FATIGUE AND PHYSICAL FUNCTION IN POSTMENOPAUSAL WOMEN, INCLUDING BREAST CANCER SURVIVORS: EXPLORING THE CONTRIBUTIONS OF BODY COMPOSITION, PHYSICAL ACTIVITY AND MUSCULAR PERFORMANCE

by

CHRISTIE LYNN WARD

(Under the Direction of Ellen M. Evans)

ABSTRACT

Determinants of feelings of energy and physical function in middle-aged women are not well characterized. In addition, middle-aged breast cancer survivors (BCS) may have compromised feelings of energy and function due to the effects of disease and treatment. This study aimed to: 1) determine the contributions of adiposity and physical activity (PA) to feelings of energy in middle-aged postmenopausal women (N=74), 2) examine associations among PA, adiposity, and muscle quality (MQ) and physical function (N=64), and 3) determine if BCS differ from age and adiposity matched controls (CON) (N=13 per group) in feelings of energy and physical function.

Body composition was measured via dual energy x-ray absorptiometry, PA via accelerometer [steps·day^{-1}, daily moderate to vigorous PA (MVPA)], vitality with the SF-36, leg strength and power via isokinetic dynamometry [60°·sec^{-1}, (KN60)], and power rig. MQ was calculated as the ratio of: 1) KN60 to upper leg lean mass (MQ-KN60), and 2) power to lower body lean mass (MQ-Power). Physical function was evaluated with timed up and go (UPGO), 30-sec chair stand (CHR), and 6-minute walk (WALK).

MVPA independently explained 8% of variance in vitality. Age and MQ-KN60 were independently related to CHR. Age and MQ-Power were significantly associated with UPGO. Total medical conditions, MQ-KN60, steps·day^{-1}, and adiposity were predictors of WALK. Fatigue, energy, and PA were similar in BCS and CON; however, CON performed better than BCS on UPGO (15.8%, p=.05). In BCS and CON, group was a significant predictor of UPGO, group and MQ-KN60 were related to CHR, and adiposity explained 12% of WALK variance; however, when substituting MQ-Power into the regression analyses, steps·day^{-1} were related to UPGO and CHR, while adiposity explained 10% of WALK. Middle-aged women, including BCS, should engage in recommended amounts of PA to preserve feelings of energy, regardless of weight status, and maintain MQ for better physical function.

INDEX WORDS: physical function, body composition, physical activity, fatigue, muscle quality, postmenopausal women, breast cancer survivors

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DEDICATION

I dedicate this document to my parents, Linda and Jim, who have always supported every crazy adventure I have taken in the name of "education;" my husband, Chris, who makes my heart smile, and reminds me every day that "it's such an amazing thing to be loved for who you are;" and my Aunt Peggy, whose quiet courage I will always admire, and whose beautiful spirit inspires my research pursuits and reminds me to live well, laugh often, and love deeply.

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CHAPTER 1

INTRODUCTION

1.1 Significance

Interventions designed to enhance the health status of postmenopausal women are of high public health interest due to the increasing number of women in this population [1], who are physically inactive [2], and overweight and/or obese [3]. The decline in estrogen during this life stage is often accompanied by increased risk for chronic metabolic diseases including diabetes mellitus and cardiovascular disease [4, 5]. Indeed, the menopausal transition has been associated with weight gain and increases in adiposity, especially in the central depot, and reductions in lean mass [4, 6-9]. Postmenopausal women have been shown to exhibit decreased physical activity (PA) levels [2], experience increases in fatigue [10] and reductions in physical functional ability [11, 12] and quality of life [13] compared to both their premenopausal and male counterparts.

There have been a number of studies that have examined the relationships among body composition, PA, feelings of fatigue and physical functional ability in postmenopausal older women, aged 65 years and older [11, 12, 14-16]. Fewer studies have focused on the middle-aged menopausal women, aged 45-65 years [17, 18]. As midlife represents the intersection of menopause and aging, lifestyle behaviors in midlife including weight management, dietary intake and PA level, may have significant implications for disability and loss of independence in older age and therefore represent the ability of postmenopausal women to age successfully. The implications of reductions in PA and adverse changes in body composition and subsequent changes in physical function and fatigue for middle-aged postmenopausal women, ages 45-65, are not well characterized in the literature due to the following: 1) studies examining fatigue and physical function in postmenopausal women focus on cohorts of older women, aged 65 years or older [17], 2) PA is not reported [19] or self-report methods are often used to assess PA [20, 21] and physical function [20, 22, 23] rather than objective measures, and 3) few studies examine body composition, especially regional measures, via DXA or other validated techniques and instead rely on body mass index (BMI) to categorize weight status [23]. To our knowledge, there is minimal reported data regarding the contributions of objectively measured PA and body composition, on measures of perceived fatigue and objective physical function in postmenopausal women 45 to 65 years of age.

In this context, the overarching aim of this project is determine the associations among body composition, PA, and feelings of fatigue and energy and profiles of physical function in middle-aged postmenopausal women. To accomplish this aim, a cross-sectional design will be used and postmenopausal women, aged 45-65 years, will complete assessments for PA, body composition, muscular capacity, physical functional performance, and fatigue/energy. The longer-term goal of this project is to generate data that would be influential in enhancing the design of a clinical trial comparing the effectiveness of PA, and/or weight loss to enhance health status and quality of life, specifically physical function and fatigue, in middle-aged postmenopausal women.

Similar patterns of physical inactivity, weight gain, fatigue and inflammation and declines in physical function have been observed in samples of pre and postmenopausal breast cancer survivors (BCS) compared to healthy controls [24]. Many BCS who are diagnosed and undergo treatment before menopause become menopausal as a result of breast cancer treatment [25], creating an accelerating aging process. Postmenopausal women diagnosed with BC may also experience earlier declines in factors associated with the aging process due to breast cancer treatment related effects. Older BCS may be at an increased risk for disability due to declines in physical functional ability and increases in fatigue, in part due to adverse changes in body composition and declines in PA.

The implications of reductions in PA and adverse changes in body composition and subsequent changes in physical function and fatigue for the postmenopausal BCS are not well characterized in the literature for similar reasons there are limitations in the literature for middle-aged postmenopausal women. These limitations are as follows: 1) studies examining fatigue and physical function in BCS use samples of both pre- and postmenopausal BCS, without the inclusion of matched controls [26-28], 2) self-report methods are often used to assess PA [27, 29, 30] and physical function rather than objective measures [31, 32] when examining PA in BCS, and 3) few studies examine body composition, especially regional measures, via DXA or other validated techniques and instead rely on body mass index (BMI) to categorize weight status when examining body composition in BCS [27, 29]. To our knowledge, there is no study that has examined the contributions of objectively measured PA level and body composition, on measures of perceived fatigue and objective physical function in postmenopausal women with and without breast cancer. It is highly probable, but still unclear, if BCS have greater risk for fatigue and physical disability due to additive and/or synergistic effects of aging and breast cancer disease and/or treatment. If BCS experience greater fatigue and risk for physical disability, compared to their age and adiposity matched controls, the determinants of this difference need to be identified toward the end of informing the design of more effective interventions for this cohort.

In this context, the secondary aim of this project is to determine if BCS differ from their relatively healthy postmenopausal counterparts in fatigue and physical function, and relatedly, determine the relationships among PA and body composition in these measures of health status. To accomplish this, a cross-sectional design will be used and BCS, who are six months to 10 years post treatment, will complete the same battery of assessment used in postmenopausal women. The longer-term goal of this project is to generate data that would be influential in enhancing the design of a clinical trial comparing the effectiveness of PA and/or weight loss to enhance health status and quality of life, specifically physical function and fatigue, in BCS.

1.2 Specific Aims

Specific Aim 1: To examine the independent associations among PA and adiposity and feelings of fatigue and energy in middle-aged postmenopausal women. It is anticipated that middle-aged postmenopausal women who exhibit greater adiposity, and lower PA will report greater fatigue, after controlling for important covariates (i.e. medication use, depressive symptoms, sleep quality, and perceived stress).

Specific Aim 2: To examine the independent associations among PA, adiposity and muscular performance and physical functional ability in middle-aged postmenopausal women. It is anticipated that middle-aged postmenopausal women who exhibit greater adiposity, lower PA, poorer muscular performance and poorer muscle quality will exhibit poorer physical function.

Secondary Aim 1: To determine if BCS differ in fatigue compared to their age (chronological and menopausal) and adiposity matched healthy counterparts (CON). It is anticipated that: 1) BCS will report greater fatigue and less energy when compared to their healthy counterparts, 2) lower PA and greater adiposity will be positively related to greater fatigue, after controlling for important covariates (i.e. anemia, medication use, depressive symptoms, sleep quality, and perceived stress), in both BCS and CON, but the associations will be stronger in BCS.

Secondary Aim 2: To determine if BCS differ in physical functional performance compared to their age (chronological and menopausal) and adiposity matched healthy counterparts (CON). It is anticipated that: 1) BCS will have poorer physical functional performance compared to their healthy counterparts, 2) lower PA and a less favorable body composition will be related to poorer physical performance in both BCS and CON, but the associations will be stronger in BCS.

1.3 Public Health Related Significance

Postmenopausal women in the early stage of menopause are at the intersection of aging and menopause, and the majority of these women are in a life stage where they have a variety of responsibilities and stressors in many domains (child care, employment, care taking, etc.). It has been reported that women, ages 45-65, years of age report greater feelings of psychological distress and feelings of fatigue compared to their older female counterparts and in addition and have poorer physical functioning than their younger female counterparts. The role that PA and body composition play in determining these outcomes is still unclear within this age group of postmenopausal women.

Postmenopausal breast cancer survivors may have exacerbated detriments in fatigue and physical function due the negative side effects of cancer treatment combined with the age associated independent effects on body composition and PA and dietary behaviors seen in postmenopausal women. While some evidence suggests that postmenopausal BCS experience similar changes in body composition, PA levels and physical function as those experienced by otherwise healthy postmenopausal women, others suggest that BCS have significant deficits compared to their healthy counterparts. It is not well established if significant differences in fatigue and physical function between BCS and controls exist and if these differences are mediated by breast cancer, and the cancer treatment process, by normal aging, or through a combination of both.

The current literature is limited for two primary reasons: 1) research examining the relationships among PA, body composition, fatigue and physical function have been completed primarily with samples of postmenopausal women who are over the age of 65 and, 2) much of the work to date has relied on subjective measures of PA, weight status and physical function, rather than utilizing objective, specifically criterion, measures. Therefore, the primary aim of this interdisciplinary project is to examine the relationships and independent contributions of adiposity, and PA to fatigue and physical function in postmenopausal women ages 45-65. Due to similar limitations within the BCS literature, our secondary aim is to evaluate fatigue and physical function in postmenopausal women and BCS and determine the presence and magnitude of difference in these outcomes. Relatedly, we will examine if the relative strength of associations and the independent contributions of PA and body composition, on fatigue and physical function are similar in postmenopausal women and BCS. This interdisciplinary project will generate critical informative data for the design of effective interventions to reduce fatigue and enhance physical function in postmenopausal middle-aged women, including BCS.

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CHAPTER 2

LITERATURE REVIEW

2.1 Menopause: Physical Activity, Body Composition and Health Status

Midlife is the intersection of menopause and aging [1] and as such, the middle aged postmenopausal woman faces a myriad of physiological and psychological changes as a consequence of these processes. Menopause is marked by the reduction and eventual cessation of estrogen production and median age of occurrence ranges from 49-52 years depending on race and country of origin [2]. The decline in estrogen that signifies the menopausal process, in addition to naturally ending reproductive ability, is associated with a host of detrimental health effects, including an increased risk for osteoporosis, increasing visceral adiposity, and increased risk for metabolic syndrome, diabetes mellitus and cardiovascular disease [3, 4]. Menopause is also associated with a decrease in muscle mass (sarcopenia) [5, 6] and muscular strength (dynapenia) [7], decreases in physical activity (PA) [8], and a decline in physical functional ability [9], which can contribute to a loss of independence and decreased quality of life for this cohort of women. From a behavioral perspective, PA levels have been shown to decline with age [8] and there is some evidence to suggest that the adverse health outcomes associated with the menopausal transition are linked to reductions in PA [3]. It is well established that higher levels of PA are associated with a more favorable body composition, decreased risks of chronic disease and better health status with regard to fatigue, body composition and function including, lower feelings of fatigue [10], greater feelings of energy [10], lower body fat [11], increases in lean mass [11], and better physical functional performance [12].

2.2 Menopause and the Breast Cancer Survivor: Physical Activity, Body Composition and Health Status

While adjusting to life after menopause can be a difficult transition for otherwise healthy women, postmenopausal breast cancer survivors (BCS) may have exacerbated declines in age and menopause-related conditions due to their combined effects. Many BCS who are diagnosed and undergo treatment before the onset of natural menopause are medically induced into a menopausal state as a result of common breast cancer treatments, creating a hormonal environment of accelerated aging. In women treated for breast cancer, medically induced menopause occurs in 50% of women 35 years or younger, 80% of women 35-44 years of age and nearly 100% of women over age 45 who undergo CMF (cytoxan, methotrexate, fluorouacil) chemotherapy treatment [13]. Those women diagnosed with breast cancer post-menopause may also experience earlier declines in outcomes often associated with the aging process due to breast cancer treatment related effects [14]. Regardless of how menopause occurs, BCS may have exacerbated declines in PA and physical function and increases in fatigue, with the latter being related to systemic inflammation [15], due to the combined effects of the breast cancer disease processes, treatments and the processes of aging. Indeed, there is growing evidence to suggest that BCS also experience detrimental changes in body composition, including decreases in lean mass along with increases in adipose tissue, as a result of changes in dietary and PA patterns, and as a consequence of their disease and/or treatment [16]. It is also relatively well-established that higher levels of PA are associated with reduced overall mortality and breast cancer mortality in women with a history of breast cancer diagnosis [17].

2.3 Incidence and Prevalence of Breast Cancer among Women in the United States

Breast cancer is the most prevalent cancer among women in the United States and it has an estimated yearly incidence rate of 191,410 women [18]. The median age of diagnosis was 61 from 2004-2008, with approximately 47% of cases being diagnosed in women between the ages of 45 and 64 [18]. With improved screening and treatment, mortality rates have significantly decreased or remained stable among women of all races in the United States, increasing the number of postmenopausal BCS, resulting in breast cancer as the leading diagnosis within the population of cancer survivors [19].

2.4 Fatigue in Postmenopausal Women

Fatigue is a public health concern, as the general population reports fatigue to their primary care physicians in 7 – 45% of visits [20] and the prevalence of fatigue has been estimated as high as 47% in older adults [21]. In adults, age 18-45 years of age, who presented with fatigue as a first time single complaint, 70% were women and only 27% were given an explanatory diagnosis (common diagnoses were anemia, vitamin B12 deficiency, infectious disease, pregnancy, anxiety, depression, post-traumatic stress disorder) [22]. Fatigue is one of the most common symptoms reported by middle-aged menopausal women [23, 24]. Recently, the CDC reported that women (15.3%) were more likely than men (10.1%) to report "often feeling very tired or exhausted on most days or every day over the past three months" and that women aged 45-64 years of age were most likely to report "often feeling very tired or exhausted" (15.9%) [25]. In addition, at all ages, women were more likely than men to report experiencing serious psychological distress over the past 30 days and women 45-64 years of age were the most likely to report experiencing serious psychological distress during the past 30 days [26]. Fatigue, independent of age, has also been associated with disability and loss of independence [27]. Though its presence is vast [28], a universal definition of fatigue is still elusive [29]. Due to its prevalence among older adults, a National Institute on Aging focus group convened to discuss fatigue and defined fatigue and fatigability as a perceived lack of physical or mental energy and the degree of fatigue associated with activity in any dimension including physical, mental, emotional and/or social, respectively [29]. Exercise physiologists interested in physical performance focus on fatigue in terms of skeletal muscle action and associate fatigue with a decrease in muscular performance caused by physiologic limitations [30]. From a psychosocial perspective, fatigue as a construct exhibits itself through physical and/or psychological aspects [31]. Chronic fatigue is a subjective experience for each individual and unique in that it is persistent, not always alleviated by rest or proper nutrition, interferes with the ability to perform activities of daily living, decreases quality of life and is often associated with disease and/or treatment [32].

2.5 Fatigue in Postmenopausal Breast Cancer Survivors

The National Comprehensive Cancer Network Fatigue Committee defines cancer related fatigue as "an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning [33]." Cancer survivors have been found to report greater feelings of fatigue compared to their healthy counterparts [27]. Breast cancer and its associated treatments impact multiple aspects of health including physical, emotional and psychosocial domains, including increased feelings of fatigue and low feelings of energy. Feelings of fatigue can have a large impact on quality of life in BCS [34, 35] and some BCS report that limiting levels of fatigue can last for up to 10 years after cessation of treatment [36]. As cancer related fatigue has been found to be independently related to markers of inflammation [37, 38], the weight gain, body composition changes and reductions in PA associated with menopause and breast cancer treatment may combine to produce an environment conducive to producing greater feelings of perceived fatigue. Importantly, physical activity/exercise has been shown to independently play a protective role against cancer related fatigue during and after treatment [39]. In addition to adiposity and PA, there are other factors that must be considered when discussing feelings of fatigue and energy for postmenopausal women and BCS, including bodily pain, sleep disturbances, depressive symptoms and anemia [40].

2.6 Physical Function and Muscular Performance in Postmenopausal Women

Physical functional performance has been examined extensively in older men and women (65 years and older) [41-43]. Due to declines in PA [8] and unfavorable changes in body composition associated with aging [44, 45], older postmenopausal women may be at an increased risk for decreased physical function status. Work from our own labs [41] found that body composition is a significant contributor to objectively measured physical function, as a higher amount of fat mass and decreased lean mass are associated with poorer functional performance in older women. Poorer physical functional performance has also been correlated with loss of independence, chronic disease and mortality [46-48]. Physical functional status and its implications are less clear in middle-aged women, especially for those in early menopause (~40-65 years of age) [49]. Tseng et al. [9] found that in women 45-57 years of age, postmenopausal women reported greater physical function limitations as assessed by the physical function scale of the SF-36, compared to premenopausal women. The presence of poorer physical function in this cohort of postmenopausal women was found to be independent of age, and was only partially explained by higher BMI and increased depressive symptoms, leading the authors to conclude that the physiological changes that accompany menopause may significantly contribute to physical function limitations in postmenopausal women. Associations between psychological status and physical function have also been explored when evaluating functioning in younger postmenopausal women. For example, Bromberger et al. [50] found that depression and impaired physical function may be exacerbated during the menopausal transition, as this often marks a time when physical roles are reduced for women.

2.7 Physical Function in Postmenopausal Breast Cancer Survivors

The evidence for physical functional declines as a result of breast cancer diagnosis and treatment are equivocal, as some studies support greater difficulty completing physical functional tasks for BCS compared to controls [14], while other studies have found no physical functional performance differences between BCS and healthy controls [51, 52]. One study examining self-reported physical function in postmenopausal BCS, 5 years post diagnosis, reported that ~30% BCS have difficulty with functional mobility and an inability to do heavy household chores, compared to ~25% of women without BC [7]. An important factor to consider when evaluating physical function in BCS is the presence of lymphedema, swelling that occurs when lymph nodes are significantly damaged in the cancer treatment process and no longer allow for adequate lymph fluid drainage. Physical and psychological function may be impaired differently among BCS with and without a history of lymphedema [53]. Chachaj et al. [54] found that BCS with increased disability scores, due to decreased arm mobility, pain in the breast and upper limb, lymphedema of the hand and/or a history of infection, reported lower quality of life and higher levels of psychological distress. They also found that age, BMI, and severity and localization of the lymphedema to the dominant limb were not significantly related to physical or psychological impairment in BCS. Those BCS without a history of lymphedema may be at decreased risk for these impairments and may be quite similar to their disease free age matched counterparts. It is important to note that disability and physical function were measured using a multitude of self-report questionnaires in the above-mentioned studies, without objective physical function measures.

