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Aspects of Muscle Performance, Mobility Limitations, Exercise Interventions and Cognitive Functioning in Older Adults

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A thesis submitted for the degree of Doctor in Philosophy

(Clinical Medicine)

Supervisor: Dr. Michael A. Conway

Submitted to the University of Dublin, Trinity College, April 2014

Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university. I declare that this thesis is my own work, however, given the high volume of data findings summarised for this thesis, it was necessary to seek the assistance of others at various stages of data collection and analysis. In this respect, I wish to specifically acknowledge the following individuals: Robert Carabello, B.S., David Clark, Ph.D., Cynthia Hau, M.P.H., Brandon Kim, B.S., Dylan Kirn, B.S., Kimberly Martin, M.P.H., and Evan Pasha, B.S. for assistance with muscle performance testing and analysis, computed tomography imaging analysis and the delivery of exercise training interventions. I wish to acknowledge Roger Fielding, Ph.D., who performed all of the muscle biopsies and Walter Frontera M.D., Ph.D., for analysis of the muscle biopsy single fiber experiments presented in this thesis. I also wish to acknowledge Gheorghe Doros, Ph.D. and Michael Walkup M.S. for their assistance with the statistical analyses for this thesis.

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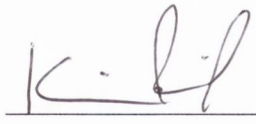

Kieran F. Reid

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List of Abbreviations

ACCORD	Action to control cardiovascular risk in diabetes
BMI	Body mass index
CSA	Cross sectional area
CS-FPP	Continuous scale physical functional performance
CT	Computed tomography
DSST	Digit symbol substitution test
EMG	Electromyography
HI	Power training performed at high intensity (70% of the 1RM)
HU	Hounsfield units
InCHIANTI	Invecchiare in Chianti study
InVEST	Program of weighted vest exercise performed at a high velocity
KE	Seated unilateral knee extension
LIFE	Lifestyle interventions and independence for elders study
LIFE-P	Lifestyle interventions and independence for elders pilot study
LLFDI	Late life function and disability instrument
LO	Power training performed at low intensity (40% of the 1RM)
LP	Seated bilateral leg press exercise
MMSE	Folstein mini-mental state examination
MyHC	Myosin heavy chain
N	Newtons
N/cm^2	Specific strength
PA	Physical activity intervention
P_0	Peak force
RAVLT	Rey auditory verbal learning test

List of Abbreviations (continued)

ROM	Range of motion
SA	Successful aging intervention
SD	Standard deviation
SE	Standard error
SF	Specific force
SL	Sarcomere length
SPPB	Short physical performance battery test
Stroop	Modified stroop test
W	Watts
W/cm^2	Specific peak power
V_0	Shortening velocity
Yrs	Years
1RM	One repetition maximum
3MSE	Modified mini-mental state examination

Summary

In section A, two studies were conducted to systematically investigate and compare the cross sectional and longitudinal physiological determinants of the age-related loss of lower extremity muscle power in healthy and mobility-limited older adults (n = 93). Computed tomography was utilised to assess mid-thigh body composition and measures of muscle quality. Surface electromyography was used to assess neuromuscular function and muscle biopsies were taken to evaluate intrinsic single muscle fibre contractile properties. In the cross sectional study, peak muscle power, strength, muscle cross-sectional area and rate of neuromuscular activation were significantly lower among mobility-limited elders compared to healthy middle-aged and healthy older adults ($P \leq 0.05$). Mobility-limited older participants also had greater deposits of intermuscular adipose tissue ($P < 0.001$). However, single fibre contractile properties of type I and type IIA muscle fibres were preserved in mobility-limited elders relative to both healthy groups. In the longitudinal investigation, experimental procedures were repeated in healthy older and mobility-limited older participants after approximately 3 years (n = 48). At follow-up, the overall magnitude of muscle power loss was similar between groups: mobility-limited: -8.5% vs. healthy older: -8.8%, $P \geq 0.8$. Mobility-limited elders had significant reductions in muscle size (-3.8%, $P< 0.01$) and strength (-5.9%, $P< 0.05$), however, these parameters were preserved in healthy older ($P \geq 0.7$). Neuromuscular activation declined significantly within healthy older but not in mobility-limited participants. Within both groups, the cross sectional areas of type I and type IIA muscle fibres were preserved while substantial increases in single fibre peak force (~ 30%), peak power (~ 200%) and unloaded shortening velocity (~ 50%) were elicited. Taken together, these studies suggest that divergent physiological mechanisms contribute to the loss of lower extremity muscle power in healthy older and mobility-limited older adults. Neuromuscular changes may be the critical early determinant of muscle power deficits with aging, while concomitant reductions in muscle quality are important physiological mechanisms contributing to muscle power deficits and mobility limitations. In response to whole muscle decrements, even among older adults with overt mobility problems, maintenance of the contractile properties of surviving muscle fibres occurs in an attempt to restore overall muscle power and function with advancing age.

In section B, the comparative effects of two uniquely different muscle power resistance training interventions on muscle performance, functional ability, neuromuscular function

and muscle mass in mobility-limited elders were evaluated. Fifty-two older adults (78 ± 5yrs) were randomised to either 16 weeks of low intensity (LO) or high intensity (HI) power training. Both groups completed 3 sets of leg & knee extension exercises at maximum voluntary contraction velocity, 2 times per week, at 40% of 1-repetition maximum (1RM) in LO or 70% of 1RM in HI. At follow-up, both LO & HI exhibited significant within-group increases of peak muscle power (32 ± 11% vs. 43 ± 11%), contraction velocity (15 ± 7% vs. 20 ± 7%), muscle strength (16 ± 4% vs. 21 ± 4%) and short physical performance battery score (1.4 ± 0.3 vs. 1.8 ± 0.3 units), respectively (all $P < 0.03$). Between-group differences were not evident for any change in muscle performance or functional ability ($P > 0.25$). Similarly both groups elicited comparable improvements in neuromuscular activation and notable increases in muscle mass after 16 weeks of power training (between group $P \geq 0.25$). This study suggests that two distinct high velocity power training interventions performed at low or high intensity can yield significant and comparable improvements in muscle performance and clinically meaningful gains in mobility among mobility-limited older adults. Such improvements, together with enhanced neural function and muscle hypertrophy, demonstrate the utility of high velocity power training and its therapeutic potential for addressing a major clinical and physiological issue affecting older adults.

In section C, a study was performed to investigate whether measures of baseline cognitive function predict subsequent adherence to a long term physical activity (PA) intervention among older adults with mobility limitations. Data were evaluated from participants randomised to the PA arm of the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study (n=50; age: 76.9±5 yrs). Tests of executive and global cognitive functioning, working memory and psychomotor speed were administered at baseline. Median rate of center-based attendance to 1-year of multi-modal PA was used to dichotomise participants into low or high adherence groups. However, no differences existed for any measure of baseline cognitive function between adherence groups (all $P \geq 0.13$). Furthermore, weak and non-significant univariate relationships were elicited between all measures of cognition and overall PA adherence levels (r values ranged: -0.20 to 0.12, $P \geq 0.14$). These data suggest that initial cognitive function is not a determinant of long term PA adherence in mobility-limited older adults. Inherent components of the PA intervention in LIFE-P, such as counseling sessions to promote long term PA adherence, may have influenced these observations. Additional studies in larger cohorts are warranted to verify these findings.

Chapter 1

Introduction

1.1 Introduction

The world population is rapidly ageing. Current projections indicate that between 2000 and 2050, the global population of older adults aged 60 years or older will double from 11% to 22%, corresponding to an absolute increase from 605 million to 2 billion over the same period (Boyle et al. 2001). In most parts of the world, the 80 years-or-older age group is growing faster than any other population segment, and will quadruple in size to almost 400 million by 2050 (Wimo et al. 2003). Consequently, as the population of older adults continues to increase, the maintenance of health and independence for older persons has emerged as a major clinical and public health priority. Unless adequate interventions, therapeutic strategies and scientific knowledge are developed to address the challenges posed by population ageing, unprecedented demands will be placed on healthcare systems, economies and social services (Anderson and Hussey 2000; Restrepo and Rozental 1994).

A critical factor in an older person's ability to function independently is mobility, i.e. the ability to move without assistance. Limitations in mobility have been defined as difficulty in performing ambulatory physical tasks such as walking, rising from a chair or climbing a flight of stairs (Gardener et al. 2006; Guralnik et al. 1995). Older persons who lose mobility experience a poorer quality of life, are less likely to remain in the community and have higher rates of falls, chronic disease, and mortality (Guralnik et al. 2000; Guralnik et al. 1995).

To capture and assess mobility limitations among older adults, several objective tests of physical performance and mobility have been developed and have been shown to be highly predictive of subsequent disability, institutionalisation, and mortality (Guralnik et al. 1995;

Guralnik et al. 1994). Limitations in mobility affect almost one in four community-dwelling older adults and three quarters of older adults that reside in long term care institutions (Fried and Guralnik 1997; Gardener et al. 2006; Melzer et al. 2005). As the population of older adults is exponentially increasing, corresponding increases in the prevalence and incidence of mobility limitations are inevitable unless additional research is conducted to improve our understanding of the major determinants of mobility loss and dependence. Furthermore, enhanced knowledge for the development and implementation of effective therapeutic interventions to preserve mobility and independent living for older adults is urgently required.

Of particular importance is the understanding of the impact of changes in muscle structure and function on the preservation of physical independence. According to the disablement model, impairment refers to a loss or abnormality at the tissue, organ and body system level (Nagi 1964; Verbrugge and Jette 1994). At an individual level, physiologic impairments can progress to mobility limitations and to subsequent disability and loss of independence. A more comprehensive understanding of the specific physiological mechanisms that potentially mediate mobility limitations may enable us to further refine treatment and preventive strategies for preserving mobility and independence among older persons.

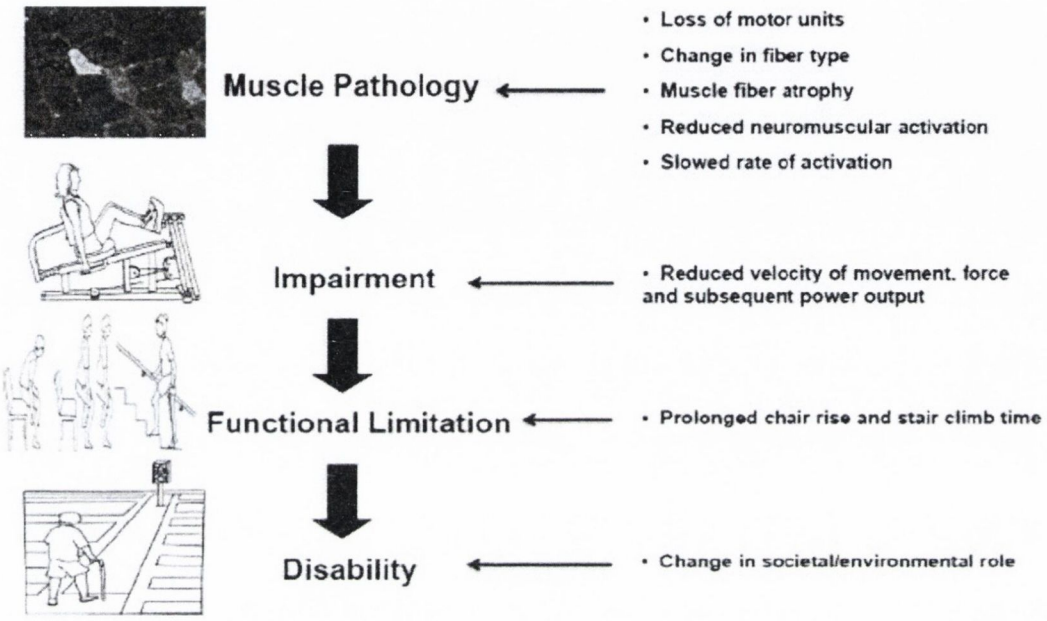
Although a large number of studies have established the role of muscle strength (the ability to generate maximal muscle force) as an early determinant of mobility limitations in older adults, skeletal muscle power (the product of the force and velocity of muscle contraction) has been shown to decline earlier and more precipitously throughout the life span (Aagaard et al. 2010; Metter et al. 1997). Previous investigations have also shown that impairments in

muscle power are important factors limiting mobility in community-dwelling elders (Bean et al. 2002b; Cuoco et al. 2004; Foldvari et al. 2000) and in nursing home residents (Bassey et al. 1992). Theoretically, muscle power may be related to mobility in many ways such as rapidly generating force to maintain balance following a perturbation or while performing a time-dependent task such as crossing a street before the light changes. Importantly, studies that have compared muscle power and strength impairments and their relative contribution to important mobility-related tasks in older adults, suggest that muscle power may be a more critical physiological attribute than muscle strength (Bean et al. 2002b; Foldvari et al. 2000).

1.2 Aim of Thesis

The major aim of this thesis is to examine lower extremity muscle power as a more critical variable for understanding the inter-relationships between impairments, mobility limitations, and resultant disability with advancing age (Figure 1.1).

Figure 1.1 Power driven pathway to age-associated disability



To date, no study has systematically investigated the underlying physiological determinants of lower extremity muscle power output in older adults. A greater understanding of the underlying physiological mechanisms that contribute to muscle power loss with advancing age is particularly warranted as the preservation of lower extremity muscle power may enhance functional impendence and greatly decrease the risk of disability among older adults. In addition, initial resistance training interventions specifically targeted at improving lower extremity muscle power in older adults have been shown to be well tolerated, safe and effective, even among very frail older adults. However, additional research is needed to identify the optimal resistance training regimens for improving lower extremity muscle power and restoring mobility in older adults.

Within this thesis, two studies will be conducted to specifically and systematically examine the underlying physiological determinants associated with the age-related loss of lower extremity muscle power output in older adults. These studies will present novel investigations into the age-related physiological determinants of lower extremity muscle power in healthy and mobility-limited older adults. Using an initial cross sectional study approach, the mechanisms that contribute to age-associated declines in peak muscle power and mobility impairments will be examined and compared across three distinct study populations: healthy middle-aged (40-55 yrs), healthy older (70-85 yrs) and mobility-limited older adults (70-85 yrs). Comprehensive experimental procedures will be performed to assess lower extremity muscle power, strength, neuromuscular activation, muscle size and composition, and an intricate evaluation of the intrinsic single muscle fiber properties of skeletal muscle will also be performed. To compliment this cross-sectional study, an in-depth longitudinal follow-up investigation will be performed to provide definitive evidence on the physiological determinants of muscle power and physical functioning with advancing age among individual cohorts of healthy and mobility-limited older adults.

In addition, this thesis will describe a study that will examine the physiologic and functional effects of a randomized, controlled, single-blind power training exercise intervention trial in a community-based group of elderly men and women with mobility-limitations. Using specialised lower extremity resistance training equipment, the effects of two uniquely different power training interventions performed at low intensity or high intensity will be quantified. For the first time, the comparative impact of these distinct power training

interventions for restoring mobility, muscle power, strength, muscle mass and neuromuscular activation in mobility-limited older adults will be examined.

In addition to mobility loss, cognitive decline is the other major age-related factor that can lead to loss of independence and institutionalisation among older adults (Aguero-Torres et al. 2002). However, participation in regular physical activity may be one of the most important health behaviours associated with the prevention and management of chronic disease among older adults. It is now recognised that higher quantities of physical activity have beneficial effects on numerous age-related conditions, including mobility-decline and cognitive impairment (Williamson and Pahor 2010). Despite this evidence, little is known about the major determinants of adherence to long term physical activity interventions in older populations. For the first time, this thesis will also describe an investigation into whether measures of cognitive function predict adherence to a long term physical activity intervention among older adults with mobility-limitations. Data will be used from the cognitive sub-study of the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study (Espeland et al. 2007). The influence of four domains of baseline cognitive function will be evaluated on subsequent long term (12 month) physical activity adherence.

1.3 Thesis Format

Chapter 2 presents a review of the literature that includes a summary of the studies that have identified skeletal muscle power as a critical physiological determinant of physical functioning and mobility limitations in older adults. In addition, a summary of the therapeutic resistance training intervention strategies designed to restore muscle power, and the impact of these interventions on functional performance, will be reviewed. In section A,

chapter 3 and chapter 4 document the respective cross-sectional and longitudinal studies examining the underlying physiological determinants of lower extremity muscle power output with advancing age. In section B, chapter 5 describes the comparative physiologic and functional effects of two distinct power training resistance training interventions specifically designed to improve lower extremity muscle power in mobility-limited older adults. In section C, the relationships between baseline levels of cognitive function and subsequent adherence to a 12 month program of multi modal physical adherence in the LIFE Pilot study are summarized in chapter 6. Within sections A-C, each individual chapter contains an introduction and study rationale section that also reviews relevant literature followed by a comprehensive description of the methods used for each investigation. A detailed presentation of the study results is followed by a study discussion and conclusions section that describes the novelty, importance and scientific relevance of each study contained in this thesis. Finally, chapter 7 in section D presents a brief general discussion of the overall findings described in sections A-C, and concludes this thesis.

Chapter 2

Review of Literature

2.1 Assessment of lower extremity muscle power in older adults

It is only since the 1990's, that skeletal muscle power has been examined as an outcome variable distinct from muscle strength (Bassey et al. 1992). Dynamic muscle strength typically represents the greatest load lifted during a 1- repetition maximum (1RM) testing protocol. Muscle strength can also be reliably assessed using isokinetic or isometric dynamometry. Evaluation of muscle power output using lower extremity pneumatic resistance training equipment has recently emerged as an accurate and valid muscle power assessment modality, particularly as this methodology can reliably capture the force and velocity components of muscle power output (Fielding et al. 2002; Reid et al. 2008). A recent systematic evaluation of this methodology demonstrated that peak power assessment with a multiple attempt protocol using pneumatic resistance equipment yields significantly higher performance and better reliability than protocols involving a single attempt at varying external resistances on pneumatic equipment in older adults (Callahan et al. 2007). This multiple attempt protocol maximizes the achievement of maximal contraction velocity and subsequent maximal muscle power output and is feasible for the assessment of lower extremity muscle power in frail older populations. As displayed in Figure 2.1, when muscle power is assessed in the older adult across a range of external resistances (40%-90% of 1RM), peak muscle power is typically yielded at approximately 70% of the 1RM while maximal contraction velocity typically occurs at the lowest external resistance (40% of 1RM) (Callahan et al. 2007; Cuoco et al. 2004; Fielding et al. 2002). Similarly, in younger adults (age range: 21-29 yrs), when muscle power is assessed across a range of external resistances (30% - 90% of 1RM), peak muscle power has also been shown to be elicited at approximately 70% of the 1RM (Thomas et al. 1996).

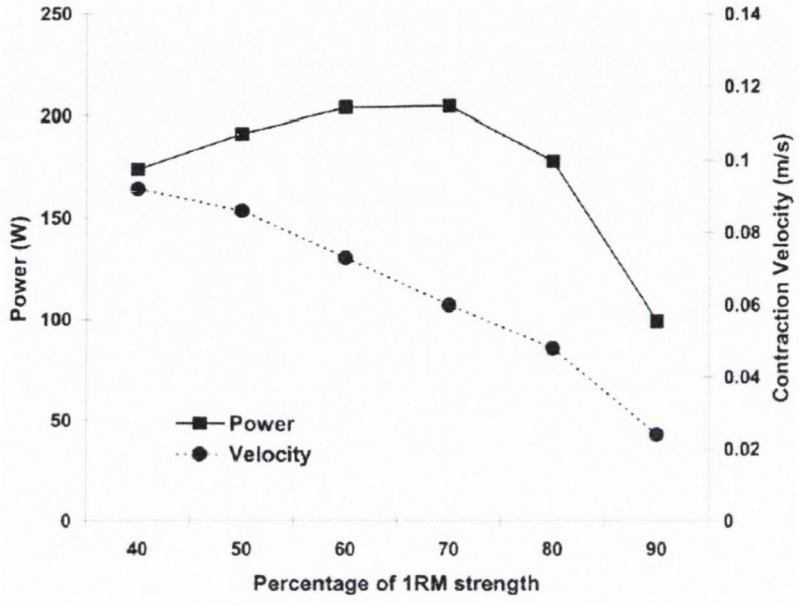


Figure 2.1 Muscle power and contraction velocity at various percentages of 1RM. *Representative data presented are from a 77-year old male study volunteer (Cuoco et al. 2004)*

Additional methods that have been developed to assess lower extremity muscle power in older individuals include vertical jump on a force platform, unloaded leg extensor power evaluation and isokinetic dynamometry.

2.2 Lower extremity muscle power and functional performance

The seminal investigation by Bassey and coworkers (Bassey et al. 1992) examined the contribution of muscle power to various functional tasks in frail institutionalised elders and demonstrated that leg extensor peak power was predictive of chair rise performance, stair

climbing and gait speed. Foldvari *et al.* (Foldvari et al. 2000) further explored the relationships between muscle power, muscle strength and other physiologic factors relevant to functional independence among 80 elderly community-dwelling women with self-reported disability. Peak muscle power ($r = 0.47$) was superior to muscle strength ($r = 0.43$) and aerobic capacity ($r = 0.40$) in determining functional status and independently predicted functional dependency even after accounting for additional neuropsychological and health status indicators.

In a similar population of elderly women with self-reported limitations in function, Suzuki *et al.* (Suzuki et al. 2001) compared the respective associations of muscle power and strength on performance based functional tasks such as the length of time necessary to rise from a chair ten times or to ascend a flight of stairs as fast as possible. Compared to muscle strength, muscle power of the ankle flexors was a stronger predictor of chair rise ($r = 0.58$ vs. 0.32) and stair climb performance ($r = 0.49$ vs. 0.37). Furthermore, muscle power remained an independent predictor of functional performance in multivariate analyses after accounting for muscle strength and additional self-report measures of health status and physical functioning.

It is important to note that inherent limitations may be associated with the ascertainment of self-reported functional status and level of mobility-disability, as older adults may underestimate or overestimate their functional capabilities. To overcome this bias, standardised and objective tests of physical performance such as the Short Physical Performance Battery test (SPPB) have been developed (Guralnik et al. 1994). The SPPB has been well-validated and widely used in large-scale epidemiologic studies and offers

additional advantages over self-report measures of functional status in terms of applicability and reproducibility. While numerous other objective physical performance tests have also been developed and are widely used to assess individual domains of physical functioning in older adults (e.g. timed up and go test, Berg balance scale), the SPPB provides a composite characterisation of several measures of lower extremity function using timed measures of standing balance (side-by-side stand, tandem and semi-tandem positions), gait speed (timed 8-ft walk) and lower extremity strength (timed test of five chair rises). Scores obtained on a 12 point summary scale indicate a gradient of functional decline that has been shown to be highly predictive of subsequent mobility-related disability, institutionalisation, and mortality (Figure 2.2) (Guralnik et al. 1994). In the majority of recent trials that have enrolled mobility-limited older adult, participants were classified as "mobility-limited" if a SPPB summary performance of ≤ 9 was obtained (Bean et al. 2010; Bean et al. 2008; Clark et al. 2011; Cuoco et al. 2004; Mayson et al. 2008).

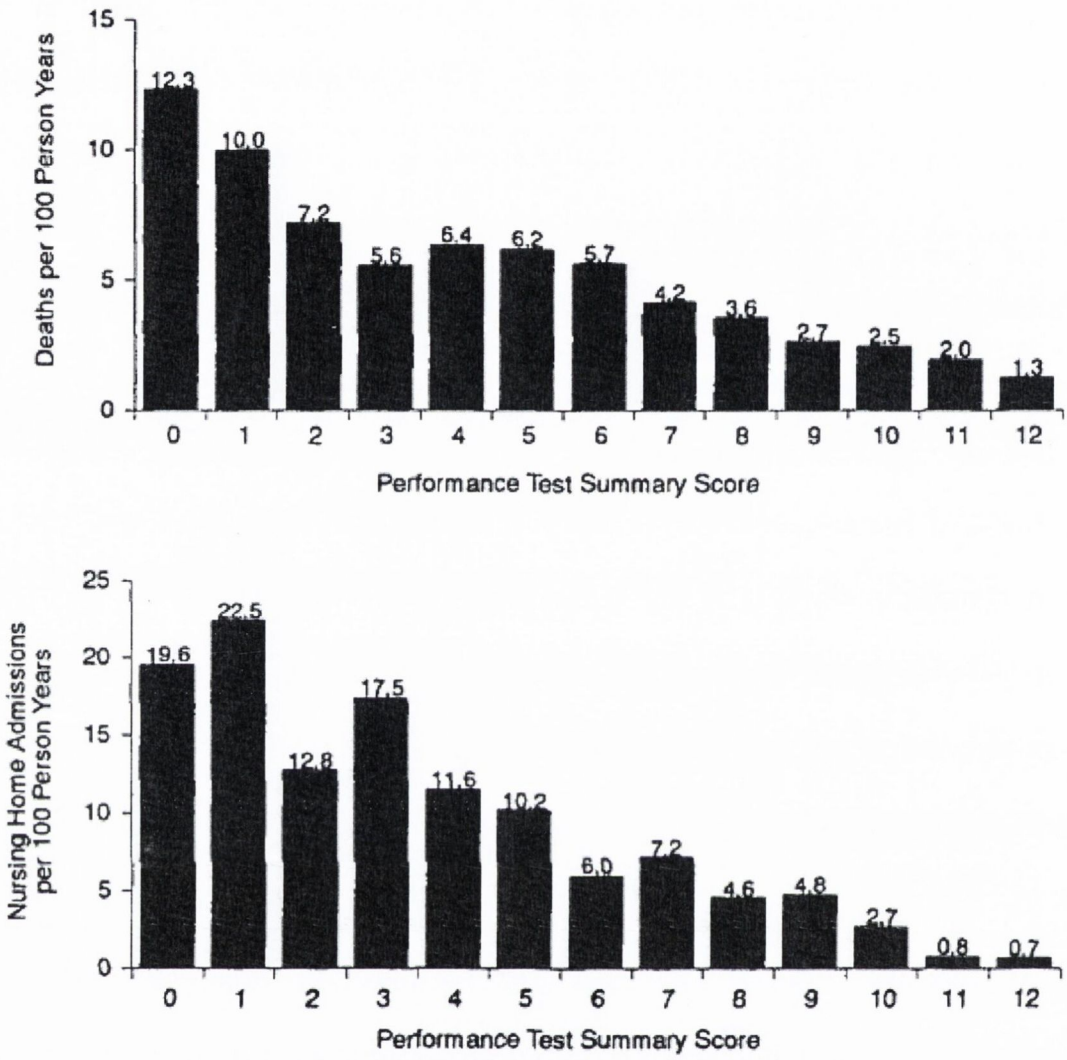


Figure 2.2 Age- and sex-adjusted mortality and nursing home admission rates according to SPPB score *(n = 5,174). Representative data from the Established Populations for Epidemiologic Studies of the Elderly (Guralnik et al. 1994).*

Many of the more recent studies examining the relationship between muscle power on functional performance in older adults have employed the SPPB as study eligibility criteria or as a study outcome measure (Bean et al. 2008; Reid et al. 2008). Bean *et al.* (Bean et al. 2002b) examined the relative contribution of muscle power and strength on various measures of physical performance among community-dwelling older men and women with

objective mobility-limitations. Compared to muscle strength, leg power consistently explained a greater proportion of the variance (2-8%) on all measures of physical performance (stair climb and chair stand performance, gait speed and the SPPB) assessed in these mobility-limited participants. Bean *et al.* (Bean et al. 2003) replicated these observations in a large cohort of 1032 older adults from the *Invecchiare in Chianti* (InCHIANTI) study and demonstrated that impairments in muscle power were more influential proximal determinants of mobility performance than impairments in muscle strength. Older adults with low muscle power output had a 2-3 fold greater risk of significant mobility impairments compared to individuals with low muscle strength.

The independent influence of the velocity component of muscle power and functional performance has been established by several important studies. Compared to muscle strength, contraction velocity of leg extensors has been shown to be a stronger predictor of performance on lower intensity functional tasks such as habitual walking speed ($r^2 = 0.18$ vs. 0.06) (Sayers et al. 2005). Cuoco and colleagues (Cuoco et al. 2004) investigated the relationship between peak muscle power generated at high (40% 1RM) and low (70% 1RM) contraction velocities on functional performance in older men and women with mobility-limitations. Power output at 40% 1RM explained more of the variability in habitual gait velocity than did peak power at 70% 1RM (59% vs. 51%) and consistently accounted for higher respective percentages of the variance in other functional tasks such as chair rise performance (28% vs. 24%) and stair climb performance (43% vs. 42%). More recently, Mayson and coworkers (Mayson et al. 2008) further illustrated the importance of muscle contraction velocity on balance performance. Among community dwelling older adults with mobility limitations, higher leg press contraction velocity (generated at 40% 1RM) was

associated with better performance on several composite measures of balance that are predictive of falling. In the same study population, contraction velocity was shown to be independently predictive of mobility (Bean et al. 2008). Higher contraction velocity was also associated with higher SPPB status and superior in predicting mobility performance compared to traditional rehabilitive impairments such as aerobic capacity and obesity. This investigation also highlighted the emergence of limb contraction velocity as an important rehabilitive impairment and specific target for therapeutic intervention.

2.3 Physiological determinants of muscle power and mobility limitations with advancing age

As muscle power is the product of force and contraction velocity, factors that lead to a reduction in either of these parameters, or both, will contribute to reduced muscle power output. Decrements in muscle power production with advancing age can be attributed to well-described changes in muscle quantity and quality. Such factors include a quantitative loss of muscle mass and alterations in the properties of individual muscle fibres, in particular, the selective reduction in the number and size of type II muscle fibres with advancing age which have the ability to generate four times the power output of type I fibres (Lexell 1997). Additionally, muscle power loss in older adults is influenced by increases in muscle fat infiltration, changes in neuromuscular function, muscle architecture, alterations in hormonal status, protein synthesis and inflammatory mediators (Aagaard et al. 2010; Lexell 1997). However, among older adults with mobility limitations, a paucity of information exists on the specific underlying physiological mechanisms that contribute to the loss of muscle power.

2.4 Changes in muscle mass and quality

To date, no studies have examined the longitudinal changes in muscle mass among mobility-limited older adults. However, in relatively healthy older subjects, previous studies have reported a significant reduction of 14.7% in thigh muscle cross sectional area (CSA) after a 12 year follow-up period (mean initial age: 65 yrs) and a 5.6% reduction after an 9 year follow-up period (mean initial age: 71 yrs) (Frontera et al. 2008). Goodpaster *et al.* (Goodpaster et al. 2006) examined the longitudinal changes (~3 yrs) in muscle mass among 1880 relatively healthy older adults in the Health, Aging and Body Composition Study (mean initial age: 73.5 yrs; range: 70-79 yrs). In this cohort, annualised rates of muscle mass decline were approximately 2% per year. This investigation also noted that the decline in muscle performance (muscle strength) was on average 3-fold higher than the loss of muscle mass over this period, suggesting a decline in muscle quality.

2.5 Skeletal muscle contractile properties

The examination of single muscle fibre properties can directly quantify the contractile elements of muscle cells, without the potential confounding effects of factors such as neural influences or muscle architecture. Several studies have shown that surviving single muscle fibre contractile function may be preserved in older adults despite the presence of significant reductions in whole muscle size and composition (Frontera et al. 2008). However, these previous studies have been limited by small sample sizes and have typically included relatively healthy and physically active older subjects. No study to date has adequeatly quantified single muscle fibre properties in mobility-limited older adults.

2.6 Neuromuscular activation

Neuromuscular activation impairments may impact movement velocity and muscle coordination leading to a reduction or a longer time to reach peak force, and thus a decline in muscle power generation. A number of studies using electromyography (EMG) have reported reduced maximal motor unit discharge rates in agonist muscles with aging, and these findings are related to deficits in maximal torque production (Klass et al. 2008). Deficits in torque and power have also been linked to reduced maximal rate of agonist EMG rise in older adults >70 years compared with those ≤70 years, in less active older adults, and in older adults who have limited mobility function compared with those with high mobility function (Clark et al. 2010, 2011).

2.7 Relationship between vascular dysfunction, physical function and resistance training interventions in older adults

There is now growing evidence from clinical studies indicating that vascular dysfunction is directly associated with physical function and performance of activities of daily living in older adults (Credeur et al. 2009; McDermott et al. 2013; Welsch et al. 2008). Manifestations of vascular dysfunction implicated in this relationship include endothelial dysfunction and arterial stiffness (Seals et al. 2009). Impaired functioning of the endothelium can ultimately lead to a reduced blood flow to the working muscle, and impaired lower limb blood flow is evident in older adults both at rest and during exercise (Dinenno et al. 2001). More recent large-scale studies have demonstrated a significant association impaired walking ability and other indices of vascular dysfunction such as increased central vascular stiffness and abnormal ankle-brachial index (Gonzales 2013; McDermott et al. 2013; Watson et al. 2011).

In a recent clinical study of 24 older adults aged 70-85 years, measures of brachial artery endothelial function and vascular stiffness were significantly correlated with leg muscle power (r= 0.43 and 0.42, respectively) but not muscular strength (Heffernan et al. 2012). These findings warrants further investigation as, to date, no studies have examined the potential vascular and blood flow responses to resistance training interventions that have been specifically designed to improve muscle power output in older adults. Other studies using more traditional resistance training strategies have determined that, in 11 previously sedentary men (age 60–67 yrs), 3 months of knee extension strength training improved endothelial function without inducing any additional arterial stiffening (Maeda et al. 2006). Similarly, in healthy postmenopausal women (age 67 ± 5 yrs), a 12-week progressive resistance training program using elastic bands significantly increased basal leg blood flow (31%) and vascular conductance (34%) (Egana et al. 2010).

