min while plasma tubes remained on ice, and all tubes were centrifuged at 1200 x g for 15 minutes at 4°C and serum and plasma were stored at -80°C until analysis. Several measures of systemic inflammation were assessed, including CRP (hs-CRP), IL-6 (hs-IL-6), and sIL-6R using commercially available ELISA kits (R & D Systems, Minneapolis, MN). Our intra-assay CV was determined to be <10% across the range of concentrations. The functional sensitivity of the assay was determined by the manufacturer to be 0.1mg/l, 0.04 pg/ml and 6.5 pg/ml for CRP, IL-6, and sIL-6R, respectively.

Inclusion of multiple markers is useful to substantiate inflammatory analyses. Furthermore, these markers in particular provide both acute phase protein and innate immune cytokine analyses, and have been successfully used to assess immune responses in behavioral disorders (24). Participants were queried regarding any acute illnesses during the 48-hours prior to the blood draw and again one week following this laboratory visit to ensure inflammatory status was not falsely elevated. CRP values >12 mg/L, indicative of acute illness, were eliminated (N = 2). In addition to inflammatory markers, a CBC profile was completed on whole blood to screen for illness, evaluate anemia (low Hemoglobin), and white blood cell (WBC) counts were used as a marker of inflammation.

Statistical Analyses

Data were analyzed with PASW for Windows version 18.0 (SPSS, Inc., Chicago IL). Means and standard deviations were calculated for all participant characteristics and primary outcome variables, and distribution statistics were computed to ensure data were normally distributed. CRP and IL-6 were non-normally distributed and were log transformed, using log base 10, which normalized the data. The non-transformed CRP and IL-6 values are presented in tables, figures, and text to enhance readability and clarity. Independent-samples t-tests were used to examine sex differences in variables of interest. The Mann-Whitney U Test was used to test for differences in categorical variables, including co-morbidities and medication use between sexes.

Partial correlation analyses, controlling for sex and age, were used to examine the relations between physical activity, fatness, inflammation and fatigue. To further evaluate the influences of adiposity and physical activity status on fatigue, participants were categorized based upon BMI: normal weight ($18 < \text{BMI} < 24.9$), overweight ($\text{BMI} > 25.0$) and obese ($\text{BMI} > 30.0$). High- and low-activity groups were created based on median division, using average accelerometer counts/min, as no standard cutoffs have been defined for older adults. The main effects of physical activity and fatness and the presence of PA-fatness interactions on fatigue were determined using two-way ANCOVA, adjusting for age and sex. Analysis of variance (ANOVA), with *post hoc* Tukey, was performed to assess differences in fatigue status between activity-fatness groups.

To test whether physical activity, adiposity, and inflammation, as well as psychosocial variables, were independently related to fatigue, we conducted a series of hierarchical linear regression (HLR) analyses. All analyses were controlled for sex and age, prior to entering other factors into the model. Secondly, we controlled for use of medications known to influence inflammation and/or fatigue, including anti-inflammatories (aspirin and NSAIDs), statins, β -blockers, calcium-channel blockers, and selective serotonin reuptake inhibitors (SSRIs). We next accounted for the number of co-morbid conditions present out of the following list: including cardiovascular disease, pulmonary disease, arthritis, anemia, diabetes, sleep apnea, and cancer history. Next, we entered psychosocial variables, including sleep quality (PSQI), depression (GDS), and perceived stress (PSS) into the model, to control for these influences on fatigue. As the primary objective of the present study was to evaluate the contributions of behavioral and physiologic factors on fatigue, these factors were entered into the model last, to control for all other covariates first, and test for the independent contribution of these factors on fatigue. Corresponding to the proposed hypothesis, these were entered in the following order: adiposity (% Body Fat), physical activity, and inflammation (CRP, IL-6, sIL-6R and WBC). All significance tests were conducted at the $p < 0.05$ level.

3.3 Results

Subject characteristics are presented in Table 3.1. Men and women were similar in age and BMI, but differed in prevalence of CVD and arthritis, with men reporting higher prevalence of these comorbidities, as well as aspirin and statin use (Table 3.2). As expected, women were shorter and lighter, and had greater adiposity (%Fat) than men (all $p < 0.05$). There were no differences in global sleep quality, depression, or fatigue between men and women, with the exception of mental fatigue, with women reporting higher levels ($p < 0.05$). Women had higher levels of sIL-6R ($p < 0.05$), but did not differ in CRP ($p = 0.06$) or IL-6 ($p > 0.1$).

Physiologic and Psychosocial Variables Associated With Fatigue

Partial correlations for the associations of adiposity, physical activity, inflammation, psychosocial factors and fatigue, controlling for sex and age, are shown in Table 3.3. Adiposity was related to general fatigue, physical fatigue, and reduced activity (r range = 0.21 to 0.42, all $p < 0.05$). Similarly, physical activity (PASE and accelerometer counts) was inversely associated with all dimensions of fatigue, except for mental fatigue (r range = -0.18 to -0.37, all $p < 0.05$). Sleep quality, depression scores and perceived stress were each related to fatigue as well. Circulating levels of CRP and IL-6 were positively associated with general and physical fatigue (r range = 0.17 to 0.26), whereas sIL-6R was not related to any dimensions of fatigue. WBC count was related to physical fatigue and reduced motivation ($r = 0.22$ and 0.21 , respectively).

Relations Between Physiologic and Psychosocial Variables

After controlling for the influence of age and sex, physical activity was inversely related to measures of adiposity (r range = -0.30 to -0.39; Table 3.4), and depression (PASE, $r = -0.18$). Both adiposity and physical activity were associated with inflammatory markers. Adiposity was not related to any psychosocial measures. Psychosocial variables were all related to one another, but were not correlated with inflammation, with the exception of sleep quality and perceived stress with WBC ($r = 0.19$ and 0.18 , respectively). Inflammatory markers, except for sIL-6R, were all inter-related (r range = 0.27 to 0.45).

Physical Activity and Adiposity on Fatigue

Results comparing fatigue across activity-fatness groups are shown in Figure 3.1. No interactions existed between activity and adiposity on component of fatigue (all $p > 0.5$). There was a main effect of adiposity status on general and physical fatigue ($p = 0.02$ and $p < 0.01$, respectively). There was also a main effect of activity status on general and physical fatigue and reduced activity ($p = 0.04$, $p < 0.01$, $p = 0.04$, respectively). There was no effect of either adiposity or activity status on reduced motivation or

mental fatigue. These relationships remained when controlling for depression, sleep quality, stress and medication usage (data not shown).

Influence of Inflammation on Fatigue

To further characterize contributions to fatigue, we compared individuals reporting lower levels of general fatigue (general fatigue <10 on the 20-point scale) to those with higher levels of fatigue. CRP and IL-6 were 58% and 29% higher in individuals with higher levels of fatigue than low-fatigued individuals (see Figure 3.2; $p < 0.05$).

Independent Predictors of Fatigue

The independent contribution of adiposity, physical activity and inflammation on dimensions of fatigue were evaluated by a series of hierarchical linear regression analyses (Table 3.5). Sleep quality, depression and adiposity were all independent predictors of general fatigue, physical fatigue, and reduced activity after controlling for all other covariates. Sex was an independent predictor of general fatigue, physical fatigue and reduced activity whereas age was an independent predictor of reduced activity. Only sleep quality and depression were independently associated with reduced motivation. Independent predictors of mental fatigue were age, statin use, depression, and physical activity.

3.4 Discussion

This study represents an examination of the relations among adiposity, physical activity, systemic inflammation and fatigue in a community sample of older adults. To our knowledge, the influences of body composition, physical activity, and inflammation on different dimensions of fatigue has not been previously evaluated in healthy community-dwelling older adults. The major novel findings of this study are: 1) adiposity was associated with several aspects of fatigue, including general fatigue, physical fatigue, and reduced activity, independent of other related risk factors, such as depressive symptoms, sleep quality, perceived stress and physical activity, 2) physical activity was inversely related to most dimensions of fatigue, and independently predicted mental fatigue, and 3) inflammation was correlated with several dimensions of fatigue; however, this relationship was not independent of other related variables. In the present study, fatigue was assessed by the Multidimensional Fatigue Inventory (MFI). The utility of this instrument is the ability to assess five different fatigue domains.