2.8 Summary

As middle-aged postmenopausal women are at risk for experiencing greater feelings of fatigue and low energy and greater physical functional decline and disability compared to both their male counterparts and premenopausal peers, research focused on identifying the most influential predictors of feelings of fatigue and energy and functional performance for middle-aged postmenopausal women is needed. Postmenopausal BCS may have greater declines in age and menopause-related conditions, including increases in fatigue, reduced feelings of energy, and decreases in physical function, compared to their non-BCS counterparts, as a result of the combined effects of the disease and its associated treatments. As this population of women continues to grow, studies focused on identifying the presence of differences and the determinants of these differences between BCS and their relatively healthy peers in feelings of energy and functional performance is also warranted.

As low levels of PA and high levels of obesity are present within both of these cohorts, it is vital to develop a more comprehensive understanding of the contributions of PA and body composition to feelings of fatigue and energy and physical function. A greater understanding of the independent and interactive effects of PA and adiposity on feelings of fatigue and energy may allow for more efficacious intervention design for these populations of women. Additionally, while the relationships between PA, body composition, and muscle capacity measures have been studied in older adults, there is a paucity of data focused on the middle-aged postmenopausal women. Identifying the independent and interactive nature of PA, adiposity, and muscle strength and power on objectively measured physical function, may inform the design of interventions that would be effective in improving function and possibly delaying the onset of disability in aging women.

2.9 References

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CHAPTER 3

FEELINGS OF ENERGY IN MIDDLE-AGED POSTMENOPAUSAL WOMEN: RELATIONSHIPS WITH ADIPOSITY AND PHYSICAL ACTIVITY

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3.1 Abstract

Feelings of fatigue and low energy are widespread among middle-aged women and have been shown to significantly affect health and quality of life. The aim of the present study was to examine the influence of adiposity (%Fat) and physical activity (PA) on feelings of fatigue and energy in postmenopausal women. Middle-aged postmenopausal women (N=74, age=58.9 ± 3.8 years) were assessed for %Fat via dual energy x-ray absorptiometry, PA via accelerometer [steps·day^{-1} and minutes of moderate to vigorous PA per day (MVPA)], feelings of vigor via the Profile of Mood States and vitality via the SF-36 Vitality scale. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). Depression was assessed using the Beck Depression Inventory (BDI), and perceived stress was evaluated using the Perceived Stress Scale (PSS). Adiposity was negatively related to steps·day^{-1} (r=-.55, p<.05) and MVPA (r=-.48, p<.05). Adiposity was not significantly related with vigor, vitality, or any other psychological measures. Greater vitality was associated with lower total number of prescription medications (r=-.31, p<.01), greater steps·day^{-1} (r=.28, p<.05), and greater MVPA (r=.37, p<.01). Feelings of vigor were not significantly associated with any variable of interest. Regression analyses revealed that MVPA independently explained 8% of the variance in vitality, while PSQI was also a significant predictor of vitality, and along with BDI and PSS explained 28% of the variance (both p<.05). Our results suggest that middle-aged women should engage in recommended amounts of MVPA to preserve feelings of energy, regardless of weight status.

3.2 Introduction

Feelings of low energy and fatigue are a public health concern, as the general population reports fatigue to their primary care physicians in 7-45% of visits [1]. In adults ages 18-45 years, who presented with fatigue as a first time single complaint, 70% were women and only 27% were given an explanatory diagnosis (common diagnoses were anemia, vitamin B12 deficiency, infectious disease, pregnancy, anxiety, depression, post-traumatic stress disorder) [2]. Fatigue is one of the most common symptoms reported by middle-aged menopausal women [3, 4]. Recently, the CDC reported that women were more likely than men to report "often feeling very tired or exhausted on most days or every day over the past three months" and that women aged 45-64 years of age were most likely to report "often feeling very tired or exhausted" [5]. Jungahaenel et al. [6] also found that participants, ages 45-60 years, reported more fatigue and less vitality compared to adults aged 60 and older. In addition, findings from the Nurse's Health Study also demonstrate that women ages 62-66 years of age report greater feelings of vitality, compared with women ages 45-51 years of age [7].

Fatigue and feelings of low energy, along with sleep disturbances and anxiety, have been shown to significantly affect quality of life in postmenopausal women [4]. Women in this age group are susceptible to feelings of low energy, as midlife is often a time when women are faced with a number of responsibilities and challenges in a variety of domains, including those related to employment and family [8, 9]. The physiological and psychological consequences of menopause also coincide with this time frame, and the menopausal transition is associated with decreases in physical activity (PA), increases in body weight and adiposity and the emergence of chronic disease conditions [8], all of which may contribute to feelings of low energy and fatigue.

There is a growing body of literature that suggests that increased levels of PA and adoption of regular programs of exercise are associated with lower feelings of fatigue and greater feelings of energy. It has been reported that physically active adults have a 40% reduced risk for reporting feelings of fatigue and low energy compared to their sedentary peers [10], and that habitual exercise programs increase feelings of energy and decrease feelings of fatigue as effectively, if not more so, than drug treatment and cognitive behavioral therapy [11]. Specifically in middle-aged women, increasing amounts of PA have been associated with increases in feelings of energy, as assessed by the vitality scale of the Medical Outcomes Survey Short Form-36 (SF-36) [12]. In addition, a six month randomized control trial conducted with sedentary overweight and obese middle-aged women found that feelings of vitality significantly improved from baseline in all exercise groups compared to the control group, independent of changes in weight, and those women who were exposed to the highest dose of exercise experienced the greatest improvement in vitality [13].

While strong evidence is continuing to accumulate for the relationship between PA and feelings of energy, the independent effect of adiposity and/or the interactive effects of PA and adiposity on feelings of energy and fatigue are less well characterized. Obesity, classified by body mass index (BMI), has been shown to be associated with poorer health related quality of life in adults [14], including lower feelings of energy and vitality [7, 15, 16]. In a recent review, Jones et al. [15] reported that energy and vitality scores were significantly lower in obese middle-aged and older postmenopausal women, compared to their normal and overweight counterparts (classified using BMI cut points), and that this domain was the most negatively affected aspect of health related quality of life after adjusting for age, race, education, smoking and alcohol intake. Valentine et al. [17] found that adiposity, relative fat mass (%Fat) measured using dual energy x-ray absorptiometry (DXA), was independently related to both general and physical fatigue in older men and women.

As higher levels of PA are often associated with more optimal body composition and are also associated with reducing the adverse effects of adiposity on health in those who are "fat but active" or "fit but fat," [18] the independent and interactive effects of adiposity and PA on feelings of fatigue and energy are vital areas of interest. At this time, the independent and interactive effects of PA and adiposity on feelings of energy are incompletely characterized and are of particular interest due to rising obesity rates [19], low numbers of middle-aged women reaching recommended levels of PA [20], and the increasing number of postmenopausal women reaching middle-age due to the aging of the baby boom generation [21].

In this context, the primary objective of the present study was to examine the associations among PA, adiposity and feelings of energy. We hypothesized that those who were more active would report greater feelings of energy, compared to those women who were less active. We also hypothesized that those women who had healthier levels of adiposity would report greater feelings of energy compare to those with greater relative fat mass. In addition, those women who had both optimal adiposity and higher PA levels would report the highest levels of vitality. Identifying the determinants of feelings of energy in middle-aged postmenopausal women is essential for designing optimal physical activity and nutritional interventions for women within this life stage.

3.3 Methods and Materials

Participants

Postmenopausal women, ages 45-65, were recruited for this study through e-mail advertisements delivered to faculty, staff and alumni organizations of a major university and flyers placed throughout the community. For study inclusion, participants had to be non-smoking for at least two years prior to study participation, weight stable (within 2 kg) for the past three months, medications stable for the past three months, free of uncontrolled pulmonary, cardiovascular or metabolic disease, and free of symptomatic joint abnormalities, and symptomatic nervous disorders. Participants also had to be willing to wear an activity monitor for seven days and undergo body composition analysis via DXA. All procedures were approved by the Institutional Review Board of the University and prior to enrollment all participants signed an IRB approved informed consent form.

Procedures

Potential participants were screened via telephone, and those eligible were scheduled for two appointments 7-10 days apart to allow for PA monitoring. Prior to Visit 1, participants were provided with a copy of the informed consent via e-mail. At Visit 1 participants completed consent forms, fasting blood draw, anthropometric measures, DXA scanning and a series of questionnaires. Participants were provided with a snack (crackers, granola bar, etc.) and drink (fruit juice, vegetable juice, etc.) immediately following the blood draw. All questionnaires concerning mood were answered in the laboratory during the participant's first visit. In the 7-10 day period between visits, participants were asked to complete a series of questionnaires addressing their health history and wear a PA monitor. At Visit 2, all questionnaires completed at home were reviewed for completeness.

Health History

Participants were asked to report the presence of medical conditions including arthritis, asthma, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, degenerative disc disease, osteoporosis, and peripheral arterial disease. In addition, participants were asked to report all prescription and over the counter medications and supplements.

Body Composition

Weight was measured using a calibrated digital scale (Tanita, Model WB-110A) and standing height, measured to the nearest 0.1cm, was obtained using a stadiometer (Seca, Model 242), while wearing light-weight clothing and no shoes. Whole body soft tissue was measured using DXA (Lunar iDXA, v 11.30.062, GE Healthcare, Madison, WI) with relative fat mass (%Fat), and central adiposity (%Fat-C) being obtained per manufacturer guidelines.

Physical Activity and Sedentary Time

An accelerometer (New Lifestyles-1000, Barebones Pedometer, New Lifestyles, Inc., Lees Summit, MO) was used to measure objective PA level, both as steps per day and minutes spent engaged in moderate to vigorous PA (MVPA). MVPA was defined as activity completed above a moderate intensity threshold, which corresponds to approximately 3.6 METs. Participants were instructed to wear the accelerometer on the non-dominant hip, fastened to their waistband, during all waking hours, except when bathing or swimming. Participants recorded the time spent wearing the activity monitor, steps taken each day and number of MVPA on a written log, which were verified by a staff member using the memory feature of the NL-1000. Ten hours of wear time was required for a valid day, and at least four valid days were required for the participant to be included in the analysis. Step counts were calculated using the average step count from valid wear days, and minutes spent in MVPA per day were calculated as the average time spent in MVPA from valid wear days. The Global Physical Activity Questionnaire (GPAQ) was used to assess self-reported time spent sedentary, specifically time during sitting or reclining during a typical day (SED) [22].

Feelings of Energy

The Profile of Mood States 30 item short form (POMS-SF) was used to assess overall mood and six specific mood states including feelings of energy during the prior week. Five adjectives are used to tap each specific mood state (e.g., Vigor = energetic, full of pep, vigorous, active and lively) and the intensity of moods are scaled using five categories (not at all, a little, moderately, quite a bit, and extremely) [23]. Item scores (0-4) are summed to yield subscale scores. The SF-36 Health Survey, a 36 item self-administered questionnaire, assesses the following eight health attributes: general physical functioning, role limitations due to physical health, bodily pain, general health, social functioning, role limitations due to emotional problems, mental health and vitality [24]. The vitality scale of the SF-36 was used to assess frequency of feelings of energy over the past month and consists of four items asking how often one has felt full of pep, full of energy, tired or worn out.

Covariates of Feelings of Energy

Assessments for known confounders of feelings of energy were administered in order to control for their potential effects. Depressive symptoms during the past two weeks were assessed using the Beck Depression Inventory-II (BDI) [25], and higher scores indicate a greater severity of depressive symptoms (range 0-63). Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), which assesses overall quality over the past month [26]. Total scores >5 on the PSQI indicate impaired sleep quality. Perceived stress was measured using the Perceived Stress Scale, in which higher scores (range 0-40) indicate higher stress [27].

Hemoglobin (Hemocue Hb 201$^+$, Hemocue America, CA) and hematocrit levels (CS22 – CritSpin with Digital Reader, Statspin, Norwood, MA) were analyzed from venous blood samples obtained using standard procedures. Normal clinical limits for hemoglobin and hematocrit were defined as 12-16 g/dL and 36-48%, respectively [28]. Two samples were assessed for each blood outcome and the average used in subsequent analysis and the coefficient of variation for hemoglobin and hematocrit levels was 2.2% and 1.5% respectively.

Statistical Analyses

Data were analyzed with IBM SPSS Statistics for Windows Version 21.0. (IBM Corp: Armonk, NY). 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.

Bivariate correlations were conducted to examine the relationships between age, total number of medical conditions, total number of prescription medications, total number of depression and anxiety medications, body composition, PA, SED, PSQI, BDI, PSS, vigor and vitality. The independent contribution of total number of medical conditions, total number of prescription medications, sleep quality, depressive symptoms, perceived stress, MVPA and %Fat on vitality were also evaluated by hierarchical linear regression analysis.

A 2x2 (PA status [less than 30 min MVPA daily vs. 30 or more min MVPA daily] x adiposity category [healthy fat vs. overfat and obese]) ANCOVA, controlling for total number of medical conditions, total number of prescription medications, sleep quality, depressive symptoms, and perceived stress, were conducted to examine the main and interactive effects of PA and adiposity on vitality. All data are presented as mean ± SD, except figures, which show mean ± SE, and statistical significance was set at the $p \leq .05$ level.

3.4 Results

A total of 191 women contacted our laboratory in response to our recruitment efforts, of those who contacted us, 91 qualified for participation. Reasons for exclusion included: did not respond to follow up contact (41), chose not to participate due to time commitment (19), currently smoking (2), not currently postmenopausal (17), outside of the age range for participation (8), BMI >35.0 (5), injury precluding completion of physical function testing required for additional arm of the current study (2), refused to undergo DXA scanning (2), and not weight stable (4). Of the 91 women who completed visit 1, 17 were excluded in the final analysis due to the following: BMI< 18.0 (1), BMI >35.0 (3), incomplete questionnaire data (5), incomplete objective PA data (5), objective PA values, both steps·day^{-1} and MVPA, exceeding 3SD from the mean (1), and vitality scores lower than 3SD from the mean (2). Participant characteristics (n=74) are presented in Table 3.1. The sample was 92% white, highly educated (18±4 years), and 90% of the sample was employed outside of the home. Approximately 30% of the sample reported taking antidepressant and/or anxiety medication, and only one participant reported taking sleeping medication. Arthritis (38.4%) and degenerative disc disease (21.9%) were the predominant medical conditions reported by participants. On average, the sample was overweight and overfat based on BMI and adiposity cut points [29], and 30% and 41% of the sample met the recommendations for 10,000 steps·day^{-1} [30] and at least 30 minutes of MVPA per day, respectively. Of those who had a complete week of activity monitoring, 63% achieved at least 150 minutes of MVPA in a 7-day period.

While data were collected for the fatigue scale of the POMS-SF, 60% of our sample reported a fatigue score of zero, indicating that they have no fatigue. The large number of participants reporting a score of zero contributed to our data violating the assumption of normal distribution, and as scores of zero are not amendable to statistical transformation, no further analyses using this outcome were conducted.

The mean vitality score for the participants was above the mean normative value for females ages 55-64 [31] (see Table 3.2). The majority of participants, 85%, reported minimal depressive symptoms as assessed by the BDI, and mean scores for the PSS were lower than the normative values for both women and adults ages 55-64 [32]. The mean values for both hemoglobin and hematocrit levels were within normal limits for women in this age group [28] .

Presented in Table 3.3, age was inversely related to depressive symptoms (r=-.28, p<.05), while increasing number of medical conditions was related to poorer sleep quality, more perceived stress, and lower vitality (r range -.27 to .31, all p<.05). An increasing total number of prescription medications was positively and moderately associated with sleep quality, depressive symptoms, and perceived stress (r range .28 to .37, all p<.05), and negatively correlated with vitality (r =-.31, p<.01). The use of antidepressant medication was negatively associated with MVPA (r=-.28), and positively associated with PSQI, BDI and PSS (r range .28 to .35, all p<.05). As expected, both %Fat and %Fat-C, were inversely related to PA measures (both p<.05), and both steps·day^{-1} and MVPA were positively and significantly related to vitality (r=.28, r=.37, respectively). With regards to confounding variables, PSQI, BDI, and PSS were strongly negatively related to vitality (r range -.51 to -.58, all p<.01).

Regression analyses examined the independent contributions of total number of medical conditions, total number of prescription medications, PSQI, BDI, PSS, and MVPA, %Fat, and MVPA on vitality. MVPA and PSQI were the only significant predictors of vitality (R^2=.50, $F_{6,68}$=10.13, p<.001). MVPA independently explained 8% of the variance in vitality, while PSQI, BDI, and PSS collectively explained 28% of the variability (Table 3.4).

Figure 3.1 shows adjusted scores comparing vitality across activity (less than 30 min MVPA vs. 30 minutes or more of MVPA), and adiposity groups (healthy fat vs. overfat and obese), when controlled for total number of medical conditions, total number of prescription medications, PSQI, BDI and PSS. No interaction existed between meeting MVPA guidelines and adiposity on vitality (p=.33). In the absence of a main effect for adiposity classification (p=.67), there was a main effect for PA on vitality (less than 30 min MVPA=66.67±13.35, 30 min or more MVPA=73.18±11.85; p=.03; Effect size d=0.52).

3.5 Discussion

The present study represents an examination of the relationships among PA and adiposity and feelings of energy, controlling for well-established influences including total number of medical conditions, total number of prescription medications, sleep quality, depression and perceived stress in a community sample of middle-aged postmenopausal women. Along with reinforcing the strong relationship between sleep quality, depressive symptoms, perceived stress and feelings of energy, as measured by the vitality scale of the SF-36, our data also add to the growing literature supporting the beneficial effect of PA on feelings of energy in this cohort. Unexpectedly, adiposity was unrelated to feelings of vigor and vitality in this cohort.

Our data corroborate previous cross sectional findings that PA is positively associated with feelings of energy [33-36]. Similar to our findings, Heesch et al. [36] found that middle-aged women who approached, met or exceeded PA recommendations reported greater vitality than those women who were sedentary or completed very low to low amounts of total PA, when PA is self-reported. Coakley et al. [7] also found that self-reported PA was the most important predictor of vitality in women ages 46-72 years participating in the Nurse's Health Study. One advantage of the current study is the use of an objective measure of PA, which allowed us to measure both total PA using steps per day and minutes per day of moderate to vigorous PA. Our data support that both daily steps·day^{-1} and daily MVPA are significantly and independently related to feelings of vitality. However, as MVPA was more strongly related to vitality and explained a greater amount of the variance in vitality compared to steps·day^{-1} (data not shown), accurate and objective measure of both total activity and intensity of activity is warranted in future studies, especially in light of current public health guidelines recommending intensity specific physical activity goals for adults [37]. It is also important to note that the type of activity monitor used in our study measures only weight bearing lower extremity aerobic activity. Because resistance exercise can improve feelings of energy [38], future work examining the relationship between PA and mood should also attempt to try to capture how activities requiring both the upper and lower extremities, including resistance training, affect feelings of energy.