2.8 Resistance training interventions to restore muscle power in older adults

Early studies evaluating whether resistance training interventions could increase lower extremity muscle power in older individuals reported minimal improvements. This was primarily because the traditional resistance training interventions employed were performed at relatively slow velocities, thus lacking the training specificity to improve peak muscle power within these populations. However, recent randomised trials designed to maximise muscle power output have generally demonstrated that high velocity power training is feasible, well tolerated, and can effectively improve lower extremity muscle power in healthy older men and women, older women with self-reported disability (Fielding et al. 2002; Marsh et al. 2006), older adults with mobility limitations (Reid et al. 2008) and in older women aged over 80 years (Aagaard et al. 2010). This distinct type of resistance

training is characterised by participants performing the concentric phase of each repetition as fast as possible.

Earles *et al.* (Earles et al. 2001) reported a 50-141% increase in leg power following 12 weeks of high velocity resistance training in combination with moderate intensity non-resistance exercise compared to a structured walking program in older men and women. Fielding *et al.*(Fielding et al. 2002) examined high velocity lower extremity resistance training compared to traditional slow velocity resistance training in older women with self-reported disability. After 16 weeks of training, they observed an 84% greater increase in leg press power in the high velocity training group compared to the low velocity group.

The comparative effects of 12 weeks of high velocity resistance training and traditional strength training on lower extremity muscle power were evaluated in 45 older adults with self-reported mobility limitations (Marsh et al. 2006). Improvements in knee and leg extensor muscle power after high velocity power training were approximately twofold greater compared to gains in muscle power as a result of strength training. Among older adults with mobility-limitations, a 12-week high-velocity resistance training intervention increased lower extremity muscle power (~25%), although these gains were comparable to improvements resulting from traditional slow velocity strength training in this population (~21%) (Reid et al. 2008). However, in this study, high velocity training was associated with significantly greater improvements in specific leg extensor muscle power (46%) compared to the induced gains from traditional strength training (20%).

While all of the aforementioned studies employed high velocity resistance training coupled with a relatively high external resistances (~70% of 1RM), only one study to date has

examined high velocity training at varying external resistances. de Vos *et al.* (de Vos et al. 2005) examined changes in leg power in response to 12 weeks of high velocity resistance training in healthy older adults randomised to one of three different external resistances: 20% 1 RM; 50% 1 RM; or 80% 1 RM. Peak power output improved similarly (14-15%) across all training intensities suggesting that power output can be increased with high velocity training at low and high external resistances. In addition, this study demonstrated a dose-response relationship between the respective training intensities and concomitant improvements in muscle strength (20%) and muscle endurance (185%) elicited when using the highest loading intensity (80% 1RM). Simultaneous improvements in strength and endurance aspects of muscle performance, in addition to muscle power improvements, are likely to play an important role in preserving functional performance in older adults. More recently, 12 weeks of explosive heavy resistance training, with a loading intensity of 75-80% 1RM, demonstrated substantial improvements in muscle power (28%) and marked gains in rapid muscle force generating characteristics in healthy older women aged 80-89 years (Aagaard et al. 2010).

2.9 Impact of muscle power training on physical function

A number of randomised trials have evaluated the effect of power training interventions on changes in physical functioning in older adults (Table 2.1). The majority of these studies compared the effects of high velocity resistance training to conventional strength training or control interventions on functional outcomes. It is evident from Table 2.1 that the magnitude of muscle power gains and function gains vary substantially across studies.

Study	Participants* (number and mean age)	Power Training Intervention	Frequency & Duration	Muscle Power Increase	Physical Function Gains in Power Training Intervention Arm	Physical Function Gains in Control Group (Traditional Strength Training Interventions)
High Velocity Resistance Training						
(Sayers et al. 2003)	15 women with self-reported disability, 73 yrs	Bilateral leg press, knee extension resistance training performed at 70% 1RM. 3 sets x 8 repetitions (concentric phase at maximal velocity)	3 x wk, 16 wks	Leg press: 97%	Balance: 5% Stair climb time: 13%	Balance: 11% Stair climb time: 10%
(Henwood et al. 2008)	19 males and females,71 yrs	6 multi-joint upper & lower body resistance training at 40%-75% 1RM. 3 sets x 8 repetitions (concentric phase at maximal velocity)	2 x wk, 24 wks	Leg extension: 62% Leg press: 58%	Stair climb time: 7% 6 m fast walk time: 15% 5-Chair stand time: 13% Functional reach test: 9%	Stair climb time: 2% 6 m fast walk time: 6% 5-Chair stand time: 11% Functional reach test: 16%
(Miszko et al. 2003)	11 older adults with low physical functioning and reduced muscle power, 72 yrs	6 multi-joint upper & lower body resistance training at 50%-70% 1RM for first 8 weeks (slow contraction velocities), changed to 40% 1RM for remaining 8 weeks. 3 sets x 6-8 repetitions (concentric phase at maximal velocity)	3 x wk, 16 wks	Peak anaerobic power (Wingate Test): 8%	Performance on CS-PFP test & sub domains scores: CS-FFP Total: 15% Balance/coordination: 21% Endurance:17%	Performance on CS-PFP test & sub domains scores: CS-FFP Total: 4% Balance/coordination: -0.4% Endurance:5%
(Bottaro et al. 2007)	11 healthy males, 67 yrs	6 multi-joint upper & lower body resistance training at 40%-60% 1RM. 3 sets x 8-10 repetitions (concentric phase at maximal velocity)	2 x wk, 10 wks	Leg press: 31% Chest press: 37%	8-Feet up-and-go: 15% 30-sec chair stand: 43% Arm curl test: 50%	8-Feet up-and-go: 1% 30-sec chair stand : 6% Arm curl test: 3%

Table 2.1 Summary of randomised trials investigating the effects of power training on physical functioning.

** = characteristics of participants randomised to power training intervention arm only; CS-FPP: Continuous Scale Physical Functional Performance;*

Study	Participants* (number and mean age)	Power Training Intervention	Frequency & Duration	Muscle Power Increase	Physical Function Gains in Power Training Intervention Arm	Physical Function Gains in Control Group
High Velocity Resistance Training						
(Orr et al. 2006)	112 healthy, high-functioning males and females, 69 yrs	5 multi-joint upper & lower body resistance training randomised to 3 intensities: 20% (LOW) 50% (MED), 80% (HIGH) of 1RM. 3 sets x 8 repetitions (concentric phase at maximal velocity)	2 x wk, 8-12 wks	Leg press, leg extension: LOW: 9%, 14% MED: 14%, 18% HIGH: 12%, 14%	Balance Performance: LOW: 11% MED: 2% HIGH: 3%	**Inactive control intervention** Balance Performance: 5%
(Earles et al. 2001)	21 healthy males and females, 77 yrs	Hip and knee extensor, plantar & hip flexor resistance training performed between 50-70% 1RM. 3 sets x 10 repetitions at usual, ramped or maximal velocities. An additional 45mins of walking/moderate activity (step-ups, chair rises) was also included	3 x wk, 12 wks	Leg press: 22%	6-minute walk distance: 20 meters SPPB score: 0.7 unit	**Walking intervention** 6-minute walk distance: 13 meters SPPB score: 0.1 unit

Table 2.1 continued Summary of Randomised Trials Investigating the Effects of Power Training on Physical Functioning.

** = characteristics of participants randomized to power training intervention arm only; SPPB: Short Physical Performance Battery Test;*

Study	Participants* (number and mean age, SPPB score)	Power Training Intervention	Frequency & Duration	Muscle Power Increase	Physical Function Gains in Power Training Intervention Arm	Physical Function Gains in Control Group
Interventions without Resistance Training Equipment						
(Bean et al. 2002a)	23 males and females with mobility limitations, 71 yrs (SPPB score: 9.7)	Weighted stair climbing: subjects ascended & descended a flight of stairs (10 steps) while wearing a weighted vest. 3 sets x 4 flights. Vest weight was adjusted to add progressive resistance throughout intervention	3 x wk, 12 wks	Leg press: 17% Stair climb power: 12%	SPPB score: 1.1 units Stair climb time: 11%	**Walking intervention** SPPB score: 0.4 units Stair climb time: 8%
(Bean et al. 2004; Bean et al. 2002b)	10 females with mild to moderate mobility limitations, 77 yrs (SPPB score: 7.7)	Weighted vest training (InVest) with exercises designed specific to mobility tasks including chair stands, toe raises, pelvic raises, step ups, chest press. 3 sets x 10 repetitions. (concentric phase of repetition performed at maximal velocity). Vest weight was adjusted to add progressive resistance throughout intervention	3 x wk, 12 wks	Leg press: 12-36%	SPPB score: 2.7 units 5-Chair stand time: 44% Gait speed: 16% Unilateral stance time: 50%	**Slow-velocity, low resistance chair-based exercise intervention** SPPB score: 2.2 units 5-Chair stand time: 29% Gait speed: 10% Unilateral stance time: 35%
(Bean et al. 2009)	72 males and females with mobility limitations, 75 yrs (SPPB score: 8.8)	InVest exercise training	3 x wk, 16 wks	Leg press: 10%	SPPB score: 1.8 units LLFDI: 2.6 units	**Traditional strength training intervention with barbells/ankle weights** SPPB score: 1.4 units LLFDI: 1.0 unit

Table 2.1 continued Summary of Randomized Trials Investigating the Effects of Power Training on Physical Functioning.

** = characteristics of participants randomized to power training intervention arm only; SPPB: Short Physical Performance Battery Test; LLFDI: Late Life Function and Disability Instrument.*

Sayers *et al.* (Sayers et al. 2003) evaluated 16 weeks of high velocity power training in older women with self-reported disability and noted modest improvements in dynamic balance and stair climbing performance after large improvements in muscle power. However, equivalent improvements in functional performance were observed in the group randomised to traditional resistance training. Similarly, Henwood *et al.* (Henwood et al. 2008) also compared high velocity varied resistance training to strength training on functional performance in healthy older adults. They demonstrated similar improvements in muscle power with both training protocols after a 24-week intervention period. These gains were also accompanied by better performance on several functional measures, including stair climb and chair rise time, although the magnitude of these improvements were not different between intervention groups. Two power training intervention studies have demonstrated that high velocity resistance training is associated with greater improvements in functional performance compared to conventional strength training. Among older adults with low muscle power, 16 weeks of high velocity power training elicited significant improvements in a battery of whole body functional performance tasks (Miszko et al. 2003). These gains were significantly greater than those elicited after a corresponding program of traditional strength training. Similarly, Bottaro *et al.*(Bottaro et al. 2007) also reported that 10 weeks of high velocity resistance training significantly improved several functional performance measures after modest improvements in leg muscle power in sedentary older males. An intervention of traditional resistance training had no effect of the functional parameters assessed in this study.

Orr *et al.* (Orr et al. 2006) reported improvements in measures of dynamic balance in high functioning older men and women randomised to 8-12 weeks of high velocity resistance

training and compared to an inactive control group. Power training performed at low intensity (20% of 1RM) was associated with the greatest improvements in balance performance compared to training performed at 50% and 80% of the 1RM. A 12-week program of high velocity resistance training resulted in a 22% increase in leg power with a corresponding increase of 20 meters in total distance walked during the six-minute walk test and a 0.7 unit increase in SPPB score in healthy older adults (Earles et al. 2001). These improvements in function were greater than those elicited from a self-paced walking program. A 20 meter improvement in 6 minute walk time and a respective 0.5 and 1.0 unit increase in SPPB score correspond to clinically meaningful and substantial improvements in physical performance measures among older adults (Perera et al. 2006).

Several studies have evaluated different types of exercise interventions that did not depend on specific resistance training equipment or isokinetic dynamometry but emphasised explosive power. These have included modified weighted stair climbing and weighted vest exercise. Bean *et al.* (Bean et al. 2002a) compared 12 weeks of a weighted stair climbing program to a walking program in older adults with baseline mobility limitations. They reported that the stair climbing intervention increased leg power by 17% with a corresponding 12% increase in stair climbing power. Significant improvements in stair climb time and SPPB scores were observed, although these gains were not statistically greater compared to those observed following a walking intervention. In older women with mobility limitations, the same investigators also examined the effects of a program of weighted vest exercise performed at a high velocity (InVEST) compared to a program of upper and lower body chair-based exercises performed at slow velocity (Bean et al. 2004; Bean et al. 2002b). Lower extremity power and chair rise time increased to a greater extent

after InVEST compared to the slow velocity program. InVEST training was also associated with a substantial increases in SPPB score and gait speed (Perera et al. 2006). More recently, Bean and colleagues compared the effects of a 16 week program of InVEST training versus a progressive resistance training program advocated by the National Institute on Aging among mobility-impaired older adults (Bean et al. 2009). InVEST training elicited significantly greater gains in limb muscle power compared to the conventional program. Substantial improvements in SPPB score and self-reported function were also induced after InVEST, although these improvements were not significantly greater than the traditional resistance training program. In a secondary analysis of this study, Bean *et al.* used multivariate regression models to delineate how the changes in leg power were significantly and independently associated with the clinically meaningful differences observed in SPPB and gait speed (Bean et al. 2010).

2.10 Summary

In summary, several, but not all, carefully conducted randomised trials have demonstrated that high velocity resistance training is more effective for improving muscle power compared to traditional slow velocity training. However, there is considerable variability across randomized trials when comparing the overall magnitude of both muscle power and functional performance improvements following high velocity training compared to gains after traditional slow velocity training or walking exercise. Several factors that may contribute to this variability across studies include: differences in the frequency, duration and intensity of power training interventions, differences in muscle power assessment and functional performance testing modalities; differences in study sample sizes and inherent differences in the characteristics of study participants across studies including varying age

ranges, levels of physical functioning and gender distributions. In general, high velocity resistance training is safe and well tolerated even in mobility-limited older adults and persons aged > 80 years. However, the efficacy and feasibility of high velocity power training in older adults with chronic conditions such as osteoarthritis and osteoporosis have yet to be fully determined. There is now clear evidence that short term interventions of high velocity resistance training and other more practical power training modalities using weighted vests can induce substantial improvements in physical functioning and restore mobility in frail older adults. Studies with larger sample sizes are needed to clearly establish whether high velocity power training is more effective for enhancing functional outcomes in older adults. Additional studies are also needed to elucidate the longer term benefits of power training in older adults, specifically for maintaining active life expectancy, preventing falls and maintaining mobility into old age.

2.11 Conclusion

Muscle power is a more discriminant predictor of functional performance in older adults than muscle strength. A distinct biological basis for the precipitous decline in muscle power with aging has yet to be determined. However, additional research should attempt to elucidate the interrelationships between impairments in muscle power, the neuromuscular system, muscle contraction velocity, and the onset of mobility limitations with advancing age. Exercise interventions targeted at improving lower extremity muscle power have been well tolerated, and are safe and effective even among frail older adults. Improvements in muscle power are greater with resistance training interventions that emphasise high versus low contraction velocity. In addition, there is emerging evidence that higher velocity lower intensity resistance training, and several types of exercise programs performed at high

velocity, can improve physical functioning in older adults to a greater extent than traditional slow velocity resistance training.

Section A

Chapter 3

Muscle power failure in mobility-limited older adults: preserved single fibre function despite lower whole muscle size, quality and neuromuscular activation

3.1 Introduction and study rationale

Lower extremity muscle power, the product of dynamic muscular force and contraction velocity, declines earlier and more rapidly with advancing age compared to muscle strength (Metter et al. 1997; Skelton et al. 1994). Peak muscle power has also emerged as an independent and potent predictor of physical performance, functional mobility, and risk of falling in older adults (Bassey et al. 1992; Bean et al. 2002b; Kuo et al. 2006; Skelton et al. 1994; Suzuki et al. 2001). Despite this evidence, limited knowledge exists on the major physiological determinants of lower extremity muscle power with advancing age. A more definitive understanding of these mechanisms is necessary and may provide more discriminant information on the specific factors that mediate mobility limitations in older persons.

Similar to the age-related loss of muscle strength, deficits in muscle power production are related to the consequences of sarcopenia (Evans 1995). The progressive muscle atrophy with aging is associated with a loss of overall muscle power and changes in the force and power generation of the remaining muscle fibres (Brooks and Faulkner 1994). However, there are several additional physiological mechanisms that accompany the phenomenon of sarcopenia that may specifically influence muscle function and power production with advancing age. Recent evidence has shown that an increased adipose tissue accumulation around and between muscle fibres concomitant with a reduced muscle cross-sectional area occurs with aging, and this skeletal muscle attenuation is inversely associated with muscle performance in older adults (Borkan et al. 1983; Goodpaster et al. 2001). Marked age-related changes in the nervous system may also have a substantial role in the age-associated decline in muscle power generation (Aagaard et al. 2010). These include loss of motor

neurons and concomitant remodeling of motor units through collateral reinnervation (Lexell 1997), impairment of neuromuscular activation observed as decreased maximal motor unit firing rates (Kamen et al. 1995) and uncoordinated patterns of intermuscular neural activation (Hakkinen et al. 1998a).

In addition, changes in individual muscle fibre composition and intrinsic contractile properties may influence the decline in muscle power among older adults. Cross sectional observations suggest that reductions in muscle power may be related to muscle fibre composition and, in particular, the selective atrophy of type II muscle fibres with aging (Larsson et al. 1979; Martin et al. 2000). Specific changes in the intrinsic ability of aged muscle to generate force have also been observed. A decreased specific force (force normalised per cross sectional area) and unloaded shortening velocity in type I and IIA fibres in older males compared to young controls have been previously reported (Frontera et al. 2000b; Larsson et al. 1979). Conversely, recent longitudinal evidence has demonstrated that despite reductions in whole muscle cross sectional area, single muscle fibre contractile function is preserved with advancing age as existing fibres may compensate to partially correct these deficits and maintain optimal force-generating capacity (Frontera et al. 2008). Further evaluation of the relationship between the intrinsic force and shortening velocity characteristics of aging skeletal muscle and their associations with whole muscle peak power is also warranted.

Important gender-related differences in lower extremity muscle power have also been reported. Across all age groups, females produce significantly less muscle power compared to males (Bassey et al. 1992; Caserotti et al. 2001; Metter et al. 1997). In addition,

significant gender differences in the magnitude of muscle power loss with advancing age have been identified. Among 65- to 85-year old males and females, maximal leg extension power was found to deteriorate at a rate of 3% per year in men and 1.7% per year in women (Skelton et al. 1994). A greater understanding of the physiological mechanisms underlying these gender-specific differences in muscle power is also necessary.

The purpose of this study was to provide a comprehensive examination of the major age-related physiological mechanisms that contribute to peak muscle power production among three distinct populations: healthy middle-aged adults, healthy older adults and older adults with mobility limitations. Given the strong association between measures of functional performance and leg extensor power output, we hypothesised that leg muscle power would be significantly lower in mobility-limited older adults relative to both healthy groups. As previous epidemiologic evidence has shown that muscle power is largely preserved until approximately age 40 (Metter et al. 1997), we employed this experimental design to investigate differences in muscle power generation within a more focused age range that would provide greater specificity to our potential findings. To delineate the major physiological mechanisms contributing to muscle power deficits with advancing age, we conducted a comparative assessment of lower extremity muscle power, strength, muscle size and quality, neuromuscular activation and also evaluated intrinsic single muscle fibre contractile properties. In addition, because of the significant gender differences that exist for leg muscle power, we also characterised the influence of gender on the determinants of lower body power production within these populations.

3.2 Methods

3.2.1 Study participants

This study employed a cross-sectional design and participants were recruited into three experimental groups: healthy middle-aged adults (aged 40-55 years), healthy older adults (aged 70-85 years) and older adults with mobility limitations (aged 70-85 years). Subjects were recruited from the Greater Boston area through local advertisements, community newsletters, and were initially screened for eligibility in-person or by telephone (See Appendix A for pre-screening telephone questionnaire).

Participants considered for either healthy group were community dwelling, not taking any prescribed medications, and scored ≥ 10 on the Short Physical Performance Battery test (SPPB) (Guralnik et al. 2000; Guralnik et al. 1995; Guralnik et al. 1994). Older mobility-limited subjects were community-dwelling and demonstrated objective functional limitations as evidenced by an SPPB score ≤ 9. The SPPB is a performance test assesses lower extremity function using measures of gait speed, standing balance, and lower extremity strength (Guralnik et al. 1994). Volunteers were evaluated for their ability to balance during three different balance tests: a side-by-side stance, a semitandem stance, and a full-tandem stance. To assess gait speed, participants were timed from a standing start and asked to walk at their normal pace over a 4-m course. To assess lower extremity strength, volunteers were asked to cross their arms in front of their chest and rise from a chair as quickly as they could five times. Each test was scored on a 0- to 4-point scale. A summary performance score of 0 to 12 was then obtained by summing the scores of the three tests. Scores obtained using the SPPB have been shown to be highly predictive of subsequent

disability, institutionalization and mortality (Guralnik et al. 2000; Guralnik et al. 1995; Guralnik et al. 1994).

After meeting the initial study eligibility criteria, all eligible subjects completed a medical history questionnaire (Appendix B) and underwent a physical examination and medical screening by the study physician. During the medical screening, a blood sample was drawn from each subject by venipuncture and all subjects provided a urine sample. Standard blood chemistries and urinalysis were included as part of the screening and included a complete blood count with differential screening biochemistry. A resting electrocardiogram was also performed. Subjects were excluded from participation if they had a body mass index (BMI) less than 19 kg/m^2 or greater than 33 kg/m^2, acute or terminal illness, myocardial infarction or upper/lower extremity fracture in the previous 6 months, unstable cardiovascular disease or other medical condition, upper or lower extremity amputation, cognitive impairment according to the Folstein Mini-Mental State Examination (MMSE) (score < 23) (Folstein et al. 1975), current participation in regular endurance or resistance training exercise (> 3×/week), or unwillingness to complete the study requirements. Other exclusion criteria included uncontrolled hypertension (>150/90 mmHg), the presence of neuromuscular disease or medications affecting neuromuscular function, anti-coagulation therapy, hormone replacement therapy, and women who were pregnant, planning to become pregnant, or breastfeeding. Participants who presented with lower extremity joint pain were also excluded. Subjects meeting the study entry criteria and given medical clearance by the study physician and written approval from their primary care physician were deemed eligible for participation. Prior to enrollment all volunteers signed an informed consent form and were made aware of all potential risks associated with the study procedures (Appendix A). This study was

approved by the Tufts Medical Center and Tufts University Health Sciences Institutional Review Board.

3.2.2 Lower extremity muscle strength, power and velocity

Strength and power testing took place on two occasions, at the same time of day separated by approximately one week. Each participant was given the opportunity to familiarise themselves with the testing equipment through the use of a visual demonstration and practice at low resistances. Participants were seated on the bilateral leg press apparatus with knees flexed to 90 degrees and hips flexed to approximately 110 degrees (Leg Press A420, Keiser Corporation, Fresno, CA) (Figures 3.1 & 3.2). Knee angle was measured using an electrogoniometer (ADInstruments, Colorado Springs, CO). Force, position, and velocity of each piston were sampled at 400 Hz and saved to disk for offline analysis. Using software provided by the manufacturer, these data were then converted to force, position and velocity at the footplate (Software Release 7.8, Keiser Corporation, Fresno, CA).

Figure 3.1 Keiser leg press A420

Figure 3.2 Older adult undergoing lower extremity strength and power testing

Leg extensor muscle strength was quantitatively assessed using the one-repetition maximum (1RM) technique and was defined as the maximum load that could be moved only once throughout the full range of motion (ROM) while maintaining proper form (Callahan et al. 2007). Subjects were instructed to perform several warm-up repetitions at minimal resistance to familiarise themselves with the apparatus. Each participant's ROM was determined during performance of a minimally loaded repetition prior to each test. An ultrasonic system measuring position, and therefore relative motion, aided examiners in establishing a subject's ROM by observing the excursion of a lighted bar on the output screen during performance of the measure with minimal resistance. Starting at a relatively low level, the examiner progressively increased the resistance after each successful repetition until the participant could no longer move the lever arm one time through their full ROM (optimally within 6-8 repetitions). Subjects performed the concentric phase, maintained full extension, and performed the eccentric phase of each repetition over 2, 1, and 2 seconds, respectively. To aid in accurate establishment of the 1RM, the subject's self-perceived level of exertion was also assessed after each successful repetition using the Borg

scale (Borg 1970). If the subject's rating was ≤ 15, a rest period of 30-60 seconds was provided between repetitions. A rest period of 2 minutes was provided if the subject's rating was ≥ 15.

After measurement of the 1RM, assessment of leg extensor peak muscle power was made after a 5 minute rest period. Performance of this multiple attempt peak power test has been previously described and validated (Callahan et al. 2007). Each participant was instructed to complete a total of five repetitions each separated by 30 seconds as quickly as possible through their full ROM at 70% of the 1RM. The highest measured power output was recorded as the leg extensor peak power. From the two data collection sessions, the highest value for 1RM and peak power was used as the baseline value.

3.2.3 Neuromuscular activation

Muscle activation of the vastus lateralis was assessed by surface electromyography (EMG) using a commercially available data acquisition system (Delsys Bagnoli-8, Delsys, Boston, MA) (Figure 3.3) by placing single differential surface electrodes (Delsys 2.1, Delsys, Boston, MA) (Figure 3.4) with 1cm inter-electrode distance over the muscle belly. Muscle activation was quantified on the second baseline visit during the multiple attempt peak power test performed at 70% of 1RM. Participants also exerted an isometric maximal voluntary effort with their legs constrained to the starting position of the leg press. Vastus lateralis EMG was recorded at a sampling rate of 1 kHz using a Powerlab/16SP A/D system and Chart software (ADInstruments, Colorado Springs, CO) and data were analysed using a custom analysis program created in MATLAB (version 7.0, The Mathworks, Natick, MA). The EMG was de-biased and then filtered using a zero-phase lag first-order Butterworth

band-pass filter (10-200Hz). Rate of activation was quantified as the mean derivative of the normalised EMG between the onset of activation (determined as resting EMG amplitude plus three standard deviations) and the onset of movement (Figure 3.5). EMG normalisation involved expressing EMG amplitude relative to peak EMG acquired during maximal voluntary isometric contraction (defined by the root-mean-square average over the 100ms window with greatest activation magnitude). For each subject, the rate of activation was averaged across trials 2, 3 and 4. Trial 1 was considered a practice trial while trial 5 was eliminated due to the potential effects of short-term fatigue.

The testing procedures and data variables summaries for the lower extremity muscle strength, power and neuromuscular activation assessments in this thesis were conducted by the following Research Technicians: Kieran Reid, M.Sc., Cynthia Hau, B.S., Evan Pasha, B.S. and David Clark, B.S.)

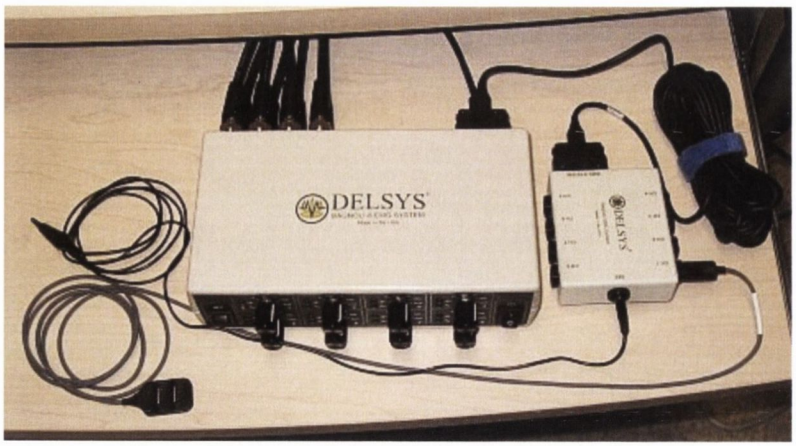


Figure 3.3 Delsys bagnoli-8 EMG system

Figure 3.4 Delsys single differential surface electrodes

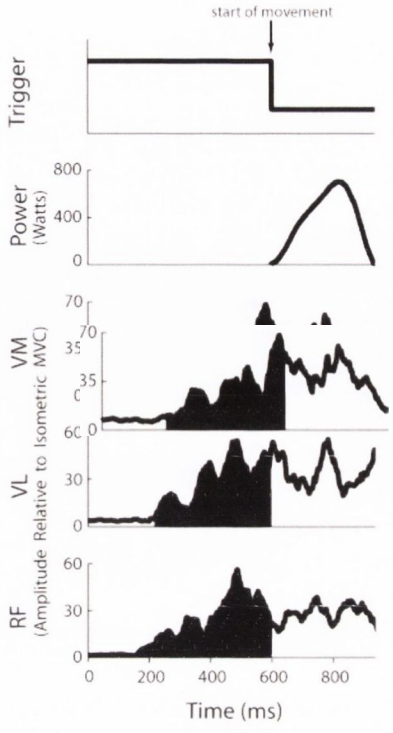


Figure 3.5 Rate of activation – onset of muscle activation and onset of movement

3.2.4 Muscle size and composition

A computed tomography (CT) scan of the nondominant thigh was performed at the midpoint of the femur for each subject. All CT scans were performed within the Department of Radiology, Tufts Medical Center, Boston, USA, by a trained and certified Radiographer. Subjects underwent the CT scan only after a minimum of 3 days after completion of all strength, power and neuromuscular activation testing. The length of the femur was determined from a coronal scout image as the distance between the intercondylar notch and the trochanteric notch. Scans were obtained using a Siemens Somotom Scanner (Erlangen, Germany) operating at 120 kV and 100 mA, with slice width of 10 mm and a scanning time of 1 s. All scans were analysed by a research technician (Kieran Reid, M.Sc., Cynthia Hau, B.S. or Evan Pasha, B.S.) in a blinded manner using SliceOmatic v4.2 software (Montreal,

Canada). Images were reconstructed on a 512 x 512 matrix with a 25-cm field of view. From the images, the cross sectional areas (CSAs) for normal density muscle and low density muscle, subcutaneous adipose tissue, and intermuscular adipose tissue were measured using manual tracing. Muscle CSA was measured in the range of 0-100 Hounsfield units (HU) and calculated as the sum of low-density muscle and normal-density muscle CSA. Adipose tissue areas were measured in the range of -190 to -30 HU. Intermuscular adipose tissue was defined as adipose tissue lying between and among muscle groups (Figure 3.6). The reliability of the CT measurement analyses have been demonstrated as excellent as the intraclass correlation coefficients for repeated analyses from 10 subjects range from 0.95 – 0.99) (Lustgarten et al. 2013). The CT methods have been previously described (Goodpaster et al. 2001; Kelley et al. 1991).

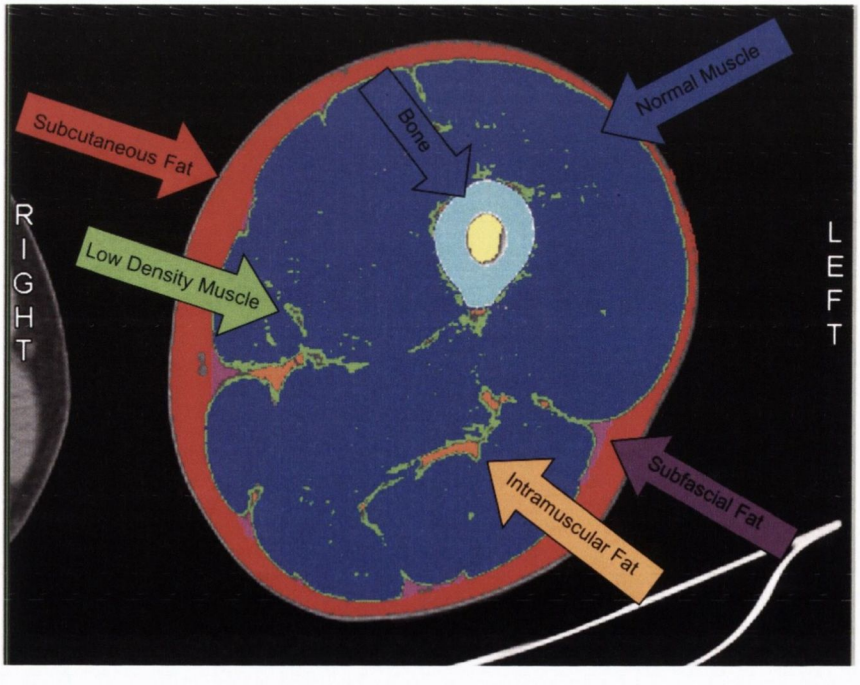


Figure 3.6 Typical SlicOmatic CT image depicting composition of mid-thigh

3.2.5 Specific muscle power and strength

The absolute leg extensor peak power and 1RM values obtained were adjusted for total muscle CSA to yield estimates of specific peak power (W/cm^2) and specific leg extensor strength (N/cm^2) (Goodpaster et al. 2001; Reid et al. 2008).

3.2.6 Muscle biopsy and single muscle fibre experiments

Muscle biopsies were taken from the vastus lateralis muscle at the level of the CT scan using a 5-mm Duchenne biopsy needle and suction (Figure 3.7) (Bergström 1962; Evans et al. 1982). All biopsies were performed by the study Principal Investigator (Roger Fielding, Ph.D.) with suction and general assistance for each biopsy procedure performed by a research technician (Kieran Reid, M.Sc). The specimen was placed in relaxing solution (see below) at 4°C within 1-2 min of being obtained. Bundles of ~30 fibre segments were dissected free from the samples and then tied with surgical silk to glass capillary tubes at slightly stretched lengths. The fibre segments were chemically skinned for 24 h in relaxing solution containing 50% (vol/vol) glycerol at 4°C and were subsequently stored at –20°C for up to 4 wk before use.