Contrary to our hypothesis we found no significant sex disparity in fatigue (with the exception of mental fatigue). It has been suggested that women may exhibit a greater degree of fatigue and/or perceptions of fatigue, particularly as they age (1;25); however, this finding is equivocal (2;26). The use of the MFI provided an assessment of fatigue severity rather than the presence or absence of fatigue,

precluding the determination of prevalence rates obtained using dichotomous variables of reported fatigue or no fatigue. The lack of sex-differences in fatigue status is in support of results from Corwin and colleagues who found similar levels of fatigue in younger men and women using the MFI (27). Sex differences in fatigue severity and in differing functional domains of fatigue (i.e., physical, mental, etc.) in older adults have not been well characterized. Indeed, after controlling for other factors, sex did make an independent contribution to general fatigue, physical fatigue, and reduced activity, with being male associated with higher levels of fatigue.

The relationship between adiposity status and fatigue appears to be fairly robust, with %Fat remaining a predictor of fatigue in older adults, even after accounting for other contributors (see Table 3.5). This appears particularly true for physical fatigue, as within the low-activity sub-group normal-weight individuals report less fatigue than overweight individuals (Figure 3.1). Recently, the American Geriatrics Society and the National Institute on Aging held a research conference for “Idiopathic Fatigue and Aging” (29). With specific focus on physical fatigue, researchers identified likely contributors, including oxidative stress, inflammation, mitochondrial function and energy utilization (28). In regard to energy utilization at the whole body level, it was proposed that there is a fixed, limited level of energy availability based primarily on aerobic fitness. With age, declines in fitness result in reductions in total energy, while completion of activities of daily living requires greater energy due to changes in biomechanical efficiency. It is speculated that energy imbalance results in the perception of physical fatigue (28). Interestingly, each of the hypothesized mechanisms for physical fatigue is also applicable to obesity, as obesity is associated with increases in inflammation (29), oxidative stress (30), mitochondrial dysfunction (31), and biomechanical inefficiency during daily tasks (32), as well as reductions in aerobic fitness. Coupled together, these age and adiposity related changes clearly place the obese elderly at greater risk for fatigue.

Several research groups have examined the relationship between systemic inflammation and fatigue, however this has been mainly limited to clinical populations, such as cancer and chronic fatigue syndrome (CFS) (33;34), or younger individuals (27;35;36), with limited evidence regarding this association in the general aging population. Some reports have failed to find differences in IL-6 between fatigue groups, such as individuals with CFS compared to healthy counter-parts (34), or between CRP and somatic symptoms (37). The sparse evidence supporting a relation between inflammation and fatigue in healthy humans has been primarily obtained from single-item questions to assess perceived fatigue and/or energy (38;39) and fatigue has often been evaluated as a dichotomous variable, i.e., the presence or absence of fatigue, rather than the degree of fatigue. We aimed to expand upon previous findings by providing a more comprehensive appraisal of fatigue, by assessing multiple dimensions of fatigue. In

addition, most previous work in this area has been limited to primarily sedentary individuals (38), precluding the ability to detect the influence of varying physical activity levels on fatigue.

Insufficient levels of physical activity have also been associated with reported fatigue in both men and women (14), and subsequently, increased physical activity may attenuate perceptions of fatigue, at least in younger adults and cancer patients (15;16). Our data extend this inverse relationship between physical activity and fatigue to older adults, even in the presence of higher levels of adiposity. This relationship is likely bi-directional, as fatigue is reported as one of, if not the most important reason for restricting physical activity, particularly in older adults (7;40). Notably however, there is compelling evidence that physical activity lessens feelings of fatigue. Speculated links between physical activity and fatigue include: the anti-inflammatory effect of exercise (13), the influence of physical activity on self-efficacy (41), or the effectiveness of physical activity mitigating the adverse effects of adiposity on fatigue, similar to other health hazards (17).

Our data corroborate previous reports in other populations (33), as both CRP and IL-6 were associated with fatigue and other somatic symptoms in relatively healthy older adults (38;42;43). Furthermore, individuals reporting higher levels of fatigue also had greater systemic inflammation, represented by higher concentrations of CRP and IL-6. Whether a threshold exists, whereby systemic inflammation exceeding a specific concentration increases perceptions of fatigue, similar to the clinical cutoff of 3.0 mg/l for CRP and cardiovascular disease (44), has not yet been established. In the present study, inflammation was not an independent predictor of any dimension of fatigue when controlling for other related factors. Lim and colleagues used a similar approach in evaluating the relations among adiposity, inflammation, depression and multiple dimensions of fatigue in a young adult population (mean age 36 yr) (26). Our results are similar, as their group also found an independent contribution of depression on all dimensions of fatigue, and of adiposity on general and physical fatigue as well as vigor. Consistent with our results, inflammation did not make an independent contribution on fatigue in young adults (26). Interestingly, in contrast to a growing body of literature establishing a relationship between inflammation and depression (45), our data do not support an association between adiposity or inflammation with depression (see Table 3.4). This lack of relation between inflammation and depression may explain the divergent results from the current study and other published work.

It should be noted, that the inflammatory measures in the current study were captured from a single blood-draw at a single time-point. Most circulating inflammatory markers vary according to circadian rhythms (46), and levels can be influenced acutely by a variety of means, such as accumulated or recent sleep deprivation (47;48), and stress (49). However, the validated questionnaires used to assess psychosocial variables are related to longer states, including lately (MFI), in the past week (GDS), or during the past month (PSQI). Therefore, these series of questionnaires may not reflect very recent

occurrences, such as a night of poor sleep, which may affect reported fatigue. It is also possible that the cross-sectional snapshot of this relationship does not account for the long-term consequences of chronic low-grade systemic inflammation. Cho and colleagues recently demonstrated, prospectively, a significant association between baseline CRP concentrations and fatigue levels at a fifteen year follow-up in younger individuals (36). Longitudinal studies evaluating the interactions of physical activity, adiposity and inflammation with fatigue are merited.

The present study is not without further limitations. First, our study included relatively healthy community-dwelling older adults. In order to maintain a balance between internal and external validity exclusion criteria were limited to diseases and/or medication usage that are known to substantially alter immune function or fatigue status. Furthermore, our study sample resembles that of the general population, with similar prevalence to national averages in several co-morbidities, including arthritis (49% vs. 50%), diabetes (6% vs. 8%), and heart disease (10% vs. 12%) for our data and national averages, respectively. We have elected to statistically control for covariates rather than exclude based on them, which would substantially impact external validity. Thus, our results may not extend to other populations with more severe and/or additional co-morbidities. Secondly, the markers used to assess systemic inflammatory status are not exhaustive, and anti-inflammatory cytokines were not evaluated. However, the balance between pro- and anti-inflammatory cytokines may have important relevance in relation to fatigue. Similarly, the link between inflammatory cytokines and sickness behavior is through the central nervous system (50), which cannot be assessed solely by systemic inflammation. Finally and importantly, the cross-sectional design of the current study precludes any inference regarding causality.

In conclusion, in relatively healthy older adults, women and men report similar levels of fatigue. Sleep quality, depression symptoms and perceived stress all influence fatigue status in both sexes. However, after accounting for these psycho-social influences adiposity, physical activity, and markers of inflammation were all associated with fatigue. Both lower classification of obesity status and higher levels of physical activity beneficially influence fatigue. Results suggest that increasing the physical activity levels of older adults may have important implications for reducing their levels of fatigue, even in the presence of obesity. Given the high prevalence and associated health detriments of fatigue in older adults, longitudinal studies involving reductions in adiposity and increasing physical activity as possible prevention and treatment strategies are warranted.

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Table 3.1 Subject Characteristics

Characteristics	Women (N=84)	Men (N=98)	All (N=182)
Age (years)	69.6±6.5	68.9±6.8	69.2±6.7
Height (m)	1.6±0.6	1.8±0.7*	1.7±0.9
Weight (kg)	70.3±14.2	84.0±14.8*	77.7±16.0
BMI (kg/m ²)	26.7±5.2	27.1±4.5	26.9±4.8
Body Fat (%)	37.8±6.6	26.3±5.7*	31.6±8.4
PASE ¹	147.5±71.0	161.9±73.6	155.1±72.6
CRP (mg/l)	3.0±3.2	2.1±2.3	2.5±2.8
IL-6 (pg/ml)	1.8±1.1	1.9±1.7	1.9±1.4
sIL-6R (ng/ml)	49.0±13.7	42.2±10.7*	45.3±12.6
WBC (k/μl)	5.4±1.4	5.6±1.5	5.5±1.4
Activity (Counts/min) [†]	269±110	322±131*	297±124
<i>Psychosocial Measures</i>			
General Fatigue ²	8.6±3.3	8.3±3.2	8.4±3.3
Physical Fatigue	8.5±3.4	8.4±3.4	8.4±3.4
Reduced Activity	8.6±3.3	8.8±3.5	8.7±3.4
Reduced Motivation	7.0±2.6	7.1±2.7	7.1±2.7
Mental Fatigue	8.6±3.5	7.6±2.9*	8.1±3.2
Pittsburg Sleep Quality Index ³	5.2±3.5	5.0±3.1	5.1±3.2
Geriatric Depression Scale ⁴	4.3±4.2	3.8±4.6	4.1±4.4
Perceived Stress Scale ⁵	10.5±6.0	9.4±5.3	9.9±5.6

*Sex difference (p<0.05). †N=165 for valid data.