Prolonged sedentary time is emerging as a distinct risk factor for chronic disease and mortality, independent of PA levels [39, 40]. Recent findings suggest that a lower amount of sedentary time is associated with lower feelings of fatigue, but does not impact feelings of energy, even in the absence of meeting public health guidelines for PA, in a cohort of young and middle-aged women [41]. Our data did not support a relationship between SED and feelings of energy, and notably, the strength of the relationship between SED and PA in our sample was lower than those published previously [41]. These differences may be the result of our measurement instrument, as we did not objectively measure sedentary time and the instrument used asked participants to report total sedentary time, during waking hours, in a 24 hour period. Hence, we do not have any information on the length of each sedentary bout.

Contrary to our hypothesis, we found no significant relationship between adiposity and feelings of energy measured by the vigor or vitality scales. These findings are supported by Han et al. [42], who found that vitality was similar among three tertiles of waist circumference in women 20-59 years of age. As Valentine et al. [17] demonstrated an independent contribution of adiposity to fatigue, these data contradict our findings. These differences may be attributable to several methodological differences. First, their sample consisted of older men and women compared to our middle-aged cohort. Second, feelings of fatigue, both general and physical, were measured using the Multidimensional Fatigue Inventory, which attempts to assess fatigue in five distinct dimensions, which are unipolar in their design, unlike the SF-36, which measures fatigue and energy using the bipolar vitality scale. Findings from Coakley et al. [7] also suggest that as BMI increases, vitality decreases, and in addition, BMI was an independent predictor of vitality, second only to PA, in a cohort of women aged 45-71 years. Feelings of vitality may also vary along the weight status/BMI continuum, as Doll et al. [16] showed a curvilinear relationship between BMI and SF-36 vitality scores, with the lowest scores being present in those who were underweight and those who were morbidly obese, among a sample of men and women 18-64 years of age.

An alternate explanation could be that the influence of adiposity on feelings of fatigue may differ in middle-aged and older women, as the relationship may be time dependent and with increasing age comes increased exposure to many factors, including obesity and its associated markers. For example, increased adiposity has been associated with increased chronic inflammation [17, 43], and an increase in the presence of inflammatory markers has been linked to greater feelings of fatigue [17]. However, as we did not measure markers of inflammation in the current study, we are limited in our ability to make conclusions regarding this relationship.

We found “fat but active” status to confer benefit in feelings of vitality in this sample. While this is a positive finding for those individuals in the “fat but active” category, only a small number of individuals in our sample qualify for this distinction, with only 13% of overweight women and 6% of obese women being engaged in recommended levels of PA in the current study. Supporting the low prevalence of “fit but fat” individuals, data from NHANES shows that only 8.9% of obese and 17.4% of overweight adults classified by BMI standards can be classified as “fit and fat” [44]. As mentioned above, no measures of systemic inflammation or metabolic health, which can both be affected by both PA [45] and adiposity levels [46], were available for analysis for the present study. These metabolic and inflammatory markers may have implications for feelings of energy, which are more important than adiposity or PA levels per se. It should be appreciated that although there was virtually no relationship between adiposity and feelings of energy, there was a robust relationship between adiposity and PA. As it is well established that habitual PA enhances weight management and optimal body composition [47], it may be that the PA masks the effects of adiposity on feelings of energy. Moreover, adiposity is the energy balance summary reflective of a longer period of time compared to our PA measures, which reflect movement within a recent time period similar to our measures of feelings of energy. Notably, our recruited sample had a high level of PA and vitality compared to national averages for this cohort, which may have also influenced the magnitude of the associations of adiposity and PA on feelings of energy.

Although our data are of interest, our study is not without limitations. Due to the cross sectional nature of our investigation, causality cannot be inferred based on our findings. As our sample included only relatively healthy community dwelling middle-aged postmenopausal women, it is difficult to apply the results to the general population. Our study also required two visits to the measurement laboratory and the completion of a battery of objective physical function assessments for another aim of our investigation. As our sample reported high levels of energy, it is possible that the women willing to participate in our investigation were quite robust and the requirements of our study, including two visits to the laboratory, PA monitoring and physical function testing, may have been too taxing for members of this age group who experience lower levels of energy (i.e. self-selection bias). In addition, there were no medication specific exclusion or inclusion criteria; therefore, women taking antidepressants, anti-anxiety medications, sleep aids, and HMG-CoA reductase inhibitors were not excluded from the present study. Although the use of such medications was controlled statistically, they may have affected the level of energy reported by the sample. Similarly, we did not include or exclude participants based on the presence and/or absence of conditions known to be associated with feelings of low energy, such as a sleep disorder.

In conclusion, in relatively healthy middle-aged postmenopausal women, sleep quality, depressive symptoms, perceived stress, comorbid conditions and antidepressant medication all are associated with feelings of energy. In addition, PA, but not adiposity, appears to be significantly and independently associated with feelings of energy, as higher daily levels of both total PA and MVPA are associated with greater feelings of positive energy. Our results suggest that middle-aged women should engage in recommended amounts of MVPA to preserve feelings of energy. Longitudinal studies examining the independent and interactive effects of PA and adiposity on feelings of energy are merited, especially in light of the current prevalence rates of obesity and physical inactivity and reports of lack of energy in this growing sector of the population.

3.6 References

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Table 3.1. Participant characteristics

	Mean ± SD N=74	Range
Age (years)	58.9 ± 3.8	50-65
Total Medical Conditions*	1	0-8
Total Prescription Medications*	1	0-6
Depression/Anxiety Medications	30%	0-2
Hormone Replacement Therapy	15.1%	0-2
Weight (kg)	68.3 ± 11.7	49.1-102.2
Height (cm)	163.5 ± 5.9	150.5-181.6
BMI ($kg \cdot m^{-2}$)	25.6 ± 4.0	18.1-35.1
Whole Body Adiposity (%)	38.5 ± 5.9	27.7-52.8
Central Adiposity (%)	43.9 ± 9.7	21.9-64.4
Physical Activity: $steps \cdot day^{-1\#}$	8,814 ± 3,352	2,632-17,393
10,000 or more $steps \cdot day^{-1}$ *(%)*	30%	
Physical Activity: $MVPA \cdot day^{-1\#}$	28.0 ± 19.0	5.0-81.0
30 or more $MVPA \cdot day^{-1}$ *(%)*	41%	
150 or more $MVPA \cdot week^{-1¥}$ *(%)*	63%	
Sedentary Time ($min \cdot day^{-1\wedge}$)	284.0 ± 151.0	60.0-660.0

*Median value; #N=70; ¥N=41; ^N=64.

Table 3.2. Mood measures

		Mean ± SD N=74	Range
POMS-SF			
Vigor		8.7 ± 4.6	0-20
Fatigue		1.5 ± 2.4	0-12
Tension		0.81 ± 1.4	0-5
Depression		0.41 ± 1.1	0-6
Anger		0.23 ± 0.71	0-4
Confusion		3.1 ± 1.6	0-8
SF-36	Normative Values for 55-64 year old women[31]		
Vitality	58.1	68.4 ± 15.7	25.0-100
Physical Function	73.1	85.0 ± 17.4	20.0-100
Role Physical	71.6	87.3 ± 18.6	0-100
Bodily Pain	66.6	79.8 ± 17.7	12.0-100
General Health	62.9	80.6 ± 15.4	30-100
Social Function	79.4	91.6 ± 16.7	37.5-100
Role Emotional	79.5	89.8 ± 17.3	8.3-100
Mental Health	73.4	82.6 ± 13.8	45.0-100
PSQI		5.8 ± 3.4	0-14
Impaired Sleep		50%	
Beck Depression Inventory		6.9 ± 6.8	0-30
Perceived Stress Scale		10.7 ± 7.1	0-30
Hemoglobin (g/dL)#		13.3 ± 0.9	11.3-15.7
Within Normal Limits	12-16 g/dL[28]	96%	
Hematocrit (%)#		42.9 ± 3.2	32.3-50.0
Within Normal Limits	36-48%[28]	97%	

POMS=Profile of Mood States-Short Form; PSQI=sleep quality as measured by the Pittsburgh Sleep Quality Index; BDI=depressive symptoms as measured by the Beck Depression Inventory-II; PSS=perceived stress as measured by the Perceived Stress Scale.
#N=70.

Table 3.3. Bivariate correlations for vigor and vitality

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Age	1.0	.08	-.05	.10	.04	.01	.07	.09	.08	.07	.12	-.08	-.28*	-.07	-.11	.03
2	Med Conditions		1.0	.21	.05	.04	.03	-.02	-.03	.09	-.01	.01	.31†	.23	.29*	-.20	-.27*
3	Total Meds			1.0	.59†	.18	.16	-.18	-.17	.22	-.13	-.31*	.47†	.38†	.28*	.03	-.31†
4	Dep Meds				1.0	.14	.11	-.24	-.28*	-.08	.10	-.23	.35†	.33†	.28*	.13	-.20
5	%Fat					1.0	.93†	-.55†	-.48†	.15	.11	-.19	-.12	-.03	-.06	.03	-.04
6	%Fat-Central						1.0	-.45†	-.43†	.14	-.12	-.27*	-.14	.01	-.05	-.05	-.02
7	steps·day^{-1}							1.0	.88†	-.07	.19	.48	-.12	-.06	-.05	.11	.28*
8	MVPA								1.0	.10	.30*	.47	-.15	-.09	-.16	.13	.37†
9	SED									1.0	-.01	-.06	.03	.05	.03	-.08	.03
10	Hemoglobin										1.0	.59†	-.09	-.09	-.11	-.22	.02
11	Hematocrit											1.0	-.02	-.02	-.02	-.17	-.03
12	PSQI												1.0	.55†	.55†	-.15	-.58†
13	BDI													1.0	.77†	-.16	-.51†
14	PSS														1.0	-.18	-.52†
15	Vigor															1.0	.34†
16	Vitality																1.0

Med conditions=total number of medical conditions; Total Meds=total number of prescription medications; Dep Meds=total number of depression/anxiety medications; %Fat=whole body adiposity; %Fat-Central=central adiposity; MVPA=minutes of moderate to vigorous physical activity per day; SED=minutes per day of sedentary time; PSQI=sleep quality as measured by the Pittsburgh Sleep Quality Index; BDI=depressive symptoms as measured by the Beck Depression Inventory-II; PSS=perceived stress as measured by the Perceived Stress Scale. $^{*}p$<.05, $^{\dagger}p$<.01.

Table 3.4. Linear regression analyses

Vitality	R^2	Predictors	β	Beta	95% CI
Step 1	$0.14^{\dagger}$				
		Total Medications	-0.25^{*}	-2.50	[-4.81, 0.20]
		Medical Conditions	-0.23^{*}	-2.39	[-4.77, -0.01]
Step 2	$0.42^{\dagger}$				
		Total Medications	-0.03	-0.32	[-2.45, 1.80]
		Medical Conditions	-0.08	-0.86	[-3.00, 1.23]
		PSQI	$-0.41^{\dagger}$	-1.84	[-2.98, 1.23]
		BDI	-0.17	-0.38	[-1.05, 0.29]
		PSS	-0.11	-0.27	[-0.98, 0.44]
Step 3	$0.50^{\dagger}$				
		Total Medications	0.01	0.07	[-1.94, 2.09]
		Comorbidities	-0.10	-0.98	[-3.00, 0.98]
		PSQI	$-0.39^{\dagger}$	-1.75	[-2.82, -0.67]
		BDI	-0.12	-0.26	[-0.90, 0.37]
		PSS	-0.15	-0.36	[-1.02, 0.31]
		MVPA	$0.28^{\dagger}$	0.23	[0.08, 0.38]

Order of analyses: Step 1: Total number of medical conditions and total number of prescription medications; Step 2: Pittsburgh Sleep Quality Index Score (PSQI), Beck Depression Inventory Score (BDI) and Perceived Stress Scale score (PSS); Step 3: Minutes of moderate to vigorous intensity physical activity per day (MVPA). β=standardized regression coefficients; Beta=unstandardized regression coefficients. $^{*}p<.05$, $^{\dagger}p<.01$.

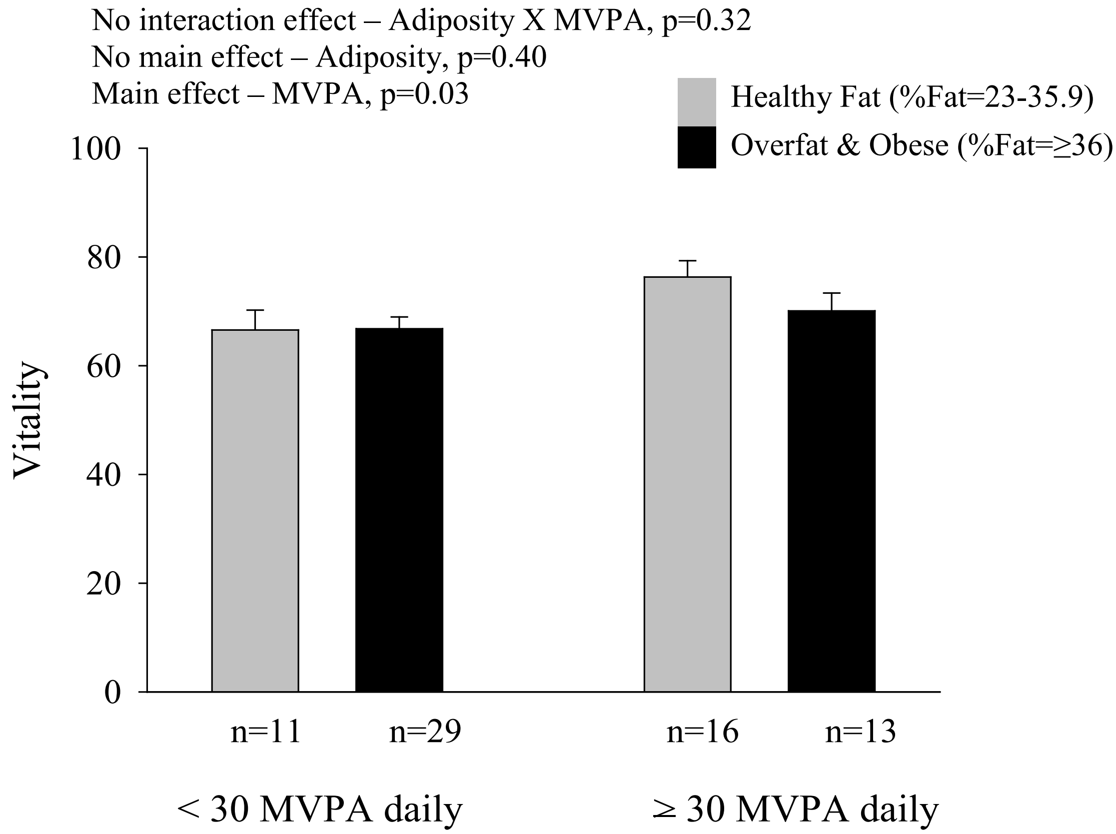

Figure 3.1. The main and interactive effects of adiposity classification and activity status on vitality as measured by the SF-36, controlled for total number of medications, Pittsburgh Sleep Quality Inventory score, Beck Depression Inventory-II score, and Perceived Stress Scale score. Mean±SE.

CHAPTER 4

PHYSICAL FUNCTION PERFORMANCE IN MIDDLE-AGED POSTMENOPAUSAL WOMEN: RELATIONSHIPS WITH ADIPOSITY AND PHYSICAL ACTIVITY

[1]Ward CL, Adrian AL, Johnson MA, Rogers LQ, Evans EM. To be submitted to *Menopause.*

4.1 Abstract

Physical function status and its determinants are not well characterized in middle-aged women. As poor function has been significantly associated with disability and quality of life, identifying the primary factors associated with adequate physical function are pertinent. Therefore, the aim of the present study was to objectively evaluate physical function and examine the contributions of adiposity, physical activity (PA), muscular strength, muscular power and muscle quality (MQ) to functional performance. Body composition [whole body adiposity, leg lean mass] was measured via dual energy x-ray absorptiometry, PA via accelerometer [steps·day^{-1}, daily minutes of moderate to vigorous PA], and physical function with timed up and go (UPGO), 30-sec chair stand (CHR), and 6-minute walk (WALK). Leg strength was assessed using isokinetic dynamometry at 60°·sec^{-1} (KN60). Leg power was assessed with the Nottingham Leg Extensor Power Rig. Muscle quality (MQ) was calculated as: 1) ratio of KN60 to upper leg lean mass (MQ-KN60), and 2) ratio of power to total lower body lean mass (MQ-Power). Regression analyses revealed: 1) age and MQ-Power are independently related to UPGO, explaining 12% and 11% of the variance, respectively ($p<.05$), 2) in addition to age, MQ-KN60 is independently related to CHR, explaining 12% and 10% of the variance, respectively ($p<.05$), and 3) number of medical conditions, MQ-KN60, steps·day^{-1}, and adiposity were independent predictors of WALK, collectively explaining 51% of the variance. A 2X2 ANCOVA [PA status (<10,000 steps·day^{-1} vs. ≥10,000 steps·day^{-1}) X adiposity (23-35.9% vs. ≥36%)] controlled for total number of medical conditions and MQ-KN60 found that in the absence of an interactive effect between adiposity classification and PA status (p=.14) and main effect for PA status (p=.11), there was a main effect for adiposity (p=.003) on WALK performance. Postmenopausal women

should strive for optimal body composition, including adiposity and lean mass, engage in PA, and maintain muscular strength and MQ for better functional performance at midlife.

Keywords: physical function, physical activity, body composition, muscle quality

4.2 Introduction

Midlife is the intersection of menopause and aging [1] and as such, the middle-aged postmenopausal woman experiences a number of physiological changes with concomitant increased risk for osteoporosis, metabolic syndrome, diabetes mellitus and cardiovascular disease [2, 3]. The menopausal transition is also associated with reductions in physical activity (PA) [4]. Both menopause and aging are associated with increasing adiposity [5, 6] and concomitant decreases in muscle mass, sarcopenia [7-9], muscular strength, dynapenia [9], and muscular power [9]. These detrimental changes in PA, body composition, and muscular performance have been associated with a decline in physical function ability [10]. The implications of poorer physical function performance are vast, as physical function has been correlated with loss of independence, decreased quality of life, and an increased risk for chronic disease and mortality [11-13].

Physical function performance has been examined extensively in older men and women (65 years and older) [14-17], and it is well established that older women have a reduced physical function and a higher risk for physical disability compared to their male counterparts [18, 19]. However, physical function status and its implications are less clear in middle-aged women, especially for those in early menopause, ~45-65 years of age [20]. In a female cohort aged 45-57 years of age, compared to premenopausal women, postmenopausal women reported greater physical function limitations, as assessed by the physical function scale of the SF-36 [10]. Sowers et al. reported that approximately 10% of women aged 40 to 55 experience some limitation in self-reported physical function, while an additional 9% reported substantial limitations in function [21]. Additionally, data from the Study of Women's Health Across the Nation indicate that a third of the women evaluated did not meet walking velocity guidelines that would allow them to cross safely at an intersection [22]. Per the Nagi disablement model, disability is the result of functional limitations, which follow physiological/mental impairment [23]. Thus, if functional limitations are increasing due to reductions in PA and increases in obesity in the middle-aged female population, the number of individuals predicted to become disabled is expected to increase. Importantly, this greater number of individuals, given our aging demographics, will also experience disability at an earlier age, and for a longer portion of their lifetimes.