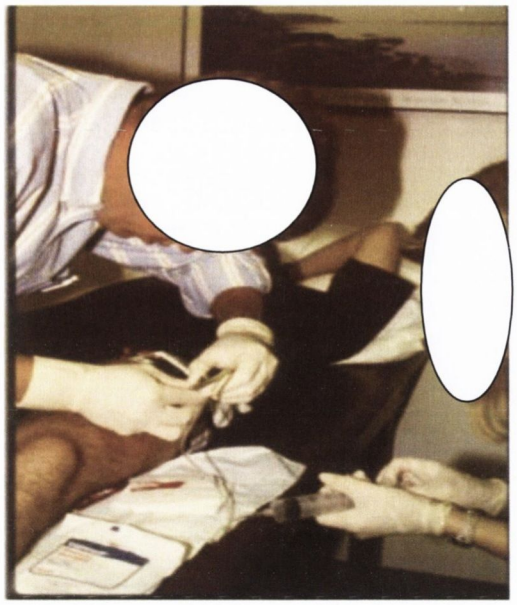
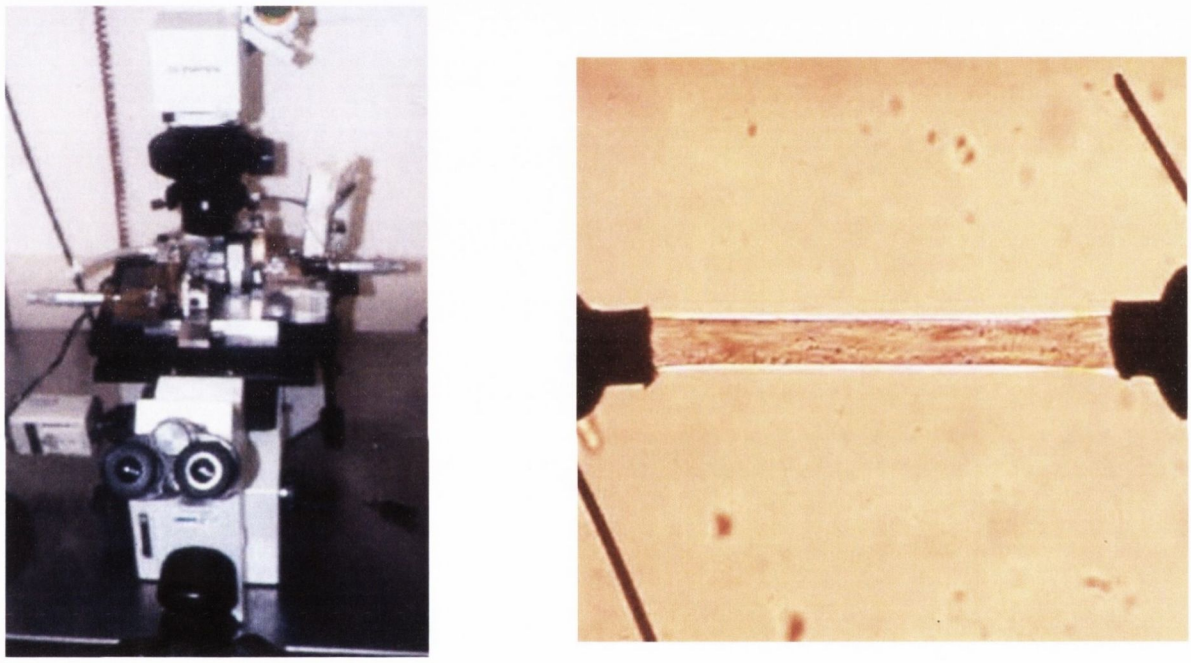


Figure 3.7 Representative image of percutaneous needle biopsy of the vastus lateralis muscle

All muscle fibre experiments were conducted within the Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, USA, under the supervision of Walter Frontera, M.D., Ph.D. Results are generated from the average number of muscle fibres studied per participant from each study group. This contrasts with previous studies that have presented data on single fibre experiments based on the total overall number of muscle fibres evaluated from a study group (Frontera et al. 2008; Trappe et al. 2003). A detailed explanation of the general methods used for the single muscle fibre experiments in this thesis has been published by others (Larsson and Moss 1993). On the day of an experiment, fibre segments were placed for 30 min in relaxing solution containing 0.5% Brij-58 (polyoxyethylene 20 cetyl ether; Sigma, St. Louis, MO) before mounting in an experimental apparatus, similar to that described previously (Moss 1979) (Figure 3.8). A fibre segment length of 1-2 mm was left exposed to the solution

between connectors leading to a force transducer (model 400A; Aurora Scientific, Aurora, Ontario, Canada) and a DC torque motor (model 308B; Aurora Scientific). The apparatus was mounted on the stage of an inverted microscope (Olympus IX70, Tokyo, Japan). While the fibre segments were in relaxing solution, sarcomere length (SL) was set to 2.75-2.85 μm by adjusting the overall segment length (Figure 3.8).



A B

Figure 3.8 Single fibre experimental apparatus (A) and single human fibre (B)

The sarcomere length, the segment diameter, and the length of segment between the connectors were measured with an image analysis system (Image-Pro Plus, Media Cybernetics, Silver Spring, MD). Fibre depth was measured by recording the vertical displacement of the microscope nosepiece while focusing on the top and bottom surfaces of the fibre. The focusing control of the microscope was used as a micrometer. The coefficient

of variation for three measurements done by the same observer is 0.5% for diameter and 3.7% for depth (Frontera et al. 2003). Fibre cross-sectional area was calculated from the diameter and depth, assuming an elliptical circumference. Maximum force (P_0) was adjusted for fibre cross-sectional area after adjusting fibre area for the 20% swelling that is known to occur during skinning (Godt and Maughan 1977; Moss 1979).

Relaxing and activating solutions contained (in mM) 4 MgATP, 1 free Mg^{2+}, 20 imidazole, 7 EGTA, 14.5 creatine phosphate, and KCl to adjust the ionic strength to 180 mM. The pH was adjusted to 7.0. The concentrations of free Ca^{2+} were 10^{-9} M (relaxing solution) and $10^{-4.5}$ M (maximum activating solution) and are expressed as pCa (–log [Ca^{2+}]). Apparent stability constants for Ca^{2+}-EGTA were corrected for temperature (15°C) and ionic strength (180 mM) (Fabiato 1988). A computer program was used to calculate the concentrations of each metal, ligand, and metal-ligand complex (Fabiato 1988).

Immediately preceding each activation, the fibre was immersed for 10–20 s in a solution with a reduced Ca^{2+}-EGTA buffering capacity. This solution was identical to the relaxing solution except that EGTA was reduced to 0.5 mM, which resulted in a faster attainment of steady tension during subsequent activation. P_0 was calculated as the difference between the total force in activating solution (pCa 4.5) and the resting tension measured in the same segment while in the relaxing solution. All contractile measurements were carried out at 15°C. Fibres with visible tears and fibres demonstrating a loss of force >10% of the baseline value were not used for the analysis. Maximum unloaded shortening velocity (V_0) was measured using the slack test (Edman 1979).

After mechanical measurements, each fibre was placed in SDS sample buffer in a plastic microfuge tube and stored at –20°C for up to 1 wk or at –80°C if the gels were to be run later. The myosin heavy chain (MyHC) composition of single fibres was determined by SDS-PAGE (Laemmli 1970). The acrylamide concentration was 4% (wt/vol) in the stacking gel and 6% in the running gel, and the gel matrix included 30% glycerol. Sample loads were kept small (equivalent to ~0.05 mm of fibre segment) to improve the resolution of the MyHC bands (types I, IIA, IIB). The conditions in which the SDS-PAGE were run include constant current (24 mA) for 5.5 h. Proteins were identified using a combination of human myosins from vastus lateralis muscles and from reports in the literature (Figure 3.9) (Larsson and Moss 1993).

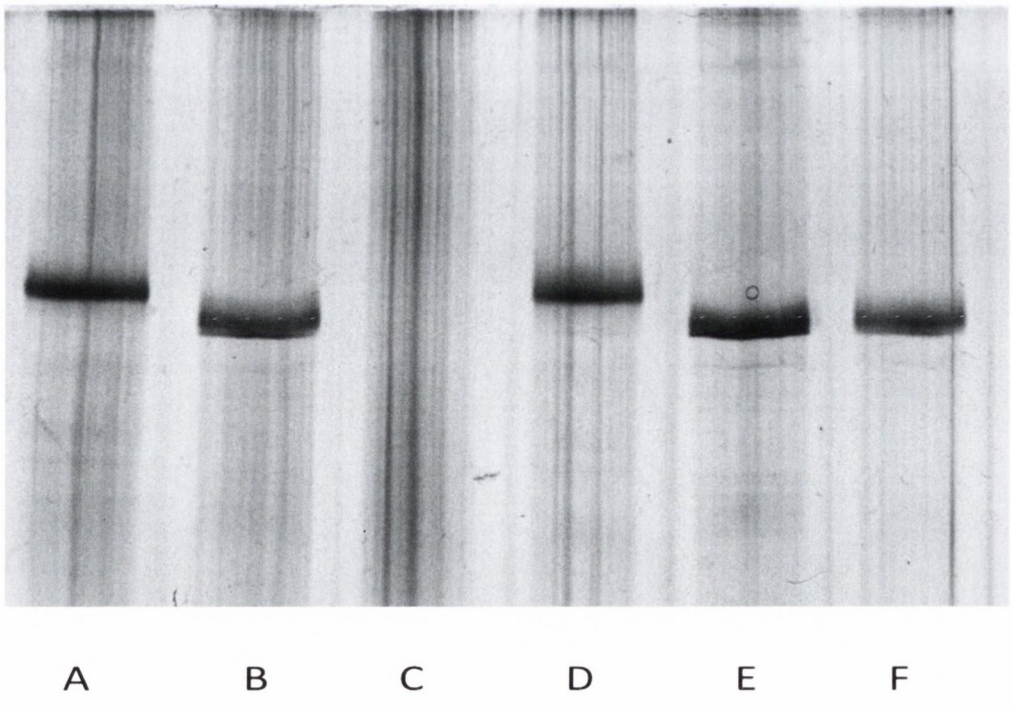


Figure 3.9 Representative SDS-PAGE gel of human single muscle fibres for MyHC identification from a healthy older subject. *Lanes B, E and F correspond to type I fibres. Lanes A and D correspond to type IIa fibres. Lane C is empty.*

3.2.7 Statistical analysis and statistical power estimates

Data analysis was conducted using SAS statistical software (Version 9.2, SAS Institute Inc., Cary, North Carolina) and all variables were examined for normality both graphically and statistically. A log transformation was used for those variables where normality did not hold. A two-way analysis of variance test was used to compare differences between the three study groups and gender groups. For each outcome, the models included gender, study group and their interaction as covariates. An analysis of whether the differences among groups were equivalent for men and women was then performed through regression models incorporating the interaction term between gender and group. A test for the interaction term provided a measure of whether men and women differed within their differences across groups. If the interaction term was significant, differences between the gender groups were estimated at each group level; otherwise an overall gender effect was estimated. Exploratory, post hoc Pearson correlation analyses were used to assess the relationships between intrinsic muscle fibre properties and whole muscle parameters in males and females. Data is presented as mean ± SD and statistical significance was accepted at $P \leq 0.05$. Marginal statistical significance was accepted at $P < 0.1$.

We evaluated statistical power for this study by focusing on the primary outcome measure, leg extensor muscle power. For sample size estimates and power calculations, we examined a two-group contrast using a two-sample t test with alpha equal to 0.017 (conservatively, as there were 3 groups). From preliminary studies of leg extensor power, we estimated the standard deviation to be 100 watts and the estimated meaningful between-group differences (healthy middle-ages vs. healthy older; healthy older vs. mobility-limited older) to be greater than or equal to 100 watts. With sample size projections of thirty individuals in each study

group, we found that we had 60% power to detect a difference of 0.7 standard deviation unit, 74% power to detect a difference of 0.8 standard deviation unit, 84% power to detect a difference of 0.9 standard deviation unit and 92% power to detect a difference that is equivalent to one standard deviation unit (100 watts).

3.3 Results

3.3.1 Study Participants

A total of 93 (46 males) subjects were enrolled into the respective study groups: healthy middle-aged (n = 31, 14 males); healthy older (n = 28, 16 males); mobility-limited older (n = 34, 16 males). Descriptive characteristics are displayed in Table 3.1. Age was significantly greater among mobility-limited older participants (77.8 ± 4.5 yrs) compared to both healthy middle-aged (47.2 ± 4.8 yrs, $P < 0.001$) and healthy older participants (74.0 ± 3.6 yrs, $P = 0.009$) ($F = 456.98$, $P < 0.001$). Mobility-limited individuals had significantly lower SPPB scores (7.9 ± 1.3) compared to healthy middle-aged (11.7 ± 0.5) and healthy older subjects (11.0 ± 0.9), ($P < 0.001$). No significant group x gender interaction was evident for any of the baseline general characteristics ($P > 0.1$). A significant overall gender effect was found for BMI, with males having consistently higher BMI values ($P = 0.01$).

Table 3.1 Subject characteristics

Variable	Healthy Middle-Aged (Male: 14, Female: 17)		Healthy Older (Male: 16, Female 12)		Mobility-Limited Older (Male: 16, Female 18)	
Age, yrs *	46.5 ± 4.5	47.8 ± 5.1	73.8 ± 3.5	74.3 ± 3.9	78.9 ± 3.8	76.8 ± 5.0
BMI, $kg/m^{2\dagger}$	26.5 ± 3.2	25.1 ± 2.7	26.0 ± 3.1	22.0 ± 7.8	26.8 ± 2.5	25.9 ± 3.7
Medical Diagnoses, n	-	-	-	-	2.6 ± 2.3	1.8 ± 1.4
Number of Medications, n	-	-	-	-	3.6 ± 2.4	2.4 ± 2.1
SPPB score *	11.8 ± 0.4	11.7 ± 0.5	11.2 ± 0.8	10.8 ± 0.9	7.9 ± 1.2	8.0 ± 1.4

Values are mean ± SD. BMI: body mass index; SPPB: Short Physical Performance Battery
* significant overall group differences
† significant overall gender difference

3.3.2 Lower extremity muscle strength, power and velocity

Mobility-limited older participants had significantly lower (all $P < 0.001$) values for leg extensor peak power ($F = 26.10$, $P < 0.001$), contraction velocity ($F = 23.61$, $P < 0.001$), and 1RM strength ($F = 13.80$, $P < 0.001$) compared to both healthy groups (Table 3.2). Healthy older adults also had significantly lower measures of peak power ($P < 0.001$), contraction velocity ($P = 0.04$) and 1RM strength ($P < 0.001$) compared to healthy middle-aged subjects. There was a significant group x gender interaction for leg extensor peak power ($P < 0.001$). The differences between males and females for peak power were 274 ± 51 W in healthy middle-aged ($P < 0.001$), 383 ± 53 W ($P < 0.001$) in healthy older and 137 ± 49 W ($P < 0.001$) in mobility-limited older participants. An overall gender difference was evident for peak power contraction velocity ($P < 0.001$). A marginally significant group x gender interaction for leg extensor strength ($P = 0.06$) was observed. The magnitude of the respective differences between males and females for 1RM strength were 513 ± 96 N in healthy middle-aged ($P < 0.001$), 737 ± 102 N ($P < 0.001$) in healthy older and 403 ± 95 N ($P = 0.001$) in mobility-limited older participants.

Table 3.2 Measures of leg extensor muscle power, contraction velocity and 1RM strength

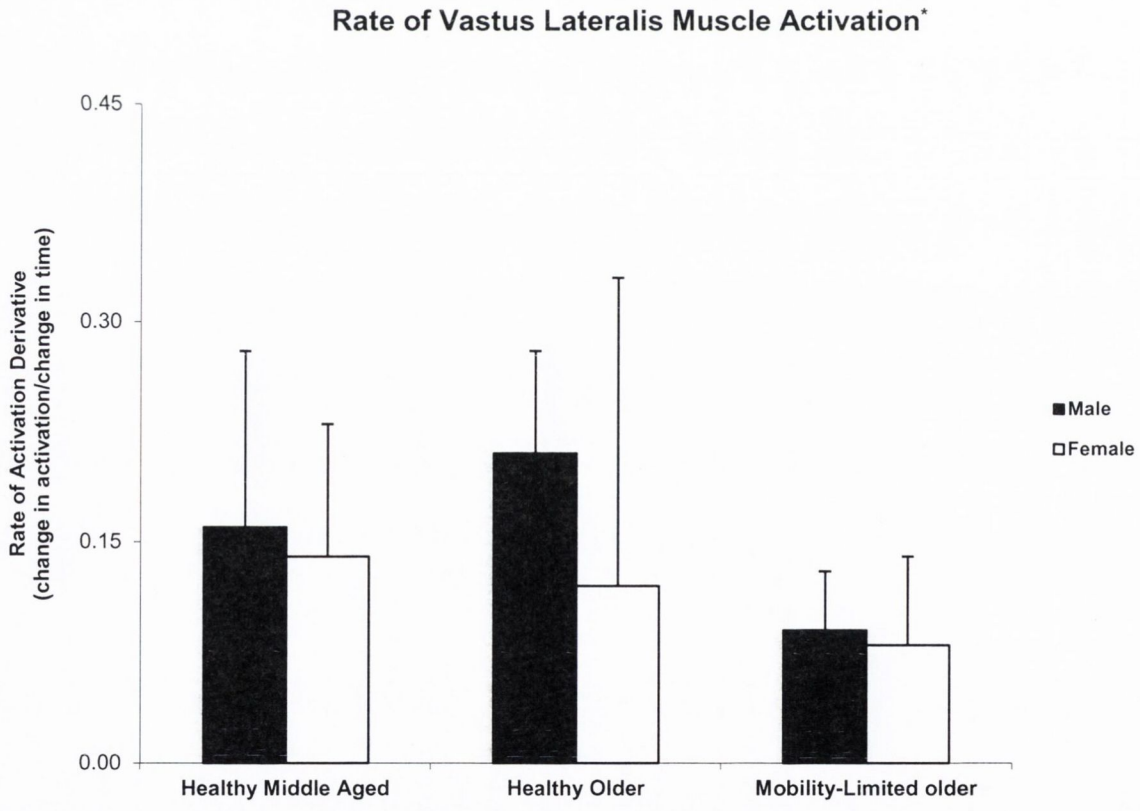
	Healthy Middle-Aged (Male: 14, Female: 17)		Healthy Older (Male: 16, Female 12)		Mobility-limited Older (Male: 16, Female 18)	
Peak Power, W*†	724 ± 213	450 ± 124	640 ± 146	256 ± 71	365 ± 159	228 ± 77
Contraction Velocity, m/s*‡	0.53 ± 0.15	0.47 ± 0.11	0.51 ± 0.11	0.37 ± 0.09	0.37 ± 0.12	0.32 ± 0.08
1RM Strength, N*§	1591 ± 265	1078 ± 243	1555 ± 280	818 ± 229	1183 ± 387	780 ± 147

Values are mean ± SD.
* significant overall group differences
† significant group x gender interaction
‡ significant overall gender difference
§ marginally significant group x gender interaction

3.3.3 Neuromuscular activation

Figure 3.10 displays the vastus lateralis neuromuscular activation data. Mobility-limited older participants had reduced levels of muscle activation when compared to healthy middle-aged (- 47.7%, P = 0.05) and healthy older (- 52.9%, P = 0.02) participants *(F* = 2.35, P < 0.05). Rate of muscle activation was similar between both healthy groups (P > 0.1). No significant group x gender interaction (P > 0.1) or a significant overall gender effect (P > 0.1) was evident.

Figure 3.10 Rate of vastus lateralis muscle activation*
Values are mean ± SD.
** significant overall group differences.*



3.3.4 Muscle size and composition

Mid-thigh muscle size and composition values are reported in Table 3.3. Significant group effects were found for total mid-thigh CSA ($F = 5.33$, $P < 0.001$), total muscle CSA ($F = -7.22$, $P < 0.001$), total normal density muscle CSA ($F = 13.26$, $P < 0.001$) and total intermuscular adipose tissue CSA ($F = 5.20$, $P < 0.001$). Healthy middle-aged participants had significantly larger mid-thigh CSA compared to healthy older ($P < 0.001$) and mobility-limited older participants ($P < 0.001$). Mobility-limited elders had significantly lower total muscle CSA compared to healthy middle-aged subjects (- 24.9%, $P < 0.001$) and healthy older participants (- 13.1%, $P = 0.02$). The mobility-limited group also exhibited significantly lower normal density muscle CSA and higher deposits of intermuscular adipose tissue compared to both healthy groups ($P < 0.001$). Healthy middle-aged subjects had significantly greater levels of total muscle CSA (13.6%, $P < 0.001$) and normal density muscle CSA ($P < 0.001$) compared to healthy older participants. No significant differences in intermuscular adipose tissue CSA were found between healthy middle-aged and healthy older participants ($P > 0.1$). A marginally significant group x gender interaction was elicited for total mid-thigh CSA ($P = 0.07$), with the differences between males and females across the 3 respective study groups being 5.9 cm^2 ($P = 0.7$), 7.4 cm^2 ($P = 0.6$) and -29.1 cm^2 ($P = 0.02$), respectively. Overall gender effects were evident for each of the remaining measures of mid-thigh muscle composition ($P < 0.001$). Mobility-limited older males and females had equivalent differences in total muscle CSA (- 24.2% vs. - 25.7%, respectively) compared to healthy middle-aged males and females.

Table 3.3 Comparison of mid-thigh muscle area & composition using computed tomography

	Healthy Middle-Aged (Male: 14, Female: 17)		Healthy Older (Male: 16, Female 12)		Mobility-limited Older (Male: 16, Female 18)	
Total mid-thigh CSA, cm^{2}*†	203 ± 36	197 ± 30	176 ± 20	168 ± 41	161 ± 24	190 ± 53
Total muscle CSA, cm^{2} *‡	146 ± 26	108 ± 18	129 ± 15	82.5 ± 10.0	111 ± 13	80.0 ± 17.4
Total normal density muscle CSA, cm^{2}*‡	121 ± 22	88.1 ± 17.7	102 ± 15	64.6 ± 10.0	84.3 ± 21.5	57.1 ± 13.6
Total low density muscle CSA, cm^{2}‡	25.2 ± 8.7	19.6 ± 7.9	26.8 ± 8.0	17.9 ± 7.4	26.1 ± 9.2	22.8 ± 7.5
Total subcutaneous adipose tissue CSA, cm^{2}‡	49.2 ± 19.1	79.5 ± 29.9	38.6 ± 11.9	77.7 ± 32.4	40.5 ± 17.0	99.0 ± 38.1
Total intermuscular adipose tissue CSA, cm^{2} *‡	3.1 ± 1.6	2.5 ± 1.7	3.7 ± 2.6	2.2 ± 1.6	4.6 ± 2.3	3.9 ± 1.5

Values are mean ± SD. CSA, cross sectional area.
* significant overall group differences
† marginally significant group x gender interaction
‡ significant overall gender difference

3.3.5 Specific muscle power and strength

Figures 3.11 and 3.12 display the muscle quality calculations. Mobility-limited older participants exhibited significantly reduced specific leg extensor peak power compared to both healthy middle-aged ($P < 0.001$) and healthy older participants ($P < 0.001$) ($F = 15.59$, $P > 0.001$). Specific power values were similar between healthy groups ($P > 0.1$). A significant group x gender interaction was elicited for specific peak power ($P = 0.04$). The differences between males and females for specific leg extensor power were 0.88 ± 0.39 W/cm^2 in healthy middle-aged ($P = 0.03$), 1.9 ± 0.4 W/cm^2 ($P < 0.001$) in healthy older and 0.45 ± 0.38 W/cm^2 ($P > 0.1$) in mobility-limited older participants. Specific leg extensor strength (Figure 3.12) was similar across groups ($P > 0.1$) with no group x gender effect ($F = 1.29$, $P > 0.1$), although a significant overall gender difference was found ($P = 0.01$).

Figure 3.11 Specific peak power*†.
Values are mean ± SD.
** significant overall group differences. † significant group x gender interaction*

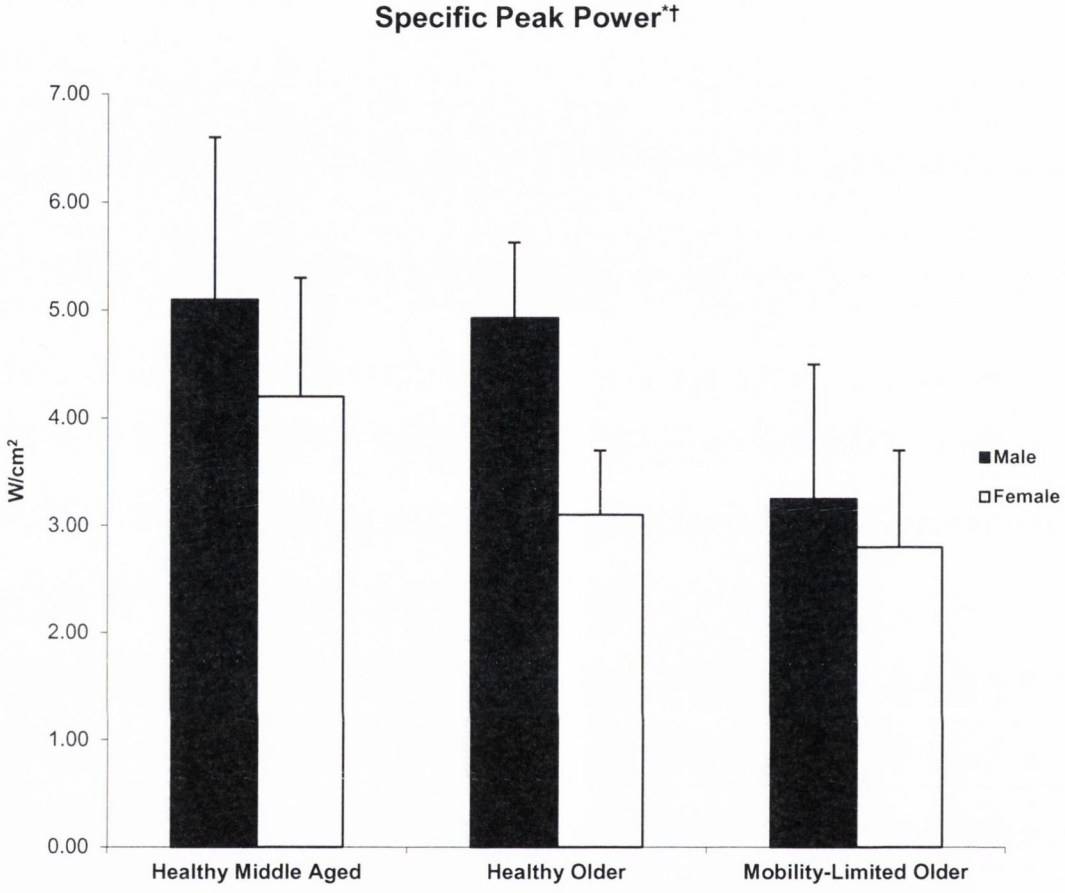
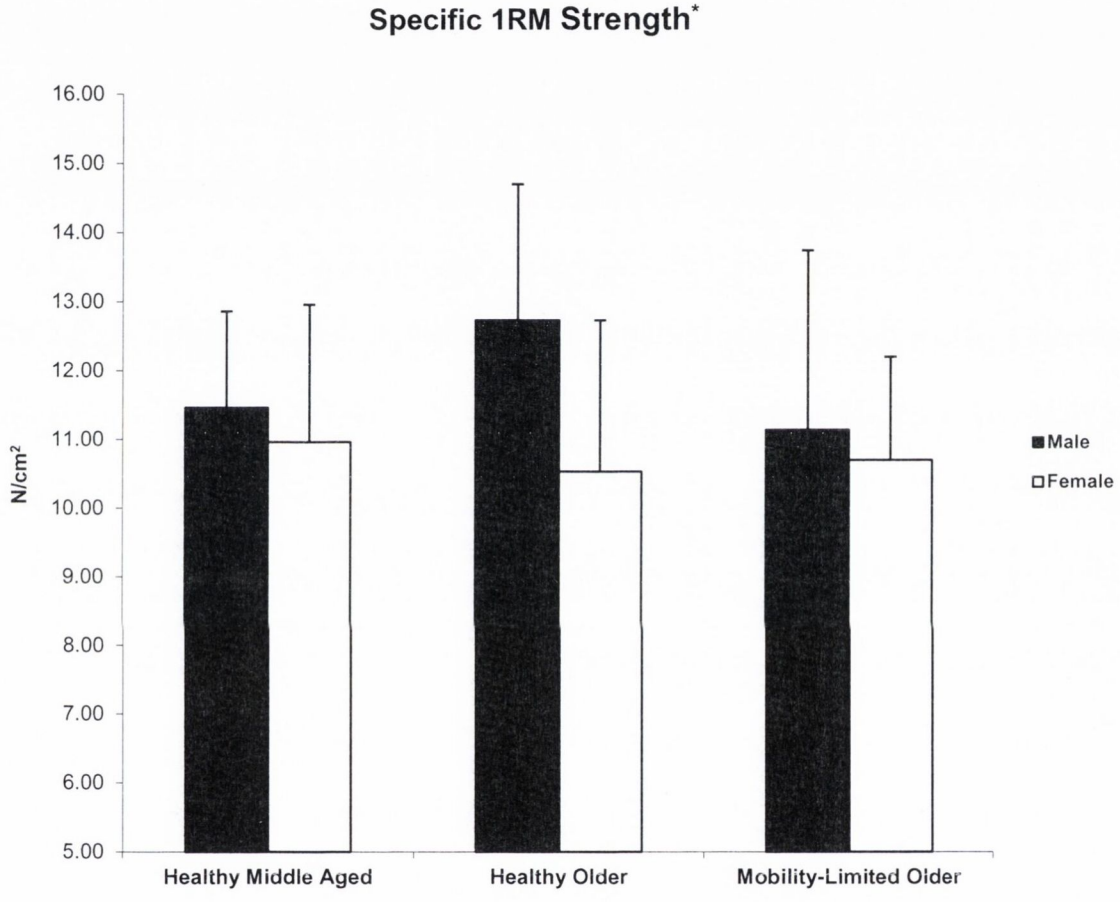


Figure 3.12 Specific 1RM strength*.
*Values are mean ± SD. * significant overall gender difference*



3.3.6 Muscle biopsy and single muscle fibre experiments

The findings from the single muscle fibre experiments are presented in Tables 3.4 and 3.5. An average of 13.0 ± 4.4 type I single fibres were studied in healthy middle-aged participants, 14.2 ± 3.2 in healthy older adults and 13.2 ± 3.4 in mobility-limited elders. The average number of type IIA single fibres studied was 6.7 ± 2.8 in healthy middle-aged participants, 4.1 ± 4.0 in healthy older and 3.5 ± 2.2 in mobility-limited elders. There was a significant group effect for type I fibre peak power ($F = 11.54$, $P < 0.001$), with healthy middle-aged participants demonstrating higher fibre peak power values compared to healthy older ($P = 0.02$) and mobility-limited older participants ($P = 0.01$). No significant group, group x gender or overall gender effects were found for the other type I fibre properties reported ($P \geq 0.1$) or for any of the type IIA fibre size or contractile properties displayed in Table 3.5 ($P > 0.1$). The additional exploratory, post-hoc correlation analysis between intrinsic fibre properties and whole muscle parameters (all groups combined) revealed significant associations between type I fibre P_0 and total muscle CSA ($r = 0.48$, $P < 0.001$) and 1RM strength ($r = 0.46$, $P < 0.001$) in females, with a weaker association found between type I fibre P_0 and leg extensor strength in males ($r = 0.33$, $P = 0.04$). For type I fibre peak power, stronger correlations were elicited with total muscle CSA ($r = 0.46$, $P = 0.01$), leg extensor peak power ($r = 0.59$, $P < 0.001$) and leg extensor strength ($r = 0.49$, $P < 0.001$) in females, with no significant associations found in males. No consistent relationship was elicited between any type IIA fibre contractile property and whole muscle CSA, power or strength.