¹ Physical Activity Scale for the Elderly. ² Multidimensional Fatigue Inventory subscales range from 4-20, with higher scores indicating higher levels of fatigue. ³ The Pittsburgh Sleep Quality Index ranges from 0-21, higher scores reflecting poorer sleep quality. ⁴ The Geriatric Depression Scale ranges from 0-30, with higher scores corresponding to greater levels of depression. ⁵ The Perceived Stress Scale ranges from 0-40, with higher scores representing a higher level of stress.

Table 3.2 Prevalence of co-morbidities and medication usage

Characteristics	Women N (%)	Men N (%)	All N (%)
<i>Co-morbidities</i>			
CVD ¹	4 (5%)	15 (15%)*	19 (10%)
Rhythm Disorders	9 (11%)	5 (5%)	14 (8%)
Pulmonary Disease	6 (7%)	4 (4%)	10 (5%)
Sleep Apnea	5 (6%)	10 (10%)	15 (8%)
Diabetes	2 (2%)	9 (9%)	11 (6%)
Arthritis	51 (61%)	42 (43%)*	93 (51%)
Cancer History	13 (16%)	24 (25%)	37 (20%)
Anemia	1 (1%)	4 (4%)	5 (3%)
<i>Medications</i>			
Aspirin	32 (38%)	58 (59%)*	90 (49%)
NSAIDs	16 (19%)	14 (14%)	30 (16%)
Anti-hypertensives	34 (40%)	35 (36%)	69 (38%)
β-blockers	13 (15%)	14 (14%)	27 (15%)
Calcium-channel blockers	7 (8%)	11 (11%)	18 (9%)
Statins	24 (28%)	47 (48%)*	71 (39%)
Anti-depressants	12 (14%)	11 (11%)	23 (13%)
SSRIs	6 (7%)	6 (6%)	12 (7%)
Thyroid	18 (21%)	6 (6%)*	24 (13%)

*Sex difference (p<0.05).

¹ Cardiovascular disease included history of myocardial infarction, bypass surgery, or other treatment (such as stent placement).

SSRIs – selective serotonin reuptake inhibitors

Table 3.3 Relation between adiposity, physical activity, inflammation, psychosocial variables and fatigue in older adults.

	General Fatigue	Physical Fatigue	Reduced Activity	Reduced Motivation	Mental Fatigue
Age	0.108	0.083	0.276*	0.156	0.092
BMI	0.209*	0.340*	0.224*	0.142	0.031
%Fat	0.248*	0.423*	0.329*	0.199*	-0.029
PASE	-0.279*	-0.367*	-0.320*	-0.221*	-0.047
Activity	-0.209*	-0.353*	-0.318*	-0.181*	0.146
CRP	0.170*	0.212*	0.104	0.153*	0.062
IL-6	0.194*	0.258*	0.211*	0.129	-0.025
sIL-6R	0.029	0.101	0.03	0.019	-0.046
WBC	0.147	0.223*	0.154	0.213*	-0.104
PSQI	0.528*	0.383*	0.282*	0.340*	0.161
GDS	0.430*	0.402*	0.385*	0.451*	0.368*
PSS	0.384*	0.306*	0.273*	0.379*	0.367*

* Significant correlation at $p < 0.05$.

All correlations controlled for age and sex (age-correlations controlled for sex).

Table 3.4 Relations between physiologic and psychosocial variables

	%Fat	PSQI	GDS	PSS	CRP	IL-6	sIL-6R	WBC
PASE	-0.304*	-0.084	-0.175*	-0.047	-0.141	-0.187*	0.011	-0.203*
Activity	-0.385*	-0.158	-0.139	-0.077	-0.106	-0.069	-0.087	-0.306*
BMI	0.730*	0.066	-0.081	0.073	0.320*	0.311*	0.154*	0.347*
%Fat		0.037	0.062	0.052	0.413*	0.351*	0.113	0.404*
PSQI			0.306*	0.326*	0.006	-0.008	0.094	0.193*
GDS				0.616*	0.026	-0.006	0.035	0.021
PSS					0.033	0.120	-0.008	0.180*
CRP						0.452*	-0.119	0.274*
IL-6							<0.001	0.378*
sIL-6R								0.152

* Significant correlation at $p < 0.05$.

All correlations controlled for age and sex.

Table 3.5 Linear regression analyses of independent predictors of fatigue

Subscale	R	R ²	ΔF	Significance, ΔF	Variables	β	P Value
General Fatigue							
F _{17,135} = 6.378 P < 0.001	0.667	0.445	6.378	<0.001	Sex	0.205	0.045
					PSQI	0.428	<0.001
					GDS	0.250	0.006
					%Fat	0.301	0.011
Physical Fatigue							
F _{17,135} = 6.250 P < 0.001	0.664	0.440	6.250	<0.001	Sex	0.318	0.002
					PSQI	0.188	0.010
					GDS	0.363	<0.001
					%Fat	0.459	<0.001
Reduced Activity							
F _{17,135} = 4.715 P < 0.001	0.610	0.294	4.715	<0.001	Sex	0.299	0.006
					Age	0.192	0.020
					PSQI	0.151	0.050
					GDS	0.317	0.001
					%Fat	0.351	0.006
Reduced Motivation							
F _{17,135} = 3.515 P < 0.001	0.554	0.307	3.515	<0.001	PSQI	0.174	0.032
					GDS	0.346	0.001
Mental Fatigue							
F _{17,135} = 3.301 P < 0.001	0.542	0.292	3.301	<0.001	Age	0.183	0.036
					Statins	0.178	0.034
					GDS	0.290	0.004
					Activity	0.250	0.007

All regression analyses were run in the following order: Step 1, age and sex; Step 2, medications (anti-inflammatories, statins, β-blockers, calcium channel blockers, and SSRIs); Step 3, number of co-morbidities; Step 4, psychosocial variables (PSQI, GDS, PSS); Step 5, activity (accelerometer counts/min) and adiposity (%Fat); Step 6, inflammatory markers (CRP, IL-6, sIL-6R, WBC).

General Fatigue: At Step 1, entering age and sex, R² = 0.011. Step 2, entering medications, R² = 0.045. Step 3, entering the number of co-morbidities, R² = 0.108. Step 4, entering psychosocial variables, R² = 0.398. Step 5, entering activity counts and %Fat, R² = 0.441. Step 6, entering inflammation, R² = 0.445.

Physical Fatigue: At Step 1, entering age and sex, R² = 0.011. Step 2, entering medications, R² = 0.072. Step 3, entering the number of co-morbidities, R² = 0.112. Step 4, entering psychosocial variables, R² = 0.300. Step 5, entering activity counts and %Fat, R² = 0.437. Step 6, entering inflammation, R² = 0.440.

Reduced Activity: At Step 1, entering age and sex, R² = 0.088. Step 2, entering medications, R² = 0.133. Step 3, entering the number of co-morbidities, R² = 0.143. Step 4, entering psychosocial variables, R² = 0.285. Step 5, entering activity counts and %Fat, R² = 0.366. Step 6, entering inflammation, R² = 0.373.

Reduced Motivation: At Step 1, entering age and sex, R² = 0.037. Step 2, entering medications, R² = 0.083. Step 3, entering the number of co-morbidities, R² = 0.087. Step 4, entering psychosocial variables, R² = 0.275. Step 5, entering activity counts and %Fat, R² = 0.294. Step 6, entering inflammation, R² = 0.307.

Mental Fatigue: At Step 1, entering age and sex, R² = 0.047. Step 2, entering medications, R² = 0.101. Step 3, entering the number of co-morbidities, R² = 0.102. Step 4, entering psychosocial variables, R² = 0.227. Step 5, entering activity counts and %Fat, R² = 0.274. Step 6, entering inflammation, R² = 0.294.