The most influential determinant of physical function is still elusive in this cohort as PA, body composition, including weight status, adiposity, lean mass and the interaction of these components, and muscle capacity including strength and power, have all been identified as correlates of physical function. From a behavioral perspective, PA levels have been shown to decline with age [4] and there is some evidence to suggest that the adverse health outcomes associated with the menopausal transition are linked to reductions in PA [2]. Relatedly, it is well established that higher levels of PA are associated with more favorable body composition, including lower fat mass [24], greater lean mass [24], and decreased risks of chronic disease [25]. PA has also been found to be independently and positively related to physical performance in late middle-aged women [26].

Obesity has been associated with mobility related disability in late middle-aged women [27], and functional differences between pre and postmenopausal women, independent of age, have been explained by higher body mass index (BMI) and increased depressive symptoms [10]. Work from our own lab found that both adiposity and lean mass are significant contributors to objectively measured physical function, as a higher amount of fat mass and decreased lean mass negatively impact performance in older women [14].

In addition to adiposity and habitual PA, muscular performance and quality should also be considered when evaluating correlates and independent determinants of physical function [9]. As lean muscle mass generally decreases with age, the muscle's ability to generate both strength and power also decreases, but this decline occurs at varying rates, and is not linear in relation to the reduction in muscle mass [9, 28]. Some authors suggest that the menopausal transition, which is correlated with reductions in PA, and adverse changes in body composition (i.e. increases in adiposity and reductions in lean mass) are the beginning of the decline in women [2-4]. Importantly, most work in this area has not been completed in middle-aged women, but rather in older adults with a focus on women, as they are known to be at higher risk for physical disability compared to men.

Limited literature indicates similar relations among muscle capacity measures and physical function in middle-aged adults compared to older adults. For example, regarding the link between muscular strength and functional performance, Ostchega et al. [29] reported that, in adults aged 50 and older, greater isokinetic strength of the right knee extensor was associated with greater distance covered during a timed walking assessment. In addition, Brill et al. [30] found that a high level of strength at baseline, calculated as a composite score from bench press, leg press and sit up tests, was associated with a lower number of self-reported functional limitations over 5 years in women with an average age of 44 years at baseline. Another muscle capacity measure of interest, leg extensor power has been found to be significantly related to physical function in older women, as power, in addition to self-reported PA, explained 40% of the variance in self-reported functional status in women aged 74.8±5.0 years [31]; however few studies have examined the contributions of muscular strength and no studies, to our knowledge, have explored the contributions of leg muscle power to function in middle-aged postmenopausal women. Moreover, the expression of muscle capacity in relation to amount of lean mass, termed muscle quality (MQ), in relation to physical function has not been explored in this cohort.

Muscle quality has been examined as a determinant of physical function in older adults. Muscle quality, isokinetic leg capacity (strength or power) normalized for leg lean mass, has been identified as the strongest independent predictor of objectively measured physical function in older men and women, 69.3±5.5 years of age, explaining 29-42% of the variance in performance [32]. Barbat-Artigas et al. [9] report that MQ is an important predictor of functional performance, but advise that calculating MQ as leg extensor power normalized for leg lean mass may be the most comprehensive, and therefore the optimal method, for calculating MQ. The authors further assert that using a power measure accounts for the shortening velocity of muscle, in addition to the force producing capability and lean mass area of the muscle, providing the most complete picture of muscle capability [9]. Importantly, calculating muscle quality, using either approach, allows the muscle capacity to be expressed in relation to the muscle mass responsible for completing the physical functional task of interest. For example, rising from a chair or walking performance are both important for adequate completion of activities of daily living; however, each task the musculature of the lower body in different ways, and MQ expressed using strength or power may differentially account for variance in performance in each of these tasks.

Although warranted, the implications of PA, body composition, muscular performance, MQ, and physical function in middle-aged postmenopausal women are not well characterized in the literature due to the following; 1) work examining these outcomes in middle-aged women is limited, as the majority of the current literature focuses on these outcomes in older adults, aged 65 and older [20], 2) PA is not reported [10] or self-report methods are used to assess PA [26, 33], 3) self-reported physical function is often used in place of objectively measured assessments of functional ability [26, 30, 34], 4) few studies examine body composition via DXA or other validated measurement techniques and instead rely on body mass index (BMI) to categorize weight status [34], and 5) few studies measure both muscular strength and power, limiting the ability to determine which muscle capacity measure or which MQ measure is more highly related to function [9, 29, 30].

In addition, the interactive effects of adiposity, PA and muscular performance on physical function are incompletely characterized, and given the low PA rates [4, 35] and current obesity rates for older women in the U.S. adult population [36], these relationships are of particular interest. Karvonen-Gutierrez [27] recently reported that 25% of late middle-aged women report moderate or severe global disability (i.e. a summary score of disability domains including the tasks of ambulation and self-care) and that obesity was independently associated with mobility disability. A better understanding of the relationships among PA, body composition, muscular performance and physical function, particularly in sedentary and overweight/obese individuals at increased risk of disability toward the end of designing effective weight management and PA interventions for physical functional preservation in this cohort. To our knowledge, no study has examined the independent or interactive contributions of objectively measured PA, body composition, and muscle capacity and quality measures to objectively measured physical function in middle-aged postmenopausal women.

In this context, the primary aim of this study was to determine the associations of objectively measured PA, body composition and muscular performance and quality with objectively measured assessments of physical function in relatively healthy middle-aged postmenopausal women. We hypothesized that lower PA, poorer body composition, and poorer muscular performance, including MQ, would be related to poorer physical function. As a secondary aim we sought to evaluate the relative strength of associations of MQ calculated using isokinetic strength and leg extension power with physical function. We hypothesized that MQ calculated using upper leg strength would be related to functional tasks relying primarily on leg strength, including walking tasks, while MQ calculated using leg power would be mostly highly associated with functional tasks requiring speed and agility.

4.3 Materials and Methods

Participants

Community-dwelling postmenopausal women ages 45-65 were recruited by placing flyers throughout the community and through e-mail advertisement delivered amongst faculty, staff and alumni organizations of a major university. Participants had to be non-smoking for at least the past two years, weight stable (within 2.6 kg) for the past three months, completion of any cancer related treatment at least five years prior to enrollment, and free of uncontrolled pulmonary, cardiovascular or metabolic disease, symptomatic joint abnormalities, and symptomatic nervous disorders, in addition to any medical conditions that would not allow for participation in any muscular performance and/or physical function assessments. The Institutional Review Board (IRB) of the University approved all procedures employed in the study and prior to enrollment participants completed an IRB approved informed consent.

Procedures

Potential participants were screened via telephone and eligible participants were scheduled for two visits to the laboratory 7-10 days apart to allow for PA monitoring. Visit 1 required participants to complete consent documents, anthropometric measures, dual energy x-ray absorptiometry (DXA) scanning, and a series of questionnaires. In the 7-10 day period between visits, participants completed questionnaires on their home computer addressing their health history and wore a PA monitor. Participants were sent a reminder e-mail prior to Visit 2 with instructions to refrain from vigorous activities/structured exercise on the day of testing and to wear clothes and shoes suitable for exercise. At Visit 2, all questionnaires were reviewed for completeness, and participants completed assessments of muscular performance and physical function.

Health History

Participants were asked to report all prescription and over the counter medications and supplements. In addition, they were asked to self-report the presence of chronic medical conditions including arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease, cardiovascular disease, peripheral arterial disease, diabetes, and degenerative disc disease.

Body Composition

Standing height and weight were measured while wearing light-weight clothing and no shoes. Height was measured to the nearest 0.1cm using a stadiometer (Seca, Model 242), and weight was measured using a calibrated digital scale (Tanita, Model WB-110A). Whole body soft tissue was measured using DXA (Lunar iDXA, v 11.30.062, GE Healthcare, Madison, WI) and in addition to relative whole body fat mass (%Fat), lean mass of the upper legs and total lean mass of the lower body were obtained.

Objective Physical Activity

Objective PA was determined using an accelerometer (New Lifestyles-1000, Barebones Pedometer, New Lifestyles, Inc., Lees Summit, MO). Participants were instructed to wear the monitor on the non-dominant hip, fastened to their waistband, during all waking hours, except when bathing or swimming. Using a written log, participants recorded the time spent wearing the activity monitor, the number of steps and MVPA, which were verified by a member of the research team using the memory feature of the NL-1000. A valid wear day included at least ten hours of wear time and four valid days were required for inclusion in analyses. Step counts were calculated using the average step count from valid wear days ($steps \cdot day^{-1}$), and minutes spent in MVPA per day were calculated as the average time spent in MVPA from valid wear days. MVPA was defined as activity completed above a moderate intensity threshold, which corresponds to approximately 3.6 METs.

Subjective Sedentary Time

The Global Physical Activity Questionnaire V2 (GPAQ), developed by the World Health Organization, was used to measure self-reported sedentary time (SED) [37]. The GPAQ asks "How much time do you usually spend sitting or reclining on a typical day?" and provides examples such as sitting or reclining at work, at home, getting to and from places, etc. Participants reported daily sitting and/or reclining time in total minutes.

Muscular Performance and Leg Muscle Quality

Muscular strength was assessed using an isokinetic dynamometer (System 4 Pro, Biodex Medical Systems, Inc., Shirley, NY) and bilateral measurements for knee flexion and extension were obtained. Isokinetic strength was measured for the knee at $60^{\circ} \cdot sec^{-1}$ (KN-60) with 2 sets of 4 repetitions for each limb. Participants were instructed to push and pull as hard and as fast as possible during each repetition of isokinetic testing and the trials that resulted in the greatest peak torque for the right and left limbs were totaled to calculate total peak torque for the joint of interest. The Nottingham Leg Extensor Power Rig (The University of Nottingham, Nottingham, UK) was used to assess leg power. Prior to assessment, seat position was adjusted for individual leg length to allow for a 5° bend in the knee when the leg was at full extension. Participants were instructed to keep their arms across their chest and to allow the inactive leg to remain flexed at

90°, with their inactive foot on the floor. Participants were instructed to push out as hard and as fast as possible with each repetition and performed up to 10 trials per leg. The highest power achieved for the right and left leg was summed as total leg power, and this value was used for analysis. Muscle quality was calculated in two ways: 1) the ratio of KN-60 to upper leg lean mass was calculated to examine muscle quality (MQ-KN60) and, 2) the ratio of leg power to total lower body lean mass (MQ-Power) was calculated to examine the relationships between muscle strength and leg muscle mass [32] and muscle power and leg muscle mass, respectively [9].

Objectively Measured Physical Function

Performance-based physical function was assessed using the timed up-and-go (UPGO), the 30-second chair stand (CHR), and 6-minute walk (WALK). The UPGO required participants to begin the assessment seated in a chair, arms crossed over their chest, and feet flat on the floor. Participants were instructed to volitionally stand and walk, as quickly as possible, around a cone placed eight feet in front of the chair and return to a seated position [38]. Participants performed two timed UPGO trials, and the fastest trial was used for analysis. The CHR assessment required participants to start in a seated position with their arms crossed over their chest and feet flat on the floor [39]. On the command "go," participants completed as many repeated chair stands as possible over a 30-second period. The WALK assessment was administered to evaluate functional endurance, and this test asked participants to safely cover as much distance as possible, over the course of the six minutes [39].

Statistical Analyses

Data were analyzed with IBM SPSS Statistics for Windows Version 21.0. (IBM Corp: Armonk, NY). 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.

Partial correlations, controlling for age and total number of medical conditions, were conducted to examine the associations between, body composition (%Fat), PA, SED, measures of muscular performance, including muscle strength and muscle power, MQ and measures of physical function. To assess the independent contributions of adiposity, PA and MQ on physical function, a series of hierarchical linear regression analyses were also conducted. Due to known effects of age and chronic medical conditions on function, analyses controlled for these measures. Regression analyses were conducted in the following order: Step 1, age and number of total number of medical conditions; Step 2, muscle quality (MQ-KN60); Step 3, PA (steps·day^{-1}); Step 4, adiposity (%Fat). A second set of regression analyses were conducted with MQ-Power in place of MQ-KN60 in Step 2.

Additionally, a 2X2 ANCOVA (PA status [less than 10,000 steps·day^{-1}vs. 10,000 steps or more steps·day^{-1}] [40] X adiposity category [healthy fat vs. overfat and obese] [41]), controlling for total number of medical conditions and MQ-KN60, was conducted to examine the main and interactive effects of PA and adiposity on WALK performance. All data are presented as mean±SD. Statistical significance was set at the $p \leq .05$ level.

4.4 Results

A total of 191 women contacted our laboratory in response to our recruitment efforts, of those who contacted us, 91 qualified for participation. Reasons for exclusion included: did not respond to follow-up contact (41), chose not to participate due to time commitment (19), currently smoking (2), not currently postmenopausal (17), outside of the age range for participation (8), BMI >35.0 (5), injury precluding completion of physical function testing required for additional arm of the current study (2), refused to undergo DXA scanning (2), and not weight stable (4). Of the 91 women who completed visit 1, 27 were excluded in the final analysis due to the following: cancer survivor recruited for alternate arm of the study (15), BMI< 18.0 (1), incomplete questionnaire data (1), incomplete objective PA data (3), incomplete physical function data (3), and incomplete isokinetic strength data (4).

The sample was 92% white and highly educated (18.5 ± 3.4 years), with participant characteristics presented in Table 4.1. Self-reported medical conditions included: cardiovascular disease, peripheral vascular disease, pulmonary disease, diabetes, and osteoporosis, and the most commonly reported conditions were arthritis (40%), depression (20%), degenerative disc disease (18%), and anxiety (17%). Mean values were within the overweight and overfat categories for BMI and %Fat, respectively [41, 42]. Notably, PA levels, when examined objectively in steps·day^{-1} or MVPA, approached and exceeded recommended daily goals of 10,000 steps [40] and 30 min MVPA per day [43], respectively.

Isokinetic peak torque of the knee extensors and flexors at 60°·sec^{-1} are shown in Table 4.2, along with values for leg power, MQ-KN60, and MQ-Power. Participants who did not complete the full battery of muscle capacity due to previous knee injury were excluded from analyses including these outcomes. Table 4.2 also includes the results for the physical function assessments.

Greater adiposity, as measured by BMI and %Fat, was negatively related to PA, both steps·day^{-1} and MVPA (r range -.27 to -.54, all p<.05), with %Fat demonstrating the strongest relationships among the two adiposity measures. Higher %Fat was significantly related to poorer functional performance (r range -.29 to -.50). Steps·day-^{1} was significantly related to leg power (*r*=.30) and MQ-Power (*r*=.32). Greater steps·day^{-1} and greater MVPA were related to better functional performance (steps·day^{-1} *r* range -.35 to .58; MVPA *r* range -.32 to .50, all $p<.05$). As expected, KN60 and leg power were significantly related to MQ-KN60 and MQ-Power (all $p<.01$). Greater muscular strength conferred better functional performance for all tasks (KN60: UPGO *r*=-.27, CHR *r*=.33, WALK *r*=.48; all $p<0.05$), while greater muscular power was significantly associated with UPGO (*r*=-.28) and CHR (*r*=.29), only. Greater MQ-KN60 was significantly associated with better UPGO (*r*=-.30), CHR (*r*=.35), and WALK (*r*=.42) performance, while greater MQ-Power was significantly associated with UPGO (*r*=-.32) and CHR (*r*=.31), only. (Table 4.3)

Regression analyses found that age was independently related to UPGO performance ($F_{5,58}$=3.47, p=.009; Table 4.4.A). Age and MQ-KN60 were identified as significant predictors of CHR performance ($F_{5,58}$=4.40, p=.002). Total number of medical conditions, MQ-KN60, PA (steps·day^{-1}) and %Fat were independent predictors of WALK performance ($F_{5,58}$=11.28, $p<.001$). Table 4.4.B, shows that both age and MQ-Power are independently related to UPGO performance ($F_{5,59}$=11.34, $p<.001$), with 11% of the variance explained by MQ-Power. Age was also identified as a significant predictor of CHR performance ($F_{5,59}$=4.95, p=.001). Total number of medical conditions, PA (steps·day^{-1}) and %Fat were independent predictors of WALK performance ($F_{5,59}$=11.27, $p<.001$).

In the absence of an interactive effect between adiposity classification and PA status (p=.14) and main effect for PA status (p=.11) when controlled for total number of medical conditions and MQ-KN60, there was a main effect for adiposity (healthy fat=705.92±79.72 ; overfat and obese= 633.13±95.16; p=.003) on WALK performance. (Figure 4.1)

4.5 Discussion

Our findings add to the accumulating literature investigating the relationships among PA, body composition, muscular performance and quality, and physical function in middle-aged women. The most notable findings in the present study are 1) MQ-KN60 is independently related to lower body tasks requiring endurance and 2) MQ-Power independently predicts performance on lower body tasks requiring speed and agility. Furthermore, our data also support associations between lower levels of %Fat and higher daily levels of both total PA and MVPA and better functional performance.

In an attempt to fully capture the contribution of muscular capacity on function, we evaluated muscular capacity using isokinetic strength and leg extension power. Additionally, our battery of functional assessments was deliberately chosen to include a multitude of functional challenges, as UPGO, CHR, and WALK assessment evaluate differing aspects of the capacity of the lower body musculature. As both measures of MQ were independently related to functional performance measures, our data support the importance of obtaining objective measures of muscle mass of the legs, muscular strength and power of participants when attempting to elucidate determinants of objectively measured physical function in this age group of early postmenopausal women [9].

The extent to which PA independently affects functional performance in middle-aged women remains unclear. Greater amounts of PA have been associated with better functional status and functional performance in older women [16, 31], and in adults ages 51-61 [26] and 40-60 [44] when both PA and function were measured via self-report. Lang et al. also found that greater amounts of self-reported PA were protective against impaired objectively measured physical function in men and women ages 50-69 years [45]. In agreement with the literature, the current findings support a positive relationship between higher amounts of objectively measured PA, both steps·day^{-1} and MVPA per day, and better performance on objectively measured physical function targeting the lower body. Furthermore, regression analyses found that total PA (steps·day^{-1}) was an independent predictor of WALK performance, supporting the importance of regular aerobic movement in maintaining gait related function. Notably, when MVPA was used in regression models in place of steps·day^{-1}, MVPA explained less variance in UPGO performance, explained no additional variance in CHR performance and was not a significant predictor of WALK performance compared to steps·day^{-1} (data not shown). Contrary to these findings, Lahti et al. [44] concluded that vigorous activity may confer greater benefit than moderate intensity activity on self-reported physical health functioning in women aged 40 to 60 years. The current findings may differ from those of Lahti et al. [44], as they did not report the contribution of total amount of physical activity on function, only that of self-reported moderate and vigorous intensity activity. In addition, when examining the contribution of intensity of exercise on functional ability in the present study, we were only able to assess the contribution of combined amounts of daily moderate and vigorous activity to physical function, as our the accelerometer used to measure daily MVPA does not allow for separate measurement of minutes of moderate activity and minutes of vigorous activity, just the combined amount of moderate and vigorous activity completed over the moderate intensity threshold.