Table 3.4 Type I single muscle fibre size and contractile properties

	Healthy Middle-Aged (Male: 12, Female: 11)		Healthy Older (Male: 16, Female 7)		Mobility-Limited Older (Male: 12, Female 13)	
CSA, μm^2	5334 ± 1254	4880 ± 993	4999 ± 931	4407 ± 1174	4989 ± 1152	4747 ± 887
P_0, μN	578 ± 137	520 ± 129	512 ± 79	453 ± 141	479 ± 142	478 ± 111
SF, N/cm^2	16.5 ± 4.6	15.8 ± 1.4	15.4 ± 2.9	15.9 ± 4.1	14.7 ± 4.5	15.4 ± 3.6
V_0, FL/s	0.60 ± 0.16	0.60 ± 0.09	0.62 ± 0.13	0.65 ± 0.21	0.68 ± 0.18	0.62 ± 0.22
Peak Power, μN*FL/s*	24.6 ± 10.5	22.8 ± 11.0	19.7 ± 5.8	15.7 ± 8.9	18.1 ± 8.1	17.2 ± 4.3
Specific Power, kN/m^2*FL/s	7.2 ± 4.0	6.5 ± 2.2	6.1 ± 2.2	5.4 ± 2.6	5.7 ± 2.0	5.7 ± 1.8

Values are mean ± SD. CSA, cross sectional area; P_0, peak force; SF, specific force; V_0, shortening velocity
* significant overall group differences

Table 3.5 Type IIA single muscle fibre size and contractile properties

	Healthy Middle-Aged (Male: 11, Female: 11)		Healthy Older (Male: 14, Female 6)		Mobility-limited Older (Male: 13, Female 9)	
CSA, μm^2	5354 ± 1411	4016 ± 1312	4902 ± 1500	4619 ± 949	4055 ± 794	4110 ± 1646
P_0, μN	481 ± 217	411 ± 124	428 ± 151	457 ± 155	332 ± 87	391 ± 191
SF, N/cm^2	13.9 ± 6.5	14.0 ± 2.1	13.0 ± 3.8	14.9 ± 6.3	12.7 ± 3.8	15.7 ± 8.3
V_0, FL/s	1.3 ± 0.2	1.3 ± 0.3	1.5 ± 0.6	1.4 ± 0.5	1.6 ± 0.6	1.2 ± 0.6
Peak Power, μN*FL/s	54.6 ± 27.8	44.4 ± 16.3	43.1 ± 21.7	47.1 ± 30.5	36.4 ± 16.6	36.7 ± 12.5
Specific Power, kN/m^2*FL/s	17.3 ± 11.1	16.4 ± 4.8	13.2 ± 6.5	16.2 ± 12.3	16.2 ± 7.6	18.3 ± 17.5

Values are mean ± SD. CSA, cross sectional area; P_0, peak force; SF, specific force; V_0, shortening velocity

3.4 Discussion

Limited knowledge exists on the underlying mechanisms contributing to the decline in muscle power with advancing age. This is the first study to compare the major physiological and gender determinants of lower extremity muscle power between healthy middle-aged, healthy older and mobility-limited older adults and provides new insight into the major characteristics associated with the reduction in muscle power and loss of mobility. The main observations are: 1) mobility-limited older adults have significant deficits in lower extremity muscle power compared to healthy middle-aged and healthy older adults; 2) muscle power impairments among mobility-limited elders are associated with concomitant reductions in leg extensor muscle strength, contraction velocity, muscle size, muscle quality and neuromuscular activation; 3) mobility-limited older adults demonstrate relative preservation and maintenance of intrinsic single muscle fibre size and contractile function despite the deficits observed at the whole muscle level; 4) male mobility-limited elders exhibit greater impairments in leg extensor muscle power and specific muscle power output compared to females. Additional notable findings from our analyses include the inherent similarities in muscle quality and neuromuscular function between healthy middle-aged and healthy older participants, despite an average age difference of ~ 25 years.

3.4.1 Muscle quantity and quality

Our cross sectional analyses using CT technology and muscle attenuation characteristics revealed that mobility-limited elders had significantly lower whole muscle and normal density muscle CSA and greater intermuscular adipose tissue deposits compared to both healthy groups. Previous findings from the Health ABC cohort have shown that the attenuation of skeletal muscle decreases with age concomitant with an increase in

intermuscular fat accumulation among high-functioning older adults (Delmonico et al. 2009; Goodpaster et al. 2001). Our data extend these observations in mobility-limited older adults with significant muscle power impairments. Furthermore, the significant deficits in specific leg extensor power among the mobility-limited participants suggest that the attenuation of skeletal muscle is associated with impairments in muscle power and mobility limitations independent of the reduction in muscle CSA. This discrepancy between the reduction in muscle power and muscle size indicates that other factors, distinct from muscle atrophy, are major contributors to the deficits in muscle power impairments among mobility-limited participants. Conversely, the similarities in specific leg extensor strength across all participants in the current study suggests that the preservation of muscle strength with aging has greater dependence on the maintenance of muscle mass in both healthy and mobility-limited individuals. Previous investigations have shown the strong association between the loss of muscle mass and muscle strength with aging, however, many of the older participants studied were healthy or reported no limitations in physical functioning (Delmonico et al. 2009; Frontera et al. 1991; Goodpaster et al. 2006).

3.4.2 Neuromuscular activation

Peak muscle power represents the integration of neural and muscular function. The present study provides evidence for the role of neuromuscular activation as a potential modulator of the age-related decline in muscle power output. As shown in Figure 3.10, vastus lateralis neuromuscular activation was significantly lower among mobility-limited elders compared to both healthy groups. Previous studies have shown that several underlying mechanisms can contribute to impairments in neuromuscular function: the loss of motor neurons (Lexell 1997); decreased maximal motor unit firing rates (Kamen et al. 1995); and aberrant patterns

of intermuscular coordination (Hakkinen et al. 1998a). It is plausible that the activation impairments observed in the mobility-limited participants impact movement velocity and muscle coordination leading to a reduction or a longer time to reach peak force, and thus a decline in muscle power generation. In separate analyses performed on the current study participants, we have previously demonstrated using surface EMG on the quadriceps and hamstring musculature that mobility-limited elders have significant impairments in torque, power and agonist muscle activation during maximal isokinetic dynamometry testing (Clark et al. 2010). Similarly, we have also shown that composite measures of pre-movement time (duration between EMG onset and movement onset) and the rate of EMG rise (duration and relative amplitude of muscle activation) of the quadriceps musculature during maximal leg extensor power testing were markedly lower in mobility-limited older adults compared to both healthy groups (Clark et al. 2011). Overall, our findings indicate that impairments in neuromuscular function may be critical determinants of muscle power deficits and subsequent mobility limitations among older adults.

3.4.3 Single fibre contractile properties

Previous studies investigating intrinsic fibre properties of skeletal muscle with aging have been limited by small sample sizes and selection bias through the inclusion of relatively healthy and physically active older subjects (Frontera et al. 2000a; Frontera et al. 2008; Frontera et al. 2000b; Trappe et al. 2003). The current study overcomes these limitations using larger and more heterogenous study groups and we also report novel information on specific force and single fibre contractile properties from mobility-limited elders. Despite the significant reductions in whole muscle performance, size and quality in mobility-limited participants, our findings suggest that the surviving muscle fibres in this population are

maintained and single fibre contractile performance (force production, single fibre quality) is preserved. A similar disassociation between changes in muscle performance at the whole muscle level compared to the single fibre level with aging has been reported previously in a longitudinal investigation of 12 older, healthy and physically active participants (Frontera et al. 2008). In the present study, there was also corresponding preservation of single muscle fibre size and contractile function in healthy older participants compared to healthy middle-aged participants, despite significant differences in leg extensor peak power, strength and contraction velocity but notable similarities in whole muscle quality and neuromuscular activation. Although a specific timecourse for surviving muscle fibre preservation with aging has yet to be determined, these data suggest that adaptations may occur within the surviving fibres of healthy older populations in response to emerging deficits in whole muscle performance with advancing age.

Among the contractile properties evaluated, type I fibre peak power was significantly higher in healthy middle-aged participants compared to both older groups, however these differences were not apparent after normalisation for fibre size. This observation is consistent with previous studies reporting the elimination of age-related differences in single fibre contractile performance after adjustment for fibre or cell size (Frontera et al. 2000b; Trappe et al. 2003).

3.4.4 Gender

Our gender analyses revealed that males generally exhibited higher values for all parameters measured except for mid-thigh CSA and subcutaneous adipose tissue. However, significant group x gender interactions were elicited for both leg extensor peak power and specific leg

extensor peak power and further investigation revealed that mobility-limited male participants had greater decrements in absolute measures of peak muscle power and specific muscle power.

There may be several plausible explanations for these novel gender-specific differences. Given that mobility-limited males and females had equivalent reductions in whole muscle CSA compared with healthy middle-aged males and females, our data suggest that additional and divergent gender-specific physiologic mechanisms influence the loss of muscle power among older adults with mobility impairments. For the first time, we have demonstrated that mobility-limited females exhibit maintenance and preservation of the intrinsic quality of their single muscle fibres. Furthermore, female mobility-limited elders showed preservation of type IIA fibre CSA and notable increases in specific force and specific power of these fibres (Table 3.5). To our knowledge, this is the largest study to-date to quantify gender related differences and compare interrelationships between measures of whole muscle performance and the properties of single muscle fibres. In addition, female gender was also associated with a stronger overall relationship between the contractile properties of type I fibres and several of the whole muscle performance measures assessed.

The attenuated differences in specific muscle power among mobility-limited females also further indicate that neuromuscular factors are important mechanisms contributing to the decline of muscle power among older males with mobility limitations. Although no statistically significant gender differences were revealed for vastus lateralis muscle activation, it is evident from our data (Figure 3.12) that male mobility-limited participants had greater deficits in neuromuscular activation compared to females. An additional

mechanism for this gender effect not quantified in this study may include unmeasured hormonal factors and sex-specific alterations in circulating steroid hormones (Macaluso and De Vito 2004). A recent cross-sectional population based study reported that reduced levels of sex hormones were associated with impaired mobility and lower muscle performance in older men, but not in older women (Schaap et al. 2005).

3.4.5 Study limitations

One of the major strengths of this study was the use of specific eligibility criteria that facilitated a comparative assessment of the determinants of muscle power among three distinct populations. We also incorporated the use of robust, well-established and intricate measurement techniques and our study also had adequate statistical power to detect differences between groups as we attained the enrollment goals for the pre-study sample size estimates. The comparison of older adults to middle-aged adults (rather than young adults) also allowed for the identification of the pertinent mechanisms contributing to muscle power loss and mobility limitations across a more specific age range. However, the major limitation of this study is the cross-sectional design as it precludes definitive causal inferences about muscle power deficits and any of the physiological variables measured. In addition, the current study design assumes that the reported age-related losses in muscle power, contributory mechanisms and subsequent mobility limitations are linear in occurrence and our analyses cannot quantify any temporal changes or adequately identify any anisotropic adaptive mechanisms that may be compensating for reductions in muscle power. Another limitation of this study is that the mobility-limited participants were significantly older than the healthy older group (~ 3.8 yrs), which may have influenced the overall study findings. Furthermore, several additional factors that may contribute to the

age-associated decline and gender differences in skeletal muscle performance were not assessed in this study. These include physical activity levels, caloric and protein intake, and the influence of additional circulatory mediators such inflammatory factors and protein synthesis activators. It is also important to recognise that the properties of skinned muscle fibres assessed in vitro during the single muscle fibre experiments may be different from the physiological properties of living fibres in vivo. Two final limitations of this study relate to the rate of activation experiments. First, no test-retest measurements were performed for neuromuscular activation testing and therefore no reliability parameters for this technique can be estimated. Second, the normalisation procedure may lead to underestimation of activation deficits in older adults who are not fully capable of voluntarily activating the quadriceps during an isometric contraction. However, previous evidence that we have reported from these same participants indicates that all groups produced similar vastus lateralis activation during isometric contractions using the currently presented leg press task (Clark et al. 2011), as well as during an isolated knee extension task (Clark et al. 2010). This is consistent with other studies that have found little, if any, deficits in voluntary activation amplitude during isometric contractions with aging (De Serres and Enoka 1998; Kent-Braun and Ng 1999). Longitudinal analysis of the physiological mechanisms contributing to the loss of muscle power and mobility limitations in the same cohort of participants would provide more definitive evidence.

3.5 Conclusion

In conclusion, this study has provided a comprehensive analysis of the physiological determinants of lower extremity muscle power in healthy middle-aged, healthy older and mobility-limited older adults. In addition to reductions in muscle mass, the significant

deficits in muscle power and subsequent loss of mobility with advancing age are associated with impairments in neuromuscular activation and a concomitant reduction in muscle quality. The dissociation between age related changes at the whole muscle and single fibre level indicate that minimal single fiber deterioration occurs in an attempt to preserve overall muscle function even among older adults with overt mobility impairments. Additional longitudinal studies should examine and delineate the contributions and interrelationships between neuromuscular function, muscle quality, single fibre properties and their gender-specific associations with muscle power deficits and the subsequent loss of mobility with advancing age

Section A

Chapter 4

Longitudinal decline of lower extremity muscle power in healthy and mobility-limited older adults: influence of muscle mass, strength, composition, neuromuscular activation and single fibre contractile properties

4.1 Introduction and Study Rationale

The ability to successfully generate skeletal muscle power, defined as the product of dynamic muscular force and contraction velocity, is critical for activities that require human movement and locomotion (Bassey et al. 1992; Reid and Fielding 2012). Among older adults, a decline in lower extremity muscle power output with advancing years has important implications for independent physical functioning in later life. Compared to traditional measures of muscle performance such as muscle strength (the ability to generate maximal force), impairments in peak lower extremity muscle power are superior predictors of functional tasks involving mobility and ambulation (Bassey et al. 1992; Bean et al. 2002b; Bean et al. 2003; Cuoco et al. 2004; Foldvari et al. 2000; Suzuki et al. 2001). Lower extremity muscle power is also a more influential determinant of falls, which accelerate other adverse outcomes in older populations, including disability and mortality (Moreland et al. 2004; Skelton et al. 2002).

Cross-sectional studies have described a multitude of physiological mechanisms that are associated with reduced muscle power output in aging humans. The well described decline in skeletal muscle size that occurs with aging, and changes in the properties of remaining muscle fibres, contribute to reduced muscle power in older adults (Brooks and Faulkner 1994; Doherty 2003). In particular, the selective atrophy and loss of type IIA muscle fibres with advancing age, which have the ability to generate four-six times more power output than type I fibres, may severely limit the successful development of dynamic muscle power during human movement (Larsson et al. 1979; Martin et al. 2000; Trappe et al. 2003). Alterations in neural function, such as the loss of motor neurons, decreased maximal motor unit firing rates and impaired neuromuscular activation inhibit muscle power output in older

adults (Aagaard et al. 2010; Clark and Fielding 2012; Clark et al. 2010). Furthermore, the infiltration of adipose tissue into skeletal muscle is inversely associated with muscle performance and higher accumulation of intermuscular adipose tissue has been linked with an inability to fully activate muscles during dynamic contractions (Goodpaster et al. 2001; Yoshida et al. 2012). In Chapter 3, the most comprehensive cross sectional examination to date of the major physiological determinants of muscle power was conducted in healthy middle-aged, healthy older and mobility-limited older adults.

However, definitive understanding of the specific physiological mechanisms that cause a decline in muscle power with advancing age is limited. The aforementioned cross sectional studies preclude definitive causal inferences about the factors causing muscle power loss and are also particularly limited by survival effect bias (Frontera et al. 2008; Goodpaster et al. 2006). This bias may lead to inaccurate estimates of the loss of muscle power over time as persons with greater muscle power may have a better chance to survive to old age and be included in cross sectional investigations. A true understanding of the nature and underlying physiological determinants of lower extremity muscle power loss in older adults can only be established using longitudinal evaluation of the same group of individuals. To date, no longitudinal investigation has examined the magnitude and major determinants of lower extremity muscle power output with advancing age. Furthermore, no study has compared the underlying mechanisms contributing to longitudinal changes of lower extremity muscle power among healthy and frail older adults. Such knowledge may be critical for identifying specific physiological factors that mediate functional loss and disability in older adults.

The purpose of this study was to comprehensively examine and quantify the longitudinal determinants of lower extremity muscle power in two distinct groups of healthy older and

mobility-limited older adults. We systematically compared the changes in leg extensor muscle power and concurrent changes in lower extremity muscle size, strength, muscle quality, neuromuscular activation and the intrinsic single muscle fibre contractile properties over a three year period in both groups. By examining several physiological domains that contribute to motor performance, we sought to identify key deficits in specific physiological systems that contribute to the age-related decline in muscle power output. Because of the significant relationship between impairments in lower extremity muscle power and mobility-related tasks, we hypothesised that mobility-limited older adults would have significantly greater reductions in lower extremity muscle power compared to healthy older adults. We also sought to examine whether different physiological mechanisms would mediate the respective changes of lower extremity muscle power in healthy older and mobility-limited groups.

4.2 Methods

4.2.1 Study participants

A total of sixty-two older subjects (28 healthy older, 34 mobility-limited) initially completed the study protocol at baseline between 2006 - 2008. The full description of the baseline recruitment and eligibility criteria has been described previously (section 3.2.1). Briefly, participants were considered eligible for the healthy older group if they were community dwelling, aged 70-85 years, not taking any prescribed medications and scored ≥ 10 on the Short Physical Performance Battery test (SPPB). Older mobility-limited subjects were considered eligible if they were community-dwelling, aged 70-85 years and demonstrated objective functional limitations as evidenced by an SPPB score ≤ 9. The SPPB characterises lower extremity function by assessing gait speed, balance and strength and is highly predictive of subsequent disability, institutionalisation, and mortality (Guralnik et al. 2000; Guralnik et al. 1995; Guralnik et al. 1994). Prior to enrollment at baseline and follow-up, all volunteers signed an informed consent form (see Appendix C) and were made aware of all potential risks associated with the study procedures. This study was approved by the Tufts University Health Sciences Institutional Review Board.

4.2.2 Experimental Procedures

The following experimental procedures have been previously described in greater detail (Sections 3.2.2 – 3.2.6). All testing procedures were performed at baseline and repeated after 3.0 ± 0.5 years of follow-up.

4.2.3 Lower extremity muscle power, strength, muscle size and quality

See previous sections 3.2.2 – 3.2.4 for description of methods.

4.2.4 Specific muscle power and strength

See previous section 3.2.5 for description of methods.

4.2.5 Neuromuscular activation

See previous section 3.2.3 for description of methods.

4.2.6 400 meter Walk

The test consisted of walking 10 laps around a pair of cones that were separated by 20 meters. Participants were instructed to walk at their typical speed and standardized verbal encouragement was given on each lap, directing participants to maintain their pace, and indicating the number of laps remaining.

4.2.7 Muscle biopsy and single muscle fibre experiments

See previous section 3.2.6 for description of methods. The same biopsy site was used at follow-up as it was possible to identify the scar of the baseline biopsy in all subjects.

4.2.8 Statistical analysis and statistical power estimates

Data analysis was performed using SAS statistical software (Version 9.2, SAS Institute Inc., Cary, North Carolina). Data are presented as mean ± SD or adjusted mean ± SE. Statistical significance was accepted at $P \leq 0.05$. A trend for statistical significance was accepted at $P \leq$

0.10. For each parameter the change between the follow-up and baseline was used as an outcome and paired analyses were performed within variables. The association between the outcome and study group (operationalised as Healthy Older vs. Mobility-limited Older) was assessed using linear regression. Baseline value, gender, and interaction between gender and risk group was included in the model. First the interaction between gender and study group was tested. If significant, the adjusted mean change difference between the two groups was calculated for both males and females and across the two gender groups. If the interaction was not significant the adjusted mean change difference between the two groups was calculated across the two gender groups. Exploratory, post-hoc bivariate correlations (Pearson) were calculated within each study group to investigate potential associations between the longitudinal change in lower extremity muscle power and concurrent changes in the major physiological domains associated with muscle power.

We evaluated statistical power for this this study using the same methods as those described in Section 3.2.8 and focusing on the primary outcome measure, leg extensor muscle power. We anticipated that we would have an 80% retention rate in the two groups over the 3 year follow up period and thus, we expect approximately 25 subjects in each of these two groups to complete the longitudinal portion of this study. From our preliminary studies of leg power, we estimate that a between-group muscle power difference of approximately 100 watts will be evident after 3 years of follow-up, with the mobility-limited older adults exhibiting a greater decline than healthy older participants. Considering a one standard deviation difference of 100 watts for this measure between groups, we estimate that we will have 80% power to detect a difference of approximately 100 watts over the 3 year period with the projected retention rates and sample size.

4.3 Results

4.3.1 Study Participants

In 2009-2011, attempts were made to contact all of the initial 64 older study participants. Of the healthy older participants, 1 had died and 1 subject could not be located. From the mobility-limited older group, 2 were physically unable to attend the laboratory, 3 subjects elected not to participate, 2 had died and 5 subjects could not be located. Searches at the Massachusetts Department of Vital Statistics, Massachusetts Department of Motor Vehicles, Social Security Death Index, and telephone directories were used to locate individuals who were no longer living at their original address. The remaining subjects were eligible for the study and a total of 26 healthy older (92.9% of initial group, 12 females) and 22 mobility-limited participants (64.7% of initial group, 12 females) enrolled and participated in the follow-up testing. The characteristics of the study participants are displayed in Table 4.1.

Table 4.1 Baseline subject characteristics

Variable	Healthy Older (male 14, female 12)	Mobility-limited Older (male 10, female 12)	Between- group difference
Age, yr	74.1 ± 3.7	77.2 ± 4.4	0.01
BMI (kg/m^2)	24.3 ± 6.0	26.9 ± 3.4	0.07
Medical Diagnoses, n	-	2.2 ± 1.9	-
Number of Medications, n	-	2.8 ± 2.4	-
SPPB score	11.0 ± 0.9	7.9 ± 1.3	0.01
Duration of follow-up, yr	3.0 ± 0.7	2.9 ± 0.4	0.54

Values are mean ± SD. BMI: body mass index; SPPB: Short Physical Performance Battery

4.3.2 Lower extremity muscle power, strength, muscle size and quality

Table 4.2 and Figure 4.1 display the longitudinal changes in muscle performance, muscle composition and quality for healthy older and mobility-limited subjects. All subjects completed the strength and power testing and CT scans were obtained at both time points from 26 healthy older 19 mobility-limited participants. Within both groups, significant and comparable losses of peak power were evident at follow-up (healthy older: -8.8% vs. -8.5% in mobility-limited). Similarly, significant decrements in contraction velocity were also apparent in both groups. 1RM strength declined significantly only among mobility-limited subjects (-5.9%). There was a trend for a significant between-group difference in the magnitude of total muscle CSA decline ($P = 0.08$). Among mobility-limited participants, a significant loss in total muscle CSA was observed (-3.8 %, $P = 0.003$) compared to a minimal reduction of -0.8% within healthy older participants ($P = 0.4$). In addition, there was also a significant group x gender interaction evident for total muscle CSA, with mobility-limited females losing significantly greater total muscle CSA compared to healthy older females ($-9.6 \pm 3.0\%$, $P < 0.01$). Total intermuscular adipose tissue depots were substantially increased in both groups (healthy older: $31.7 \pm 15.2\%$, $P = 0.2$; mobility-limited older: $27.2 \pm 17.0\%$, $P = 0.002$). Both groups lost specific muscle power (within-group changes: $P < 0.05$), although the comparative magnitude of this decrement was not different between groups ($P = 0.5$). No significant changes between or within groups were evident for bodyweight, BMI or specific 1RM strength ($P > 0.17$, data not shown).

Table 4.2 Comparative 3 year longitudinal changes in lower extremity muscle performance, muscle composition and quality

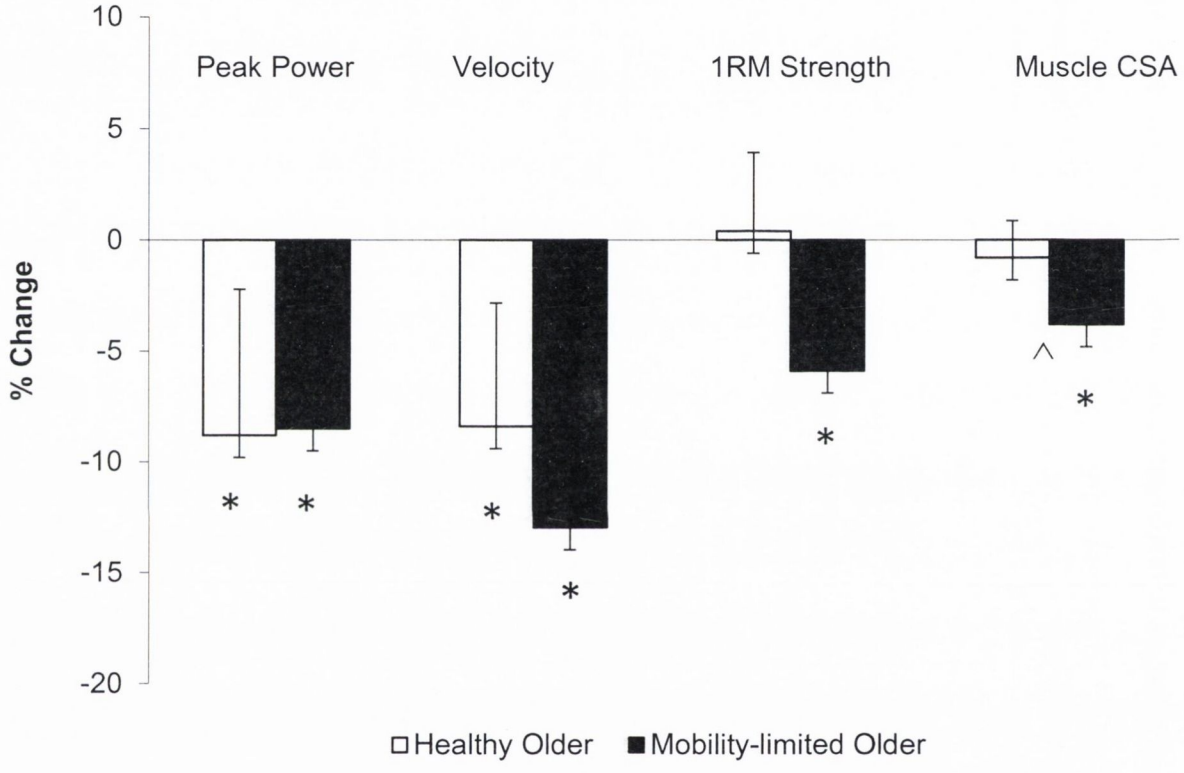
Variable	Healthy Older			Mobility-limited Older			
	Baseline value ($\bar{x} \pm SD$)	Delta^ ($\bar{x} \pm SE$)	% Change^ ($\bar{x} \pm SE$)	Baseline value ($\bar{x} \pm SD$)	Delta^ ($\bar{x} \pm SE$)	% Change^ ($\bar{x} \pm SE$)	Group difference P
Peak power (W)	471 ± 232	-69.8 ± 22.2*	-8.8 ± 6.6	291 ± 116	-65.6 ± 25.1*	-8.5 ± 7.5	0.91
Contraction velocity (m/s)	0.45 ± 0.13	-0.06 ± 0.02*	-8.4 ± 5.6	0.34 ± 0.11	-0.08 ± 0.02*	-13.0 ± 6	0.42
1RM strength (N)	1278 ± 436	-19.6 ± 43.8	0.4 ± 3.5	1080 ± 343	-102 ± 50*	-5.9 ± 4.1	0.23
Total muscle CSA (cm^2) ¥	109 ± 27	-1.2 ± 1.4	-0.8 ± 1.7	95.1 ± 22.7	-5.1 ± 1.6*	-3.8 ± 1.9	0.08
Total intermuscular CSA (cm^2)	2.9 ± 2.3	0.30 ± 0.24	31.7 ± 15.2	4.4 ± 2.2	0.90 ± 0.27*	27.2 ± 17.0	0.11
Specific peak power, (W/cm^2)	4.1 ± 1.2	-0.41 ± 0.20*	-4.2 ± 6.0	3.0 ± 1.0	-0.63 ± 0.24*	-11.3 ± 7.1	0.49

^Values are adjusted means ± SD or SE. *Significant within group difference ($p < 0.05$). ¥ Group x gender interaction ($P = 0.02$)

Figure 4.1 Longitudinal changes (%) in muscle power, velocity, 1RM, muscle CSA

Values are adjusted mean % changes after 3 year follow-up

** = significant within-group difference, P ≤ 0.05 ^ = trend for between-group difference, P = 0.08*

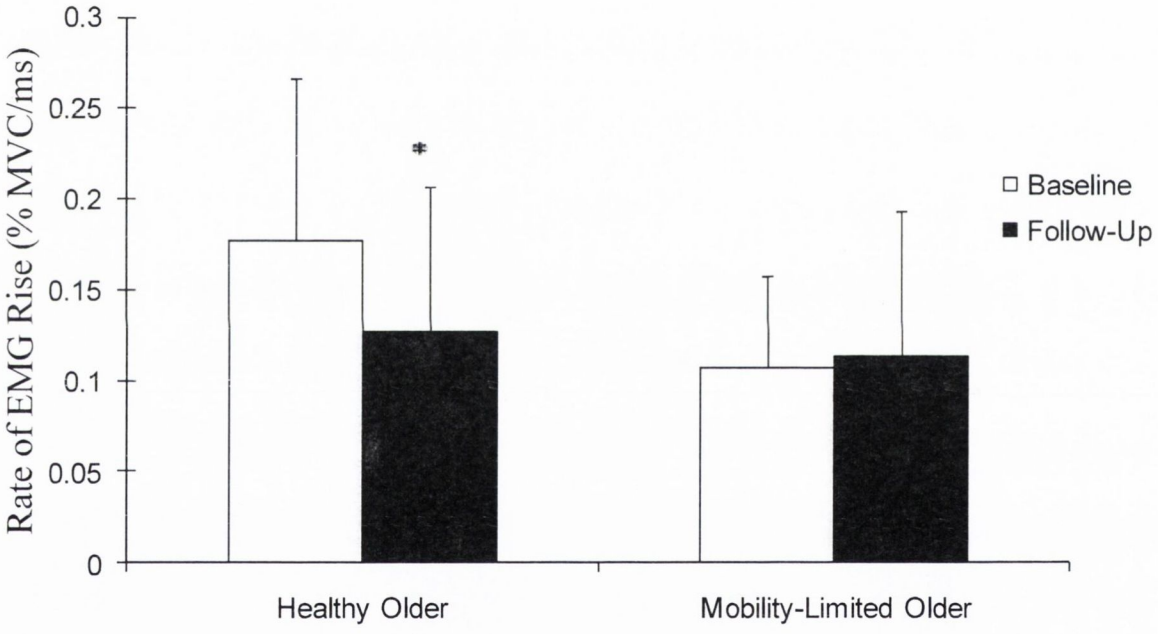


4.3.3 Neuromuscular activation

Vastus lateralis rate of neuromuscular activation data was only included if deemed of high quality after custom software analysis and secondary visual inspection of all raw data. At each time point, a significant amount of signal noise obscured reliable identification of the onset of muscle contraction, resulting in valid data from 21 healthy older and 11 mobility-limited participants at baseline or follow-up. Figure 4.2 displays the vastus lateralis rate of neuromuscular activation data obtained at both time points, from a final total of 14 healthy older participants (5 females) and 6 mobility-limited participants (2 females). Within-group analyses revealed that the rate of EMG rise was significantly reduced among healthy older participants (-25.6 ± 14.0%, $P = 0.004$). Rate of EMG rise among mobility-limited participants did not change ($P = 0.8$). A trend for a statistically significant between group difference was evident for rate of EMG rise ($P = 0.10$). No significant group x gender interaction was evident. Within this subset of participants with valid neuromuscular activation data, the magnitude of peak power loss in healthy older ($n = 14$) was -18.7 ± 5.5% ($P = 0.003$) and -20.1 ± 9.8% ($P = 0.05$) in mobility-limited participants ($n = 6$) (between group difference: $P > 0.9$).

Figure 4.2 Rate of vastus lateralis muscle activation.

*Values are mean ± SD. * within-group change: $P < 0.05$*

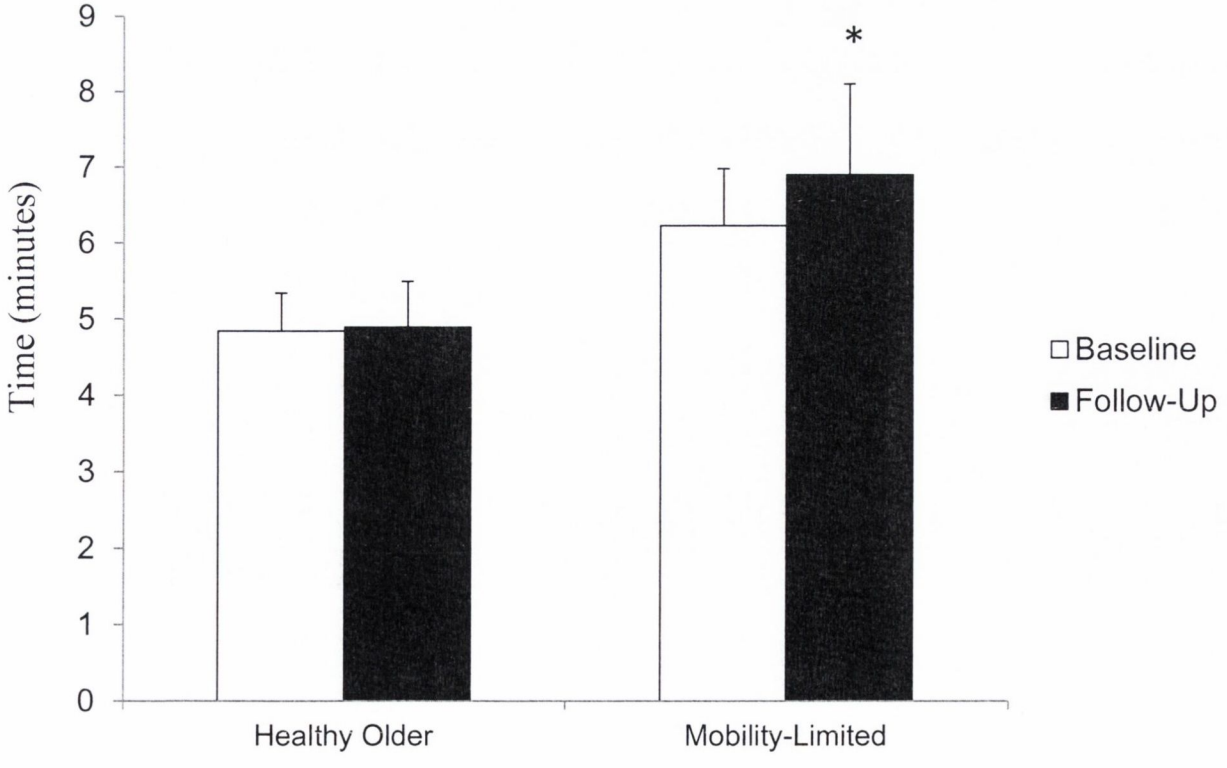


4.3.4 400 metre walk

Figure 4.3 displays the 400 metre walk data obtained at both time points from a final total of 25 healthy older participants and 20 mobility-limited participants. Three participants (1 healthy older and 2 mobility-limited) were unable to complete the 400 metre walk at follow-up and were excluded from the analysis. Within-group analyses revealed that the time to complete the 400 metre walk increased significantly among mobility-limited participants (13.4 ± 12.2%, P = 0.04). Time to complete the 400 metre walk among the healthy older participants did not change (P > 0.5). A trend for a statistically significant between group difference was evident for time to complete 400 metre walk (P = 0.08). No significant group x gender interaction was evident.