Figure 3.1 The interactive and main effects of adiposity and activity status on (A) general fatigue, (B) physical fatigue and (C) reduced activity. Values are displayed as mean±SEM. Numbers inside of bars represent the number of participants falling into each category, which is consistent across dimension of fatigue. * Indicates a significant difference from the high-activity/normal-weight group ($p < 0.05$). † Indicates a significant difference from the low-activity/over-weight group ($p < 0.05$).

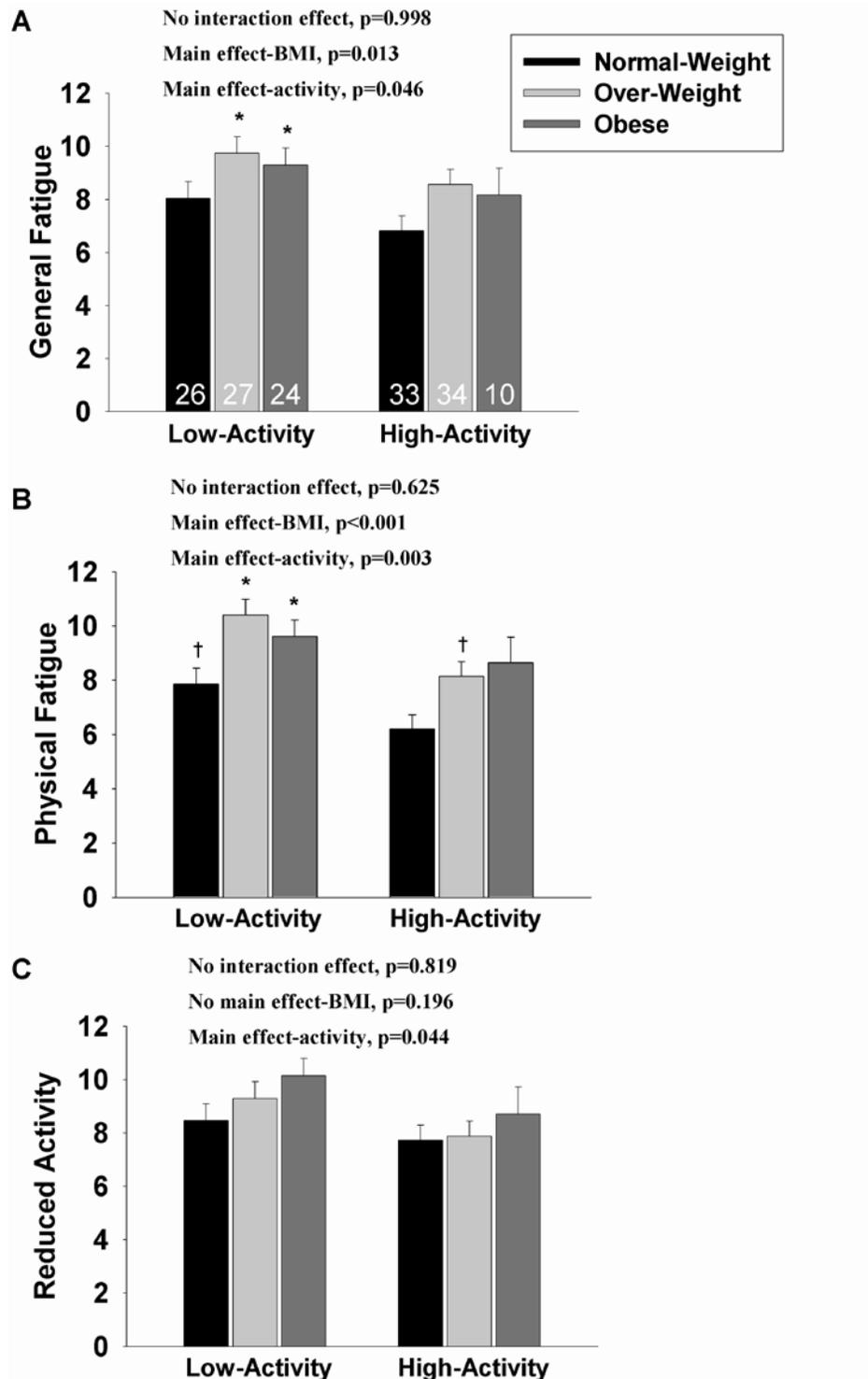
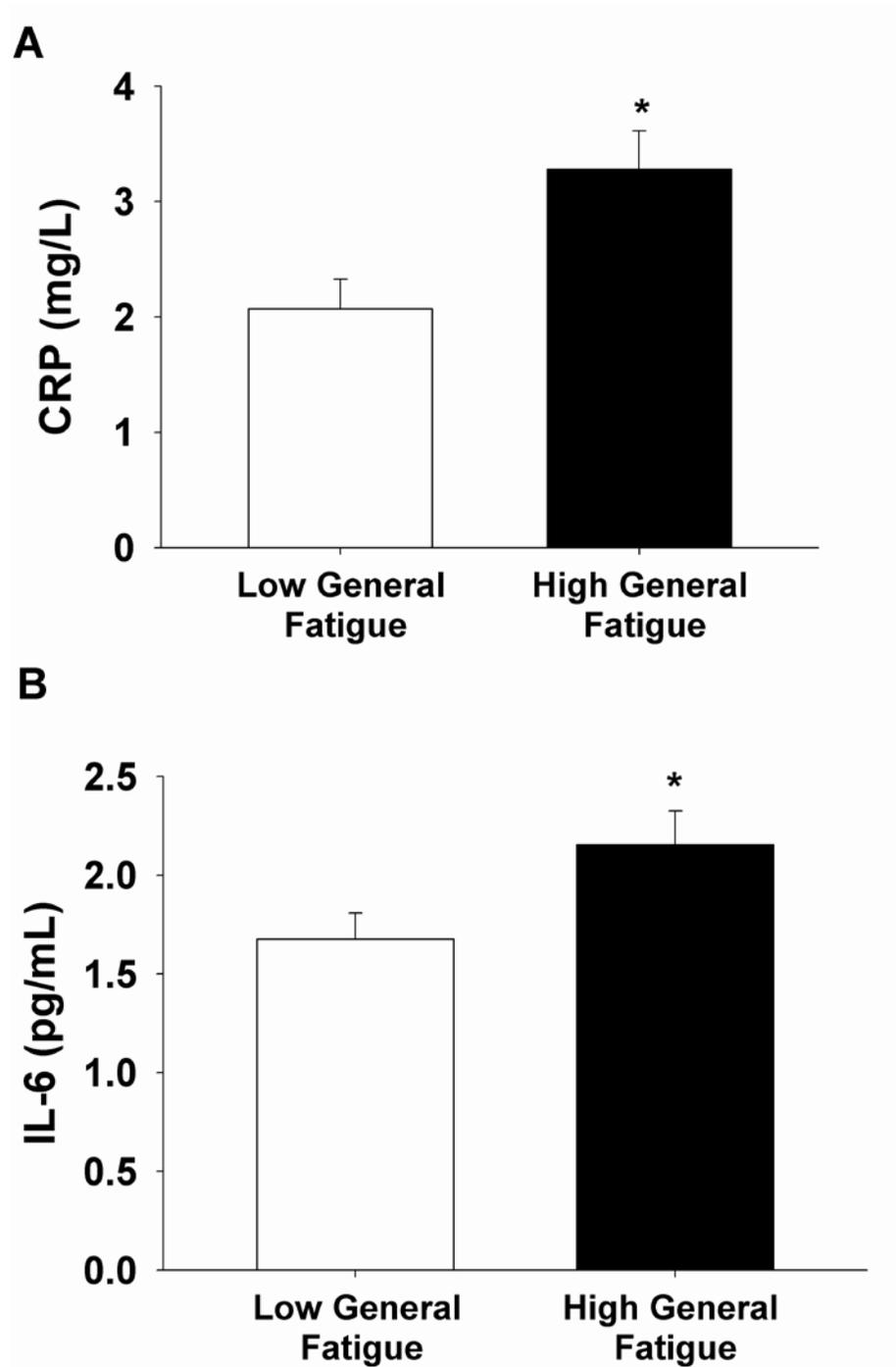


Figure 3.2 C-reactive protein (CRP) (A) and Interleukin-6 (IL-6) (B) in older adults reporting higher levels of general fatigue compared to those reporting low levels of fatigue. Mean±SEM.

* Indicates a significant difference from the low-fatigued group ($p < 0.05$).