Our finding that a greater level of total activity may positively affect gait related functional performance is encouraging for those individuals who are unable to accumulate recommended amounts of moderate to vigorous intensity activity [43]. Furthermore, regular PA has been found to be effective at ameliorating the effects of higher BMI on physical function in middle-aged men and women [26, 45]. Lastly, it is important to note that while we attempted to objectively measure PA, our method did not allow for the objective measurement of activities that were not aerobic and weight bearing in nature. Future work evaluating function may be improved by including methods that allow for measurement of non-weight bearing activities and resistance training, as these activities would theoretically contribute to functional performance.

Independent of PA level, prolonged sedentary time is emerging as a risk factor for chronic disease and mortality [46, 47], and meeting PA recommendations has been found to be unrelated to amounts of daily sitting time in middle-aged and older women [48]. Though our findings were not statistically significant, our data suggest that increasing amounts of sedentary time were related to poorer CHR performance. There is data to support a longitudinal relationship between sedentary time and function, as women, aged 50-79 years, with more than 6 total hours per day of self-reported sedentary time reported experiencing poorer physical function between baseline and follow up testing, when controlled for age, BMI, PA, socioeconomic status and total number of chronic medical conditions [49]. Our cross sectional data may not have shown a robust relationship between sedentary time and functional performance due to the nature of the assessments used to evaluate sedentary time and function in the present study. The GPAQ asks participants to self-report total sedentary time, during waking hours, in a 24-hour period, and does not capture any information on the length of each sedentary bout [37]. Alternatively, the high level of PA in our cohort may have offset any amount of sedentary time. Future work examining the role of sedentary time on physical function should employ objective measures for both sedentary time and physical function to further delineate this relationship.

The relationship between function and weight status and/or adiposity has been examined more extensively along the lifespan, from midlife to older age [18, 22, 50, 51]. A recent review found that performance of functional tasks, including walking, stair climbing and chair rise, was poorer in older adults with greater adiposity [18]. Our own data [50] also found that adiposity was the strongest independent predictor of objectively measured functional performance, including WALK, UPGO and CHR in community dwelling older adults aged 60-85 years of age; however, leg strength or power was not reported. In postmenopausal women, younger than 75 years of age, Lebrun et al. [51] found that fat mass, not muscular strength, was the primary determinant of walking composite measures. Specific to middle-aged women (mean age of 47 years), Sowers et al. [22] found that total fat mass was more consistently associated with poorer gait measures (i.e. shorter stride length, lower velocity, greater time in double support) and poorer gait composite scores (which included performance on a timed 12.3 meter walk), compared to skeletal muscle mass and quadriceps strength. In the current study, while adiposity was identified as a significant predictor of WALK performance and explained the largest amount of variance in WALK, it was not independently related to any other measures of function requiring quick explosive movements. As the sample of women in the current study were a) younger than the older adults employed above [22, 51], b) most likely more physically active than the other samples (not all studies cited assessed PA), and c) assessed using different methodology for gait related function as the middle-aged women referenced above (i.e. a timed 12.3 meter walk is not aerobically similar to the 6 minute walk [22]), differences in our findings may reflect differences in methodology and/or cohorts. Muscle mass, strength, power and the interaction thereof (i.e. MQ) may play a dominant role in middle-aged women for gait endurance tasks before detrimental changes in adiposity, including increases in subcutaneous and visceral fat, become great enough to be the dominant determinant of physical function in middle-aged women.

From a methodological perspective, when evaluating the strength of univariate associations between weight and adiposity status and physical function, it was demonstrated that adiposity, rather than BMI, was more highly correlated with functional performance variables, especially with WALK. These results support the importance of obtaining objective measures of body composition, including adiposity and lean mass, when evaluating determinants of physical function in middle-aged women [52]. Though BMI may be effective as a surrogate measure of adiposity for estimating mortality risk [53], BMI does not account for composition changes, including increases in fat mass and decreases in lean muscle mass, that occur with aging in this cohort of women, which clearly have implications for functional ability.

In addition to body composition factors, muscle capacity measures have been identified as instrumental factors associated with physical functional performance in both middle-aged and older adults. Leg strength, leg muscle power and muscle quality, leg strength or power normalized for leg lean mass have all been significantly associated with physical function [9, 22, 30, 31]. In a longitudinal examination, Brill et al. [30] found that women with greater composite strength scores at baseline (mean age 45 years) were less likely than their weaker counterparts to self-report functional limitations approximately 5 years later, supporting the role of muscular strength in prevention of functional decline with aging. In middle-aged women, quadriceps strength was identified as a significant correlate of stair climbing tasks [22], though both Brill et al. [30] and Sowers et al. [22] did not measure leg muscle power. Foldvari et al. [31], who measured both leg press strength and power, found that in addition to habitual PA, leg muscle power, was independently related to self-reported functional status, and more strongly associated with functional status than leg strength in older women aged 70-80 years. While our univariate results demonstrate a moderate relationship between leg extension power and objectively measured assessments of function, KN60 demonstrated stronger relationships. The differences between the current findings and those of Foldvari et al. [31] could be the result of their older sample of women and their use of self-report to assess a composite score of physical function addressing activities of daily living and mobility.

One strength of our study design is that we obtained objective measures of leg lean mass, muscular strength and muscular power, allowing for the calculation of measures of MQ expressed using both leg strength and power. This approach allowed for the examination of which MQ measure was more strongly related to functional performance and to determine the independent contribution of MQ-KN60 and MQ-Power, in addition to that of adiposity and PA to functional performance. Misic et al. [32] found that MQ, calculated as MQ-KN60 was in the present study, explained the greatest amount of variance in function tasks assessing a range of skills, including stair ascent and descent, UPGO, and 7 meter walk, in community dwelling older adults. Straight et al. [17] reported that MQ, calculated as MQ-Power was in the present study, explained up to 26% of the variance in physical function, including the tasks of UPGO and CHR after adjustment for covariates, including age, comorbid conditions, and PA in older adults. The present study found that MQ-KN60 is independently related to both CHR and WALK, tasks which require greater muscle endurance, while MQ-Power was most highly related to UPGO, the task requiring the most power, speed and agility. Collectively, this emphasizes that in middle-age both adequate muscle mass and the ability to generate both strength and power contribute to physical functional ability.

The present study is not without limitations. As our approach was cross sectional, we are unable to make inferences about causality. In addition, our participant sample only included ambulatory, community-dwelling, middle-aged women therefore the relationships present may not reflect those found in less able bodied women of the same age. Notably in our sample, mean values for steps $\cdot day^{-1}$ and MVPA are just under the recommendations for 10,000 steps $\cdot day^{-1}$ [40] and meet the recommendations for at least 30 minutes of moderate intensity activity per day [42], reflecting that our sample may be more physically active than the general population.

Furthermore, while both MQ-KN60 and MQ-Power were shown to be important determinants of physical function in the present study, the optimal method for calculating MQ is still being established as the optimal speed of isokinetic testing, the optimal capacity measure (strength vs. power) and whether to use of the values generated by one leg or the sum of values from both legs one or both legs is still under debate [9]. In addition, calculating MQ using lean mass values obtained via DXA does not account for the presence of fat infiltration within muscle mass, which may be a limiting factor, as this infiltration has been associated with the decreased mobility in older adults [15]. Thus, additional measures of lean mass from imaging modalities for use in the calculation of MQ are warranted.

In summary, our results suggest that in relatively healthy, community-dwelling middle-aged postmenopausal women, MQ appears to be a major correlate of physical functional ability; with MQ calculated using isokinetic strength important for tasks requiring endurance and MQ calculated using leg extension power most essential for tasks requiring speed and agility. Identifying the most influential factors contributing to functional performance is instrumental for the development and implementation of effective prevention and treatment strategies for middle-aged women, in hopes of preventing future disability. Our data suggest that preserving and improving MQ may be the primary target for future weight management and PA interventions aimed at improving function among postmenopausal middle-aged women.

4.6 References

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Table 4.1. Participant characteristics

	Mean ± SD N=64	Range
Age (years)	58.6 ± 3.6	50-65
Total Number of Medical Conditions	2.0 ± 1.5	0-5
Total Prescription Medications	2.0 ± 2.0	0-6
Hormone Replacement Therapy (%)	15%	
Menopause Duration (months)	106.0 ± 60.5	20-252
Body Mass (kg)	69.6 ± 13.1	49.1-102.8
Height (cm)	163.6 ± 6.0	150.5-181.6
Body Mass Index ($kg{\cdot}m^{-2}$)	26.0 ± 4.5	18.1-37.0
Whole Body Adiposity (%)	38.8 ± 6.1	27.7-52.8
Upper Leg Lean Mass (kg)	9.5 ± 1.5	7.0-13.8
Total Leg Lean Mass (kg)	20.4 ± 2.7	15.9-28.5
Physical Activity: $steps{\cdot}day^{-1}$	9076.2 ± 3,822	2,632-21,275
Meet 10,000 $steps{\cdot}day^{-1}$ (%)	30%	
Physical Activity: $MVPA{\cdot}day^{-1}$	30.0 ± 20.8	5.0-94.63
Meet 30 $MVPA{\cdot}day^{-1}$ (%)	42%	
Meet 150 $MVPA{\cdot}week^{-1}$ (%)$^{\#}$	66%	
GPAQ – Sedentary Time ($min{\cdot}day^{-1}$) $^{\wedge}$	294.5 ± 145.6	60.0-660.0

MVPA= minutes per day of moderate to vigorous physical activity; GPAQ= Global Physical Activity Questionnaire. $^{\#}$N=35; $^{\wedge}$N=53.

Table 4.2. Muscular performance, muscle quality and physical function performance

	Mean ± SD N=63	Range
Quadriceps Peak Torque $60^{\circ}\cdot sec^{-1}$ (Newton-Meters)^	253.9 ± 63.8	79.0-379.1
Leg Extension Power (Watts)	233.5 ± 67.9	114.2-415.0
Muscle Quality – Isometric $60^{\circ}\cdot sec^{-1}$ (Newton-meters$\cdot kg^{-1}$)^	26.5 ± 6.9	3.1-42.5
Muscle Quality – Leg Extension Power (Watts$\cdot kg^{-1}$)	11.6 ± 3.3	5.1-19.0
Timed Up and Go (seconds)	4.5 ± 0.8	3.0-6.7
30 Second Chair Stand (repetitions)	21.8 ± 6.9	12.0-41.0
6 Minute Walk (meters)	651.5 ± 104.2	448.0-982.8

^n=62.

Table 4.3. Partial correlations, controlled for age and total number of medical conditions, for body composition, physical activity, muscle capacity measures, muscle quality, and physical function

	BMI	%Fat	Steps·day^{-1}	MVPA	SED	KN60	Power	MQ-KN60	MQ-Power	UPGO	CHAIR	WALK
BMI	1.0	.78†	-.27*	-.35†	-.03	.12	.18	-.20	-.09	.25	-.11	-.31*
%Fat		1.0	-.54†	-.52†	.01	-.09	.01	-.23	-.10	.30*	-.29*	-.50†
Steps·day^{-1}			1.0	.86†	-.12	.25	.30*	.22	.32*	-.35†	.41†	.58†
MVPA				1.0	-.03	.24	.24	.23	.29*	-.32*	.38†	.50†
SED					1.0	.01	-.12	-.13	-.14	.07	-.23	-.14
KN60						1.0	.55†	.76†	.39†	-.27*	.33*	.48†
Power							1.0	.46†	.91†	-.28*	.29*	.25
MQ-KN60								1.0	.51†	-.30*	.35†	.42†
MQ-Power									1.0	-.32*	.31*	.25
UPGO										1.0	-.58†	-.47†
CHAIR											1.0	.58†
WALK												1.0

BMI=body mass index; %Fat=whole body adiposity; MVPA=minutes per day moderate to vigorous physical activity; SED=minutes per day of sedentary time; MVC=maximal voluntary contraction for knee flexion and extension at 60° (0°·sec^{-1}); KN60=isokinetic peak torque of the knee at 60°·sec^{-1}; Power=leg extension power; MQ-KN60=muscle quality calculated using KN60 (isokinetic peak torque of the knee at 60°·sec^{-1}); MQ-Power=muscle quality calculated using leg extension power; UPGO=Timed Up and Go; CHAIR=30 second chair stand; WALK=6 minute walk. $^*p\leq.05$; $^\dagger p\leq.01$.

Table 4.4.A. Regression analyses of independent predictors of physical function

	Timed Up and Go				30 Second Chair Stand				6 Minute Walk			
	R^2	β	Beta	95% CI	R^2	β	Beta	95% CI	R^2	β	Beta	95% CI
Step 1	0.11*				0.12*				0.16†			
Age		0.28*	0.06	[0.01, 0.11]		-0.27*	-0.51	[-0.98, -0.03]		-0.11	-2.98	[-9.65, 3.70]
Medical Cond		0.15	0.08	[-0.05, 0.21]		-0.18	-0.86	[-2.05, 0.33]		-0.38†	-25.50	[-42.23, -8.77]
Step 2	0.18*				0.22*				0.31†			
Age		0.28*	0.06	[0.01, 0.11]		-0.27*	-0.51	[-0.96, -0.06]		-0.11	-3.03	[-9.65, 2.98]
Medical Cond		0.11	0.06	[-0.07, 0.19]		-0.14	-0.65	[-1.80, 0.49]		-0.32	-21.95	[-34.68, -5.58]
MQ-KN60		-0.27*	-0.03	[-0.06, -0.003]		0.32†	0.32	[0.07, 0.56]		0.38	5.43	[6.09, 15.52]
Step 3	0.23				0.29*				0.48†			
Age		0.29*	0.06	[0.01, 0.11]		-0.28*	-0.53	[-0.97, -0.10]		-0.13	-3.54	[-8.43, 1.90]
Medical Cond		0.11	-0.02	[-0.07, 0.18]		-0.13	-0.62	[-1.71, 0.49]		-0.31†	-21.11	[-33.04, -6.82]
MQ-KN60		-0.21	-4.60^{-5}	[-0.05, 0.004]		0.25†	0.25	[0.01, 0.49]		0.27†	3.91	[-3.46, 12.49]
Steps·day^{-1}		-0.23	0.06	[0.000, 0.000]		0.27*	0.000	[0.000, 0.001]		0.43†	0.01	[0.005, 0.02]
Step 4	0.25				0.29				0.52*			
Age		0.29*	0.03	[0.01, 0.11]		-0.29*	-0.54	[-0.98, -0.10]		-0.14	-3.76	[-18.53, 1.55]
Medical Cond		0.07	-0.02	[-0.10, 0.17]		-0.11	-0.51	[-1.68, 0.65]		-0.25†	-16.78	[-29.37, -2.64]
MQ-KN60		-0.20	-3.10^{-5}	[-0.05, 0.006]		0.24*	0.24	[-0.003, 0.48]		0.25†	3.52	[2.85, 11.75]
Steps·day^{-1}		-0.16	0.02	[0.000, 0.000]		0.23	0.000	[0.000, 0.001]		0.31†	0.008	[0.002, 0.01]
%Fat		0.15	0.01	[-0.02, 0.06]		-0.09	-0.10	[-0.43, 0.24]		-0.25*	-4.13	[-7.65, 0.02]

Analyses conducted in this order: Step 1- Age and Medical Cond (total number of medical conditions); Step 2-MQ-KN60=muscle quality calculated using KN60 (isokinetic peak torque of the knee at 60°·sec^{-1}); Step3-Steps·day^{-1}; Step 4-% Fat. β=standardized regression coefficients, Beta=unstandardized regression coefficients. *$p \leq .05$, †$p \leq .01$.

Table 4.4.B. Regression analyses of independent predictors of physical function

	Timed Up and Go				30 Second Chair Stand				6 Minute Walk			
	R^2	β	Beta	95% CI	R^2	β	Beta	95% CI	R^2	β	Beta	95% CI
Step 1	0.12*				0.12*				0.18†			
Age		0.31*	0.07	[0.01, 0.12]		-0.29*	-0.55	[-1.02, -0.08]		-0.11	-3.07	[-9.73, 3.59]
Medical Cond		0.10	0.05	[-0.08, 0.18]		-0.16	-0.72	[-1.87, 0.43]		-0.39†	-26.55	[-42.95, -10.16]
Step 2	0.23†				0.21*				0.24*			
Age		0.24*	0.05	[0.001, 0.10]		-0.23	-0.43	[-0.89, 0.02]		-0.06	-1.65	[-8.24, 4.94]
Medical Cond		0.10	0.05	[-0.07, 0.17]		-0.16	-0.73	[-1.82, 0.37]		-0.39†	-26.62	[-42.52, -10.72]
MQ-Power		-0.35†	-0.08	[-0.14, -0.03]		0.31*	0.66	[0.15, 1.17]		0.26*	7.94	[0.56, 15.33]
Step 3	0.29*				0.31†				0.46†			
Age		0.29*	0.06	[0.01, 0.11]		-0.29*	-0.53	[-0.97, -0.10]		-0.15	-3.98	[-9.65, 1.68]
Medical Cond		0.06	0.03	[-0.09, 0.15]		-0.10	-0.46	[-1.52, 0.61]		-0.30†	-20.36	[-34.07, -6.64]
MQ-Power		-0.27*	-0.06	[-0.12, -0.005]		0.24*	0.44	[-0.08, 0.95]		0.09†	2.77	[-3.84, 9.38]
Steps·day^{-1}		-0.25	-5.35^{-5}	[0.000, 0.000]		0.33*	0.001	[0.000, 0.001]		0.51†	0.01	[0.008, 0.02]
Step 4	0.31				0.31				0.51*			
Age		0.28*	0.06	[0.01, 0.11]		-0.28*	-0.53	[-0.97, -0.09]		-0.14	-3.82	[-9.28, 1.65]
Medical Cond		0.01	0.007	[-0.12, 0.13]		-0.08	-0.35	[-1.44, 0.75]		-0.25*	-16.77	[-30.37, -3.2]
MQ-Power		-0.27*	-0.06	[-0.12, -0.006]		0.21	0.44	[-0.008, 0.95]		0.10	2.96	[-3.42, 9.34]
Steps·day^{-1}		-0.14	-2.99^{-5}	[0.000, 0.000]		0.26	0.001	[0.000, 0.001]		0.37†	0.01	[0.004, 0.02]
%Fat		0.21	0.03	[-0.009, 0.06]		-0.12	-0.13	[-0.45, 0.19]		-0.27*	-4.50	[-8.47, -0.53]

Analyses conducted in this order: Step 1-Age and Medical Cond (total number of medical conditions); Step 2-MQ-Power=muscle quality calculated using Leg Extension Power; Step 3-Steps·day^{-1}; Step 4-%Fat. β=standardized regression coefficients, Beta=unstandardized regression coefficients. $^*p \leq .05$, $^\dagger p \leq .01$.