Figure 4.3 Time to complete 400 metre walk

*Values are mean ± SD. * within-group change: P < 0.05*



4.3.5 Muscle biopsy and single muscle fibre experiments

The findings from the single muscle fibre experiments are displayed in Table 4.3 and Figure 4.4. After accounting for participants that elected not to undergo the muscle biopsy and for those who were excluded from the procedure for medical reasons, type I fibre samples were successfully obtained from 16 healthy older (5 females) and 6 mobility-limited (3 females) participants. Type IIA fibre samples were obtained at both time points from 14 healthy older (3 females) and 5 mobility-limited participants (3 females). For type I fibre properties, no significant change in type I fibre CSA were observed at follow-up. However, both groups had similar and significant within-group increases ($P \leq 0.05$) in type I fibre peak force, specific force, shortening velocity and peak power (P for between group differences: $\geq$ 0.13). Type I fibre specific power also increased in both groups, however this increase was only statistically significant among healthy older participants ($P < 0.0001$). For type IIA fibre properties, no significant change in fibre CSA were observed in either group. Significant within-group increases in peak force and shortening velocity were found among the healthy older group while peak power was significantly increased among mobility-limited participants at follow-up. Both groups had similar and significant within-group increases ($P < 0.02$) of type IIA fibre specific force and specific power (P for all between group differences: ≥ 0.13). No significant group x gender interaction was evident for any single fibre variable examined. Within this subset of muscle biopsy participants, the magnitude of peak power loss in healthy older (n = 16) was -14.3 ± 6.7% (P = 0.05) and -34.5 ± 11.4% (P = 0.007) in mobility-limited older (n = 6) (between group difference: P = 0.2). A three dimensional plot (Figure 4.4) displays the overall magnitude (% change) of the longitudinal increases in peak force and shortening velocity according to fibre type and study group.

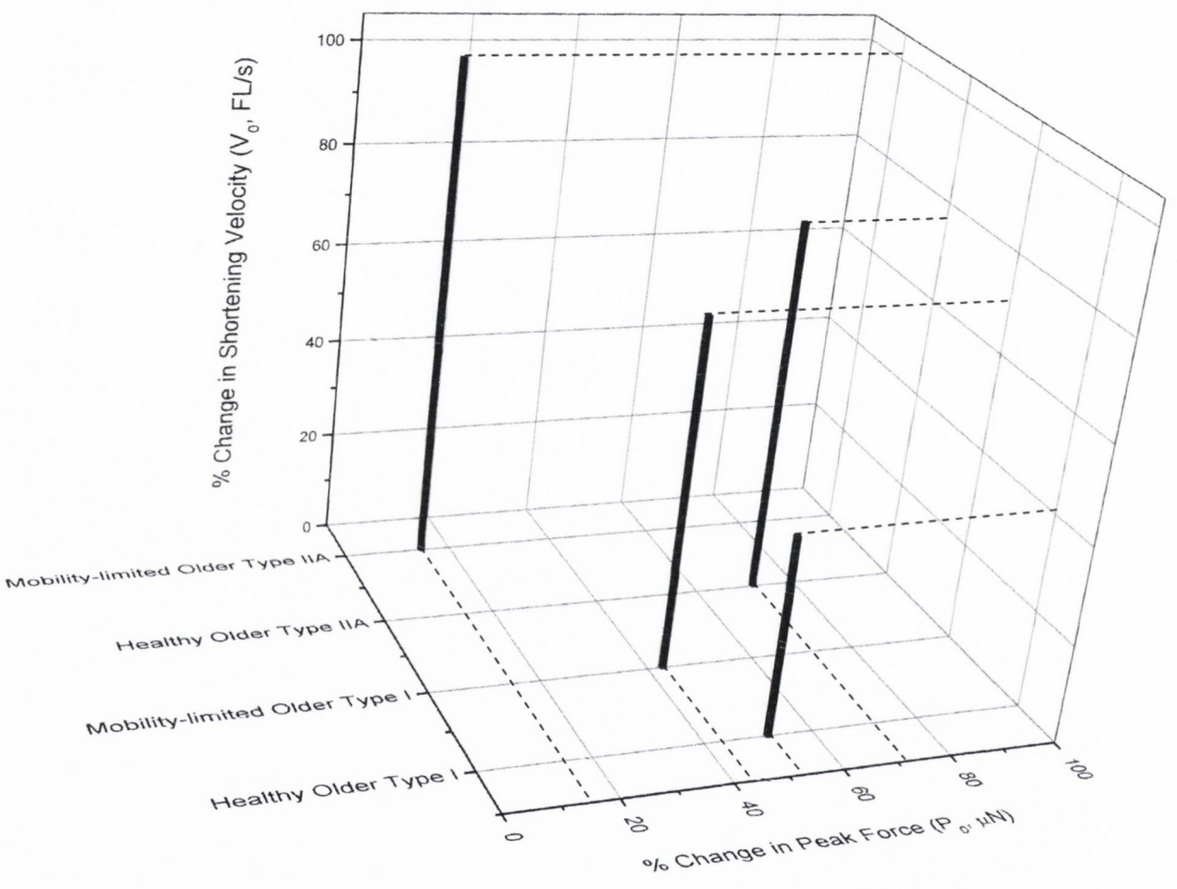
Table 4.3 - Single muscle fibre size and contractile properties

	Healthy Older			Mobility-limited Older			Between Group
	Baseline	Follow-up	P Value	Baseline	Follow-up	P Value	P Value
Type I							
Number of fibres	13.6 ± 2.6	10.4 ± 4.2		14.8 ± 2.4	9.0 ± 4.8		
CSA, μm^2	4,787 ± 1,063	4,956 ± 1,336	0.60	4,900 ± 930	4,599 ± 646	0.39	0.32
P_0, μN	488 ± 104	705 ± 245	< 0.001	488 ± 134	689 ± 202	0.05	0.50
SF, N/cm^2	15.6 ± 3.4	21.9 ± 4.8	< 0.001	15.2 ± 4.1	23.0 ± 4.1	< 0.001	0.80
V_0, FL/s	0.63 ± 0.16	0.77 ± 0.21	< 0.001	0.61 ± 0.20	0.97 ± 0.23	< 0.001	0.13
Peak Power, μN*FL/s*	18.1 ± 7.1	47.9 ± 29.1	< 0.001	18.1 ± 7.2	45.2 ± 14.8	0.03	0.86
Specific Power, kN/m^2*FL/s	5.8 ± 2.4	16.3 ± 13.5	< 0.001	5.7 ± 2.2	14.9 ± 3.9	0.10	0.86
Type IIA							
Number of fibres	4.2 ± 3.2	7.4 ± 4.8		4.5 ± 2.5	4.6 ± 1.8		
CSA, μm^2	4,817 ± 1,339	4,881 ± 1,710	0.60	4,469 ± 1,014	3,603 ± 869	0.16	0.13
P_0, μN	437 ± 149	644 ± 248	< 0.001	386 ± 170	504 ± 211	0.56	0.39
SF, N/cm^2	13.6 ± 4.6	20.1 ± 2.9	< 0.001	12.7 ± 4.3	21.0 ± 3.4	< 0.001	0.14
V_0, FL/s	1.5 ± 0.5	2.2 ± 0.7	< 0.001	1.3 ± 0.5	2.0 ± 0.7	0.11	0.60
Peak Power, μN*FL/s*	44.3 ± 23.9	99.3 ± 58.5	0.05	35.5 ± 13.3	153 ± 188	0.02	0.20
Specific Power, kN/m^2*FL/s	14.1 ± 8.4	30.4 ± 10.6	< 0.001	14.5 ± 7.1	35.1 ± 21.8	0.02	0.69

Values are mean ± SD. CSA, cross sectional area; P_0, peak force; SF, specific force; V_0, shortening velocity

Figure 4.4 Three-dimensional plot comparing the longitudinal increases in peak force vs. shortening velocity in Type 1 and Type IIA single fibres.

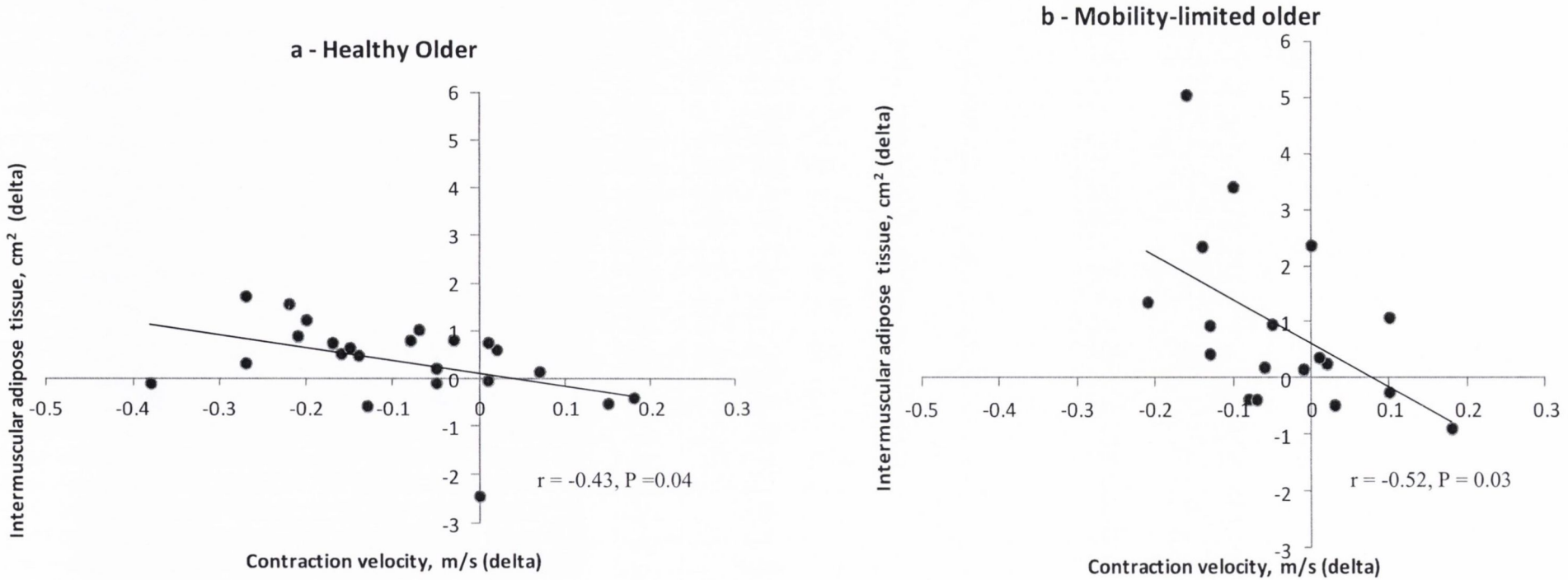
Values are mean percentage changes



Among healthy older participants, post-hoc correlation analyses revealed significant relationships between the decline in leg extensor power and the corresponding decline in contraction velocity ($r = 0.78$, $P < 0.001$) and the increase in intermuscular adipose tissue infiltration ($r = -0.45$, $P = 0.03$). No relationship existed between the change in muscle power and muscle size within this group ($r = 0.08$, $P = 0.7$). Among mobility-limited participants, significant relationships were evident for the decline in muscle power and corresponding declines in contraction velocity ($r = 0.84$, $P < 0.001$) and 1RM strength ($r = 0.52$, $P = 0.03$). The longitudinal change of intermuscular adipose tissue infiltration was significantly and inversely correlated with the decline of contraction velocity among healthy older ($r = -0.43$, $P = 0.04$) (Figure 4.5a) and mobility-limited participants ($r = -0.52$, $P = 0.03$) (Figure 4.5b). No significant relationships existed between changes in subcutaneous adipose tissue and changes in muscle power or contraction velocity within healthy older or mobility-limited participants.

Figure 4.5 Correlation between changes (delta) in contraction velocity and intermuscular adipose tissue accumulation

a) healthy older and b) mobility-limited older adults



4.4 Discussion

The major finding of this investigation is that lower extremity muscle power deteriorates significantly over a 3-year interval in healthy and mobility-limited older groups. While the magnitude of this decline is equivalent in both groups, the underlying physiological mechanisms that determine muscle power loss differ between both groups. Specifically, our investigation has established that the loss of muscle power among healthy older adults is associated with significant declines in the rate of neuromuscular activation but minimal changes in muscle size, strength and physical function. Conversely, decrements in muscle power among mobility-limited elders are associated with significant declines in muscle size and muscle strength and physical function, but no additional declines in neuromuscular activation. In addition, we have identified that substantial compensatory adaptations occur within the contractile properties of surviving single muscle fibres among healthy older and mobility-limited elders in response to the declines in whole muscle power. Finally, for the first time, we demonstrate that significant increases of intermuscular adipose tissue infiltration into skeletal muscle with advancing age are inversely associated with the loss of muscle contractile velocity and power output in healthy older and mobility-limited adults.

4.4.1 Magnitude of lower extremity muscle power loss in older adults

The overall decline in lower extremity muscle power in mobility-limited elders (-8.5%) was similar in healthy older subjects (-8.8%), representing annualised rates of decline of 2.9%/yr within both groups. While this finding was contrary to our primary hypothesis, there are several plausible explanations. Mobility-limited elders had significantly lower absolute levels of leg extensor muscle power at baseline compared to healthy older participants. Therefore, one possibility is that mobility-limited elders had already reached critically low levels of muscle power at baseline, beyond which compensatory

mechanisms are activated in an attempt to restore muscle function and limit additional decrements in muscle power. Another possibility is that the 3-year time follow up period in this study may have been too short to truly capture a comprehensive trajectory of muscle power changes, particularly given the variability of changes in muscle performance observed in the current study and reported in previous studies (Delmonico et al. 2009; Frontera et al. 2008; Goodpaster et al. 2008; Goodpaster et al. 2006; Hicks et al. 2012; Hughes et al. 2001).

4.4.2 Changes in muscle strength, muscle size and neuromuscular activation

Several important findings are evident from the different longitudinal changes in muscle strength, muscle size and neuromuscular activation observed across groups in this study. Despite overall decrements in muscle power, the healthy older group maintained their strength, whereas mobility-limited elders exhibited significant reductions in muscle power and strength at follow-up. The decline in neuromuscular activation, concurrent with the maintenance of muscle size and strength in the healthy older group indicate that altered neuromuscular function is the critical early determinant of muscle power loss with aging. As coexisting deficits in contraction velocity (-8.4%) were evident at follow-up within this group, an impaired rate of activation may specifically impact muscle contractile velocity leading to a longer time to reach peak force, and thus an observed decline in muscle power generation (Aagaard et al. 2010; Clark et al. 2011). It is likely that the large discrepancy between the decline in muscle power and the changes in both muscle size and muscle strength within the healthy older group is primarily accounted for by changes in neuromuscular activation and concomitantly manifested through impairments in contraction velocity. In contrast, the significant decrements in muscle size (-3.8%), strength (-5.7%) and contraction velocity (-13%) among mobility limited elders suggest that a combination of deficits are major determinants of muscle power loss

within this group. Therefore, while mobility-limited elders exhibited no additional changes in neuromuscular activation, baseline impairments in neuromuscular activation were evident and it is possible that no further deficits were detectable, at least with the surface EMG methods employed in this investigation.

4.4.3 Single muscle fibre contractile properties

In both groups, the cross sectional areas of type I and type IIA fibres were largely preserved and emphatic increases were elicited in all single fibre contractile mechanics examined 3 years apart. A plausible explanation for these findings is that pronounced adaptations occur within the surviving single muscle fibres of both healthy and mobility-limited older adults in an attempt to restore contractile performance and compensate, albeit sub-optimally, for the major deficits in whole muscle power, size, quality and neuromuscular activation.

The magnitude of the observed myocellular contractile adaptations are directionally similar but substantially greater than reported in a previous longitudinal study by our research group. After a 9-year follow up period, Frontera et al. identified trends for increased peak force and preserved unloaded shortening velocity of type I and IIA fibres in response to significant deficits in whole muscle strength and size in a small sample (n = 9) of healthy older men and women (Frontera et al. 2008). In the current study, the substantial improvements of single fibre peak force and unloaded shortening velocity in both groups occurred during a shorter follow-up period. From these data, it can be hypothesised that there may be an initial early time course for pronounced myocellular contractile adaptations that, subsequently, become attenuated with advancing years in older persons. However, additional studies on the age related changes in single fibre properties utilising more comprehensive longitudinal analyses than those employed in

the current study would be necessary to further explore this hypothesis. Also of particular interest in the current study is the magnitude of the single fibre peak power increases in type I (~200%) and in type IIA fibres (~200 - 300%) within both groups. These values are extraordinary when put in context with studies that have been specifically designed to improve myocellular contractile function in humans. In young and healthy older adults, maximal increases in peak power of type I and type IIA fibres have been shown to increase by up to ~160% and ~60%, respectively, after several months of progressive resistance training (Slivka et al. 2008; Trappe et al. 2001; Trappe et al. 2000).

Overall, several factors may help explain the mechanisms responsible for the magnitude of the single fibre adaptations reported in the current investigation. We quantified the myocellular adaptations during a dynamic skeletal muscle loading period in two distinct groups of aging humans over a 3 year period. This relatively short term follow-up duration, concomitant with significant reductions in whole muscle power and other emerging and established physiological perturbations at the whole muscle level, represents a novel loading paradigm for the intrinsic properties of surviving single muscle fibres that has not been previously characterised in older adults. It is also possible that additional methodological considerations, such as differences in study populations, amount of fibres studied and potential confounding factors such as physical activity may contribute to differences between the current and previous investigations.

4.4.4 Adipose tissue infiltration within skeletal muscle

Both groups exhibited substantial increases of intermuscular adipose tissue and the magnitude of these increases were consistent with previous reports in healthy older and mobility limited populations (Delmonico et al. 2009; Goodpaster et al. 2008; Goodpaster

et al. 2006; Marcus et al. 2012). In addition, we demonstrate significant inverse relationships between increases of intermuscular adipose tissue infiltration and corresponding losses in muscle power and contraction velocity within both groups. The mechanism linking adipose tissue infiltration to altered muscle power remains unclear. However, it is possible that adipose tissue infiltration into skeletal muscle alters muscle fibre orientation or directly inhibits central activation and neuromuscular conductivity, thus reducing the force and contractile producing capabilities of the whole muscle (Marcus et al. 2012; Yoshida et al. 2012). Another potential mechanism is the secretion by intermuscular adipose tissue of pro-inflammatory cytokines leading to inflammation that ultimately inhibits muscle force production at a systemic level (Hardin et al. 2008). Alternatively, while no changes in body weight or BMI were evident within the two groups in the current study, we speculate that the infiltration of adipose tissue into skeletal muscle could serve as a proxy for adverse lifestyle influences on muscle function related to diet and physical inactivity among older adults. In this regard, a one-year intervention of regular physical activity has been shown to attenuate increases in muscle fat infiltration and decrements in muscle performance in mobility-limited limited older adults compared to sedentary controls (Goodpaster et al. 2008).

4.4.5 Functional Performance

The healthy older participants maintained their 400 metre walk performance after 3 years of follow-up. Despite major whole muscle changes, this finding suggests that changes in physical function among healthy older persons are preceded by decrements in muscle power and neuromuscular neuromuscular activation while minimal changes in muscle size and strength occur. Conversely, among mobility-limited participants, the decline in physical function continues to occur concomitant with losses of muscle power, muscle mass and strength.

4.4.6 Limitations

Major strengths of this investigation include the longitudinal study design and the use of specific eligibility criteria to characterise two distinct aging phenotypes. However, some limitations of the current investigation must be considered. The differential loss to follow-up rate between the two study groups may have influenced our overall findings. Approximately one-third of the original mobility-limited group did not return for reassessment, which may have limited our ability to fully examine the true magnitude and nature of muscle power loss and the generalisability of our findings within this group. Similarly, given the low number of muscle biopsies obtained at follow-up, particularly within the mobility-limited participants, suggest that the biopsy data should be interpreted with caution. In addition, the mobility-limited participants were also significantly older than the healthy older group at baseline (~ 3.1 yrs), which may have also influenced the overall study findings. Another limitation is that the current 3-year longitudinal analysis assumes that the age-related losses in muscle power, contributory mechanisms and subsequent mobility limitations are linear in occurrence. Consequently, the current study cannot adequately quantify any shorter term mechanisms that may be contributing to or compensating for reductions in muscle power. In addition, a number of unmeasured factors that may mediate the age-associated decline in muscle power and skeletal muscle performance were not assessed in this study. These include caloric and protein intake and the influence of inflammatory factors and protein synthesis activators. Finally, among older adults, level of physical activity has been shown to influence several determinants of muscle power characterised in this study (Clark and Fielding 2012; D'Antona et al. 2007; Goodpaster et al. 2006). An assessment of the interaction between physical activity on the physiological domains investigated this study may have added important supplementary information to our findings.

4.5 Conclusion

In conclusion, this is the first longitudinal investigation to comprehensively characterise the major physiological determinants of the age related loss of lower extremity muscle power in healthy older and mobility-limited older adults. The overall magnitude of muscle power loss was similar between both groups; however different underlying physiological domains determine lower extremity muscle power decrements within healthy older adults and older adults with mobility limitations. Neuromuscular activation deficits precede changes in muscle size and strength and physical function, and this may be the initial mechanism that influences muscle power loss with advancing age. Despite major and emerging physiological decrements at the whole muscle level, single muscle fibre size is preserved and the contractile properties of these surviving fibres undergo substantial compensatory mechanisms in an attempt to restore whole muscle power and physical function in older adults with and without mobility-limitations. Additional studies are needed to elucidate the mechanisms by which intermuscular adipose tissue infiltration may directly contribute to the loss of muscle power, muscle performance and subsequent loss of mobility with advancing age.

Section B

Chapter 5

Comparative effects of low intensity and high intensity power training for improving muscle power, mobility, muscle mass and neuromuscular activation in older adults with mobility limitations

5.1 Introduction and study rationale

Mobility, the ability to move without assistance, is an essential part of many fundamental activities of daily living for older adults (Guralnik et al. 2000). Limitations in mobility, typically defined as difficulty in performing ambulatory tasks such as walking, rising from a chair or climbing a flight of stairs, are estimated to affect approximately 25% of older adults aged 65 years or older (Fried and Guralnik 1997; Gardener et al. 2006; Melzer et al. 2005). Mobility-limited older adults also have higher rates of falls, chronic disease, institutionalization, and mortality (Guralnik et al. 2000; Guralnik et al. 1995; Guralnik et al. 1994). As the population of older adults continues to exponentially increase, corresponding increases in the prevalence and incidence of mobility limitations are inevitable unless therapeutic interventions for preserving mobility are identified and optimised.

Resistance training interventions have the potential to counteract the age-related decline of mobility among older adults (Fiatarone et al. 1990; Fiatarone et al. 1994; Frontera et al. 1988; Sullivan et al. 2001). In recent years, recognition of the importance of improving the muscle-power generating capacity of skeletal muscle has given rise to studies in which more powerful, high-velocity movements are employed during progressive resistance training interventions in older participants (Evans 2000; Fielding et al. 2002). Muscle power (the product of the force and velocity of muscle contraction) declines earlier and more rapidly with advancing age compared to muscle strength (the maximal force capacity of skeletal muscle) and is a more influential determinant of performance on mobility related tasks among older adults (Bean et al. 2002b; Metter et al. 1997). High velocity resistance training of the lower extremities has emerged as a particularly effective resistance training intervention for increasing muscle power in older persons (de Vos et al. 2005; Earles et al.

2001; Fielding et al. 2002; Miszko et al. 2003; Sayers 2008). This explosive form of resistance training is characterized by participants performing the concentric phase of each repetition as fast as possible.

While a number of studies have demonstrated the safety and feasibility of high velocity power training for increasing lower extremity muscle power and improving mobility, additional studies are needed to better understand and refine power training interventions among older adults. The majority of high velocity power interventions to date have been conducted in relatively healthy older adults, and greater understanding of the impact of power training in mobility-limited populations is especially warranted. In particular, further research is required to establish the optimal training stimulus during high velocity power training for maximizing muscle power gains and for optimising improvements in mobility. To date, studies have shown that high velocity power training conducted at low relative training intensities (i.e. 20-50% of the 1 repetition maximum(1RM)) or high training intensities (60-80% of the 1RM) can elicit significant improvements in lower extremity power and mobility related performance among older adults (Bottaro et al. 2007; Earles et al. 2001; Fielding et al. 2002; Henwood et al. 2008; Miszko et al. 2003; Reid et al. 2008) . Only one previous study has directly compared changes in muscle power after programs of high velocity power training conducted at varying external resistances (de Vos et al. 2005). This study, conducted in healthy older adults, demonstrated that muscle power improved similarly (14-15%) in participants randomized to 12 weeks of power training performed at low or high relative training intensities (20%, 50% or 80% of the 1RM). While these findings suggest that power output can be increased by a similar magnitude after training at low or high external resistances in healthy older adults, no study to date has specifically

examined the effects of high velocity power training at varying intensities among older mobility-limited older adults.

The purpose of this study was to compare the effects of 16 weeks of high velocity power training performed at low intensity (40% of the 1RM (LO)) or high intensity (70% of the 1RM (HI)) for improving lower extremity muscle power and mobility in older adults with mobility-limitations. We chose these two relative intensities as power training at LO specifically targets the velocity component of muscle power generation, thus facilitating greater speeds of skeletal muscle contraction but lower force output throughout training. Alternatively, power training performed at HI targets the force component of muscle power generation, yielding higher force output at lower contraction velocities throughout training. By directly comparing regimens of velocity–specific (LO) or force-specific (HI) power training, this study may provide important information for optimising the design of resistance training interventions for increasing muscle power and restoring mobility in older adults with mobility limitations. A second aim of this study was to examine the major underlying physiological mechanisms contributing to potential improvements in muscle power and mobility across both interventions. We also evaluated the comparable training induced adaptations in neuromuscular function and muscle mass after LO and HI in mobility-limited older adults.

5.2 Methods

5.2.1 Study design

This study was a single blind, randomized, 16-week exercise intervention trial comparing the effects of LO and HI on changes in lower extremity muscle power, mobility and additional physiological outcomes in older adults with mobility limitations. A computer-generated randomization scheme (developed by statistician Gheorghe Doros, Ph.D.) determined the order in which the interventions were assigned. A separate blocked randomization schedule was utilised for males and females and a block size of 10 was employed (allocating 5 subjects to LO and 5 subjects to HI). The randomization scheme administered by a research assistant not affiliated with the study and who did not have direct contact with the research participants or study assessment staff.

5.2.2 Study population

Subjects were recruited from the Greater Boston area through recruitment postings, local advertisements and community newsletters. Potential subjects were initially prescreened by telephone (see Appendix D) and were considered eligible for a screening visit if they were: aged between 70 – 85 years, community-dwelling, reported no unstable chronic medical conditions, were not currently performing any regular endurance or resistance training exercise and reported some difficulty in mobility-related tasks such as walking, rising from a chair or lifting and carrying objects. Eligible subjects were invited to the research center for a screening visit. After signing a pre-admission informed consent (see Appendix D), the individuals completed a medical history questionnaire and performed the Short Physical Performance Battery test (SPPB) for objective assessment of functional performance (Guralnik et al. 1994). Participants with an SPPB score of ≤ 9 underwent a physical

examination by the study physician. In addition, all subjects completed a resting electrocardiogram, standard blood chemistries and urine analysis. Subjects were excluded from participation if they had a BMI < 19 kg/m^2 or > 32 kg/m^2, acute or terminal illness, cognitive impairment according to the Folstein Mini-Mental State Examination (score < 23) (Folstein et al. 1975), myocardial infarction in the previous six months, symptomatic coronary artery disease, congestive heart failure, upper or lower extremity fracture in the previous six months, uncontrolled hypertension (>150/90 mmHg), neuromuscular disease or hormone replacement therapy. Subjects who met the study entry criteria and were given medical clearance by the study physician were deemed eligible for participation. All volunteers signed an informed consent form (see Appendix D) and were made aware of all potential risks and benefits associated with the procedures of the study prior to enrollment. This study was approved by the Tufts University Health Sciences Institutional Review Board.

5.2.3 High velocity power training interventions

After baseline testing, participants were randomly assigned to either the LO or HI power training group. All of the training sessions and evaluation sessions were conducted within the laboratory under the supervision of a research assistant (Kimberly Martin, M.P.H.). Blood pressure and heart rate were recorded at the beginning of each training session, followed by approximately five minutes of cycling on a stationary bicycle. All subjects trained two times per week for 16 weeks. Subjects randomized to the LO training group performed 3 sets of 10 repetitions at 40% of their 1RM for the seated bilateral leg press (LP) and seated unilateral knee extension (KE) using Keiser pneumatic resistance training equipment (Keiser Sport Health Equipment Inc., Fresno, CA). Subjects assigned to the HI

power training group performed 3 sets of 10 repetitions at 70% of their 1RM on the LP and KE. While performing the LP and KE, subjects in both intervention group were instructed to complete the concentric phase of each repetition as fast as possible, to maintain full extension of each repetition for 1 second, and to complete the eccentric phase of each repetition over 2 seconds. Rate of perceived exertion was assessed after each training set for LP and KE (Borg 1970). The resistance for each participant was adjusted every 3 weeks by repeating the 1RM measures. At the completion of each training session, participants performed a standing static quadriceps stretch, gastrocnemius stretch, and hamstrings stretch, holding each stretch for 20 – 30 seconds.

5.2.4 Testing procedures

Testing of all outcome measures described below were performed prior to randomization and repeated at week 16. An additional, interim assessment of muscle strength, power and neuromuscular activation was performed after 4 weeks of enrollment to compare early physiological responses to LO and HI in mobility-limited older adults. A previous 16-week intervention of muscle power training in older women demonstrated a rapid early rise in muscle power by 4 weeks and an additional, more-gradual increase in muscle power thereafter (Fielding et al. 2002). All assessments were conducted by an assessor blinded to intervention assignment.

5.2.5 Short physical performance battery test

See previous section 3.2.1 for description of methods.

5.2.6 Lower extremity muscle strength, power and velocity

See previous section 3.2.2 for description of methods.

5.2.7 Neuromuscular activation

See previous section 3.2.3 for description of methods.

5.2.8 Muscle size

See previous section 3.2.4 for description of methods.

5.2.9 Statistical analysis

Data analysis was performed using SAS statistical software (Version 9.2, SAS Institute Inc., Cary, North Carolina). All data were initially examined visually and statistically for normality of distribution. Data are presented as mean ± SD or adjusted mean ± SE. Statistical significance was accepted at $P \leq 0.05$ and an intention-to-treat analysis was utilized (all enrolled participants were included in the final analysis including all withdrawals). Changes in leg extensor muscle power and SPPB score were the primary outcome variables for this study. Outcome variables were assessed using repeated measures analysis of variance and covariance models to analyze the effect of time, group and time x group interactions. Independent samples *t*-tests were used to compare the training intensity between LO and HI. Specific mean differences were assessed using linear contrasts.

5.3 Results

5.3.1 Recruitment and subject characteristics

Participant screening and flow throughout the study are presented in Figure 5.1. Of the individuals who responded to recruitment efforts (n=472), 208 completed the telephone pre-screening questionnaire of whom 94 attended for a screening assessment. A total of 65 subjects met acceptable SPPB score criteria of ≤ 9, however, 10 subjects were excluded for medical reasons. Three eligible subjects dropped out before being randomized; one due to a previously unreported history of inguinal hernia, one because of muscle soreness after a baseline testing visit and one was no longer interested in participating in the study after baseline testing. Therefore, a total of 52 subjects, 11% of the original respondents, were randomized to the respective LO (n=25, 15 females) and HI (n=27) (18 females) power training groups. Baseline descriptive characteristics are presented in Table 5.1.