CHAPTER 4

Body Composition and Habitual Physical Activity Are Related with Performance Measures of Physical Function in Community-Dwelling Older Adults

Abstract

Aging is accompanied by gains in adiposity, loss of lean mass, reductions in physical activity, and loss of physical function. **Purpose:** The primary purpose of this study was to determine the influence of body composition components [adiposity and mineral-free lean mass (MFLM)] and physical activity (PA) on measures of lower-extremity physical function (LEPF) in community-dwelling older adults. **Methods:** Older adults (N=156, age=68.9±6.7 years, 85 men) were assessed for adiposity (% Fat) and lean mass [MFLM_{LEG} and Skeletal Muscle Index (SMI); appendicular MFLM/ht²] via dual-energy X-ray absorptiometry, and PA using accelerometers. LEPF was assessed by 7-m walk tests (WALK), a Timed Up and Go (Up&Go), a 30-second chair stand test (30-Chair), a 6-min walk, the Short Physical Performance Battery (SPPB) and the Star-Excursion Balance Test (STAR). **Results:** Men performed better on all LEPF tests (all p<0.05). MFLM and SMI were not related to any LEPF outcomes. In the absence of a significant interaction, main effects for adiposity were found for mobility tests of LEPF, including WALK, Up&Go, 30-Chair and 6-min walk with higher adiposity relating to poorer performance. There was a main effect of PA on 6-min walk only with greater PA conferring better performance. After accounting for influences of sex, age and number of co-morbidities, % Fat remained a significant predictor of all mobility measures and the STAR composite, as did PA for Up&Go and 6-min walk (all p < 0.05). **Conclusion:** Our results suggest that adiposity is a major determinant of both balance and gait-related physical function in relatively healthy older adults. Daily physical activity may help to prevent age-related loss of mobility.

Key Words: adiposity, lean mass, physical activity, function, mobility

4.1 Introduction

The aging process is accompanied by a progressive reduction in lean mass, increases in total adipose tissue, and increased ectopic adipose, including visceral and accumulation of lipid infiltration into the muscle, especially after menopause in women (1;2). These changes in body composition are accompanied by progressive detriments in physical function with aging. Unfortunately, these alterations in body composition and fat distribution are commonly masked when assessed by BMI as often no substantial change, if any, in BMI appears, due to a reduction in muscle mass that accompanies the increase in fat mass (3). A number of studies have demonstrated an increased discrepancy between BMI and %Fat in the aging population (4).

A rapidly growing public health concern in the aging population is a decrement in physical function. Reductions in physical function are associated with several adverse health outcomes, including further disability, fall risk, loss of independence, and mortality (5-8). Higher levels of adiposity have been linked to reductions in lower-extremity physical function (LEPF), limited mobility (9) and elevated risk for physical disability in older adults (10). This finding is inconsistent, as other reports support a role of reduced lean mass, particularly in the lower-body, rather than accumulation of fat mass as the primary determinant of functional ability (11-13). The influences of body composition components in relation to physical function are not well characterized. It is intuitive that the interaction between reduced skeletal muscle mass and increased adiposity may have the most impact on physical function. Lower levels of muscle mass may not be problematic if the load being carried (i.e., total body mass) is relatively low as well (14). On the other end of the spectrum, an individual with a high level of muscle mass, but a disproportionately elevated total body mass will likely have detriments in function. The somatotype at greatest risk for disability is a frail obese individual (relatively low levels of muscle mass in combination with elevated fat mass), which unfortunately represents a rapidly growing portion of the population (15).

There is speculation that physical inactivity may provide a more direct link between elevated adiposity, reduced muscle mass and functional decline (16). Physical activity has been consistently associated with improvements in physical function (17;18). These benefits manifest as both a prolonged time until mobility disability occurs in the lifespan as well as improvements in functional testing scores. For example, physical activity has been shown to improve status [assessed via the short physical performance battery (SPPB)] scores by >1 point which has been supported as a clinically meaningful improvement in physical function (19). Some evidence suggests that moderate-to-vigorous physical activity may be required to maintain and/or improve physical function with aging (17;18;20).

The interactive effects of physical activity and adiposity on physical function are less clear. Studies evaluating the relationship between physical activity and function often statistically account for body composition, in the form of BMI, and may be overlooking an important determinant involved in

function. A better understanding of the influence of physical activity on function, particularly in obese individuals at increased risk of disability, is warranted. In this context, the primary aim of this study was to determine the relative influences of disordered body composition (i.e., increases in adiposity relative to loss of muscle mass) and objectively measured physical activity on performance measures of physical function in relatively healthy older men and women.

4.2 Materials and Methods

Participants

One hundred fifty-six community-dwelling older adults (71 women, 85 men, 68.9 ± 6.7 years) participated in this study. Exclusion criteria included the presence of severe arthritis, human immunodeficiency virus, smoking, current diagnoses of inflammatory disease or cancer, uncontrolled metabolic or cardiovascular disease. Individuals with neurologic diseases or severe orthopedic problems at the time of recruitment were also excluded. Following eligibility screening all participants completed a university Institutional Review Board approved informed consent prior to enrollment in the study.

Physical Activity

Accelerometers (ActiGraph single-axis model, Health One Technology) were used to provide an objective measure of physical activity over 1 week. Participants were instructed to wear the monitor on the non-dominant hip, under clothing, and fastened to a belt worn around the waist during waking hours. Data were recorded and stored in 1-minute epochs. It was required that participants had five valid days of data for a reliable estimate of weekly physical activity. Valid days for accelerometer data were determined by 10 hours of wear time during the waking hours (21), defined as the moment upon getting out of bed in the morning through the moment of getting into bed in the evening. We considered the data to be spurious when counts exceed 20,000 per minute (21).

Body Composition

Standing height and weight measurements were completed with subjects wearing light-weight clothing and no shoes. Height was obtained using a stadiometer (Seca, Model 242) with measures obtained to the nearest 0.1 cm. Weight was measured on a calibrated digital scale (Tanita, Model BWB-627A). Body Mass Index (BMI) was calculated by dividing body mass (kg) by height (m) squared (kg/m^2). Whole-body and regional soft tissue composition was measured by DXA using a Hologic Discovery A bone densitometer (software version 12.7.3). Regional analyses were performed per manufacturer guidelines and involved bisecting the femoral neck to determine mineral-free lean mass (MFLM) of the legs, and the gleno-humeral joint to determine MFLM of the arms. The MFLM of the

arms and legs was summed to provide a measure of appendicular lean mass, which was then normalized by height (kg/m^2), similar to BMI to provide a skeletal muscle index (SMI). Precision for DXA measurements of interest are 1-1.5% in our laboratory.

Lower-Extremity Physical Function

A series of physical performance tests were administered to evaluate lower-extremity physical function (LEPF). The Short Physical Performance Battery (SPPB) was used to objectively evaluate physical function. This 3 item performance test consists of a combination of tests including balance, gait speed and chair stands that correlate well with degree of disability, loss of independence and mortality, and with other objective measures of strength and balance (22). Functional gait tests included a series of 7-meter walks, performed at normal walking speed (WALK), and as quickly as possible (FASTWALK). Each participant completed two trials of 7-m walks for both conditions. Participants also completed a timed up-and-go (UPGO) as quickly as possible. On the command “go” participants were told to stand from a chair, walk around a cone placed 2.5 m away and return to the chair and sit down, while being timed. Similarly, participants completed a series of as many repeated chair stands as possible over a 30-second period (CHAIR-30). Finally, a 6-minute walk was used as a measure of functional endurance which has been shown to be useful and clinically meaningful in this population.

Balance

The Star-Excursion Balance Test (STAR), also known as the Lower-Extremity Reach Test (LERT), was performed to challenge unilateral dynamic balance (23). This test involved balancing on a stance leg and reaching with the opposite leg as far as possible. Participants were instructed to maintain hands on hips and were not allowed to shift their weight from the stance leg. Following several familiarization trials, 5 reaches were completed in the anterior, medial, and posterior directions (in reference to the stance leg) (23), and the distance from the heel of the stance foot to the distal touch point of each was recorded. Reach distances were normalized to leg length of the reach leg. This distance reflects dynamic balance of each limb (23).