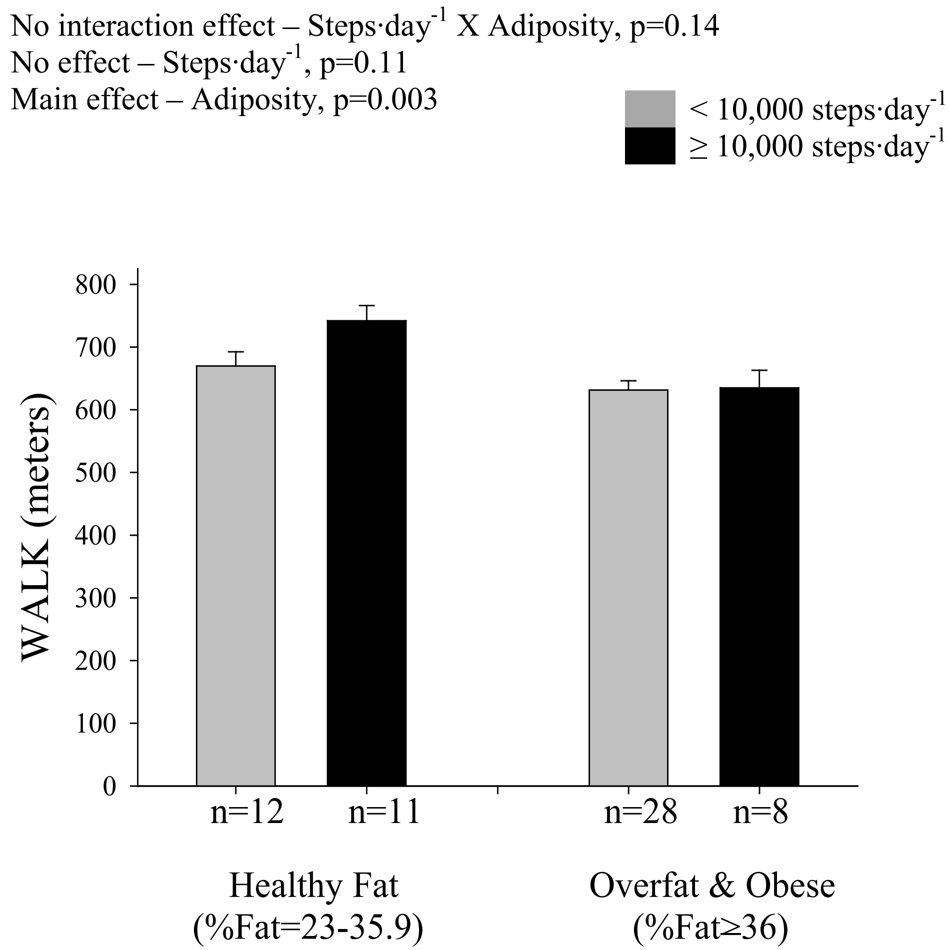

Figure 4.1. The main and interactive effects of adiposity classification and activity status on 6-minute walk performance (WALK), controlled for total number of medical conditions and muscle quality calculated using knee isometric strength at $60^{\circ}\cdot sec^{-1}$. Mean±SE.

CHAPTER 5

A PILOT STUDY EXAMINING FATIGUE AND PHYSICAL FUNCTION IN POSTMENOPAUSAL BREAST CANCER SURVIVORS AND AGE AND ADIPOSITY MATCHED CONTROLS: RELATIONSHIPS WITH BODY COMPOSITION AND PHYSICAL ACTIVITY

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5.1 Abstract

Breast cancer survivors (BCS) report less energy, more fatigue and poorer physical function compared to non-BCS; however, confounding factors are often uncontrolled. This pilot study aimed to determine if BCS differ from age (±3 yrs), body mass index (±4 $kg \cdot m^{-2}$), and adiposity (±7%) matched controls (CON) (N=13 per group) in fatigue, energy, physical activity (PA), and physical function. Body composition was measured via DXA, PA via accelerometer [$steps \cdot day^{-1}$, daily minutes of moderate to vigorous PA (MVPA)], fatigue and energy via the Profile of Mood States and SF-36 Vitality scale, and physical function with timed up and go (UPGO), 30 sec chair stand (CHR), and 6 minute walk (WALK). Leg strength was assessed using isokinetic dynamometry at $60° \cdot sec^{-1}$ (KN60) and leg power using Nottingham Power Rig. Muscle quality was calculated as the ratio of KN60 to upper leg lean mass (MQ-KN60) and ratio of power to total lower body lean mass. Feelings of fatigue and energy, $steps \cdot day^{-1}$, and MVPA were similar in BCS and CON (all $p>.05$). CON performed better than BCS on UPGO (15.8%, $p=.05$) and CHR (21.5%, $p=.15$). Regression analyses using MQ-KN60 found; 1) group was a significant predictor of UPGO, 2) group and MQ-KN60 were independently related to CHR, ($p<.05$), and 3) adiposity explained 12% of the variance in WALK. Regression analyses using MQ-Power found; 1) $steps \cdot day^{-1}$ were independently related to UPGO and CHR, 2) adiposity significantly explained 10% of WALK. Middle-aged women, especially BCS, should engage in PA and maintain muscle quality for better physical performance.

Key words: Breast cancer survivors, Physical activity, Body composition, Adiposity, Fatigue, Muscle quality, Physical function

5.2 Introduction

Midlife, often defined as ages 45-65 years, is the intersection of menopause and aging [1], and as such, the middle-aged postmenopausal woman faces a myriad of physiological and psychological changes, including an increased risk for osteoporosis, increasing visceral adiposity, and increased risk for metabolic syndrome, diabetes mellitus and cardiovascular disease [2, 3]. Menopause is also associated with decreased physical activity (PA) [4], sarcopenia, a decrease in muscle mass [5, 6], dynapenia, the loss of muscular strength [7], and a decline in physical functional ability [8]. In addition, increases in sleep disturbances, fatigue, depression, and anxiety have also been associated with the menopausal transition in midlife women [9, 10]. These changes can contribute to decreased quality of life and the eventual increase in risk of physical disability and loss of independence for this cohort of women.

While adjusting to life after menopause can be a difficult transition for otherwise healthy women, postmenopausal breast cancer survivors (BCS) may have exacerbated declines in age and menopause-related conditions due to the combined effects of breast cancer itself and breast cancer treatment. Many BCS who are diagnosed and undergo treatment before the onset of natural menopause are induced into a menopausal state as a result of common breast cancer treatments, including adjuvant chemotherapy, creating a hormonal environment of accelerated aging [11]. As the ages associated with the onset of menopause overlap with the ages in which the majority of breast cancer cases are diagnosed, 45-64 years [12], the menopausal BCS cohort in our society is growing. Improvements in screening and treatment have resulted in stable or decreasing breast cancer mortality among women of all races in the United States, resulting in breast cancer as the leading diagnosis within the cancer survivor population [13, 14].

Due to the changes in physiological and psychological health that accompany menopause and the detrimental changes that often accompany breast cancer diagnosis and treatment, including weight gain [15], reductions in PA [16], and increased feelings of fatigue [17], the menopausal BCS may be at increased risk of physical disability and decreased quality of life as a result of the combination of aging and breast cancer treatment related effects. Some efforts have been made to explore if differences exist between BCS and controls in habitual PA, body composition, feelings of fatigue and physical function ability, but findings are equivocal. Specifically, the literature suggests that similar patterns of weight gain, PA [15], fatigue [18], and physical disability [19] exist in postmenopausal BCS compared to controls; while, other evidence supports that BCS report greater feelings of fatigue [17], and have greater functional impairments [20] compared to women without a history of breast cancer. Interestingly, recent work found that while BCS engaged more frequently in PA, they also engaged in longer bouts of sedentary time when compared to individuals without a history of cancer [21].

The implications of PA level, body composition, fatigue and physical function for the middle-aged postmenopausal BCS are not optimally characterized in the literature due to the following: 1) the majority of the work published to date examining the aforementioned variables of interest in BCS has been completed without the inclusion of matched controls in the research design [22-24]; 2) work examining these outcomes in middle-aged women, with and without cancer, is also sparse, as the majority of the current literature focuses on these outcomes in older adults, aged 65 and older [25]; 3) self-report methods are often used to assess PA [23, 26, 27] and physical function [28, 29] rather than objective measures; and 4) few studies examine body composition via DXA or other validated techniques and instead rely on body mass index (BMI) to categorize weight status [23, 26]. To our knowledge, no study has examined the contributions of objectively measured PA and body composition, on measures of perceived fatigue and objective physical function in postmenopausal women with and without breast cancer. It is highly probable, but unknown, if BCS report greater fatigue and have reduced physical performance increasing the subsequent risk for physical disability due to additive and/or synergistic effects of aging and breast cancer disease and/or treatment. If BCS experience greater fatigue and poorer physical function, compared to their age matched controls, the determinants of this difference need to be identified toward the end of informing the design of effective interventions for this cohort.

In this context, the primary objective of the present pilot study was to determine if BCS differ from their age and adiposity matched controls (CON) in feelings of fatigue and energy and physical function, and relatedly examine the associations that PA and body composition have with these measures of health status. We hypothesized that BCS would report greater fatigue and less energy and exhibit poorer physical function when compared to CON. We further hypothesized that lower PA and poorer body composition, including greater adiposity and lower muscle quality, would be related to poorer physical function in both BCS and CON, but the associations would be stronger in BCS.

5.3 Methods and Materials

Participants

Community dwelling BCS (n=13) and CON (n=13), ages 45-65, were recruited for this study. Both BCS and CON were recruited by placing flyers throughout the community and through e-mail advertisement delivered amongst faculty, staff and alumni organizations of a major university. BCS were specifically recruited through advertisements delivered to cancer support centers and contact with breast cancer charity organizations and local oncology groups.

To be included in the present study, participants had to be weight stable (within 2.6 kg) for the past three months, non-smoking for at least the past two years, free of uncontrolled pulmonary, cardiovascular or metabolic disease, and free of symptomatic joint abnormalities, symptomatic nervous disorders and any medical condition that would preclude them from participating in physical assessments of function. Cancer related exclusion criteria included a current diagnosis of active cancer, breast cancer that had metastasized, and/or any type of cancer, other than breast cancer, that had been diagnosed and treated less than five years prior to study start. Breast cancer specific inclusion criteria were completion of radiation, chemotherapy, and/or surgical treatment six months to ten years prior to initial testing, and initial diagnosis of ductal carcinoma in situ (DCIS), Type I, Type II, and Type IIIA breast cancer. The Institutional Review Board of the University approved all procedures used in the study, and all participants signed an IRB approved informed consent prior to enrollment.

Procedures

Potential participants were screened via telephone and those eligible were scheduled for two appointments, 7-10 days apart to allow adequate time for PA monitoring. At Visit 1 participants completed consent forms, fasting blood draw, anthropometric measures, dual energy x-ray absorptiometry (DXA) scanning and a series of questionnaires. Participants arrived to the laboratory in a fasted state, they were provided with a snack (crackers, granola bar, etc.) and drink (fruit juice, etc.) immediately following the fasting blood draw. All questionnaires concerning mood were answered in the laboratory during the participant's first visit. In the 7-10 day period between visits, participants were asked to complete a series of questionnaires addressing their health history, including breast cancer history, if applicable, and wear a PA monitor. Participants were also sent a reminder e-mail prior to Visit 2, with instructions to refrain from vigorous activities/structured exercise on the morning of their visit and to wear comfortable clothes and shoes. At Visit 2, all questionnaires completed at home were reviewed for completeness, and participants completed a battery of physical function and muscular performance assessments. In an attempt to control for potentially important factors, BCS and CON were matched on age (±3.0 years), BMI (±4.0 $kg \cdot m^{-2}$) and category (normal weight, overweight, obese) [30], and adiposity value (±7.0%) and category (healthy fat, overfat, obese) [31].

Health history

Both BCS and CON were asked to report the presence of chronic medical conditions, excluding cancer. These conditions included arthritis, asthma, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, degenerative disc disease, osteoporosis, and peripheral arterial disease. In addition, all participants were asked to report all prescription and over the counter medication and supplement use.

Body composition

Standing height and weight were measured with participants wearing light-weight clothing and no shoes. Height, as measured to the nearest 0.1cm, was obtained using a stadiometer (Seca, Model 242), while weight was measured using a calibrated digital scale (Tanita, Model WB-110A). Whole body soft tissue was measured using DXA (Lunar iDXA, v11.30.062, GE Healthcare, Madison, WI). In addition to relative whole body fat mass (%Fat), lean mass of the upper legs (inclusive from bisection of the femoral neck to the patella), and total lower body lean mass (inclusive of lean mass from the top of the iliac crests), were obtained per manufacturer guidelines.

Objective physical activity

Objective PA was determined using an accelerometer (New Lifestyles-1000, Barebones Pedometer, New Lifestyles, Inc., Lees Summit, MO). Participants were instructed to wear the monitor on the non-dominant hip, fastened to their waistband, for at least 7-days during all waking hours, except when bathing or swimming. Participants recorded the time spent wearing the activity monitor on a written log, which was verified using the memory feature of the NL-1000. MVPA was defined as activity completed above a moderate intensity threshold, which corresponds to approximately 3.6 METs. A valid wear day included at least ten hours of wear time, and four valid days were required to be included in the analysis. Step counts were calculated using the average step count from valid wear days, and minutes spent in MVPA per day were calculated as the average time spent in MVPA from valid wear days.

Feelings of fatigue and energy

The Profile of Mood States 30 item short form (POMS-SF) was used to assess overall mood and six specific mood states including feelings of energy during the prior week. [32]. Five adjectives are used to tap each specific mood state (e.g., Fatigue = worn out, fatigued, exhausted, sluggish, and weary; Vigor = energetic, full of pep, vigorous, active, and lively) and the intensity of moods are scaled using five categories (not at all, a little, moderately, quite a bit, and extremely). Scores for each scale of the POMS-SF range from 0-20, with greater scores indicating increasing intensity in the domain of interest. The SF-36 Health Survey, a 36 item self-administered questionnaire, assesses the following eight health attributes: general physical functioning, role limitations due to physical health, bodily pain, general health, social functioning, role limitations due to emotional problems, mental health and vitality [33]. The vitality scale of the SF-36 was used to assess frequency of feelings of energy over the past month and consists of four items asking how often one has felt full of pep, full of energy, tired or worn out. Scores for the vitality scale range from 0-100 with lower scores indicating frequent feelings of fatigue and higher scores indicating frequent feelings of energy.

Covariates of fatigue

In order to control for their potential effects, assessments for known confounders of feelings of fatigue and energy were administered. Venous blood samples were obtained using standard procedures to allow for the measurement of hemoglobin (Hemocue Hb 201^+, Hemocue America, CA) and hematocrit levels (CS22 – CritSpin with Digital Reader, Statspin, Norwood, MA). Two samples were assessed for each blood outcome and the average used in subsequent analysis. The coefficient of variation for hemoglobin and hematocrit levels was 0.4% and 3.0% respectively. Normal clinical limits for hemoglobin and hematocrit were defined as 12-16 g/dL and 36-48%, respectively [34]. Severity of depressive symptoms during the past two weeks were assessed using the Beck Depression Inventory-II (BDI) [35], in which higher scores indicate greater depressive severity. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), which assesses overall sleep quality over the past month [36]. Total PSQI scores >5 indicate impaired sleep quality. Perceived stress was measured using the Perceived Stress Scale (PSS), in which higher scores indicate higher stress (range 0 – 40) [37].

Muscular performance and leg muscle quality

Muscular strength and endurance was assessed using an isokinetic dynamometer (System 4 Pro, Biodex Medical Systems, Inc., Shirley, NY). Bilateral measurements were assessed for knee flexion and extension. Isokinetic strength was measured for the knee at $60^{\circ}\cdot sec^{-1}$ (KN60) with 2 sets of 4 repetitions for each limb. Participants were instructed to push and pull as hard and as fast as possible during each repetition of isokinetic testing and the trials that resulted in the greatest peak torque for the right and left limbs were totaled to calculate total peak torque for the joint of interest. Leg power was assessed using the Nottingham Leg Extensor Power Rig (The University of Nottingham, Nottingham, UK). Prior to assessment, seat position was adjusted for individual leg length to allow for a 5° bend in the knee when the leg was at full extension. Participants were instructed to keep their arms across their chest with each repetition and to allow the inactive leg to remain flexed at 90°, with their foot on the floor. Participants performed up to 10 trials per leg and were instructed to push out as hard and as fast as possible with each repetition. The highest leg power value achieved for the right and left leg was summed, and this value, total leg extension power, was used for analysis. Muscle quality, the ratio of muscle capacity to leg lean mass was calculated as: a) the ratio of KN60 to upper leg muscle mass (MQ-KN60) [38], and b) the ratio of leg power to total lower body lean mass (MQ-Power) [39].

Objectively measured physical function

Performance based physical function was assessed using the timed up-and-go (UPGO), the 30 second chair stand (CHR), and 6-minute walk (WALK) [40]. To complete the UPGO, participants began the assessment seated in a chair with their arms across their chest and feet flat on the floor. On the command "go," participants were instructed to volitionally stand and walk, as quickly as possible, around a cone placed eight feet in front of the chair and return to a seated position [41]. Participants who were able to complete this assessment performed two timed UPGO trials, and the fastest trial was used for analysis. To complete the CHR, participants began the assessment in a seated position with their arms across their chest, feet flat on the floor and on the command "go," participants completed as many repeated chair stands as possible over a 30-second period. Functional endurance was assessed using the WALK assessment, and this test required participants to safely cover as much distance as possible over the course of the six minutes.

Statistical analyses

Data were analyzed with IBM SPSS Statistics for Windows Version 21.0. (IBM Corp: Armonk, NY). 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 examine statistical difference between BCS and CON. In addition, effect sizes, Cohen's *d* and the coefficient of determination (r^2), were calculated to evaluate clinically meaningful differences between groups and to demonstrate shared variance between two variables, respectively. An effect size of 0.50 is the value generally identified for clinical significance.

Partial correlations, controlling for menopausal duration, were conducted to examine the associations between months since completion of invasive breast cancer treatment, adiposity, PA, measures of muscular performance, MQ-KN60, MQ-Power and measures of physical function in BCS only. Associations, controlled for months in menopause, between adiposity, PA, measures of muscular performance, MQ-KN60, MQ-Power and measures of physical function were also evaluated for both BCS and CON.

The independent contributions of menopausal duration, group membership, MQ-KN60, steps·day^{-1}, and %Fat were evaluated for UPGO, CHR and WALK with a series of hierarchical linear regression analyses. Additionally, a second set of regression analyses were conducted with MQ-Power, in place of MQ-KN60. All data are presented as mean ± SD, except figures, which express variability using standard error bars. Statistical significance was set at the $p \leq .05$ level.

5.4 Results

Breast cancer survivor characteristics

Regarding BCS specifically, three BCS were diagnosed with premenopausal breast cancer and transitioned into menopause during the subsequent year of breast cancer treatment (range=1-8 months after initial diagnosis), while the remaining 10 BCS were diagnosed with postmenopausal breast cancer. All BCS were postmenopausal at the time of assessment (90.6 ± 52.3 months; range = 24-171 months menopausal). Four BCS (30.8%) were diagnosed with DCIS, six BCS (46.2%) with Type IA, one BCS (7.7%) with IIA, one BCS (7.7%) with IIB, and one BCS (7.7%) chose not to disclose. Estrogen receptor positive type tumors were diagnosed in 76.9% of BCS.