Figure 5.1 **Participant flow from initial respondents to randomization**

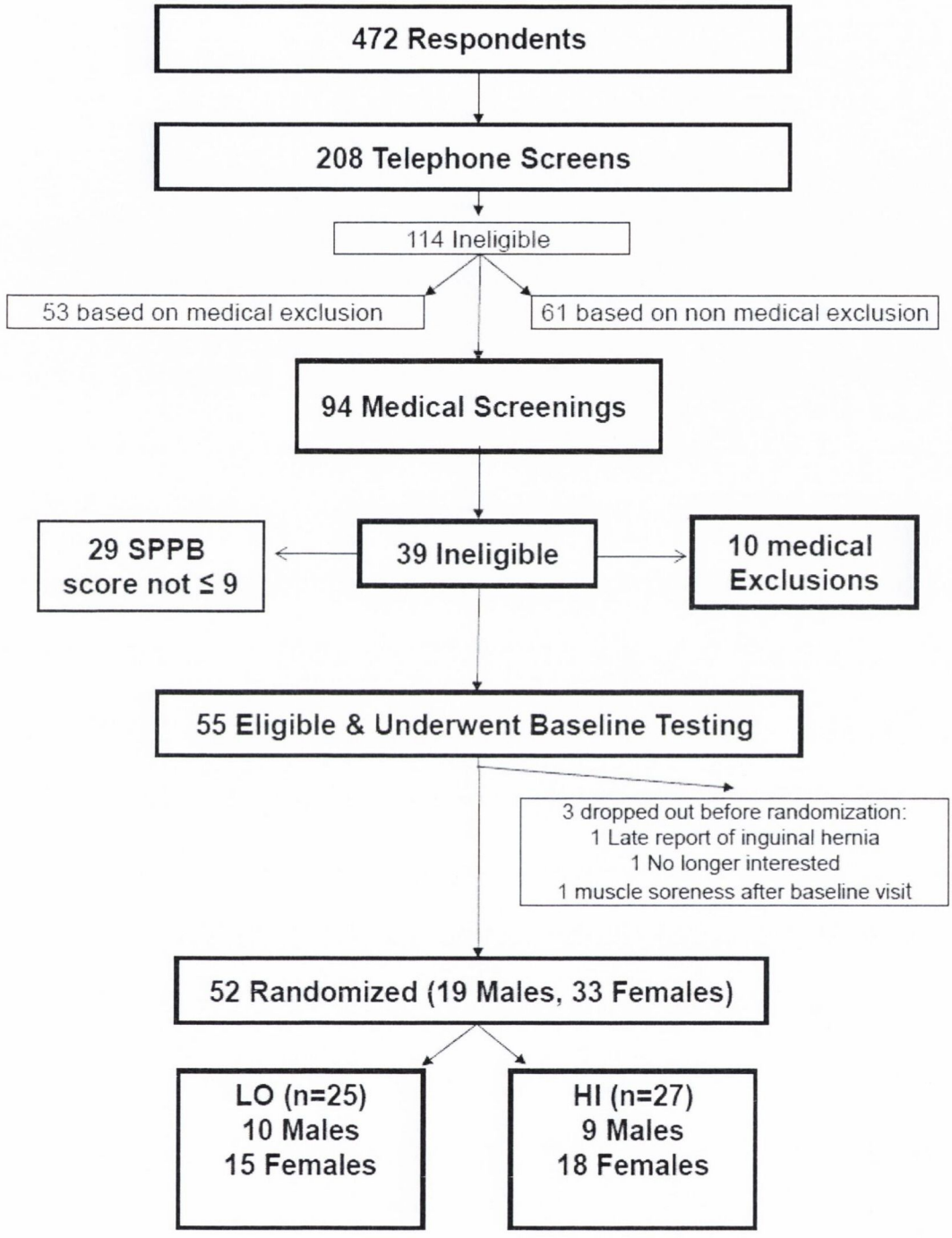


Table 5.1 Baseline subject characteristics

Variables	LO	HI	Between-group Difference (P)
Age, yrs	78.3 ± 4.8	77.6 ± 4.2	0.79
Body Mass Index, kg/m^2	25.7 ± 3.1	27.4 ± 3.2	0.88
Medical diagnosis, n	3.3 ± 2.4	3.8 ± 2.5	0.61
Medications, n	3.8 ± 3.0	4.5 ± 2.8	0.34
SPPB	8.0 ± 1.3	8.11 ± 1.2	0.80

Values are mean ± SD

5.3.2 Training intensity

To compare the relative training intensities of LO and HI throughout the duration of each intervention, training data were analyzed on representative training days after the repeat 1RM assessments that were performed every 3 weeks. Results for representative LO and HI training performed during weeks 3, 6 and 15 (average of all 3 sets) are presented in Table 5.2. For both LP and KE, it is evident that the relative training intensities were significantly different ($P < 0.05$) between LO and HI and were maintained at the respective, desired intensity levels throughout the course of the study. As intended, HI was associated with greater absolute force levels ($P < 0.05$) while LO was associated with significantly greater contraction velocities ($P < 0.05$) for both LP and KE throughout each intervention. The power output levels elicited during LP and KE training for both LO or HI were comparable throughout the study (all $P \geq 0.25$). During LP training, total work tended to be lower in LO ($P = 0.06 - 0.12$), while during KE, total work was significantly lower at each representative training session evaluated (all $P < 0.05$). In LO, rate of perceived exertion was significantly and consistently lower throughout training (all $P < 0.05$).

Table 5.2 **Comparison of training intensity between LO & HI throughout the intervention**

Training	Week 3		Week 9		Week 15	
Leg Extension	**LO**	**HI**	**LO**	**HI**	**LO**	**HI**
% 1RM	40.2 ± 0.8	70.0 ± 0.2*	40.4 ± 1.2	70.1 ± 0.5*	40.0 ± 0.0	70.0 ± 0.0*
Force, N	401 ± 108	654 ± 239*	423 ± 222	672 ± 264*	405 ± 125	660 ± 200*
Work, J	155 ± 70	203 ± 91	167 ± 84	177.3 ± 71	174 ± 59	214 ± 87
Power, W	218 ± 131	226 ± 118	222 ± 134	217 ± 124	251 ± 129	261 ± 124
Velocity, radians	0.41 ± 0.16	0.28 ± 0.10*	0.41 ± 0.13	0.27 ± 0.09*	0.47 ± 0.13	0.32 ± 0.09*
RPE	11.7 ± 1.6	14.2 ± 2.5*	11.4 ± 1.6	13.1 ± 2.4*	11.3 ± 2.1	12.9 ± 2.4*
Knee Extension	**LO**	**HI**	**LO**	**HI**	**LO**	**HI**
% 1RM	40.0 ± 0.0	70.0 ± 0.0*	40.0 ± 0.0	70.0 ± 0.0*	40.0 ± 0.0	70.0 ± 0.0*
Force, N	27.7 ± 8	44.5 ± 13*	29.4 ± 10	40.1 ± 17*	29.8 ± 10	44.2 ± 13*
Work, J	32.3 ± 13	46.9 ± 15*	34.5 ± 15	45.7 ± 16*	36.2 ± 15	47.9 ± 17*
Power, W	46.9 ± 22	56.3 ± 29	45.7 ± 27	54.7 ± 29	51.9 ± 26	60.5 ± 31
Velocity, radians/sec	1.91 ± 0.43	1.39 ± 0.37*	1.79 ± 0.66	1.47 ± 0.36	1.97 ± 0.45	1.52 ± 0.41*
RPE	13.5 ± 1.8	15.1 ± 2.1*	13.1 ± 1.2	14.7 ± 1.9*	13.2 ± 2.3	14.5 ± 1.6*

Values are mean ± SD. * = significant difference between training groups ($P < 0.05$)
RPE: Rate of perceived exertion (6-20 Borg scale)

5.3.3 Attrition and training adherence

One of the 25 subjects randomized to LO and three of the 27 subjects randomized to HI dropped out of the training interventions. The LO participant withdrew due to an illness (week 7). From HI, one subject reported a hamstring injury and back pain after a training session (week 2), one subject discontinued secondary to exacerbation of preexisting chronic obstructive pulmonary disease (week 5), and one participant had a non-injurious fall outside of the laboratory after a training visit (week 10). This participant was withdrawn from the study after consultation with the study investigators and the participant. No other adverse events were reported. Overall adherence rates (number of training session attended / total number of session), including all withdrawals, were excellent and corresponded to 88 ± 12% (range: 31% - 100%) in LO and 82 ± 23% (range: 9% - 100%) in HI.

5.3.4 Muscle power, contraction velocity, muscle strength

Absolute and relative changes in muscle power, contraction velocity and muscle strength are presented in Tables 5.3 (leg extension) and Table 5.4 (knee extension). At week 4, no significant within or between group changes were evident for any measure of LP or KE muscle power, contraction velocity or muscle strength. However, by week 16, large and statistically significant increases in LP muscle power, contraction velocity and strength were elicited within both groups. While the magnitude of these improvements were consistently greater in HI compared to LO, no statistically significant between-group differences were evident. For KE, each intervention group was associated with significant gains in all parameters measured (except contraction velocity at 70% 1RM), however, no between-group differences were evident.

Table 5.3 **Leg extensor muscle power, contraction velocity and strength: absolute and relative changes at week 4 and week 16**

			Week 4				Week 16			
	Power Training Group	Baseline Value mean ± SD	Delta^ mean ± SE	% Change mean ± SE	P (within group)	P (between groups)	Delta^ mean ± SE	% Change mean ± SE	P (within group)	P (between groups)
Peak Power (40%), W	LO	243 ± 113	10.3 ± 9.7	6.2 ± 6	0.29	0.54	50.4 ± 15	34.0 ± 11	0.002	0.26
	HI	260 ± 140	1.9 ± 9.3	6.2 ± 5	0.84		74.8 ± 15	42.1 ± 8	0.001	
Contraction Velocity (40%), m/s	LO	0.48 ± 0.13	0.01 ± 0.02	1.2 ± 5	0.76	0.47	0.06 ± 0.02	17.7 ± 6	0.005	0.55
	HI	0.47 ± 0.15	-0.01 ± 0.02	1.9 ± 5	0.47		0.08 ± 0.02	25.2 ± 7	0.0004	
Peak Power (70%), W	LO	273 ± 131	6.9 ± 12.2	5.5 ± 4.7	0.57	0.68	47.6 ± 17	32.9 ± 13	0.007	0.40
	HI	282 ± 153	-0.01 ± 11.7	4.0 ± 4.5	0.99		67.7 ± 17	41.6 ± 12	0.001	
Contraction Velocity (70%) , m/s	LO	0.35 ± 0.10	0.003 ± 0.016	1.6 ± 4.7	0.87	0.23	0.03 ± 0.02	14.6 ± 7	0.07	0.73
	HI	0.34 ± 0.11	-0.02 ± 0.02	-4.8 ± 4.5	0.12		0.04 ± 0.02	21.2 ± 9	0.02	
1RM Strength, N	LO	882 ± 258	4.4 ± 35.0	0.7 ± 3.5	0.90	0.97	116.1 ± 38.7	13.3 ± 4	0.003	0.41
	HI	940 ± 344	2.6 ± 33.7	1.1 ± 3.4	0.94		160.6 ± 37.9	19.2 ± 4	0.0001	

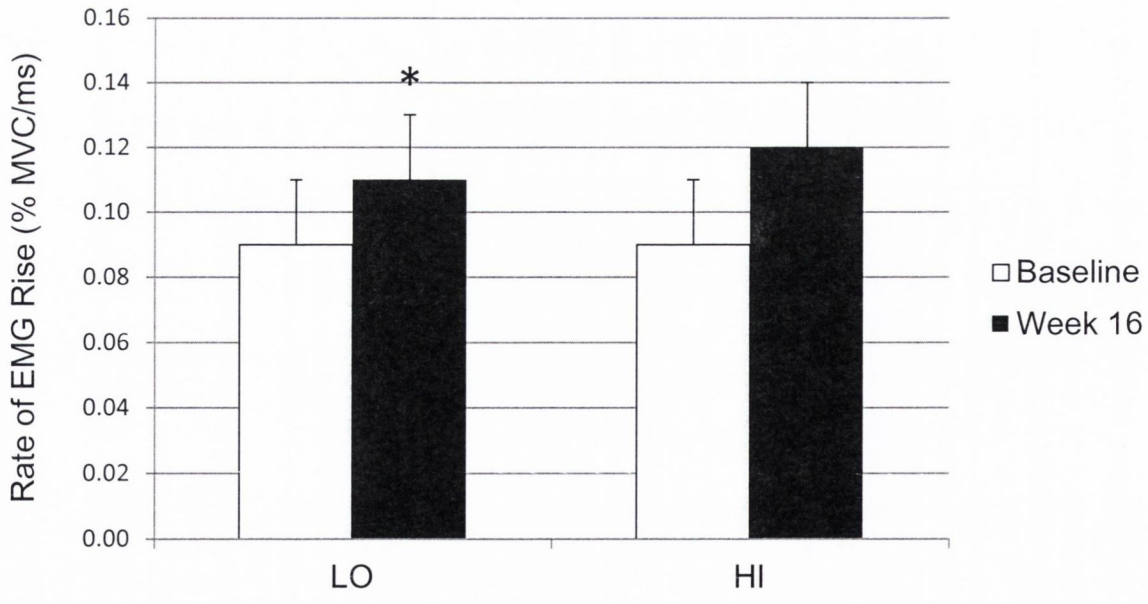
Table 5.4 **Knee extensor muscle power, contraction velocity and strength: absolute and relative changes at week 4 and week 16**

			Week 4				Week 16			
	Power Training Group	Baseline Value mean ± SD	Delta^ mean ± SE	% Change mean ± SE	P (within group)	P (between groups)	Delta^ mean ± SE	% Change mean ± SE	P (within group)	P (between groups)
Peak Power (40%), W	LO	51.8 ± 25	1.3 ± 2	6.8 ± 4	0.45	0.25	10.4 ± 3	30.3 ± 8	0.001	0.57
	HI	60.7 ± 25	0.3 ± 3	3.3 ± 4	0.91		11.7 ± 2	26.46 ± 9	0.001	
Contraction Velocity (40%), radians/s	LO	2.04 ± 0.5	0.06 ± 0.05	5.1 ± 4	0.29	0.25	0.15 ± 0.05	10.4 ± 4	0.006	0.39
	HI	2.15 ± 0.4	0.13 ± 0.07	8.6 ± 5	0.06		0.15 ± 0.07	10.0 ± 5	0.05	
Peak Power (70%), W	LO	61.6 ± 28	1.7 ± 3	8.7 ± 7	0.59	0.69	14.6 ± 4	27.1 ± 8	0.001	0.72
	HI	76.7 ± 38	3.3 ± 3	6.1 ± 4	0.25		12.1 ± 4	27.6 ± 12	0.01	
Contraction Velocity (70%) , radians/s	LO	1.64 ± 0.4	0.004 ± 0.07	2.6 ± 5	0.95	0.60	0.05 ± 0.07	4.5 ± 5	0.42	0.99
	HI	1.82 ± 0.3	0.01 ± 0.05	1.5 ± 3	0.82		-0.001 ± 0.07	1.1 ± 4	0.99	
1RM Strength, N	LO	58.1 ± 24	-2.6 ± 2	-2.9 ± 3	0.19	0.39	8.9 ± 3	20.3 ± 5	0.002	0.45
	HI	65.7 ± 25	-0.2 ± 3	-0.1 ± 4	0.92		10.9 ± 3	22.4 ± 7	0.001	

5.3.5 Neuromuscular activation

Rate of vastus lateralis neuromuscular activation (Figure 5.2) was largely unchanged at week 4 within both groups ($P > 0.77$). However, at week 16, rate of activation improved in both groups and was significantly improved in LO ($P = 0.03$), but not in HI ($P = 0.65$). No between-group differences at week 4 or week 16 were evident ($P > 0.26$). Rate of vastus lateralis neuromuscular activation was unchanged at week 4 within both groups ($P > 0.77$). However, at week 16, rate of activation increased in both groups and was significantly improved in LO ($P = 0.03$) but not in HI ($P = 0.65$) (Figure 5.2). No between-group differences were found ($P > 0.26$).

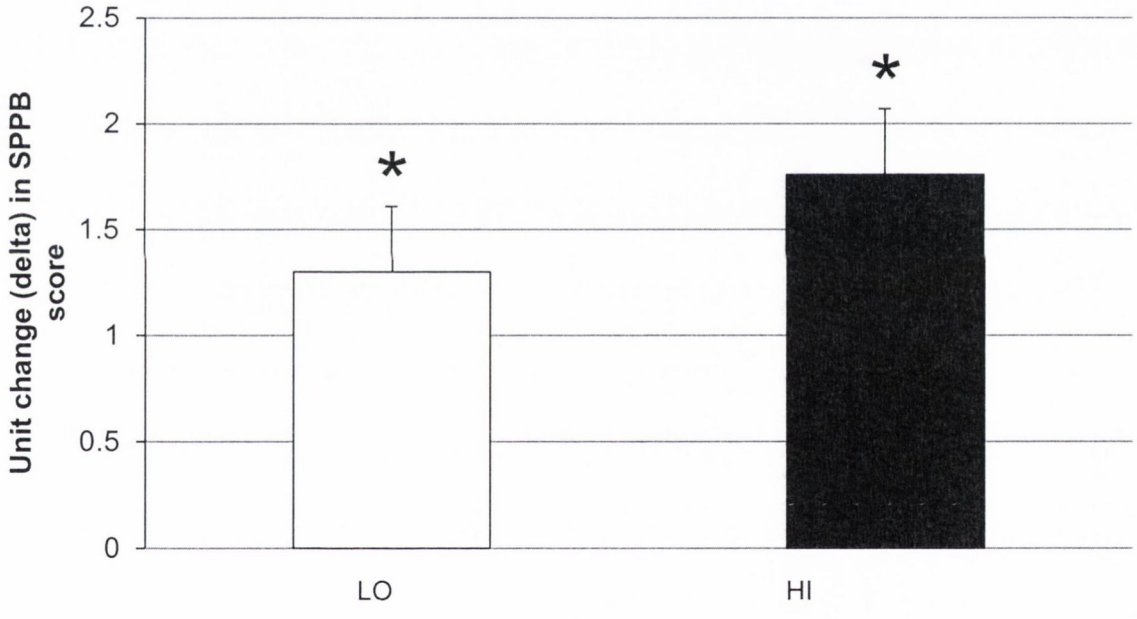
Figure 5.2 **Rate of vastus lateralis muscle activation: baseline vs. week 16 (absolute mean ± SE)**
*** = significant within-group difference ($P < 0.05$)**



5.3.6 Short physical performance battery

Significant improvements in SPPB score were elicited within both groups at week 16 (Figure 5.3). LO was associated with a 1.3 unit ($P < 0.001$) increase in SPPB score. In HI, the corresponding improvement of SPPB score was greater (1.8 unit increase, $P < 0.001$), however, overall between-group differences for this parameter were not evident ($P = 0.32$).

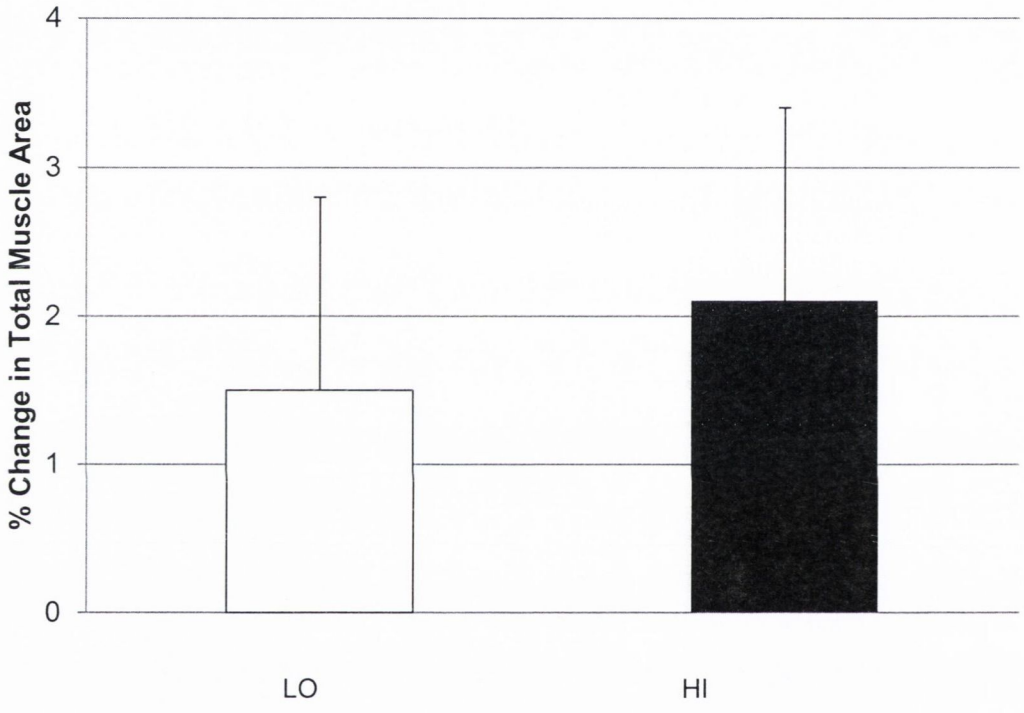
Figure 5.3 Changes in SPPB score: baseline vs. week 16
(values adjusted means ±SE)
*** = significant within-group difference ($P < 0.05$)**



5.3.7 Muscle size

Figure 5.4 displays the changes in muscle mass as a result of LO and HI. At week 16, non-significant but detectable gains in total mid-thigh muscle CSA were evident in LO (1.6%, P = 0.35) and 2.1% in HI (P = 0.17) (between-group difference: P = 0.78).

Figure 5.4 **% Change in mid-thigh muscle cross sectional area: baseline vs. week 16 (values are adjusted means ± SE)**



5.4 Discussion

This is the first study to directly compare the effects of two definitive high velocity power training interventions on changes in muscle power, mobility performance, muscle mass and neuromuscular activation in mobility-limited older adults. The major finding from this investigation is that both modes of velocity-specific (LO) and force-specific (HI) power training elicited significant and comparable improvements in lower extremity muscle power and substantial improvements in mobility performance after 16 weeks. While participants randomized to HI had markedly greater improvements in leg extensor muscle power and mobility performance compared to LO, the magnitude of these respective gains were not statistically different between groups. This study also demonstrated that both LO and HI power training interventions elicited notable changes in neuromuscular activation and muscle mass within this population of frail older adults, although these improvements were not all statistically significant.

5.4.1 Magnitude and timecourse for changes in muscle power

The magnitude of lower extremity muscle power improvements in the current investigation (~26% to ~42%) are of particular interest when compared to previous studies. Reid et al. reported improvements in knee and leg extensor power output that ranged from ~23% to ~ 30% after 12 weeks of high velocity power training (performed at 70% 1RM) in mobility-limited older adults (Reid et al. 2008). Similarly, in healthy older subjects, peak muscle power output has been shown to improve by ~15% after 12 weeks of high velocity power training at 3 different training intensities (20% 1RM, 50% 1RM, or 80% 1RM) (de Vos et al. 2005). The longer duration and volume of power training in the current study may explain the greater muscle power gains observed compared to these previous studies. However, our findings are in significant contrast to two other previous studies. In healthy older adults, 12 weeks of high velocity training (at

a resistance equivalent to 70% of body mass) resulted in emphatic gains of leg extensor muscle power of ~150% (Earles et al. 2001). Similarly, Fielding et al. demonstrated that 16 weeks of high velocity power training (at 70% 1RM) resulted in improvements of lower extremity power output ranging from ~33 to ~97% in older females with self-reported disability (Fielding et al. 2002). This study also demonstrated rapid early improvements in knee extensor and leg extensor muscle power (~15% to ~53% after 4 week). In the current study, no changes in muscle power were observed after 4 weeks of LO or HI. A limitation of this study is that additional interim assessments of muscle power were not made (e.g. at week 8 and 12) which would have provided valuable information of the timecourse of muscle power improvements to power training in mobility-limited older adults. However, taken together, our findings suggest that the training-induced adaptations that occur in response to high velocity power training in older adults with mobility limitations are not rapid. In addition, the overall capacity for muscle power improvements in mobility-limited older adults is blunted compared to healthy older adults.

5.4.2 Effects of LO and HI on mobility

The current study demonstrated that both LO and HI are associated with important and substantial improvements in mobility performance. The observed improvements in SPPB within LO (1.3 unit) and HI (1.8) are clinically relevant, as a 1-unit improvement in SPPB score is considered a meaningfully large clinical effect (Perera et al. 2006). The magnitude of SPPB improvements in the current study are higher than a previous study that has evaluated the effects of high velocity resistance training on the SPPB score. In healthy subjects with a baseline SPPB score of 10.6, a 12 week power training intervention increased SPPB score by 0.7 units (Earles et al. 2001). Our findings are also comparable or greater than several other studies that have evaluated different types of

exercise interventions that did not utilize resistance training equipment but emphasized explosive power movements (Bean et al. 2004; Bean et al. 2009; Pahor et al. 2006). These programs of weighted stair climbing and weighted vest mobility-specific exercises that incorporated high velocity movements, ranging from 12-16 weeks in duration, have been shown to improve SPPB score by 1.1 to 2.7 units in older adults with mobility limitations (Bean et al. 2004; Bean et al. 2009). In addition, the improvements in SPPB after LO and HI in the currently study are greater than improvements after longer term (6 and 12) months of multi-modal aerobic, strength and balance exercise (Pahor et al. 2006).

While there were no statistically significant differences in the magnitude of the improvements in SPPB between LO and HI groups, the adjusted mean difference in SPPB score between groups at week 16 was 0.46 units. Differences of 0.28–0.52 units have been previously reported as being clinically relevant small differences in SPPB performance (Perera et al. 2006).

5.4.3 Changes in neuromuscular activation and muscle mass

The improvements in muscle performance and mobility observed after 16 weeks of LO and HI may be attributed to both neural and muscular adaptations. Importantly, the current study suggests that the training induced adaptations in neural drive and increased muscle CSA are mechanistically similar, but of a lower magnitude, compared to adaptations shown in younger subjects and more healthy older populations (Aagaard et al. 2010). In the present study, the changes in neuromuscular activation mirrored the overall changes in muscle performance in both LO and HI groups, and interestingly, no changes in neuromuscular activation were evident after 4 weeks in either group. Previous studies in healthy younger and older adults have shown early and acute neural

adaptations to resistance training performed at various intensities and contraction velocities (Aagaard et al. 2010; Caserotti et al. 2008; Hakkinen et al. 1998b). Our data suggest however, that despite robust training stimuli for neuromuscular adaptations, mobility-limited participants elicit delayed neuromuscular responses to high velocity power training.

Previous investigations specifically designed to induce muscle hypertrophy in older individuals using high intensity resistance training have reported gains in muscle CSA ranging from 5-12% after 10-14 weeks of training (Frontera et al. 1988; Hakkinen et al. 1998b; Suetta et al. 2004). The changes in muscle CSA in the current study are modest in comparison to these previous studies. However, eliciting gains in muscle CSA was not a major goal of either the LO or HI power training employed in this study. Although HI was associated with noticeably higher improvements in muscle CSA compared to LO, this likely occurred as a result of training at significantly greater absolute force levels throughout the HI intervention (Table 5.2).

Overall, it may be important to consider the gains in neural function and muscle CSA from LO and HI in the context of some of the age-related morphology associated with mobility-limited older adult. We have recently demonstrated that mobility-limited older adults have significant deficits in neuromuscular function and more precipitous declines in muscle mass when compared to healthy middle aged and healthy older adults (Reid et al. 2012). Therefore, any therapeutic intervention, such as LO or HI, that can preserve or increase neural function or muscle mass within mobility-limited older adults may have important clinical significance.

5.4.4 Study Limitations

A limitation of this study is that additional interim assessments of muscle power were not made (e.g. at week 8 and 12). This would have provided valuable information of the timecourse of muscle power improvements to power training in mobility-limited older adults. In addition, another limitation of this study is that it was significantly underpowered to detect clinically meaningful between group differences for changes in leg power or SPPB score after LO and HI. A post-hoc power analysis revealed that the study only had 10% statistical power (alpha level: 0.05) to detect a significant difference between the changes in leg extensor muscle power at week 16 (Faul et al. 2007). On the basis of the mean, between-groups comparison effect size observed for leg muscle power in the present study (Cohen's d = 0.18), an approximate sample size of 380 participants per study group would be needed to obtain statistical power at the recommended .80 level (Cohen 1992). Similarly, post hoc power analysis revealed that the current study only had 23% statistical power to detect a significant between-group differences in SPPB score at week 16, and based on the observed mean, between-groups comparison effect size for SPPB score (Cohen's d = 0.34), a minimum sample size of approximately 108 participants per study group would be needed to obtain statistical power for this outcome measure at the recommended .80 level. Finally, the limited sample sizes in the current study may also partially explain some of the inconsistencies identified between the training intensities reported in Table 5.2 and the overall study outcome measures. The intensity of some of the training parameters (Force, work, power and velocity) did not increase progressively throughout the 16 week training period in both groups. A possible explanation for this observation, coupled with the limited samples sizes, may be due to the relatively high variably of the measured parameters at the respective time-points throughout the intervention.

5.4.5 Practical implications

In addition to the important clinical and physiological outcomes, there are important practical implications related to our study findings. Compared to HI, participants in the LO training group, using lighter resistance and moving the training loads more rapidly, attained clinically important gains in muscle power and mobility. This outcome, which were accomplished with overall lower total workloads and consistently lower rates of perceived exertion (Table 5.2), may have important implications for exercise prescription strategies for older adults as the use of lighter weights moved more rapidly may be a more practical form of high velocity power training. This may be of particular relevance for older adults with chronic conditions as arthritis, osteoporosis, or other debilitating disorders where high intensity exercise may be contraindicated or poorly tolerated. LO training has also been previously associated with lower perceived exertion when compared to traditional strength training (Sayers 2007). Additional research is necessary to encourage long term participation in various modalities of resistance training for preserving muscle power and mobility in older adults.

5.5 Conclusion

In conclusion, this study demonstrated that two distinct 16 week power training interventions, performed at low intensity or high intensity, elicited significant and comparable improvements in muscle power and clinically meaningful improvements in mobility performance in mobility-limited older adults. These improvements were associated with adaptations in neuromuscular function and small increases in muscle mass. The overall gains in muscle power, mobility, together with enhanced neural function and muscle hypertrophy, further demonstrate the utility of high velocity power training for increasing muscle power, counteracting mobility loss, and its therapeutic potential for addressing a major clinical and physiological issue affecting older adults.

Section C

Chapter 6

Cognitive function as a predictor of physical activity adherence in the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study

6.1 Introduction and study rationale

Participation in regular physical activity may be one of the most important health behaviors associated with the prevention and management of chronic disease and the promotion of health and well-being among older adults (Brassington et al. 2002; Williamson and Pahor 2010). While a significant amount of research has been conducted to explore factors related to the adoption and maintenance of physical activity in middle-aged and younger adults, few studies have examined the factors that influence physical activity participation among adults aged > 65 years (Brassington et al. 2002; King et al. 1998; Rejeski et al. 2007). Furthermore, little is known about the major determinants of adherence to physical activity among older adults during interventions over prolonged durations (> 6 months).

The Lifestyle Interventions and Independence for Elders Pilot study (LIFE-P) was conducted to examine the feasibility of conducting a large multi-center clinical trial on the effects of increasing physical activity in sedentary, older individuals at risk for mobility disability (Rejeski et al. 2005). Independent factors previously shown to influence adherence to this long term (12 month) physical activity intervention include chronic disease burden and self-reported symptoms of chronic disease (Fielding et al. 2007; Rejeski et al. 2007). The potential influence of baseline cognitive function on subsequent adherence to the LIFE-P physical activity intervention was not examined in either of these previous investigations. However, recent studies have shown that older adults with lower cognitive function (reduced executive functioning) were less adherent to a 3-month exercise based cardiac rehabilitation program. Importantly, these participants with low adherence also had poorer outcomes following from their exercise intervention (Kakos et al. 2010). Similarly, in a recent study involving older retirement village residents, impaired global cognitive function (assessed

using the Mini-Mental State Examination) was found to be a significant independent predictor of low physical activity adherence during a 6-12 month intervention period (Tiedemann et al. 2011).

The purpose of this investigation was to investigate whether measures of baseline cognitive function predict subsequent adherence to the LIFE-P physical activity intervention (PA). Data was examined form the cognitive sub-study of LIFE-P and four domains of cognitive function (global cognition, executive functioning, psychomotor speed and working memory) were evaluated (Williamson et al. 2009). We hypothesised that lower levels of cognitive functioning would be predictive of low adherence to PA. In addition, we also explored whether measures of cognition would be associated with medical suspensions during the physical activity program in LIFE-P. We also hypothesised that lower cognitive function would be associated with higher rates of medical suspensions during PA.

6.2 Methods

6.2.1 Secondary analysis of LIFE-P dataset

This study represents secondary analysis of the existing LIFE-P study dataset. In order to test the aims and hypothesis described in section 6.1, an analysis proposal was submitted to the LIFE Study Publications and Presentations Committee for review and subsequent approval (see Appendix E for approval notice). A LIFE study statistician (Michael Walkup, M.S.) conducted the statistical analysis described below. The subsequent Results (6.3) and Discussion (6.4) sections describe the findings from this secondary analysis of the LIFE-P dataset.

6.2.2 Study design

The LIFE-P study was a single-blind, multicenter, randomized controlled trial of a PA intervention compared to a successful aging (SA) intervention in sedentary older adults. The study was designed to help plan a definitive phase 3 randomized controlled trial to examine the efficacy of a program of physical activity, compared with SA on the incidence of major mobility disability in older adults. Complete descriptions of the LIFE-P study design and overall findings have been reported previously (Pahor et al. 2006; Rejeski et al. 2005; Williamson et al. 2009). Briefly, the study was conducted at four field centers across the United States (Cooper Institute, Stanford University, University of Pittsburgh, and Wake Forest University). The LIFE-P cognitive sub-study was conducted at Stanford University and Wake Forest University (Williamson et al. 2009). Participants were observed for an average of 1.2 years, and the major findings from LIFE-P were that a structured PA intervention resulted in clinically meaningful improvements in physical performance compared to SA (Pahor et al. 2006). The results from the LIFE-P cognitive sub-study

demonstrated a positive association between improvements in physical performance and enhanced cognitive function.