Statistical Analyses

Data were analyzed with PASW for Windows version 18.0 (SPSS, Inc., Chicago IL). Means and standard deviations were calculated for all participant characteristics and primary outcome variables, and distribution statistics were computed to ensure data were normally distributed. Independent samples *t*-tests were conducted to determine sex differences. Partial correlations, controlling for sex and age, were conducted to examine the associations among variables of interest. A series of hierarchical linear

regression analyses were conducted to assess the independent contributions of adiposity, $MFLM_{LEG}$, and physical activity on physical function. Due to known differences between men and women (e.g. adiposity, physical activity and function), all analyses were controlled for sex and age. Additionally, we categorized subjects based upon adiposity categories according to World Health Organization cut-points for older adults for women and men, respectively: healthy fat (24-35.9% and 13-24.9%), over-fat (36-41.9% and 25-29.9%) and obese (>42% and >30%) (24). Using the median value for activity counts, high- and low-activity groups were created. To determine the presence of an interaction of PA and adiposity on function, as well as main effects of each, a two-way ANCOVA, adjusting for age and sex was performed. Analysis of variance (ANOVA), with *post hoc* Tukey, was performed to assess differences in function between activity-fatness groups. All significance tests were conducted at the $p \leq .05$ level.

4.3 Results

Characteristics of participants are presented in Table 4.1. Men were taller and weighed more than women. Although similar in BMI and activity levels, women had significantly higher %Fat, and lower MFLM corresponding to a lower skeletal muscle index (SMI). Men were more active than women for total activity, but did not engage in more moderate-to-vigorous physical activity (MVPA). In regard to comorbidities, women reported a higher prevalence of arthritis, with no other sex differences. On functional tasks, men performed better than women on the 7-meter fast walk (7m FAST), the Up&Go, the 6-min walk, and the SPPB composite score (Table 4.2; all $p < 0.05$). On balance tests, men performed better on the medial reach only ($p = 0.04$), with posterior and composite reaches failing to reach significance ($p = 0.08$ and $p = 0.06$, respectively) compared to women.

Adiposity was inversely associated with all measures of physical function (r range = 0.20 to 0.44), however no measure of lean mass (MFLM, $MFLM_{LEG}$, or SMI) correlated with any functional measure (Table 4.3). Higher total activity counts were related to better physical function on walking tasks (r range = 0.19 to 0.36), but not chair rise tasks ($p > 0.05$). MVPA was only related to distance covered on the 6-min walk test ($r = 0.25$, $p < 0.01$).

Results comparing function measures across PA-fatness groups are shown in Figure 4.1. There was an interaction between PA and adiposity for only the 30-second chair stand test of the gait-related functional tasks. In the absence of other interactions, there was a main effect of adiposity on several functional tests, including WALK, UP&GO, 5-rep chair-stand, and 6-min walk (all $p < 0.05$). In contrast, there was a main effect of activity on the 6-min walk only ($p = 0.03$). With regard to balance tests, there was an interaction on medial, posterior and composite reach distances (interaction $p < 0.05$, see Figure 4.2). There was a main effect of adiposity on anterior reach distance ($p = 0.02$).

Regression analyses were performed to examine the independent contribution %Fat, MFLM_{LEG} and physical activity to physical function (Table 4.4). After controlling for age, sex, and number of comorbidities, %Fat remained a significant predictor of Up&Go, Chair-stand (both 5-rep and 30-second), 6-min walk, and balance performance. Physical activity was an independent predictor of the Up&Go and 6-min walk. MFLM_{LEG} did not significantly contribute to the model for any outcome of performance, and when replaced with other measures of lean mass (total MFLM or SMI) this result did not change. When total PA was replaced with time spent in MVPA there was an independent contribution of MVPA on the 6-min walk test only (data not shown).

4.4 Discussion

The results from the present study support a detrimental role of adiposity on physical function in aging men and women. We add to the mounting literature aiming to uncover the etiological factors influencing physical functional limitations in older adults. In particular, our data support adiposity, rather than lean mass as the more deleterious body composition component affecting function. Several investigations have corroborated a relationship between BMI and performance on functional tasks, including the 6-min walk and 400-m walks. However, given the discordance between BMI and adiposity in the aging population and in individuals most at risk for mobility limitations in particular, we suggest the increasing importance of measuring adiposity rather than using BMI as a surrogate. Our data underscores the importance of utilizing measures of adiposity as this field of study evolves.

The findings in the current study expand on the current literature, attempting to characterize the physical function ability of a growing population of overweight and obese older adults (9). The most intuitive reason for this decline in physical function with obesity is the physical burden of carrying an excess load, which is typically accompanied by minimal increases (if any) in muscle mass or strength. Similarly, obesity is associated with biomechanical changes in gait (25), which likely is a cause and consequence of mobility disability. This may be at least partially explained by the added energy requirement to complete a given task, particularly as accumulating activities of daily living deplete energy stores throughout the day (26).

The clear robust effect of adiposity on physical function has been largely overlooked in studies investigating the relationship between PA and function. This becomes increasingly important given the growing population of overweight and obese older adults. Limited objective exercise intensity data in regard to physical function are available. A recent report from Chale-Rush and colleagues, reported for the first time individuals reporting greater than 150 min/week of MVPA (as captured by self-report) perform better on physical performance tasks, including the SPPB and 400m walk (20). Of note, that study was limited to individuals at risk for mobility disability (SPPB < 10), and MVPA activity groups

were divided based on 150 min/wk of MVPA (20). In the current study the median split for objectively measured MVPA was < 60min/wk, substantially lower than that previously used. Our data support increases in total activity to be related to physical function performance, with no added benefit of MVPA. Perhaps setting the MVPA activity categories at a higher level of accumulating activity would allow for the functional differences to be seen. These findings that total, or light activity appear to be sufficient for higher scores of function are consistent with others using objectively measured PA (17;27;28). Our findings extend the previous relations of activity with the SPPB to additional measures of function, including the Up&Go, 6-min walk and dynamic balance tests in both men and women. In contrast to the majority of studies investigating the relations between physical activity and function, which have been limited to sedentary populations, we targeted recruitment to obtain a wide array of activity levels in order to gain a better understanding of varying levels of activity and functional decline.

Prospective studies have identified an association between physical activity and attenuation in muscle mass loss and preservation of muscle strength and function (29). Limited work has been done to identify intensity-specific associations between habitual physical activity and reductions in functional decline. However, loss of muscle strength, rather than lean mass *per se*, appears to be a more important determinant of function (30). Additionally, the relationship between physical activity and muscle quality, or strength per muscle mass, may also play a role in regard to the decline in function seen with age (31). Aging is associated with reductions in muscle quality (strength normalized per muscle size or mass), in addition to declines in strength or mass alone, and leg muscle quality is an important factor for physical function in obese frail elderly (32). Increases in obesity status are also associated with poorer muscle quality (33). Thus, age-related changes in adiposity, physical activity and muscle quality may all impact obesity-related mobility impairments. Development of treatment strategies to attenuate declines in function is imperative, as the prevalence of obesity-related disability continues to grow rapidly, with estimates suggesting > 40% of obese individuals reporting functional impairment (34).

The present study is not without limitations. The current population included a wide variety of physical activity, body composition, and functional ability levels, and may not reflect the relationships that may be present in more disabled populations. It should be noted, that our study sample is similar in obesity and co-morbidity prevalence to that of the general population. We believe this may provide a framework for the initial phases of the disablement process (19) and is relevant in regard to prevention of mobility disability. In creating the activity sub-groups, there is no consensus for clear cut-points in the older adults and we relied on median splits for high- and low-activity groups. Identification of a threshold effect, whereby accumulation of a set quantity of physical activity is necessary for achieving functional benefits has not been established. Using recognized MVPA cut-offs (> 150 min/wk) for other health benefits (35), our high-activity sample was limited to 43 participants (26%). Given that the population in

the current study was relatively health and community-dwelling, yet such a small portion accumulating > 150 min/wk of MVPA this may not be an appropriate cut-off, particularly when studying more disabled or mobility-limited populations.

In conclusion, reductions in adiposity, rather than focusing on gains in lean mass, appear to be a worthwhile target to maintain, or possibly regain, mobility in older adults. As a behavioral therapy, physical activity may have direct and indirect benefits, via weight management and maintenance of muscle mass, strength, and quality. The quantity and intensity of physical activity required to obtain benefits in function are currently not established. Our data support increases in total activity to be related to physical function performance, with no added benefit of MVPA. This finding has great public health significance, as older adults can positively influence their physical function ability simply by increasing their daily activity levels, without the burden of high-intensity ‘training’. Due to the complexity of these relationships, future work should simultaneously assess each of these factors to further our understanding the disablement process. Uncovering the key influential factors contributing to disability is essential for development and implementation of effective prevention and treatment strategies for loss in mobility.