All BCS completed one or multiple types of surgical intervention (23.1% right lumpectomy, 38.5% left lumpectomy, 7.7% right total mastectomy, 7.7% left total mastectomy, 23.1% double mastectomy, 7.7% right radical modified mastectomy). In addition to surgery, treatment included chemotherapy for 53.8% (range = 3-4 months) and radiation for 53.8% (range=24-80 treatments) of the BCS sample. Average time since treatment termination was 28.5±13.3 months (range=6-54 months). Two BCS experienced lymphedema and both were prescribed compression garments, which they wore during all physical elements of testing. Prescription medications associated with long-term breast cancer treatment included anastrozole (30.8%), letrazole (30.8%), tamoxifen (15.3%) and anastrozole and tamoxifen in combination (7.7%).

Demographic comparisons between breast cancer survivors and matched controls

Both BCS and CON groups were 92.3% white, and the remaining 7.7% in each group was comprised of participants who were black and Asian, respectively. Both groups were highly educated (BCS=19±2 years, CON=16±5 years) and 70% of BCS and 100% of CON were employed outside of the home. Participant characteristics for both groups are presented in Table 5.1. By design, BCS and CON were similar in age, BMI and adiposity. On average, BCS reported a greater number of medications (*p*=0.16) and medical conditions, excluding cancer, compared to CON (*p*=0.06). Self-reported medical conditions included: cardiovascular disease, peripheral vascular disease, pulmonary disease, diabetes, and osteoporosis, and the most commonly reported conditions were arthritis (BCS 53.8%, CON 53.8%), degenerative disc disease (BCS 46.2%, CON 15.4%), depression (BCS 46.2%, CON 23.1%), and anxiety (BCS 30.8%, CON 15.4%).

Table 5.1 displays that both BCS and CON fall within the overweight and overfat categories for BMI and %Fat, respectively [30, 31]. Both upper leg lean mass and total lower body lean mass of the legs were similar in BCS and CON (both $p>.05$). Physical activity levels, when examined objectively in steps·day^{-1} or MVPA, were also similar for both BCS and CON ($p>.05$).

Group comparisons for feelings of fatigue and energy and associated psychosocial variables

There were no differences in feelings of fatigue, vigor or vitality between groups (all $p>.05$), and effect sizes ranged from 0.11-0.34 (Table 5.2). No statistically significant differences in PSQI, BDI, PSS (all $p\geq.05$) were seen between groups, though a moderate effect for group differences was seen for PSQI with BCS reporting poorer sleep quality compared to CON ($p=.14$, Cohen's $d=0.56$). Hemoglobin and hematocrit levels were similar between BCS and CON (both $p>.05$), and all participants' average hemoglobin and hematocrit levels fell within normal clinical limits [34].

Group comparisons for muscular performance, muscle quality and physical function

There were no significant differences in muscular performance between BCS and CON (all p>.05), though BCS produced 15% more force with isokinetic testing compared to CON (Cohen's d=0.60, p=.17), and CON produced 20% more leg power compared to BCS (Cohen's d=0.61, p=.16) (Table 5.3). MQ-KN60 and MQ-Power were statistically similar between groups, but BCS had greater MQ-KN60 compared to CON (Cohen's d=0.36, p=.26), while CON demonstrated better MQ-Power compared to BCS (Cohen's d=0.74, p=.08). Two BCS were unable to complete muscular strength assessments due to previous knee injuries; therefore, they, along with their matched CON, were excluded from analyses including these outcomes. Though differences were not statistically significant, CON demonstrated a clinically meaningful difference in performance on UPGO (Cohen's d=.76, p=.05) and CHR (Cohen's d=.57, p=.15), compared to BCS (see Figure 5.1).

Physiologic and muscular performance variables associated with physical function

Lower steps·day^{-1} were related to greater adiposity in CON (r=-.62, r^2=.38, p<.01,), but not in BCS (steps·day^{-1} r=-.59, r^2=.34, p>.05,), Table 5.4.A and Table 5.4.B. Greater adiposity was strongly and significantly associated with a lower number of CHR (r=-.75, r^2=.56) and less distance covered during WALK (r=-.79, r^2=.62) in BCS (both p<.05). Steps·day^{-1} was not significantly related to any measures of muscle capacity in BCS or CON (all p>.05). Greater steps·day^{-1} was related to better performance in CHR (r=.72, r^2=.51, p<.01) and WALK (r=.76, r^2=.58, p<.01) in BCS only. MVPA was significantly related to KN60 (r=.74, r^2=.54) and MQ-KN60 (r=.89, r^2=.79) in CON, and MQ-KN60 (r=.75, r^2=.56) only in BCS (all p<.05). Greater MVPA was related to better physical function performance in CHR (r=.60, r^2=.36, p<.05) and WALK (r=.62, r^2=.38, p<.05) in BCS only. Higher KN60 and power were significantly related to better UPGO (r=-.68, r^2=.46; r=-.70, r^2=.49 respectively, p<.05) and CHR (r=.85, r^2=.72; r= .86, r^2=.74, respectively, p<.05) in CON. Greater MQ-KN60 was strongly associated with better CHR (r=.71, r^2=.50, p<.05) in CON only. Similarly, higher MQ-Power was also strongly correlated with better UPGO (r=.69, r^2=.48, p<.05) and CHR (r=.82, r^2=.67, p<.01) in CON only.

When MQ-KN60 was included in the regression models, only group membership was independently related to UPGO performance ($F_{5,21}$=4.81, p=.007). Group membership and MQ-KN60 were identified as significant predictors of CHR performance ($F_{5,21}$=6.90, p=.001), while %Fat was an independent predictor of WALK performance ($F_{5,21}$=5.83, p=.003; Table 5.5.A). When MQ-Power was included in the regression models, steps·day^{-1} was the only independent predictor of UPGO ($F_{5,21}$=4.58, p=.009) and CHR ($F_{5,21}$=5.30, p=.005), while only %Fat was an independently related to WALK ($F_{5,21}$=6.35, p=.002), (Table 5.5.B).

5.5 Discussion

The potential influences of PA and body composition on feelings of energy and fatigue and objectively measured physical function in postmenopausal BCS have not been well characterized. Novel results from the present pilot study indicate that feelings of fatigue, vigor and vitality are similar in age and adiposity matched BCS and CON who engage in similar amounts of total and moderate to vigorous objectively measured PA. We also found that functional performance is poorer in BCS compared to their matched counterparts. Additionally, group membership, total PA measured as steps·day^{-1}, MQ-KN60 and adiposity independently contributed to functional tasks relying primarily on the lower body musculature.

As our participants were intentionally matched for age, BMI, and adiposity, that there were no significant differences in adiposity or lean mass values was not unexpected. Mean values for BMI and whole body adiposity for both BCS and CON placed our sample of women in overweight [30] and overfat [31] categories, respectively. Our results also indicate that BCS of similar age and body composition, when compared to their non BCS CON, do not differ in their average level of daily PA or the intensity of their daily activity. Notably, on average neither group met recommended levels of total activity based on step counts [42] or the recommendations for at least 30 minutes of moderate intensity activity per day [30]. This is not unexpected as a low percentage of women in this age group meet recommended PA guidelines, especially when PA is measured objectively rather than with self-report [4].

Fatigue, vigor and vitality in breast cancer survivors and controls

Efforts were made to match participants such that, BCS differed from their matched controls only due to their exposure to breast cancer diagnosis and treatments, to determine if BCS and healthy controls experience similar feelings of fatigue, vigor and vitality. No statistically significant or clinically meaningful differences, based on effect sizes, were found between groups for feelings of fatigue and energy. Our findings reflect those of Bower et al. [18] who found that BCS reported similar vitality scores compared to those reported by women in the general population. It is worth noting that both BCS and CON reported mean scores for fatigue, vigor and vitality that indicate a low level of fatigue and high levels of both vigor and vitality, as vitality scores approach and exceed, for BCS and CON respectively, normative values for women ages 55-64 [43]. This may suggest that the women willing to participate in our investigation were quite robust and the requirements of our study, including two visits to the laboratory, PA monitoring and physical function testing, may have been too taxing for members of either group who experience greater levels of fatigue and lower levels of positive energy, thereby reducing their motivation for study participation. In regards to potential confounders of fatigue, there were clinically meaningful differences between groups in sleep quality, with BCS experiencing poorer sleep quality than their matched controls. As BCS have been found to have poorer sleep quality compared to age matched women without cancer [44], these results are not unexpected.

Physical function in breast cancer survivors and controls

Adiposity [8, 23, 49-51], PA [23, 50, 52, 53], and muscular performance and quality [38, 54] have all been identified as factors that explain differences in functional performance in BCS and middle-aged and older women. In an attempt to add to the growing literature examining the effects of muscle quality on physical function, we calculated muscle quality in two ways, MQ-KN60 and MQ-Power. The calculation of MQ-KN60 reflects the strength of the legs relative to the muscle mass responsible, the quadriceps and hamstrings, while MQ-Power attempts to quantify the power generating capacity with respect to the total lean muscle mass of the lower body. Differences in MQ comparing BCS and CON have not been explored previously and the respective contributions of MQ, expressed using strength or power, to physical function have also not been evaluated in middle-aged women, including BCS.

There were no statistically significant differences between BCS and matched CON in objective physical functional performance, but the magnitude of the effect size between groups exceeded 0.5, the value generally identified for clinically significant differences, for both UPGO and CHR, as BCS performed more poorly on these tasks compared to CON. As adiposity and objectively measured PA levels were similar for women in both groups, differences in these outcomes do not account for the differences in functional performance. Muscular strength, leg power, MQ-KN60 and MQ-Power were also not significantly different between groups, but the effect sizes for KN60, Power, MQ-KN60, and MQ-Power were moderate and above the threshold generally used for clinical significance. Differences in leg strength and MQ-KN60 unexpectedly favored BCS over CON, while differences for leg extension power and MQ-Power favored CON compared to BCS. These results reflected that CON demonstrate greater leg extension power compared to BCS, and may explain the moderate group effects favoring CON for functional performance on UPGO and CHR, but not WALK. As UPGO requires speed and agility, and CHR requires the participant to generate power to rise from a seated position, these assessments rely more heavily on adequate muscle power for completion. It has been suggested that muscle power may play a more significant role, compared to muscular strength, in determining functional ability in older adults, as most activities of daily living require adequate muscle power [39, 55]. As CON had superior performance on all functional tasks, especially those requiring muscle power, UPGO and CHR, our results support a role for leg muscle power in determining functional performance and the importance of measuring leg power when examining muscular capacity measures and physical function. In addition, we encouraged all participants to give their best effort for all muscle capacity and functional measures, and assessed Rating of Perceived Exertion (RPE) on the Borg 0-20 scale [30] for functional tasks (UPGO RPE: BCS=8.2±2.8, CON=8.2±3.3; CHR RPE: BCS=10.9±3.3, CON=12.8±2.7; WALK RPE: BCS=12.2±2.6, CON=12.3±3.4) and knee strength measures (RPE: BCS = 12.2±2.6, CON=12.2±2.7) to ensure that our participants were executing all tasks at safe and tolerable levels. Though we could not control motivation for task completion and effort expended by the participants, as the RPE values for each group are not statistically different, and indicate a moderate workload for both groups, these data support that muscle capacity and physical function may differ between BCS and CON. The relative influence of muscle strength and power on functional performance remains incompletely characterized in middle-aged women in general, and BCS specifically.

Evaluating independent predictors of functional performance

The most salient predictor of function is not well established in middle-aged women, especially in BCS, and MQ as an independent factor for function has not been examined in healthy middle-aged women and BCS. When examining independent predictors of function in the present study, MQ-KN60 was determined to be a significant predictor of CHR performance, emphasizing the importance of maintaining muscular strength relative to lean mass for physical function tasks requiring a combination of muscle power and muscular endurance. In work with older men and women, 69.3 ± 5.5 years, Misic et al. [38] found that MQ-KN60, calculated in the same method as the present study, explained 29-42% of the variance in objective measures of function, including UPGO, 7 meter walk, and stair ascent and descent. These data support findings that adequate muscular strength and strength per unit lean mass is related to function tasks requiring gait related tasks requiring speed and agility, but a measure of muscle power was not included [38]. Barbat-Artigas et al. [39] suggests that calculating muscle quality as the ratio of muscle power to lean muscle mass is most optimal when examining muscle quality and its contribution to functional performance, due to the fact that MQ-Power takes shortening velocity of muscle into account, in addition to the force producing capability. Our data do not support an independent role for MQ-Power in our sample of middle-aged CON and BCS. While these findings are contrary to those of Straight et al. [56], who reported that MQ-Power, as measured in the current study, explained 11- 26% of the variance in physical function, including the tasks of UPGO, CHR and WALK after adjustment for covariates, including age, medical conditions, and PA, in women 74±6 years of age, they did not report MQ-KN60; therefore, it is not possible to compare the magnitude of variance explained by muscle power and strength between the two studies. Our findings may vary from both Misic et al. [38] and Straight et al. [56] due to the younger age of the women in the current study and the common trajectory of changes in muscle power, muscle strength and muscle quality with aging, as declines in power generally occur first, followed by a loss of muscle strength and then declines in muscle mass [39]. The interactive relations among PA, muscle capacity, and body composition (i.e. lean mass) for physical functional performance remain incompletely characterized in middle-aged women, especially BCS.

Univariate correlations suggest that increased adiposity was moderately and strongly associated with poorer performance in WALK in CON and BCS, respectively, supporting other findings that body composition related components play a role in determining performance in endurance based tasks of lower extremity function in both BCS and older men and women [23, 57, 58]. Adiposity was also found to be a significant independent predictor of WALK performance in both regression models. These data are in agreement with recent results from Elme et al. [23], who identified obesity, measured by BMI, as one of the most important determinants of lower extremity physical performance, as assessed using a 2 km walking test, in BCS. Our findings also agree with those of: a) Lebrun et al. [59], who reported that in postmenopausal women, younger than 75 years of age, fat mass, not muscular strength, was the primary determinant of walking composite measures, and b) Sowers et al. [60], who found that total fat mass was more consistently associated with poorer gait measures (i.e. shorter stride length, lower velocity, greater time in double support) and poorer gait composite scores (which included performance on a timed 12.3 meter walk), compared to skeletal muscle mass and quadriceps strength in middle-aged women with an average age of 47 years.

Our data support a positive relationship between PA and physical function; greater steps·day^{-1} was associated with better lower extremity function, and steps·day^{-1} was found to be independently related to performance in UPGO and CHR, explaining the greatest amount of variance in both regression models. Greater amounts of PA have been shown to be associated with better physical functioning and health related quality of life in BCS [23, 61]. The current findings also lend evidence to the idea that total daily amounts of PA, measured as steps·day^{-1}, are protective for function in a similar magnitude as daily PA completed at moderate to vigorous intensities, as steps·day^{-1} explained similar amounts of variance in UPGO and CHR and 16% more variance in WALK compared to MVPA, when MVPA was substituted for steps·day^{-1} in each regression model (data not shown). In addition, encouragement of PA adoption and maintenance for overweight and obese women is especially important, as recent work by Tucker and others [62] found that middle-aged women who are obese, defined as %Fat ≥ 32%, decrease their total PA over time, in addition to reducing the intensity of their activity, to a greater extent than those who are not obese.

As greater amounts of steps·day^{-1} and MVPA were both related to better functional performance in both groups, it is important to note that the type of activity monitor used in our study is limited in its scope, as it measures weight bearing lower extremity aerobic activity only. In addition, the accelerometer is not able to distinguish between moderate and vigorous intensity activities as it is designed to measure minutes of activity completed above the moderate threshold. Future work with both BCS and CON should attempt to determine how activities requiring the upper and lower extremities, including resistance training, and how differing intensities of activity affect the ability to perform functional tasks.

Our results should be interpreted within the recognized limitations of our study. First, our cross sectional design does not allow inference of causality between variables of interest. As our sample of BCS is quite small, this contributed to a reduction in statistical power, though even with this small sample we were able to detect some clinically meaningful differences in functional performance, demonstrating that there may be factors differentiating BCS from their age and adiposity matched counterparts beyond body composition, PA and muscular performance and quality. Also, as our BCS sample was overweight and overfat, these results may not be indicative of those that would occur with underweight, normal weight or obese participants. As we measured fatigue, vigor and energy with questionnaires not specifically designed for cancer survivors, though these questionnaires are widely used with a variety of samples, our results may not reflect fatigue scores based on cancer fatigue assessments or as a result of cancer specific origins. However, based on the average time since treatment we believe this limitation is minimal. In addition, our study required participants to be free living, resulting in our sample to be comprised of community dwelling postmenopausal women, so our results regarding feelings of fatigue and energy and functional performance may not reflect individuals who have mobility challenges and/or cannot complete most instrumental activities of daily living. Finally, the optimal method for calculating MQ is still being established. Though previous studies have calculated MQ as leg lean mass, measured via DXA, normalized for leg strength, measured using isokinetic dynamometer [38, 54], the optimal speed of isokinetic testing is still under debate [39]. Researches are also still unsure whether to use the sum of the right and left leg values when examining muscular strength and leg power [39]. In addition, calculating muscle quality using lean mass measured via DXA does not account for fat infiltration within lean mass, which has been shown to be associated with loss of mobility in older adults [63].

In conclusion, our pilot data suggest that feelings of energy and fatigue are similar between BCS and CON when age and objectively measured body composition and PA levels are similar. This is encouraging for BCS, as these results suggest that middle-aged postmenopausal BCS, six months to approximately five years after treatment, do not experience greater feelings of fatigue or lower feelings of energy, beyond those experienced by their matched non-BCS counterparts. In regards to physical function, BCS perform more poorly compared to their matched counterparts in tasks requiring muscular endurance and power, the UPGO and CHR, which may be due in part to lower leg power. As PA, adiposity and MQ-KN60 were identified as independent predictors of functional performance, these findings emphasize the importance of adequate PA, healthy levels of adiposity, and adequate leg muscular strength per unit of leg lean mass for physical functional ability. Higher levels of adiposity, and lower amounts of PA, lean mass and muscle quality in middle age independently influence physical function performance, potentially increasing risk for disability in middle-aged women, especially those with a history of breast cancer.

5.6 References

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Table 5.1. Participant characteristics

	BCS (N = 13)	CON (N = 13)	P value	ES (*d*)
Age (years)	57.4 ± 4.3	57.7 ± 4.3	.89	0.07
Months Menopausal	90.6 ± 52.3	95.9± 54.6	.80	0.10
Total Medications	5.0 ± 5.0	2.0 ± 2.0	.16	0.74
Total Comorbidities	3.0 ± 3.0	2.0 ± 1.0	.06	0.56
Weight (kg)	71.6 ± 16.4	72.3 ± 12.1	.91	0.04
Height (cm)	163.8 ± 8.0	163.6 ± 6.0	.95	0.02
Body Mass Index ($kg \cdot m^{-2}$)	26.6 ± 4.5	27.0 ± 4.2	.80	0.10
Whole Body Adiposity (%)	40.0 ± 7.6	40.8 ± 5.3	.78	0.11
Upper Leg Lean Mass (kg)	9.6 ± 1.8	9.6 ± 0.9	.86	0.05
Total Lean Mass of the Legs (kg)	20.6 ± 3.4	20.3 ± 1.7	.82	0.09
Physical Activity-Steps$\cdot day^{-1}$	7545.3 ± 3688.1	7498.0 ± 2517.3	.97	0.02
Physical Activity-MVPA$\cdot day^{-1}$	21.2 ± 19.5	18.0 ± 7.8	.59	0.20

Mean ± SD. BCS=breast cancer survivors; CON=controls; ES=effect size; MVPA=minutes of moderate to vigorous physical activity per day.