6.2.3 Study participants

The study was approved by the local institutional review boards, participants provided written informed consent and a data safety monitoring board monitored safety and the conduct of the trial. Participants were recruited in the age range of 70–89 years. Additional inclusion criteria included a sedentary life style (< 20 min/wk spent in structured PA), able to walk 400 m within 15 minutes without sitting and without use of any assistive device, and Short Physical Performance Battery (SPPB) score 9 or less (of 12). Participants with severe heart failure, uncontrolled angina, severe pulmonary disease, severe arthritis, cancer requiring treatment in the past 3 years, Parkinson's disease or other serious neurological disorders, life expectancy of less than 12 months, or a Mini-Mental State Examination score less than 21 were ineligible. Temporary exclusion criteria were acute myocardial infarction, deep venous thrombosis, pulmonary embolism, major arrhythmias, or stroke within 6 months, recent major surgery, uncontrolled hypertension, uncontrolled diabetes, and ongoing lower extremity physical therapy.

Recruitment relied primarily on mass mailing, community outreach, and media advertising. Participants who were eligible after an initial phone screening were invited for clinic visits, during which they signed the informed consent form (See Appendix E) and completed a personal interview, the SPPB, a physical exam, an electrocardiogram, and a 400-meter walk test. Eligible participants received detailed instructions for a 1-week to 2-week behavioral run-in, during which they were asked to self-monitor specific behaviors and to complete

forms related to these behaviors. Participants who successfully completed the behavioral run-in received additional baseline assessments and were randomized to the study interventions via a web-based system. Of the 3141 persons who were initially screened by phone, a total of 424 (13.5%) were ultimately randomized to LIFE-P across the four field centers. For the cognitive sub-study, the first 50 participants at the Stanford University and Wake Forest University field centers were administered a cognitive assessment battery at baseline.

6.2.4 Physical activity intervention

The PA intervention consisted of a combination of aerobic, strength, balance, and flexibility exercises. The intervention was divided into three phases: adoption (weeks 1–8), transition (weeks 9–24), and maintenance (week 25 to the end of the trial). Each participant in the PA group received a 45-minute individualized, introductory session to describe the intervention and to provide individual counseling to optimize safety and participation. For the first 2 months (adoption), three center-based exercise sessions (40–60 min) per week were conducted in a supervised setting. During the next 4 months (transition), the number of center-based sessions were reduced (2/week) and home-based endurance/strengthening/flexibility exercises (≥3/week) were started. The subsequent maintenance phase consisted of the home-based intervention, optional once-to-twice-per-week center-based sessions, and monthly telephone contacts. The PA intervention included group-based behavioral counseling sessions (1/week for the first 10 weeks) that focused on PA participation and disability prevention, and on encouraging participants to increase all forms of PA. The PA intervention focused on walking as the primary mode of exercise. The goal was walking for at least 150 minutes over the course of the week (Rejeski et al. 2005).

Each session was preceded by a brief warm-up and followed by a brief cool-down period. To complement the walking program, participants completed lower extremity strengthening exercises, followed by lower extremity stretching exercises. Balance training was introduced during the adoption phase. The intensity of training was gradually increased over the first 2–3 weeks. Perceived exertion assessed by the Borg scale (Borg 1970) was used to regulate the intensity of exercise; moderate intensity exercise was promoted. Participants were asked to walk at a target intensity of 13 (somewhat hard), and they were discouraged from exercising at levels ≥15 (hard) or ≤11 (fairly light). Strengthening exercises were performed at a perceived exertion of 15–16.

6.2.5 Successful aging intervention

An SA health education intervention was used as the active control and was designed to provide attention and health education to participants (Rejeski et al. 2005). Participants met in small groups weekly for the first 26 weeks and then monthly to the end of the trial. Sessions included health topics relevant to older adults such as nutrition, medications, foot care, and recommended preventive services at different ages. Basic educational information related to PA was provided, but there was no content provided describing the PA intervention.

6.2.6 Outcome Measures - Cognitive assessment battery

The assessment battery was adapted from the Action to Control Cardiovascular Risk in Diabetes (ACCORD)—Memory in Diabetes trial (Williamson et al. 2007). This battery was developed specifically for the purpose of incorporating cognitive assessment as a secondary outcome in a large cardiovascular clinical trial (ACCORD). It was chosen by the LIFE study

investigators based on its broad assessment of domains of cognition likely to be affected by the LIFE-P intervention, in addition to experience gained from ACCORD study on the feasibility of administering this battery in a large clinical trial. The cognitive battery consisted of four primary components:

Modified Mini-Mental State Examination (3MSE) is a widely used measure of global cognitive functioning (Teng and Chui 1987). This is an expanded 100-point version of the original Folstein Mini-Mental State Examination (Folstein et al. 1975).

Modified Stroop test (Stroop) as a measure of processing speed, cognitive flexibility, and inhibition or disinhibition. This test consists of three subtasks: color word naming, color naming, and naming of color words printed in a different color from the color word (interference component). Participant score is the difference between tests 2 and 3.

Digit Symbol Substitution Test (DSST) as a measure of psychomotor speed and working memory (Salthouse 1978). The DSST has proven to be feasible in aging studies and large multicenter clinical trials (Launer et al. 2000). Participants are given a series of numbered symbols and then asked to draw the appropriate symbols below a list of random numbers. The score is the number of correctly made matches in 1 minute.

The Rey Auditory Verbal Learning Test (RAVLT), a test of short- and long-term verbal memory assessing the ability to learn a list of 15 common words (Estevez-Gonzalez et al. 2003). The study participant is read this list five times, and after each time, he or she immediately recalls as many words as possible. Following the fifth recall, an interference list is presented after which the participant is asked to spontaneously recall words from the original list. Then, a 10-minute interval passes and he or she is asked again to remember

spontaneously as many words as possible from the first list (delayed recall). Scoring is based on total correct words across all components.

6.2.7 Measures of adherence

Attendance at center-based physical activity sessions was reported as the percentage of attended sessions relative to the total number of possible sessions in each study phase, excluding facility closings (e.g., holidays, weather emergencies, etc.). Attendance was also calculated excluding sessions missed because of suspended status. During maintenance, adherence was also assessed by completion of the home activity logs. The dose of physical activity was examined by evaluating the intensity and duration of physical activity throughout the trial.

6.2.8 Medical suspension from physical activity

Participants were placed on suspended status if they missed three or more consecutive sessions of center-based physical activity (adoption and transition), or two or more weeks of home-based PA (maintenance) because of a health event. Participants were allowed to rejoin the PA intervention after suspension, after receiving medical clearance from their primary care physician and the development of a modified physical activity plan by the study interventionist. Study staff contacted suspended participants by telephone at least monthly to determine whether and when the health event had resolved. Evaluation to rejoin the physical activity intervention included an assessment of the functional impact of the illness and activity-limitation prescriptions provided by the participant's health care team. After clearance from the primary-care physician, the participant was reevaluated by study staff and a new level of physical activity was developed. The participants completed the duration

of the PA intervention as originally scheduled (12 months) regardless of the length of their medical suspension, and no makeup physical activity sessions were provided.

6.2.9 Statistical analysis and statistical power estimates

Data analysis was performed using SAS statistical software (Version 9.2, SAS Institute Inc., Cary, North Carolina). Statistical significance was accepted at $P \leq 0.05$ and results are reported as mean ± SD. All data variables were examined for normality both graphically and statistically. The primary outcome measures were the correlations between the four baseline measures of cognition and the levels of subsequent PA adherence. Univariate correlation analyses (Pearson) were performed to examine the associations between baseline measures of cognitive function and subsequent PA adherence. Separate analyses were conducted for each of the adoption, transition and maintenance phases of the intervention. In the adoption and transition phases, percent attendance per participant was calculated by dividing the number of sessions attended by the expected number of sessions. For the maintenance phase, the total number of sessions attended was used as the index of PA adherence. With 49 participants having data on each cognition and PA adherence variable, a post-hoc statistical power estimate revealed that this study had approximately 80% power to detect correlations of 0.40 or larger, assuming a 0.05 two-sided alpha level. To further examine the influence of baseline cognition on subsequent PA adherence, independent samples T tests were used to test whether group differences existed for baseline cognition in participants with subsequent low PA adherence compared to those with high PA adherence in the adoption, transition, and the average of adoption and transition phase PA adherence. The median level of adherence was used as the cut point to define low and high PA adherence in the respective phases of PA . Group differences were adjusted for gender and site. Linear regression

models were used to examine the relationships between baseline cognitive function and home log completion rates throughout PA. Logistic regressions models examined whether baseline cognitive function was predictive of medical suspensions during PA

6.3 Results

6.3.1 Participant Characteristics

A total of 102 participants were administered the cognitive battery at the baseline examination in LIFE-P. From these participants a total of 50 participants were randomized to the PA intervention. All participants successfully completed the cognitive assessment battery at baseline except for 1 participant who did not complete the Modified Stroop test. One participant from PA (death) did not complete the study intervention. The baseline characteristics are shown in Table 6.1.

Table 6.1 Baseline characteristics of PA participants (n = 50) in the cognitive sub-study of LIFE-P

Variable	PA Participants
Age, yr	76.9 ± 4.5
BMI (kg/m^2)	28.9 ± 5.2
Female gender, n (%)	36 (72)
SPPB score	7.9 ± 1.2

Values are mean ± SD. BMI: body mass index;
SPPB: Short Physical Performance Battery

6.3.2 Relationship between cognitive function and PA adherence

Results of the correlation analysis between the four domains of cognitive function and level of PA adherence are provided in Table 6.2. No significant relationships were found between any measure of cognitive function and subsequent level of PA adherence at any phase in LIFE-P (all $P \geq 0.14$).

Table 6.2 Correlation coefficients between domains of cognitive function and subsequent adherence to PA during LIFE–P

Variable	Adoption phase adherence (%)	Transition phase adherence (%)	Maintenance phase adherence (number of sessions)
3MSE	-0.04 (P = 0.79)	0.03 (P = 0.82)	0.03 (P = 0.86)
DSST	-0.21 (P = 0.14)	-0.11 (P = 0.45)	-0.06 (P = 0.69)
Stroop*	0.12 (P = 0.40)	0.11 (P = 0.45)	-0.10 (P = 0.52)
RAVLT	-0.13 (P = 0.38)	-0.12 (P = 0.42)	-0.12 (P = 0.41)

* One participant did not complete the Modified Stroop test at baseline

6.3.3 Cognitive function in participants with low vs. high levels of PA adherence

The median cut point for low and high PA adherence level in the adoption phase was 82.6%, transition phase was 72.3%, and combined was 77.1%. Table 6.3 displays the overall results comparing baseline measures of cognitive function across the dichotomised level of PA adherence. Compared to participants with high adherence, no significant group differences were evident in any domain of baseline cognitive function for participants with subsequent low adherence to the PA intervention (all $P \geq 0.11$).

Table 6.3 Baseline measures of cognition: low vs. high PA adherence

	PA Adherence								
	Adoption Phase Adherence^			Transition Phase Adherence ^			Combined^		
	Low (n = 24)	High (n = 25)	P-value	Low (n = 24)	High (n = 25)	P-value	Low (n = 24)	High (n = 25)	P-value
3MSE	26.4 ± 2.9	27.4 ± 2.4	0.43	26.8 ± 2.8	27.2 ± 2.5	0.64	26.4 ± 2.9	27.6 ± 2.2	0.13
Stroop*	37.7 ± 15.4	41.8 ± 25.0	0.72	39.9 ± 18.0	40.3 ± 25.0	0.98	39.3 ± 15.2	40.9 ± 26.9	0.87
DSST	47.3 ± 11.0	43.5 ± 13.2	0.11	43.6 ± 11.8	46.5 ± 13.0	0.32	45.2 ± 10.9	44.8 ± 13.9	0.93
RAVLT	6.5 ± 2.8	6.0 ± 3.4	0.84	5.9 ± 2.9	6.5 ± 3.5	0.25	6.2 ± 2.9	6.2 ± 3.5	0.58

Values mean ± SD
^Adoption phase of the intervention is weeks 1-8
^Transition phase of the intervention is weeks 9-24
^Combined is the adoption + transition is weeks 1-24
* One participant in the Low group did not complete the Modified Stroop test at baseline

6.3.4 Cognitive function vs. home log completion rate and medical suspensions

Similarly, no association between any domain of cognitive function and the number of home logs completed was evident. However, logistic regression analysis revealed that greater baseline levels of 3MSE, an index of global cognitive functioning, was associated with a reduced rate of medical suspensions from PA (Odds ratio = 0.797, P = 0.02, 95% CI (0.657, 0.965)).

6.4 Discussion

The major finding of this study is that cognitive function is not a determinant of adherence to a long-term intervention of multi modal physical activity in the LIFE-P study. We demonstrated that within this population of frail older adults, cognition performance assessed across multiple domains including executive functioning, global cognition and short and long term working memory, did not impact subsequent adherence to PA in LIFE-P. However, greater baseline global cognitive function was associated with a lower likelihood of a medical suspension during LIFE-P.

Although our primary observations were contrary to our initial hypothesis, there are important considerations associated with our findings. In LIFE-P, participants with evidence of dementia at baseline were excluded from participation (MMSE level < 21) (Pahor et al. 2006). However, participants with baseline MMSE scores from 21-25, which indicates mild cognitive impairment or mild dementia, were enrolled into the study. Therefore, the null findings of the current investigation suggest that aspects of the LIFE-P study design may have been important in limiting any potential influence of cognition and adherence to physical activity. In particular, specific components of the PA intervention may have diminished the potential influence of cognition function and PA adherence as, in addition to the multi modal physical activity regimen, the PA intervention was augmented with weekly closed-group behavioral counseling sessions that focused on physical activity adherence and the prevention of physical disability. Such behavioral groups sessions are effective for older adults in promoting commitment to physical activity and as a strategy to cope with the process of physical disablement (Rejeski et al. 2003). Previous studies that have identified cognitive function as a significant determinant of activity adherence in cardiac rehabilitation patients and among older persons in retirement villages did not include any additional

behavioral counseling sessions to support physical activity adherence (Kakos et al. 2010; Tiedemann et al. 2011). Taken together, our findings suggest that behavioral counseling, specifically targeted to promote physical activity adherence among older adults in exercise programs, may not only be important for improving the delivery and application of exercise programs, but also limiting the influence of potential barriers to physical adherence such as cognitive impairment.

Our analyses reported a relationship between global cognition and the development of inter-current illness and resulting medical suspensions during PA. As lower cognitive scores have been previously shown to predict medical events in older adults, and as the vast majority of medical suspensions in LIFE-P were not related to participation in PA, it is likely that external factors beyond the scope of this analysis, such as prevalence of co-morbid medical conditions, may help explain this association (Phillips et al. 2010; Stephan et al. 2011).

Several other factors could have influenced the findings in the present study. Due to the small sample size, the current analysis may have been underpowered to detect a true relationship between cognition and physical activity adherence. In addition, the 12 month duration of PA may not have been of sufficient duration for any potential baseline cognitive impairments to manifest into non-adherence in PA. Finally, the results of this study are limited to older adults who were motivated to volunteer for a 12 month randomized controlled trial.

6.5 Conclusion

In conclusion, the results of the study demonstrate that baseline measures of cognitive function are not predictive of subsequent adherence to PA in LIFE-P. Study design aspects, including inherent components of the PA intervention that targeted physical activity adherence, may have influenced any potential association between cognitive function and activity adherence in LIFE-P. Additional investigations, in studies with larger sample sizes and longer durations of PA (Fielding et al. 2011), are warranted to further examine cognitive function as a determinant of physical activity adherence in mobility-limited older adults.

Section D

Chapter 7

General Discussion

7.1 General Discussion

This thesis has presented four distinct original research investigations that have provided significant new information on the age-related determinants of skeletal muscle power and muscle performance, mobility limitations, exercise training interventions and cognitive function in older adults.

The primary aim of this thesis was to examine lower extremity muscle power as a more critical variable for understanding the inter-relationships between skeletal muscle impairments and mobility limitations with advancing age. Chapter 3 presented the first study of its kind to comprehensively and systematically compare several major mechanistic and gender determinants of muscle power between defined groups of healthy middle-aged, healthy older and mobility-limited older adults. This cross sectional examination provided new insights into some of the major physiological characteristics associated with the reduction in muscle power with advancing age. Mobility-limited older adults, while possessing significant deficits in muscle power compared to age-matched healthy older adults and younger middle-aged subjects, also exhibited major decrements in leg muscle strength, contraction velocity, muscle size, muscle quality, neuromuscular function and possessed significantly greater deposits of adipose tissue within their muscle tissue, compared to both healthy groups studied. However, despite these major whole muscle deficits, it was evident from chapter 3 that the function and contractile performance of the surviving single muscle fibres in mobility-limited older adults remained largely intact. Overall this study highlighted several potential etiologies associated with the age-related loss of muscle power and mobility limitations among older adults.

Longitudinal studies provide a more definitive opportunity to study the magnitude and mechanisms of muscle power and mobility loss in older adults. The fact that these types of studies are typically challenging to carry out in the same cohort of aging humans likely explain the limited number of longitudinal studies of aging in the scientific literature (Frontera et al. 2008; Guralnik and Kritchevsky 2010). However, the study presented in chapter 4 overcame many of the challenges associated with conducting longitudinal studies of aging, and represents a seminal investigation into the age-related changes of lower extremity muscle power, mobility, and concurrent changes in whole muscle and intrinsic single fibre properties in both healthy older and mobility-limited older cohorts. Overall, this investigation demonstrated that lower extremity muscle power deteriorated significantly over a 3-year interval in both cohorts, and while the magnitude of this decline was equivalent, the physiological mechanisms that determine muscle power largely differ between healthy and mobility-limited older adults. Critically, from all of the physiological parameters examined throughout this investigation in chapter 4, it would seem that neuromuscular activation deficits precede declines in muscle size, strength and physical function, and ultimately may be the primary underlying physiological mechanism that influences muscle power loss and resultant mobility decline with advancing age. Another important observation from this study was that the function and contractile properties of the surviving single muscle fires were largely preserved after 3 years of aging in both cohorts, despite major perturbations at the whole muscle level. An explanation for this phenomenon, initially identified in chapter 3, and confirmed in chapter 4, is that the surviving muscle fibres partially adapt in an attempt to restore overall whole muscle power and physical function in aging humans with and without manifest mobility-limitations. A final observation from chapter 4 described the novel correlations identified between adipose

tissue infiltration into skeletal muscle and the declines of muscle power and contraction velocity. While further research is certainly warranted to explore and further characterise these relationships, the findings suggest that adipose tissue infiltration into skeletal muscle is an important physiological alteration that may directly limit muscle performance and mobility with advancing age.

The study described in chapter 5 sought to refine the design of resistance training interventions for inducing maximum muscle power gains and physical function improvements among mobility-limited older adults. To add significant context to the overall findings presented in chapter 5, it is important to reconsider the general phenotype of the mobility-limited older adult characterised in chapter 3 and chapter 4. Considering the major physiological and physical function decrements that are present among mobility-limited older adults, the need to identify and optimise exercise interventions for restoring muscle power and mobility in older adults is of urgent importance. It is therefore extremely encouraging for geriatricians, gerontologists, exercise physiologists and indeed older adults that the major findings from chapter 5 showed that two distinct 16-week regimens of high velocity resistance training can substantially improve lower extremity muscle power and induce clinically meaningful improvements in physical function in mobility-limited older adults. Overall, the direct comparison of the effects of velocity-specific (LO) and force-specific (HI) power training revealed significant, yet comparable, between-group increases of muscle power and substantial gains in mobility performance, which appear to be mediated by improvements in neuromuscular activation and muscle mass. However, within these salient findings, chapter 5 identified important practical considerations for the optimal design of resistance training interventions for restoring muscle power and mobility in older

adults. Compared to HI, participants in the LO training group, through the use of lighter resistance and moving these training loads more rapidly, still attained substantial and clinically important gains in muscle power and mobility, with reduced total work and consistently lower perceived exertion. Ultimately, these findings suggests that LO training could be a more practical and widely applicable form of resistance training for improving muscle power, counteracting mobility loss and addressing a major clinical and physiological issue affecting older adults. These conclusions from chapter 5 also lend encouragement for the design of tolerable but efficacious resistance training interventions for improving mobility outcomes in older adults with chronic conditions such osteoarthritis and osteoporosis, and other more severe disabling diseases, where heavy resistance training loads may be contraindicated.

Consistent with the outcomes demonstrated in chapter 5, regular participation in interventions of physical activity may be one of the most important health behaviours associated with the management of chronic disease among older adults. Higher quantities of physical activity have been shown to elicit beneficial effects on numerous age-related conditions, including two of the most debilitating conditions affecting older adults: mobility-decline and cognitive impairment. However there is very limited knowledge on how older adults with mobility limitations, who may also have emerging or co-existing impairments in cognitive function, can actually adhere to long term physical activity interventions greater than 6 months in duration. The final study presented in this thesis, Chapter 6, addressed this question using a secondary analysis of data from the LIFE-P study. Traditionally, mobility limitations and cognitive impairment have been previously studied, assessed and recognised as two very distinct and different syndromes affecting the health of older adults (Montero-

Odasso et al. 2012). However, there are now numerous lines of evidence emerging from both cross-sectional and longitudinal studies indicating that cognitive function is strongly linked to physical function, and physical function may be, largely mediated by cognitive function (Boyle et al. 2010; Buchman et al. 2007; Robertson et al. 2013). It is against this backdrop that the research question addressed in chapter 6 has fulfilled an ever-increasing necessity for more studies to further explore the potential relationships and interplay between cognitive function and mobility limitations in older adults. The major findings from chapter 6 demonstrated that among mobility-limited older adults participating in a 12 month multi-modal physical intervention, initial baseline cognitive function assessed across multiple domains including executive functioning, global cognition and verbal memory, was not associated with subsequent long term physical activity adherence. This finding was notable as a proportion of the participants in LIFE-P exhibited baseline deficits in global cognitive function which would be consistent with typical clinical classifications and manifestations of mild cognitive impairment or mild dementia in older adults. While levels of baseline cognition were predictive of medical suspensions from the LIFE-P physical activity intervention, the overall results from chapter 6 are both positive and encouraging as they demonstrate that older adults with mobility limitations, and some with emerging cognitive deficits, can successfully adhere to a long term multi-modal exercise intervention. It is likely that inherent aspects in the delivery of the LIFE-P physical activity intervention, including a series of behavioural counseling sessions implemented to specifically promote physical activity adherence, contributed to these findings.

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Appendix A

Pre-screening telephone questionnaire

Informed Consent Forms

(Chapter 3)

Project title: "Lower Extremity Muscle Power and Function in the Elderly"

Study 1 - Pre-screening questionnaire:

This questionnaire will be used to determine if you potentially qualify for this study. If you do qualify based on this questionnaire and are interested in participating in this study, you will be invited to participate in additional screens and surveys to further assess your eligibility. By answering these questions, you are under no obligation to participate in this research study.

I would like to describe the study and the time commitment it would involve on your part. You are being asked to participate in a research study for approximately 2 weeks. The study will take place at the Jean Mayer Human Nutrition Research Center on Aging (HNRCA) at Tufts University. During the study, you will undergo a series of evaluations to determine your lower body muscle mass, strength, power and function. You will be required to attend for an initial screening visit. The payment for this visit is $15. If you qualify after this first visit, you will be required to attend for a further three visits over a two week period. The stipend for participation in this study is $200.

Date: _____

Subject name: _____ Sex: M___ F___

Address:_____

_____

Telephone number:_____

Where did you hear about this study? direct mailing _____ poster_____

advertisement_____ (please specify e.g. newspaper, radio, internet) _____
other_____

Please answer the following questions:

1. What is your age? _____ D.O.B? _____

   Only interviewees aged between 40-55yrs and 70-85 yrs will be invited to participate in the study. If outside these ranges, STOP pre- screening and refer to note B.

2. What is your bodyweight: _____ lbs _____ kg

   What is your height: ___ feet _____inches _____ meters (_____ m^2)

   calculate BMI: _____ kg/m^2 (convert lbs to kg: 1 lb = 0.454 kg, convert inches to meters: 1 inch = 0.0254 meters)

   Interviewees with a BMI < 19 kg/m^2 or > 32 kg/m^2 will be excluded from the study. If BMI is outside this range, STOP pre-screening and refer to note B.

3. Do you have health insurance? Yes ____ No ____ **If no, STOP pre-screening and refer to note B.**

4. Are you taking any prescribed medication? Yes ____ No ____ **If yes and aged 40-55yrs, STOP pre-screening and refer to note B.**

---

5. Do you currently exercise regularly or participate in a structured exercise program?

Yes ___ No ___ If yes, describe activities

_____

_____

(If interviewee currently performs, or has during the previous 6 months, any regular endurance or resistance training exercise > 3 times/week, STOP pre-screening and refer to note B.

6-14: If interviewee answers 'yes' to any of these questions, STOP pre-screening and refer to note B.

6. Have you had any broken bones within the past 6 months? Yes ___ No ___ If yes, please explain:

_____

7. Have you had a heart attack/myocardial infarction within the last 6 months? Yes ___ No When?

_____

8. Do you have uncontrolled hypertension (BP > 150/90 mm Hg) ? Yes ____ No ____

_____

9. Have you ever been diagnosed with or do you currently suffer from symptomatic coronary heart disease?

Yes ____ No _____

10. Do you currently suffer from any neuromuscular disease (such as muscular dystrophy, ALS/motor neuron disease)? Yes ____ No _____

11. Are you currently receiving coumadin therapy? Yes ____ No ____

12. Are you currently receiving hormone replacement therapy? Yes ____ No ____

13. **Females Only**: Are you currently receiving estrogen therapy? Yes ____ No ____

14. **Females (aged 40-55yrs) Only:** Are you currently pregnant, planning to become pregnant or are you breastfeeding? Yes ____ No ____

15. **If aged 70-85 yrs and answered yes to question 4:**

Do you have any difficulty:

a. Walking a quarter of a mile or more? Yes _____ No _____

b. Climbing a flight of stairs? Yes _____ No _____

c. Standing up from a chair? Yes _____ No _____

d. Lifting and carrying an object weighing 10 lbs? Yes _____ No _____

(If interviewee answers 'no' to a,b,c and d: STOP pre-screening and refer to note B)

Q's 16-17: Subjects answering 'yes' to any of these questions will have further details taken and their participation in the study will be discussed between the study physician, the study investigators and if necessary, the subject's primary care physician.

16. Do you currently suffer from any other illnesses? Yes ___ No ____

If yes, please explain:

_____

17. Are you currently participating in any other research studies? Yes ____ No _____ If yes, please explain:

_____

18. Can you get transportation to HNRCA, located at 711 Washington Street. The subway orange line stops one block away from the HNRCA. Yes _____ No _____

19. Are you still interested in participating in this study? Yes_____ No _____

20. Do you have any questions about anything we discussed today?

_____

Notes

A: If interviewee qualifies: Our enrollment coordinator will be contacting you shortly to schedule your screening visit.

B: If interviewee does not qualify: I am sorry, but you do not qualify for this study because _____. Thank you very much for your time and interest in this study. May we keep your name on file and contact you in the future for other research projects?

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PREADMISSION SCREENING CONSENT FORM

Title: Lower Extremity Power and Function in the Elderly: Study 1

Principal Investigator: Roger Fielding, Ph.D.

Physician: Edward Phillips, M.D.

Study Coordinator: Kieran Reid, M.Sc.

You have been invited to participate in a research study at the Human Nutrition Research Center on Aging (HNRCA) at Tufts University. In order to assess your eligibility to participate in this research study, you must go through a preadmission screening process.

You will invited to the HNRCA for a preadmission screening visit. This visit will occur at the start of a two-week study period. If you successfully complete this screening visit, you will be accepted into the study and you will be required to attend the laboratory for three additional visits within this two-week period. On these additional visits, all of the investigational procedures will be performed in the Nutrition Exercise Physiology and Sarcopenia (NEPS) Laboratory at the HNRCA.

At the first pre-entry screening visit:

You will be asked to provide information about all medications (prescription and over-the-counter) that you currently take.

You will be asked to fill out a questionnaire about your health and exercise habits. A licensed physician or nurse practitioner will conduct a brief general physical examination to best assure your fitness to participate in the strength testing, exercise testing and biopsy parts of the study.

A resting electrocardiogram (EKG) will also be performed. To do this, your chest will be rubbed clean with isopropyl alcohol and a set of 10 adhesive (sticky) electrodes (plastic discs) will be placed on the skin.

In addition, you will have 0.5 oz. (3 tsps) of blood drawn from your vein for various routine blood measurements (e.g. complete blood count). We will also ask you to provide us with a small urine sample for urinalysis.

A brief test of your memory and mental function will be administered by the physician, nurse practitioner or other staff to determine your ability to follow directions during the study and provide consent.

You will also be asked to undergo a Short Performance Physical Performance Evaluation Test. This test has three parts: You will be asked: 1.) to walk about 13 feet. 2) to stand up from a chair five times without using your arms. 3) to stand in different positions while keeping your balance. The examiner will demonstrate what to do and will be nearby to steady you if you need it. The test takes about 5 minutes to complete.

The potential risks of this screening visit are related to the EKG, blood draw and the Short Physical Performance Evaluation Test.

- EKG: There are no risks to this procedure other than occasional skin irritation from the adhesive electrodes.

- Blood Draw: There may be a slight discomfort during blood drawing and there is the possibility of a small bruise forming at the puncture site. There is also the remote possibility of a superficial inflammation (phlebitis) of the vein. There is no risk to the urine sampling.

- Short physical performance evaluation: The only risk expected to be associated with these tests is a risk of losing your balance. The examiner will remain close to help you if you are unsteady.

While this screening procedure may be of no direct benefit to you, you may receive some benefit

since the results of this medical testing (physical examination and laboratory results) may be made available to you and/or your physician for follow-up, upon your request. If any abnormalities are discovered as a result of the physical examination and laboratory results, you will be notified and referred to your doctor. The results of this screening procedure may or may not qualify you to be admitted into the research study.

If you have any questions concerning this screening, you can call Dr. Roger Fielding at 617-556-3016 or Dr Eddie Phillips at 617-573-2222.

You understand that you are being screened to participate in the above research study. If for some unforeseen reason the research study does not commence, the HNRCA is not obligated to provide you with financial compensation for the research study. In such a case, the HNRCA staff will attempt to identify an alternative research study for which you qualify and approve.

VOLUNTEER STATEMENT

I understand that the screening process may be discontinued at any time by the staff of the HNRCA. I also understand that, if for any reason I refuse to participate or discontinue my participation in this process at any time, I will be free to do so and this will have no effect upon continuation of any care or treatment I may be receiving from physicians at the Tufts-New England Medical Center.

I understand the importance of correct medical and psychosocial information in the determination of my eligibility for participation, for my own safety and benefit. I, therefore, agree to answer all questions put forth to me during this screening process accurately and to the best of my knowledge.

I understand that my medical records and data will be kept confidential, except as required by law.

I understand that, in the event I become ill or injured as a result of participating in this screening process, medical care will be provided to me. However, such medical care will not be provided free of charge even if the injury or illness is a direct result of this research study. I understand that no funds to provide financial compensation for research-related injury or illness are available.

I understand that I will be paid a stipend of $15.00 for the screening visit. This stipend is

provided to defray my travel/parking costs.

I have been fully informed of the above-described plan with its possible risks and benefits and I hereby consent to the plan set forth above. I will receive a copy of this consent form.

I have explained to_____the nature and purpose of the
Participant's Name
screening process and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____

Date Participant's Signature

_____ _____

Date Principal Investigator or Representative's Signature

JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER
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INFORMED CONSENT FORM For Research Participation

Title: Lower Extremity Power and Function in the Elderly: Study 1

Principal Investigator: Roger Fielding, Ph.D.

Study Physician: Edward Phillips, M.D.

Study Coordinator: Kieran Reid, M.Sc.

INTRODUCTION

You are being invited to participate in a research study. The purpose of the research is to evaluate the change over time of your muscle function, mass, strength and power. You are being invited to take part in this research study because you meet the study entry eligibility criteria set by the study investigators. A total of 115 subjects will be enrolled in this study. The study is supported by a grant from the National Institute on Aging.

The following tests will take place at the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University. The study involves four visits conducted over a two-week period. At the end of this 2 week period the study will be completed for all subjects aged between 40-55 years. After the initial testing, if you are aged 70 years or older we will also be contacting you approximately every six months by mail or phone (your choice) until we invite you to return for a similar round of testing in approximately four years. By agreeing to participate in this research study, you are in no way obligated to participate again in the four year follow-up.

You have previously had preadmission screening for the research study - *Lower Extremity Power and Function in the Elderly: Study 1*. This form describes the study in further detail.

STUDY PROCEDURES

If the initial screening qualifies you for the study, you will be asked to undergo the following procedures once, except for the muscle strength and power testing, which you will be asked to perform on two separate occasions, one week apart.

Questionnaires

You will be asked to fill out a series of questionnaires related to your health, mobility, memory, mood, life satisfaction, and ability to perform daily functions such as stair climbing and rising from a chair. You will be given instructions and plenty of time to complete these forms and you can choose not to answer any questions that you feel uncomfortable with for any reason. These forms will take approximately 60 minutes to fill out.

Gait, Balance and Function

You will be observed and timed as you perform maneuvers including walking at your usual pace and at a fast pace for 20 feet, standing up from a chair, walking heel-to-toe forwards and backwards, and climbing and descending a flight of stairs. The risk to these procedures is the chance that you could slip and fall. The examiner will be close to your side as you perform these tests so that you can be steadied if necessary. These tests will take approximately 40 minutes.