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Table 4.1 Subject Characteristics

Characteristics	Women (N=71)	Men (N=85)	p-value
Age (years)	69.1±6.2	68.8±8	0.837
Height (m)	1.62±0.6	1.76±0.7	<0.001
Weight (kg)	69.1±14.1	82.8±13.8	<0.001
BMI (kg/m ²)	26.3±5.1	26.7±3.9	0.570
Body Fat (%)	37.4±6.9	26.2±5.6	<0.001
SMI (kg/m ²)	6.5±1.0	8.4±1.0	<0.001
Activity counts (counts/min)	274.0±111.5	324.2±131.0	0.012
MVPA (min/week)	79.6±96.8	104.1±123.1	0.175
<i>Co-morbidities</i>			
Cardiovascular	4 (5%)	15 (15%)	0.055
Respiratory or pulmonary	9 (11%)	5 (5%)	0.232
Arthritis	6 (7%)	4 (4%)	0.037
Number of medical conditions	5 (6%)	10 (10%)	0.543
Number of medications	2 (2%)	9 (9%)	0.097

Means±SD are presented unless otherwise indicated.

Table 4.2 Lower-Extremity Physical Function Performance

<i>Dynamic Gait</i>	Women (N=71)	Men (N=85)	p-value
7-meter Walk (sec)	5.34±1.09	5.28±0.94	0.704
7-meter FastWalk (sec)	3.80±0.71	3.53±0.74	0.022
Up&Go (sec)	6.31±1.78	5.72±1.59	0.030
5-rep Chair Stand (sec)	8.58±2.68	7.65±2.97	0.050
30-sec Chair Stand (reps)	15.72±4.13	17.51±5.89	0.035
6-min walk (meters)	561±94	630±119	<0.001
SPPB Total Score	11.47±1.03	11.6±1.2	0.369
<i>Balance</i>			
Anterior Reach	1.72±0.19	1.75±0.17	0.344
Medial Reach	1.52±0.20	1.59±0.25	0.037
Posterior Reach	1.03±0.33	1.13±0.33	0.080
Composite Reach	4.27±0.65	4.47±0.67	0.064

Means±SD are presented unless otherwise indicated.

Table 4.3a Relation between adiposity, lean mass, physical activity and function in older adults.

	WALK	FASTWALK	Up&Go	5-Rep Chair	30-sec Chair	6-min Walk	SPPB Total
Age	.335*	.383*	.399*	.385*	-.361*	-.550*	-.360*
%Fat	.313*	.287*	.324*	.284*	-.386*	-.458*	-.219*
MFLM _{LEG}	.155	.077	.092	.138	-.023	-.051	-.147
SMI	.184	.148	.081	.030	.035	-.165	-.103
Activity Counts	-.236*	-.150	-.200*	-.130	.163	.351*	.181*
MVPA	-.177*	-.134	-.099	-.073	.121	.288*	.119

* Significant correlation at $p < 0.05$. All analyses were controlled for age and sex (except for age, which is controlled for sex only).

Table 4.3b Relation between adiposity, lean mass, physical activity and balance in older adults.

	Anterior	Medial	Posterior	Composite
Age	-.271*	-.327*	-.434*	-.402*
%Fat	-.315*	-.324*	-.264*	-.335*
MFLM _{LEG}	-.152	-.064	-.040	-.086
SMI	-.156	-.092	-.056	-.106
Activity Counts	.218*	.234*	.177*	.232*
MVPA	.198*	.140	.182*	.196*

* Significant correlation at $p < 0.05$. All analyses were controlled for age and sex. (except for age, which is controlled for sex only).

Table 4.4 Linear regression analyses of independent predictors of physical function

Subscale	R	R ²	ΔF	Significance, ΔF	Variables	β	P Value
Up&Go							
F _{6,158} = 12.081 P < 0.001	0.561	0.314	12.081	<0.001	Sex	0.032	0.795
					Age	0.394	<0.001
					Co-morbidities	-0.035	0.608
					%Fat	0.305	0.003
					Activity	-0.190	0.018
					MFLM _{LEG}	0.072	0.486
5-rep Chair Stand							
F _{6,156} = 12.106 P < 0.001	0.495	0.245	12.106	<0.001	Sex	-0.082	0.551
					Age	0.404	<0.001
					Co-morbidities	0.019	0.800
					%Fat	0.254	0.021
					Activity	-0.087	0.320
					MFLM _{LEG}	0.183	0.111
30-second Chair Stand							
F _{6,161} = 9.787 P < 0.001	0.524	0.275	9.787	<0.001	Sex	-0.114	0.373
					Age	-0.363	<0.001
					Co-morbidities	-0.049	0.496
					%Fat	-0.424	<0.001
					Activity	0.064	0.437
					MFLM _{LEG}	-0.019	0.862
6-min Walk							
F _{6,146} = 25.819 P < 0.001	0.725	0.525	25.819	<0.001	Sex	0.007	0.945
					Age	-0.465	<0.001
					Co-morbidities	-0.117	0.058
					%Fat	-0.396	<0.001
					Activity	0.183	0.011
					MFLM _{LEG}	-0.010	0.907
SPPB							
F _{6,155} = 7.383 P < 0.001	0.479	0.229	7.383	<0.001	Sex	0.058	0.681
					Age	-0.368	<0.001
					Co-morbidities	-0.079	0.296
					%Fat	-0.185	0.098
					Activity	0.146	0.094
					MFLM _{LEG}	-0.210	0.074
STAR Composite							
F _{6,159} = 11.734 P < 0.001	0.561	0.315	11.734	<0.001	Sex	0.016	0.902
					Age	-0.358	<0.001
					Co-morbidities	-0.162	0.022
					%Fat	-0.293	0.005
					Activity	0.142	0.081
					MFLM _{LEG}	-0.129	0.215

Figure 4.1 The interactive effects of adiposity and physical activity on (A) Up&Go, (B) 5-Rep Chair Stand, (C) 30-sec Chair Stand, (D) 6-min walk and (E) SPPB total score. Numbers in bars represent the number of participants in each group. Values are presented as means and SE. * Significant difference from the healthy-fat/high-activity group ($p < 0.05$). † Significant difference from the obese/low-activity group ($p < 0.05$).