Table 5.2. Feelings of fatigue and energy and covariates

	BCS (N=13)	CON (N=13)	P value	ES (*d*)
POMS-SF Fatigue	3.1 ± 4.2	2.9 ± 4.1	.78	0.11
POMS-SF Vigor	8.0 ± 4.7	9.7 ± 5.1	.39	0.34
SF-36 Vitality	58.2 ± 25.7	61.5 ± 17.5	.70	0.15
Above Vitality Norm	53.8%	61.5%		
PSQI	7.8 ± 3.7	5.8 ± 3.5	.15	0.56
Impaired Sleep (>5)	69.2%	38.5%		
BDI	11.7 ± 8.8	9.5 ± 8.0	.51	0.26
Depressive Symptoms				
Minimal (0-13)	69.2%	76.9%		
Mild (14-19)	7.7%	15.4%		
Moderate (20-28)	15.4%	0%		
Severe (29-63)	7.7%	7.7%		
PSS	13.2 ± 7.2	14.8 ± 7.3	.58	0.22
Hemoglobin ($g \cdot dL^{-1}$)	12.7 ± 0.8	13.2 ± 0.8	.11	0.65
Hematocrit (%)	41.7 ± 4.1	43.0 ± 2.1	.28	0.47

Mean ± SD. BCS=breast cancer survivors; CON=controls; ES=effect size; POMS=Profile of Mood States-Short Form; PSQI=sleep quality as measured by the Pittsburgh Sleep Quality Index; BDI=depressive symptoms as measured by the Beck Depression Inventory-II; PSS=perceived stress as measured by the Perceived Stress Scale.

Table 5.3. Muscular performance and muscle quality

	BCS (N=11)	CON (N=11)	P value	ES (*d*)
Quadriceps Peak Torque 60°·sec^{-1} (Newton-Meters)	261.0 ± 63.7	226.0 ± 50.2	.17	0.60
Leg Extension Power (Watts)	193.7 ± 61.4	233.5 ± 66.4	.16	0.61
Muscle Quality-KN60	26.7 ± 5.8	24.0 ± 5.2	.26	0.36
Muscle Quality-Power	9.3 ± 2.8	11.6 ± 3.1	.08	0.74

BCS=breast cancer survivors; CON=controls; Muscle Quality-KN60=muscle quality calculated using isokinetic strength at 60°·sec^{-1}; Muscle Quality-Power=muscle quality calculated using leg extension power.

Table 5.4. Partial correlations, controlled for months in menopause, between, physical activity, muscular performance, muscle quality and physical function in breast cancer survivors and controls

Breast Cancer Survivors (N = 13)										
	%Fat	Steps·day^{-1}	MVPA	KN60$^{\wedge}$	Power$^{\wedge}$	MQ-KN60$^{\wedge}$	MQ-Power$^{\wedge}$	UPGO	CHR	WALK
%Fat	1.0	-.59	-.52	.23	-.15	-.17	-.32	.38	-.75†	-.79†
Steps·day^{-1}		1.0	.91†	.36	.14	.79†	.34	-.51	.72†	.76†
MVPA			1.0	.51	.08	.75†	.20	-.55	.60*	.62*
KN60				1.0	.07	.46	-.22	-.31	.21	.08
Power					1.0	-.22	.84†	-.28	.28	.31
MQ-KN60						1.0	.06	-.54	.49	.57
MQ-Power							1.0	-.40	.37	.54
UPGO								1.0	-.79†	-.72†
CHR									1.0	.93†
WALK										1.0
Controls (N = 13)										
	%Fat	Steps·day^{-1}	MVPA	KN60$^{\wedge}$	Power$^{\wedge}$	MQ-KN60$^{\wedge}$	MQ-Power$^{\wedge}$	UPGO	CHR	WALK
%Fat	1.0	-.62†	-.44	-.11	-.06	-.42	-.28	.30	-.15	-.53
Steps·day^{-1}		1.0	.42	.38	.52	.41	.57	-.48	.57	.42
MVPA			1.0	.74*	.55	.89†	.61	-.24	.49	.35
KN60				1.0	.91†	.92†	.88†	-.68*	.85†	.26
Power					1.0	.75†	.96	-.70*	.86†	.34
MQ-KN60						1.0	.81†	-.63	.71*	.33
MQ-Power							1.0	-.69*	.82†	.43
UPGO								1.0	-.68*	-.57
CHR									1.0	.42
WALK										1.0

%Fat=percent body fat; MVPA=physical activity measured as minutes·day^{-1} of moderate to vigorous intensity activity; KN60=isokinetic peak torque of the knee at 60°·sec^{-1}; Power=leg extension power; MQ-KN60=muscle quality calculated using isokinetic strength at 60°·sec^{-1}; MQ-Power=muscle quality calculated using Leg Extension Power; UPGO=Timed Up and Go; CHR=30 second chair stand; WALK=6 minute walk. $^{\wedge}$N=11; $^{*}p<.05$; $^{\dagger}p<.01$.

Table 5.5.A. Linear regression analyses of physical activity, muscle quality (MQ-KN60), and adiposity as independent predictors of physical function in breast cancer survivors and controls

	Timed Up and Go				30 Second Chair Stand				6 Minute Walk			
	R^2	β	Beta	95% CI	R^2	β	Beta	95% CI	R^2	β	Beta	95% CI
Step 1	0.18				0.17				0.01			
Menopause		-0.06	-0.001	[-0.01, 0.009]		0.003	<0.001	[-0.06, 0.06]			0.02	[-0.95, 0.99]
Group		-0.42	-0.98	[-2.01, 0.05]		0.41	5.72	[-0.50, 11.95]		0.009	8.67	[-91.73,
Step 2	0.53†				0.57†				0.53*	0.04		109.07]
Menopause		0.04	-0.001	[-0.009, 0.007]		-0.01	-0.002	[-0.05, 0.04]			-0.02	
Group		-0.36*	-0.85	[-1.66, -0.05]		0.35*	4.92	[0.26, 9.57]		-	-5.01	[-0.70, 0.67]
Steps·day^{-1}		-0.59†	<0.001	[<0.001,<0.001		0.64†	0.001	[0.001, 0.002]		0.009	0.03	[-76.28, 66.26]
Step 3	0.60			]	0.67*				0.53	-0.02		[0.01, 0.04]
Menopause		0.02	<0.001			-0.09	-0.01	[-0.05, 0.03]		0.73†	-0.04	
Group		-0.48*	-1.12	[-0.007, 0.008]		0.49†	6.90	[2.35, 11.46]			-1.43	[-0.76, 0.69]
Steps·day^{-1}		-0.39	<0.001	[-1.96, -0.29]		0.38*	0.001	[<0.001,		-0.02	0.02	[-81.43, 78.58]
MQ-KN60		-0.35	-0.08	[<0.001,<0.001		0.43*	0.57	0.002]		-	1.02	[0.009, 0.04]
Step 4	0.60			]	0.68			[0.05, 1.08]	0.65*	0.007		[-7.96, 10.00]
Menopause		0.02	<0.001	[-0.17, 0.02]		-0.07	-0.01			0.70†	0.06	
Group		-0.48*	-1.13			0.51†	7.27	[-0.05, 0.03]		0.05		[-0.59, 0.72]
Steps·day^{-1}		-0.38	<0.001	[-0.007, 0.008]		0.27	0.001	[2.54, 11.498]			14.03	[-59.53, 87.60]
MQ-KN60		-0.36	-0.08	[-2.01, -0.24]		0.46*	0.25	[<0.001,		0.03	0.01	[-0.005, 0.03]
%Fat		0.008	0.001	[<0.001,<0.001		-0.15	-0.16	0.002]		0.07	2.56	[-5.66, 10.78]
				]				[0.07, 1.12]		0.37	-6.83	[-13.23, -0.43]
				[-0.18, 0.02]				[-0.57, 0.25]		0.13		
				[-0.08, 0.08]						-0.45*		

Analyses conducted in this order: Step 1-number of months in menopause (Menopause) and group membership; Step 2-Steps·day^{-1}; Step 3-MQ-KN60=muscle quality calculated using isokinetic strength at 60°·sec^{-1}; Step 4-%Fat. β=unstandardized regression coefficients; Beta=standardized regression coefficients. $^{*}p<.05$, $^{\dagger}p<.01$.

Table 5.5.B. Linear regression analyses of physical activity, muscle quality (MQ-Power), and adiposity as independent predictors of physical function in breast cancer survivors and controls

	Timed Up and Go				30 Second Chair Stand				6 Minute Walk			
	R^2	β	Beta	95% CI	R^2	β	Beta	95% CI	R^2	β	Beta	95% CI
Step 1	0.18				0.17				0.002			
Menopause		-0.06	-0.001	[-0.01, 0.009]		0.003	<0.001	[-0.06, 0.06]		0.009	0.02	[-0.95, 0.99]
Group		-0.42	-0.98	[-2.01, 0.05]		0.41	15.72	[-0.50, 11.95]		0.04	8.67	[-91.73, 109.07]
Step 2	$0.53^{\dagger}$				$0.57^{\dagger}$				$0.53^{\dagger}$			
Menopause		0.04	-0.001	[-0.009, 0.007]		-0.01	-0.002	[-0.05, 0.04]		-0.009	-0.02	[-0.70, 0.67]
Group		-0.36^{*}	-0.85	[-1.66, -0.05]		0.35^{*}	4.92	[0.26, 9.57]		-0.02	-5.01	[-76.28, 66.26]
Steps·day^{-1}		$-0.59^{\dagger}$	<0.001	[<0.001,<0.001]		$0.64^{\dagger}$	0.001	[0.001, 0.002]		$0.73^{\dagger}$	0.03	[0.01, 0.04]
Step 3	0.59				0.62^{*}				0.56			
Menopause		0.07	0.001	[-0.007, 0.01]		-0.12	-0.02	[-0.06, 0.03]		-0.09	-0.18	[-0.92, 0.57]
Group		-0.27	-0.64	[-1.47, -0.20]		0.26	3.62	[-1.19, 8.42]		-0.09	-19.28	[-95.45, 56.88]
Steps·day^{-1}		-0.48^{*}	<0.001	[<0.001,<0.001]		$0.52^{\dagger}$	0.001	[<0.001, 0.002]		0.65	0.02	[0.009, 0.04]
MQ-Power		-0.31	-0.12	[-0.28, 0.05]		0.31	0.71	[-0.23, 1.66]		0.23	7.85	[-7.91, 22.08]
Step 4	0.59				0.62				0.67^{*}			
Menopause		0.08	0.002	[-0.007, 0.008]		-0.11	-0.02	[-0.06, 0.04]		-0.03	-0.05	[-0.74, 0.64]
Group		-0.26	-0.62	[-1.49, 0.26]		0.27	3.72	[-1.29, 8.74]		-0.04	-9.21	[-78.93, 60.51]
Steps·day^{-1}		-0.52^{*}	<0.001	[<0.001,<0.001]		0.48^{*}	0.001	[<0.001, 0.002]		0.39	0.01	[-0.001, 0.03]
MQ-Power		-0.31	-0.12	[-0.29, 0.05]		0.31	0.71	[-0.27, 1.69]		0.22	7.49	[-6.10, 21.07]
%Fat^{-1}		-0.06	-0.01	[-0.09, 0.07]		-0.06	-0.07	[-0.51, 0.38]		-0.42^{*}	-6.39	[-12.52, -0.26]

Analyses conducted in this order: Step 1-number of months in menopause (Menopause) and group membership; Step 2-Steps·day^{-1}; Step 3-MQ-Power=muscle quality calculated using leg extension power; Step 4-%Fat. β=unstandardized regression coefficients; Beta=standardized regression coefficients. $^{*}p<.05$, $^{\dagger}p<.01$.

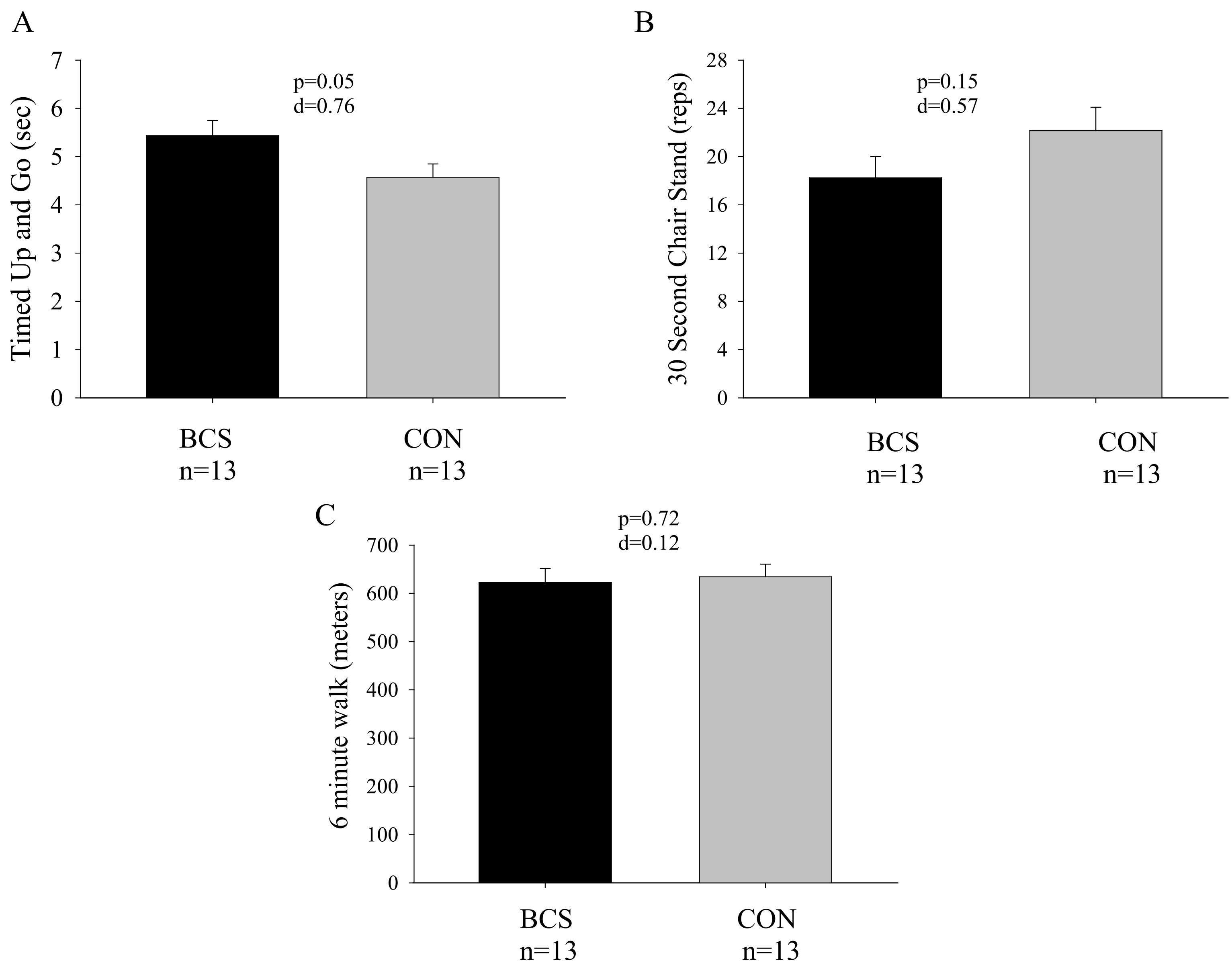

Figure 5.1.A-C. Mean values (M ± SE) for breast cancer survivors (BCS) and matched controls (CON) for physical function tasks on (A) Timed Up and Go, (B) 30 Second Chair Stand, and (C) 6 minute walk.

CHAPTER 6

SUMMARY AND CONCLUSIONS

The results from the present study add to the growing body of literature examining the determinants of feelings of fatigue and energy and physical function in middle-aged postmenopausal women, including breast cancer survivors. As women are at greater risk for feelings of low energy, physical functional decline and disability compared to their male counterparts and postmenopausal women fare less well than their premenopausal peers in these same outcomes, identifying the most salient predictors of feelings of energy and functional performance for this cohort is warranted. Moreover, high levels of physical inactivity and obesity within the population of middle-aged postmenopausal women, combined with the growing number of women within this cohort, as a result of the aging baby boomer generation, highlight the need for a more complete understanding of the contributions of physical activity (PA) and body composition to feelings of fatigue and energy and physical function.

Our findings confirm that in relatively healthy middle-aged postmenopausal women, sleep quality, depressive symptoms, perceived stress, comorbid conditions and the use of antidepressant and anti-anxiety medication influence feelings of vitality. In addition, PA, but not adiposity, appears to be significantly independently associated with feelings of vitality, as higher daily levels of total PA and moderate to vigorous physical activity (MVPA) are associated with greater feelings of vitality. Our results suggest that middle-aged postmenopausal women should engage in recommended amounts of MVPA to preserve feelings of energy.

In regards to functional performance, our results suggest that muscle quality [i.e. muscle capacity normalized for lean mass (MQ)] is a significant determinant of functional ability; with MQ, calculated using isokinetic strength normalized for lean mass of the upper legs (MQ-KN60), being most important for tasks requiring endurance and MQ, calculated using leg extension power normalized for total lean mass of the legs (MQ-Power), essential for functional tasks emphasizing speed and agility. As total daily PA and adiposity were also independently related to functional performance tasks addressing walking and aerobic endurance, attaining adequate levels of PA and maintaining optimal levels of adiposity, should also be emphasized for maintenance of functional performance for the middle-aged postmenopausal woman cohort.

Lastly, in our examination of feelings of fatigue and energy, and objectively measured function in middle-aged postmenopausal women, we also assessed these outcomes in a sub-set of middle-aged postmenopausal breast cancer survivors (BCS). BCS may have exacerbated declines in age and menopause-related conditions, including increases in fatigue, reduced feelings of energy, and decreases in physical function compared to their non-BCS counterparts due to the effects of the cancer and associated treatments. Our sample of BCS was deliberately matched to controls subjects for age, adiposity and menopausal duration in an attempt to control for the confounding variables on our primary outcomes of interest. Our findings suggest that BCS and controls, matched on these outcomes, a) engage in similar amounts of daily total and moderate to vigorous PA, b) BCS and controls have similar feelings of fatigue and energy compared to their matched counterparts, and c) BCS had poorer functional performance in tasks requiring muscular endurance and power. As PA, adiposity and MQ-KN60 were identified as independent predictors of functional performance, emphasizing the importance of adequate amounts of total PA, optimal levels of body fat, and adequate leg muscular strength per unit of leg lean mass for maintenance of physical functional ability is warranted, especially in BCS.

Results from this cross sectional investigation are projected to inform the development of behavioral interventions for middle-aged postmenopausal women, including postmenopausal BCS, toward the end of improving feelings of fatigue and energy and preserving and improving physical function, to maximize quality of life, especially in late life. Our findings highlight the need for middle-aged women to meet recommended amounts of total and moderate to vigorous PA, as PA was influential in determining feelings of energy and functional performance requiring aerobic endurance. Attention to body composition is also warranted for the postmenopausal middle-aged women, as adiposity influences walking related functional tasks and adequate leg lean mass, and the ability to use it efficiently, is necessary for optimal MQ. Optimizing body composition and PA in middle-aged women may decrease the risk of disability in older age for postmenopausal women, including BCS.