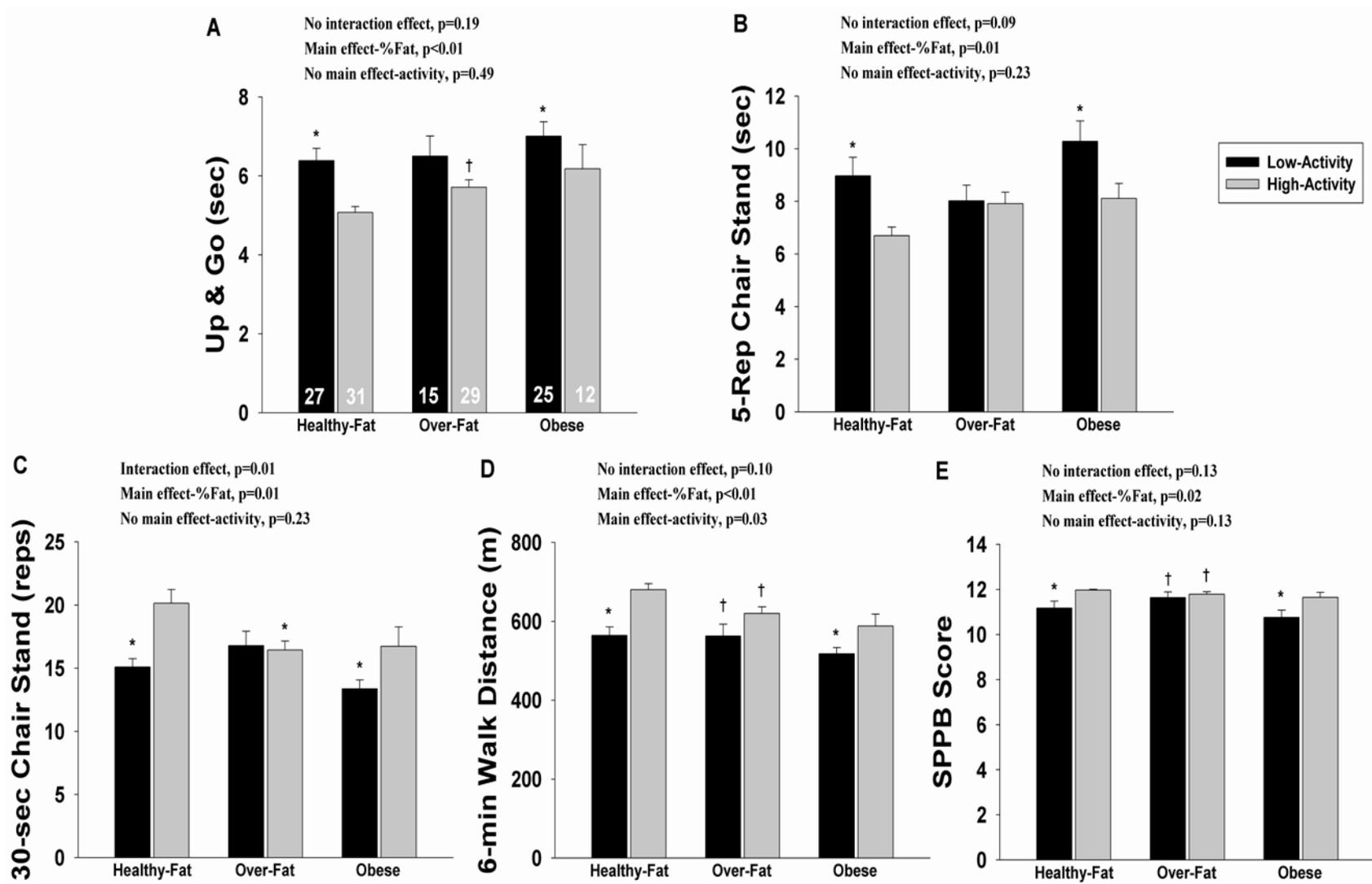
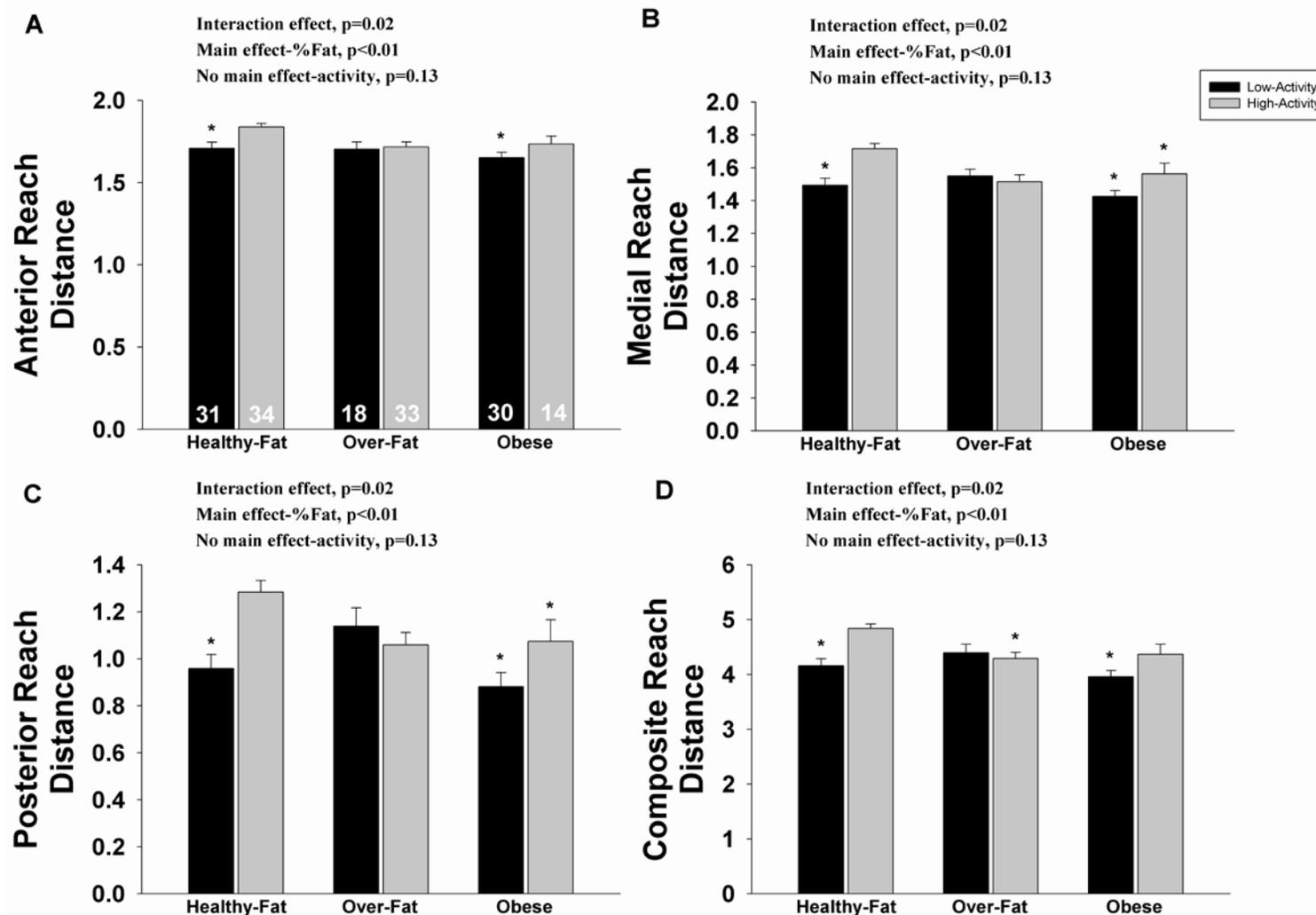


Figure 4.2 The interactive effects of adiposity and physical activity on dynamic balance, including: (A) Anterior, (B) Medial, (C) Posterior and (D) Composite reach distances, normalized to leg length. Numbers in bars represent the number of participants in each group. Values are presented as means and SE. * Significant difference from the healthy-fat/high-activity group ($p < 0.05$). † Significant difference from the obese/low-activity group ($p < 0.05$).



CHAPTER 5

Summary and Discussion

The results from the present study add to the rapidly accruing body of literature regarding the interactions between adiposity and physical activity on a multitude of health outcomes. The American demographics are progressing in concert with the rising prevalence of overweight, obesity and physical inactivity, each of which is increasing at an alarming rate. The aging process is accompanied by adverse alterations in body composition, reductions in muscle strength and function, and fatigue. The newly coined concept of inflamm-aging, and its role in the disablement process are only beginning to be fully understood. Chronic elevations in inflammatory mediators may have a causal role underpinning a variety of co-morbid states, including, but not limited to fatigue, sarcopenia, and physical dysfunction.

Only recently is there becoming an appreciation for adipose tissue as an active endocrine organ rather than simply a storage depot. The impact of excess adiposity is widely underappreciated. Results from this study exemplify the contribution of adiposity on several aspects of adverse aging, including Fatigue in multiple domains, elevations in systemic inflammation and reductions in physical function. Additional research in this area should focus on the underlying connection between obesity and fatigue.

Fortunately, physical activity is a modifiable behavior effective in treating a variety of health complications. Our data expand upon this, as being physically active appears to be beneficial for attenuating the obesity-associated perceptions of fatigue and detriments in physical function. Currently, recommendations regarding the quantity, intensity, and type of physical activity necessary to obtain the benefits on these specific outcomes have not been established. Future work should attempt to better define these activity thresholds. Results from our work suggest simply increasing daily activity levels may be sufficient in achieving the beneficial effects of exercise on fatigue and function, with no added benefit of higher intensity moderate-to-vigorous physical activity.

Identification of psycho-physiological influences governing physical activity and obesity-related behaviors is a promising area of research. Results from this cross-sectional study are intended to inform longitudinal and mechanistic investigations aimed at attenuating inflammation, fatigue and physical dysfunction. Enhancing our understanding of aging associated decrements is essential for establishing prevention and treatment strategies targeted at inactivity, physical dysfunction toward the end of maximizing the quality of life across the lifespan and into old age.

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Invited Reviewer (ad hoc)

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Instructional Experience

2006 – present University of Illinois at Urbana-Champaign

KIN 553 – Graduate Circulorespiratory Physiology Laboratory
KIN 494 – Advanced Exercise Prescription (Teaching Assistant) (undergraduate and graduate)
KIN 452 – Clinical and Applied Exercise Physiology (undergraduate and graduate)
KIN 386 – Practical Experiences – Lifetime Fitness Program
KIN 352 – Bioenergetics of Movement Laboratory
KIN 150 – Bioscience of Human Movement Laboratory

2003 – 2005 James Madison University

KIN 424 – Theories and Practices of Weight Management Laboratory (undergraduate and graduate)
KIN 421 – Exercise Testing and Prescription Laboratory
KIN 202 – Biological Foundations of Kinesiology Laboratory