Muscle Strength Testing

You will have tests of muscle strength conducted at HNRCA. You will be asked to exercise different muscles of your legs in a specially designed chair that resists movements of the joints. You will be asked to apply as much force as possible against a lever arm that controls the speed of your muscle contraction. At the end of the test your muscles will be fatigued. While the risks of this test are minimal, they might include muscle tightness, soreness and fatigue, and rarely muscle strain. During the study, this measurement will be done twice, separated by one week. This test will take approximately 30 minutes.

Muscle Power Testing

The maximal amount of power you have in your legs will be determined using weight training equipment. You will be asked to lift a series of increasingly heavier weights by pressing out your legs while your feet are resting on a footplate. You will then be asked to quickly and forcefully give one push to a pedal attached to a machine to measure leg power. You may be asked to repeat this push up to 5 times with rest periods in between, at three different levels of work. You will also be

asked to lift a series of increasingly heavier weights by pushing out your legs as rapidly as possible for each lift. In addition, the ability of your leg muscles to control a fixed level of resistance will also be measured. You will be asked to slowly push your feet against a pedal and may be required to repeat this up to 14 times. The overall risks involved with the muscle power testing may be muscle tightness, soreness, and fatigue, and rarely pulled muscles. This measurement will be done twice, on two visits separated by one week. This test will take approximately 45 minutes.

400 meter walk (¼ mile)

You will be instructed to walk at a pace you can keep up without feeling that you are too uncomfortable until you complete a ¼ mile, or can no longer continue. Rest periods are permitted while standing for up to 60 seconds, if necessary. If you cannot continue after 60 seconds rest, or if you need to sit down, the test will be terminated.

Muscle Biopsy

A muscle biopsy will be taken to enable us to get in-depth analysis of your muscle tissue. The muscle biopsy procedure will be performed by Dr. Roger Fielding in your non-dominant (opposite of your dominant hand) thigh under sterile conditions. After a local numbing medicine, similar to that used at the dentist (which may result in a brief stinging or burning sensation), is injected in the middle of your thigh, a small (1/4 inch) incision will be made, and then a muscle biopsy needle will be inserted and a small muscle specimen (about 1/100th of an ounce) will be taken. The incision will be properly covered with a sterile dressing and an elastic bandage. The dressing will remain in place for 24 hours. You will not be able take a shower for 48 hours after the biopsy. This procedure will take about 1 hour. You will be asked to stop taking any aspirin and anti-inflammatory medicine (e.g., ibuprofen or naproxen) for three days before the procedure and three days after the procedure. Documented confirmation will be obtained from your primary care physician (PCP) regarding whether or not your medication can be discontinued before obtaining your approval. You may experience a mild to moderate temporary increase in joint pain while your anti-inflammatory medication is not taken before and after the muscle biopsy. You may be exposed to a minimal, temporary increased risk of stroke or heart attack while your aspirin is being held before and after the muscle biopsy. You will be informed of your PCP's decision and any concerns regarding an increased risk. You will feel a dull pain during the procedure and some muscle soreness and tenderness from 4-12 hours after the biopsy has been taken. The muscle biopsy involves some discomfort such as redness, sensation of pressure in the area, soreness, and bruising. Rarely, infection, prolonged discomfort or numbness (1% of cases) may occur. There is a small risk of bleeding, infection, and scarring of the skin. Any bruising resulting from the procedure can be

reduced by making sure that the bandage in the site remains firm and secure and that you do not participate in any vigorous exercise in the 24 hours following the biopsy. The muscle biopsy sample will be taken at the HNRCA but transferred for evaluation at Spaulding Rehabilitation Hospital. A portion of the sample will remain at the HNRCA for analysis. Confidentiality will be ensured as all samples being transferred will be coded and made unidentifiable. Your name will not be given out with the sample.

Surface EMG Testing and Neuromuscular testing

We will make several measurements intended to provide information regarding how you control your muscle force and timing. To do this, the electrical activity of your muscles will be measured using a procedure called electromyography, also termed EMG. By analyzing the electrical activity generated when you use your muscles or move your limbs, EMG will allow us to develop a better understanding of how your nervous system control your muscles, whether it has been affected with age, and whether this control is affected by exercise. These recordings will be made by placing small sensors on the skin over the muscles on your legs. The sensors are small boxes that will be taped to your skin using non-allergenic tape. There may be slight discomfort associated with shaving the hair from the skin and cleaning the skin with alcohol, and from removing the tape from the surface sensors. Some slight skin irritation is possible, although sensors are removed carefully to reduce the likelihood of this occurrence. If skin irritation does occur, it should disappear in a few days.

We will also study your ability to produce maximal muscle force while pushing your leg against a lever arm. To do this you will be seated in a specifically designed exercise machine and we will stimulate your muscles electrically by means of surface sensors on your legs while you push against the lever as hard as you can. This is done to determine whether you are able to fully use and move your muscles under your own effort. The electrical stimulation can be described as a very concentrated period of muscle tension. While many people find it uncomfortable, the duration of each stimulation is less than a half-second. Slight irritation or redness of the skin may occur due to shaving and cleaning the stimulation site prior to testing.

Computed Tomography (CT scan): You will be asked to lie down on a bed while the CT scan of your non-dominant thigh (opposite of your dominant hand) is done. This will take about 30 minutes. This x-ray technique will be used to obtain a picture of your thigh muscles and will be done at Tufts Medical Center. This measurement will be done once during the study. The total effective radiation dose to your body is approximately the same as the normal background radiation received by an individual in 2.5 weeks, or approximately the same as the amount of radiation you would be exposed

to during a twelve hour airplane flight. This is generally regarded as safe.

TIMELINE OF STUDY PROCEDURES

Visit 1: (Screening, 3-hours)
- Complete consent form
- Cognitive screening questionnaire
- Complete a medical history questionnaire
- Medical screening by the study physician
- Resting electrocardiogram (EKG)
- Blood draw
- Short Physical Performance Battery

Visit 2: (Within 1-3 days of visit 1, 4-hours)
- Complete questionnaires:
  - Health
  - Mobility
  - Mood
  - Life satisfaction
  - Ability to perform activities of daily living.
- Gait analysis
- Balance Testing
- Muscle strength and power tests
- 400 meter walk test

Visit 3: (Approximately 7 days after visit 2, 4-hours)
- Muscle strength and power tests
- Neuromuscular testing

Visit 4: (A minimum of 3 days after visit 3, 2-hours)
- CT Scan
- Muscle biopsy of a thigh muscle

If necessary, this schedule will be changed to account for any unforeseen delays or complications

PREGNANCY AND BREASTFEEDING RISKS

Because the risks associated with these procedures during pregnancy and breastfeeding are unknown, you should not participate in this study if you are pregnant, planning to become pregnant or are breastfeeding. If you become pregnant during the course of this study, please notify the study coordinator.

BENEFITS

This research study is not being performed to benefit you directly. The benefits from your participation in this study are that your health and fitness status will be evaluated. The results of the medical screening and fitness evaluations will be made available for you and/or your primary care physician, upon your request. Others may benefit in the future from an improved understanding of the change of an individual's body composition, strength and muscle mass over time.

PAYMENT FOR RESEARCH-RELATED INJURY

Emergency medical treatment will be given to you if you are hurt or get sick as a direct result of this study. You or your insurance carrier will have to pay for any such medical care. Any needed medical care is available at the usual cost. All needed facilities, emergency treatment and professional services are available to you, just as they are to the general public. There are no plans to pay for your treatment if you get hurt or sick as part of this study. The institution has not set aside any money to pay for a research-related injury or illness.

CONTACTS

You have been told that you may reach the Principal Investigator or the study physician at any time of the day or night during the study period if you have any questions or problems related to the study. The telephone numbers are:

Roger Fielding, PhD.	(617) 556-3016	office
	(781) 284-9980	(evenings and weekends)
Edward M. Phillips, M.D.	(617) 573 2222	(Spaulding page operator)
	(617) 556 3042	(Metabolic Research Unit at HNRCA) (evenings/weekends)

If you have any questions about your rights as a research study subject, call the Tufts Medical Center/Tufts University Health Sciences Institutional Review Board (IRB) at (617) 636-7512. The IRB is a group of doctors, nurses, and non-medical people who review human research studies for safety and protection of human subjects.

PAYMENT

You will receive a screening payment of $15 if you are not eligible for the study or do not wish to participate in the study after your initial screening. If you meet the study entry criteria and are

willing to participate, you will receive an additional payment of $200 from the Human Nutrition Research Center on Aging at Tufts University at the conclusion of all four sessions of testing. If you do not complete the study, the amount of the payment will be proportional to the time you have spent in the research study (i.e. $15 for the screening test, $60 for completion of each visit 2, 3 and $80 for visit 4).

COSTS

There is no cost to you for participation in this research study.

ALTERNATIVES

Your alternative is not to participate in this research study. You may participate in other exercise programs.

WITHDRAWAL AND STUDY TERMINATION

You may change your mind about being in this study and stop being in this study at any time for any reason. If you decide to withdraw from this research study, you must inform Dr. Roger Fielding, the Principal Investigator.

The investigator or study sponsor may stop your participation in this research study without your permission for any of the following reasons:

- You do not follow the study procedures
- There has been a change in your health
- The study sponsor has ended the study due to new safety information

CONFIDENTIALITY

Medical information produced by this study will not become part of your hospital medical record, unless you request it to be. The information will be stored in the investigator's file and identified by a code number only. Information contained in your research records may not be given to anyone unaffiliated with the HNRCA, in a form that could identify you, without your written consent or as specified by law.

It is possible that your medical and research record, including sensitive information or identifying information, may be inspected and/or copied by the study sponsor (National Institute on Aging), federal or state government agencies such as the Office of Human Research Protection, or hospital

accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor or by any of these agencies, the HNRCA will use reasonable efforts to protect your privacy and the confidentiality of your medical information.

The blood, urine and muscle biopsy samples that are obtained from you will be coded such that study investigators will not know your identity. Only the principal investigator and study coordinator at the HNRCA will have access to the code. All of the information collected on you during the course of the study will remain in a secure location. The coded vials with your muscle biopsy will analyzed at Spaulding Rehabilitation Hospital and the information sent to the Principal Investigator Dr. Roger Fielding at the HNRCA. Once the study is complete, any remaining blood, urine or muscle samples may be saved for up to three years. Information relating to your participation in this study (e.g. such as the results from your exercise testing, completed questionnaires etc.) will be transferred to Boston University School of Public Health where statistical analyses of the data will be performed. Your data will be de-identified, so that your identity will remain unknown and to ensure confidentiality.

The results of this study may be published in a medical book or journal or used for teaching purposes. However, your name and any other identifying information will not be used in any publication or teaching materials.

You will have a research record with the HNRCA. Every effort will be made to maintain the confidentiality of your research records for this study by the investigators.

PARTICIPANT'S STATEMENT

Taking part in this study is totally your choice. Please read all or the following information carefully. Ask Dr. Roger Fielding or his representative, to explain any words, terms, or sections that are unclear to you. You should also ask any questions that you have about this research study. Your questions will be answered in words, or if you prefer, in writing. Do not sign this informed consent form unless you understand the information in it and have had your questions answered to your satisfaction. You should talk about this research study and the information in this informed consent form with whomever you want before you sign it.

I have read this consent form and have discussed with Dr. Fielding, or his representative the procedures described above. I have been given the opportunity to ask questions, which have been answered to my satisfaction. I understand that any questions that I might have will be answered verbally, or if I prefer, with a written statement.

I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to continue to participate. I understand that my participation is voluntary and that I may refuse to participate in this study.

I also understand that if, for any reason, I wish to discontinue my participation in the process at any time, I will be free to do so. I understand that if I discontinue my participation in the study, the amount of the payment will then be proportional to the time I have spent in the study.

Also, the Investigator or the Institution may decide, at any time and for any reason, that my participation in this study may be terminated. In this event, the payment amount will be proportional to the time I have spent in the study.

I understand that in the event I become ill or I am injured as a result of participating in this research study, medical care will be provided to me. However, such medical care will not be provided free of charge, even if the injury or illness is a direct result of this research study. I understand that no funds to provide financial compensation for research-related injury or illness are available.

If I have any questions concerning my rights as a research subject in this study, I may contact the Tufts Medical Center/Tufts University Health Sciences Institutional Review Board at (617) 636-7512.

I have been fully informed of the above-described plan with its possible risks and benefits, and I hereby consent to the procedures set forth above. I will receive a signed copy of this consent form.

I understand that as a participant in this study my identity and my medical records and data relating to this research study will be kept confidential, except as required by law, and except, for inspections by the study sponsor (National Institute on Aging), the Tufts-Medical Center Institutional Review Board and the federal Office of Human Research Protections (OHRP).

_____ _____

Date Participant's Signature

I have fully explained to _____ (Participant) the nature and purpose of the above-described procedure and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____

Date Principal Investigator or Representative's Signature

Appendix B

Health History Questionnaire

(used in Chapters 3-5)

JEAN MAYER USDA
HUMAN NUTRITION RESEARCH CENTER ON AGING AT
TUFTS UNIVERSITY
711 Washington Street, Boston, Massachusetts 02111
1-800-738-7555—volunteers-hnrc@tufts.edu

Healthy Aging
THROUGH NUTRITION RESEARCH

HEALTH QUESTIONNAIRE

The following questions are designed to obtain a thorough preliminary medical history. The information you provide will help us to make the best determination about your eligibility for a particular study or studies.
Please fill out the questionnaire and bring it with you to your next appointment. Thank you.

THIS QUESTIONNAIRE, AS WELL AS OTHER MEDICAL INFORMATION YOU PROVIDE, WILL BE KEPT CONFIDENTIAL EXCEPT WHERE REQUIRED BY LAW.

INSTRUCTIONS:
In the three spaces below, please indicate the study numbers of the research studies that interest you, beginning with your first choice.

- If a label with your name is affixed below, please make any necessary corrections.
- If no label is affixed, please PRINT your name and address in the space provided.

Please PRINT your answers to all questions in INK. For those questions requiring further information, be as complete and specific as possible. Additional space for comments is provided on the last page of the questionnaire.

I am interested in these studies: 1._____ 2._____ 3._____

Name: _____

Street Address: _____

City, State, Zip: _____

- Telephone number: Home ( )_____Work ( )_____
- Do you mind being called at work? Yes_____No_____
- Date of Birth:_____M_____F_____Social Security #:_____
- Are you currently participating in research studies outside the **HNRCA**? No_____Yes_____

  If yes, please explain:_____

- Are there times in the next 6 months when you will be unable to participate? No_____Yes_____

  If yes, please indicate the time(s):_____

Attachment 4

DEMOGRAPHICS

1. MARITAL STATUS (please check one):

___Married ___Single, never married ___Separated ___Divorced __Widowed

2. LIVING SITUATION: Where do you live? (please check one):

___House___Apartment___Shelter___Dormitory___Other, specify_____

3. RACE/ETHNICITY:

Are you Hispanic? Yes No

(please check one):

___American Indian or Alaska Native
___Black or African American
___White or Caucasian
___Native Hawaiian or Other Pacific Islander
___Asian
___Other, specify_____

4. OCCUPATION:

Are you retired? No_____Yes_____

If no, what is your current occupation:_____

If yes, what was your occupation at retirement:_____

5. EDUCATION:

Last grade completed in elementary or secondary school (high school):_____

Education since leaving elementary or secondary school:

_____None
_____Vocational school
_____Community or junior college
_____Four year college
_____Graduate school (i.e. MD, MBA)
_____Professional school

PERSONAL HEALTH HISTORY

1. Height:_____ft._____inches (without shoes) Weight:_____lbs. (without shoes)
2. Are you allergic to, sensitive to, or intolerant of any foods or medications? No_____Yes_____

Food:_____

Medication:_____

Seasonal Allergies: (what season?)_____

Other: (soap, tape, latex, lotions, etc.)_____

3. Do you currently smoke or use tobacco? No_____Yes_____

If yes: How much do you smoke?_____How long have you smoked?_____

If no: Have you ever smoked? No_____Yes_____

How long ago did you quit?_____

4. When did you last see your physician or health care provider (ob-gyn, eye doctor, etc.)?

Date:_____Reason:_____

_____

5. Do you have any chronic illnesses? If yes, please explain: No_____Yes_____

_____

_____

6. Have you ever been hospitalized or had surgery? No_____Yes_____

_____

_____

7. Are you currently taking any medication either prescribed by a doctor or purchased over the counter at least once a week? No_____Yes_____

If yes, list ALL medication use including aspirin, eye drops, creams, sleeping pills, antacids.

	Drug Name	**Amount**	**How Often?**	**How Long?**	**Reason**
Example	*Advil*	*2 tablets*	*Everyday*	*One year*	*Joint pain*
a.					
b.					
c.					
d.					
e.					
f.					

8. Do you currently take any vitamins, minerals, herbs, or health food supplements on a regular basis? No_____Yes_____

If yes, list All supplements and please indicate whether it was prescribed by a doctor or other health care provider.

	Drug Name	**Amount**	**How Often?**	**How Long?**	**Reason**	**MD?**
Example	*Vitamin E*	*400 IU*	*Everyday*	*Four years*	*General Health*	*No*
a.						
b.						
c.						
d.						
e.						
f.						

9. Would you be willing to stop your vitamins, minerals, herbs, or health food supplements if needed while participating in the study? No_____Yes_____

10. Are you currently following a special diet? (vegetarian, diabetic, lactose free) No_____Yes_____

If yes, please specify?_____

a. Is this diet being prescribed by your health care provider? No_____Yes_____

11. Where do you most often obtain your meals? (Check all that apply.)

( ) Home ( ) Home, with home delivered meals

( ) Work ( ) Restaurants

( ) Congregate meal sites ( ) Other_____

12. If accepted for a study, would you be willing to follow a diet that may vary from your current food in take? No_____Yes_____

13. Have you had a weight loss or gain in the last 6 months? No_____Yes_____

If yes, how much? _____lbs. Gain_____ Loss_____

14. Do you have any difficulty chewing or swallowing your food? No_____Yes_____

If yes, do you need your food prepared in a special way? No_____Yes_____

Please specify:_____

_____

15. Do you have dentures, bridges or implants? No_____Yes_____

16. Have you had problems with choking? No_____Yes_____

17. How many meals and/or snacks per day do you usually eat?

Meals:_____ Time of day:_____

Snacks:_____ Time of day:_____

18. Do you currently participate in *regular* physical activity? No_____Yes_____

If yes, how often and what type?_____

19. Do you have any condition that would prevent you from being physically active? No_____Yes_____

If yes, please explain:_____

20. Have you ever received counseling or psychotherapy on an outpatient or inpatient basis? No_____Yes_____

If yes, explain:_____

21. Do you currently drink alcohol? No_____Yes_____

If yes, how much: Per day:_____ Per week:_____

22. Have you ever had a drinking problem? No_____Yes_____

If yes, please explain:_____

23. Do you now use or have you ever used drugs or substances to alter mood? No_____Yes_____

If yes, please list:

Substance Name	When Used	How Much	How Often
a.			
b.			

The following is a list of health conditions.
Check yes or no and circle those conditions that apply to you.
Please indicate when you had the problem and any treatment, hospital stay, and/or follow-up required.

24. **Skin:** rashes, moles, eczema, psoriasis. No_____Yes_____

If yes, explain:_____

25. **Head:** head injury, headaches, dizziness. No_____Yes_____

If yes, explain:_____

26. **Eyes:** glaucoma, cataracts, doubled or blurred vision, infection. No_____Yes_____

If yes, explain:_____

27. **Ears:** hearing loss, ringing. No_____Yes_____

If yes, explain:_____

28. **Nose, Sinuses:** sinus trouble, nosebleeds, deviated septum. No_____Yes_____

If yes, explain:_____

29. **Mouth/Throat:** hoarseness, frequent sore throats, sores. No_____Yes_____

If yes, explain:_____

30. **Neck:** lumps, swollen glands, pain or stiffness. No_____Yes_____

If yes, explain:_____

31. **Breasts:** lumps, nipple discharge, discomfort, lumpectomy, mastectomy. No_____Yes_____

If yes, explain:_____

*Date of last mammogram:*_____

32. **Respiratory:** cough, shortness of breath, asthma, wheezing, bronchitis, pneumonia, emphysema, tuberculosis or a positive TB test. No_____Yes_____

If yes, explain:_____

*Date of last chest x-ray:*_____

33. **Heart:** chest pain or pressure, murmur, palpitations, irregular heart beat, rheumatic fever, mitral valve prolapse, history of coronary heart disease, heart attack, congestive heart failure. No_____Yes_____

If yes, explain:_____

*Date of last electrocardiogram:*_____

34. **Blood Pressure:** high or low. No_____Yes_____

If yes, explain:_____

*Last reading, if known:*_____

35. **Cholesterol:** Have you ever been told you had high cholesterol? No_____Yes_____

If yes, explain:_____

36. **Stomach:** chronic indigestion, ulcer, hiatal hernia, heartburn, reflux? No_____Yes_____

If yes, explain:_____

37. **Intestine:** constipation, diarrhea, hernia, change in bowel habits, irritable bowel disorder, colitis, polyps. No_____Yes_____

If yes, explain:_____

38. Do you use any type of aid such as laxatives, suppositories or enemas to regulate your bowel habits? No_____Yes_____

If yes, list:_____

39. **Cancer:** Have you ever had any form of cancer, skin or other? No_____Yes_____

If yes, explain:_____

_____

40. **Liver, Gallbladder:** hepatitis, gallstones, cirrhosis. No_____Yes_____

If yes, explain:_____

_____

41. **Urinary:** frequent urination, incontinence urgency, burning, blood in urine, infection, kidney stones. No_____Yes_____

If yes, explain:_____

_____

42. **Circulation:** leg cramps or pain in hands or feet, blood clots, phlebitis. No_____Yes_____

If yes, explain:_____

_____

43. **Muscles, Bones, Joints:** joint pain, swelling, weakness, disc disease, arthritis, tendonitis, bursitis, gout, backache, osteoporosis. No_____Yes_____

If yes, explain:_____

_____

44. **Back:** broken bone, stress fracture or fractured a vertebra in your back? No_____Yes_____

If yes, explain:_____

_____

45. **Neurological:** seizure, stroke, paralysis, fainting, weakness, numbness, tingling, tremors, memory loss? No_____Yes_____

If yes, explain:_____

_____

46. **Memory:** Do you have any problems with your memory? No_____Yes_____

If yes, explain:_____

_____

47. **Blood:** anemia, low blood count, bleeding, transfusions. No_____Yes_____

If yes, explain:_____

_____

48. **Glands:** diabetes or high blood sugar, over or underactive thyroid, excessive hunger, thirst. No_____Yes_____

If yes, explain:_____

_____

49. **Eating Disorders:** anorexia, bulimia, binge eating. No_____Yes_____

If yes, explain:_____

_____

50. **Do you mind having your blood drawn?** No_____Yes_____

If yes, explain:_____

_____

51. **Are you a blood, plasma, platelet donor?** No_____Yes_____

If yes, please give date of last donation:_____

52. **FOR MALES ONLY:**

Have you ever had prostate problems, enlargement, incontinence of urine or stool, hernias, testicular pain, lumps, discharge from or sores on penis? No_____Yes_____

If yes, explain:_____

_____

53. **FOR FEMALES ONLY:**

Have you ever had menstrual problems, vaginal discharge, irregular Bleeding, incontinence of urine or stool? No_____Yes_____

If yes, explain:_____

_____

Are you still menstruating: No_____Yes_____

If no, what was your age at menopause?_____

If menopausal, are you currently on estrogen replacement therapy? No_____Yes_____

Last PAP smear:_____ Number of pregnancies_____ Number of births:_____

Please provide the following information regarding your primary care doctor in the event that your screening test results need to be sent to him/her for review.

Doctor's Name_____

Address_____

City_____ State_____ Zip code_____

Telephone Number ( ) _____ Fax Number ( ) _____

COMMENTS:_____

_____

_____

PLEASE PRINT NAME:_____

SIGNATURE:_____ **DATE:**_____

FOR FURTHER INFORMATION CALL: 1-800-738-7555 or email volunteers-hnrc@tufts.edu

Last revised: August 2011

Appendix C

Informed Consent Forms

(Chapter 4)

JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER ON AGING TUFTS UNIVERSITY

PREADMISSION SCREENING CONSENT FORM

Title: Lower Extremity Power and Function in the Elderly: Study 1 (Follow-Up)

Principal Investigator: Roger Fielding, Ph.D.

Physician: Edward Phillips, M.D.

Study Coordinator: Kieran Reid, M.Sc.

You have been invited to participate in a research study at the Human Nutrition Research Center on Aging (HNRCA) at Tufts University. In order to assess your eligibility to participate in this research study, you must go through a preadmission screening process.

You will invited to the HNRCA for a preadmission screening visit. This visit will occur at the start of a two-week study period. If you successfully complete this screening visit, you will be accepted into the study and you will be required to attend the laboratory for three additional visits within this two-week period. On these additional visits, all of the investigational procedures will be performed in the Nutrition Exercise Physiology and Sarcopenia (NEPS) Laboratory at the HNRCA.

At the first pre-entry screening visit:

You will be asked to provide information about all medications (prescription and over-the-counter) that you currently take.

You will be asked to fill out a questionnaire about your health and exercise habits. A licensed physician or nurse practitioner will conduct a brief general physical examination to best assure your fitness to participate in the strength testing, exercise testing and biopsy parts of the study.

A resting electrocardiogram (EKG) will also be performed. To do this, your chest will be rubbed clean with isopropyl alcohol and a set of 10 adhesive (sticky) electrodes (plastic discs) will be placed on the skin.

A brief test of your memory and mental function will be administered by the physician, nurse practitioner or other staff to determine your ability to follow directions during the study and provide consent.

You will also be asked to undergo a Short Performance Physical Performance Evaluation Test. This test has three parts: You will be asked: 1.) to walk about 13 feet. 2) to stand up from a chair five

times without using your arms. 3) to stand in different positions while keeping your balance. The examiner will demonstrate what to do and will be nearby to steady you if you need it. The test takes about 5 minutes to complete.

The potential risks of this screening visit are related to the EKG and the Short Physical Performance Evaluation Test.

- EKG: There are no risks to this procedure other than occasional skin irritation from the adhesive electrodes.
- Short physical performance evaluation: The only risk expected to be associated with these tests is a risk of losing your balance. The examiner will remain close to help you if you are unsteady.

While this screening procedure may be of no direct benefit to you, you may receive some benefit since the results of this medical testing (physical examination and laboratory results) may be made available to you and/or your physician for follow-up, upon your request. If any abnormalities are discovered as a result of the physical examination and laboratory results, you will be notified and referred to your doctor. The results of this screening procedure may or may not qualify you to be admitted into the research study.

If you have any questions concerning this screening, you can call Dr. Roger Fielding at 617-556-3016 or Dr Eddie Phillips at 617-573-2222.

You understand that you are being screened to participate in the above research study. If for some unforeseen reason the research study does not commence, the HNRCA is not obligated to provide you with financial compensation for the research study. In such a case, the HNRCA staff will attempt to identify an alternative research study for which you qualify and approve.

VOLUNTEER STATEMENT

I understand that the screening process may be discontinued at any time by the staff of the HNRCA. I also understand that, if for any reason I refuse to participate or discontinue my participation in this process at any time, I will be free to do so and this will have no effect upon continuation of any care or treatment I may be receiving from physicians at the Tufts-New England Medical Center.

I understand the importance of correct medical and psychosocial information in the determination of my eligibility for participation, for my own safety and benefit. I, therefore, agree to answer all questions put forth to me during this screening process accurately and to the best of my knowledge.

I understand that my medical records and data will be kept confidential, except as required by law.

I understand that, in the event I become ill or injured as a result of participating in this screening process, medical care will be provided to me. However, such medical care will not be provided free of charge even if the injury or illness is a direct result of this research study. I understand that no funds to provide financial compensation for research-related injury or illness are available.

I understand that I will be paid a stipend of $15.00 for the screening visit. This stipend is provided to defray my travel/parking costs.

I have been fully informed of the above-described plan with its possible risks and benefits and I hereby consent to the plan set forth above. I will receive a copy of this consent form.

I have explained to_____the nature and purpose of the

Participant's Name

screening process and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____

Date Participant's Signature

_____ _____

Date Principal Investigator or Representative's Signature

JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER ON AGING TUFTS UNIVERSITY

INFORMED CONSENT FORM For Research Participation

Title: Lower Extremity Power and Function in the Elderly: Study 1 (Follow-Up)

Principal Investigator: Roger Fielding, Ph.D.

Study Physician: Edward Phillips, M.D.

Study Coordinator: Kieran Reid, M.Sc.

INTRODUCTION

You are being invited to participate in a research study. The purpose of the research is to evaluate the change over time of your muscle function, mass, strength, power and body composition. You are being invited to take part in this research study because you meet the study entry eligibility criteria set by the study investigators. Fifty subjects who had previously undergone similar testing approximately four years ago are being recruited for this study. The study is supported by a grant from the National Institute on Aging.

The following tests will take place at the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University. This re-evaluation study will involve four visits conducted over a two-week period.

You have previously had preadmission screening for the research study - *Lower Extremity Power and Function in the Elderly: Study 1 (Follow-Up)*. This form describes the study in further detail.

STUDY PROCEDURES

If the initial screening qualifies you for the study, you will be asked to undergo the following procedures once, except for the muscle strength and power testing, which you will be asked to perform on two separate occasions, one week apart.

Questionnaires

You will be asked to fill out a series of questionnaires related to your health, mobility, memory, mood, life satisfaction, and ability to perform daily functions such as stair climbing and rising from a chair. You will be given instructions and plenty of time to complete these forms and you can choose not to answer any questions that you feel uncomfortable with for any reason. These forms will take approximately 60 minutes to fill out.

Gait, Balance and Function

You will be observed and timed as you perform maneuvers including walking at your usual pace and at a fast pace for 20 feet, standing up from a chair, walking heel-to-toe forwards and backwards, and

climbing and descending a flight of stairs. The risk to these procedures is the chance that you could slip and fall. The examiner will be close to your side as you perform these tests so that you can be steadied if necessary. These tests will take approximately 40 minutes.

Muscle Strength Testing

You will have tests of muscle strength conducted at HNRCA. You will be asked to exercise different muscles of your legs in a specially designed chair that resists movements of the joints. You will be asked to apply as much force as possible against a lever arm that controls the speed of your muscle contraction. At the end of the test your muscles will be fatigued. While the risks of this test are minimal, they might include muscle tightness, soreness and fatigue, and rarely muscle strain. During the study, this measurement will be done twice, separated by one week. This test will take approximately 30 minutes.

Muscle Power Testing

The maximal amount of power you have in your legs will be determined using weight training equipment. You will be asked to lift a series of increasingly heavier weights by pressing out your legs while your feet are resting on a footplate. You will then be asked to quickly and forcefully give one push to a pedal attached to a machine to measure leg power. You may be asked to repeat this push up to 5 times with rest periods in between. at two different levels of work. You will also be asked to lift a series of increasingly heavier weights by pushing out your legs as rapidly as possible for each lift. The overall risks involved with the muscle power testing may be muscle tightness, soreness, and fatigue, and rarely pulled muscles. This measurement will be done twice, on two visits separated by one week. This test will take approximately 45 minutes.

400 meter walk (¼ mile)

You will be instructed to walk at a pace you can keep up without feeling that you are too uncomfortable until you complete a ¼ mile, or can no longer continue. Rest periods are permitted while standing for up to 60 seconds, if necessary. If you cannot continue after 60 seconds rest, or if you need to sit down, the test will be terminated.

Muscle Biopsy

A muscle biopsy will be taken to enable us to get in-depth analysis of your muscle tissue. The muscle biopsy procedure will be performed by Dr. Roger Fielding in your non-dominant (opposite of your dominant hand) thigh under sterile conditions. After a local numbing medicine, similar to that used at the dentist (which may result in a brief stinging or burning sensation), is injected in the middle of your thigh, a small (1/4 inch) incision will be made, and then a muscle biopsy needle will be inserted and a small muscle specimen (about 1/100th of an ounce) will be taken. The incision will be properly covered with a sterile dressing and an elastic bandage. The dressing will remain in place for 24 hours. You will not be able take a shower for 48 hours after the biopsy. This procedure will take about 1 hour. You will be asked to stop taking any aspirin and anti-inflammatory medicine (e.g., ibuprofen or naproxen) for three days before the procedure and three days after the procedure. Documented confirmation will be obtained from your primary care physician (PCP) regarding whether or not your medication can be discontinued before obtaining your approval. You may experience a mild to moderate temporary increase in joint pain while your anti-inflammatory

medication is not taken before and after the muscle biopsy. You may be exposed to a minimal, temporary increased risk of stroke or heart attack while your aspirin is being held before and after the muscle biopsy. You will be informed of your PCP's decision and any concerns regarding an increased risk. You will feel a dull pain during the procedure and some muscle soreness and tenderness from 4-12 hours after the biopsy has been taken. The muscle biopsy involves some discomfort such as redness, sensation of pressure in the area, soreness, and bruising. Rarely, infection, prolonged discomfort or numbness (1% of cases) may occur. There is a small risk of bleeding, infection, and scarring of the skin. Any bruising resulting from the procedure can be reduced by making sure that the bandage in the site remains firm and secure and that you do not participate in any vigorous exercise in the 24 hours following the biopsy. The muscle biopsy sample will be taken at the HNRCA but transferred for evaluation at Spaulding Rehabilitation Hospital. A portion of the sample will remain at the HNRCA for analysis. Confidentiality will be ensured as all samples being transferred will be coded and made unidentifiable. Your name will not be given out with the sample.

Surface EMG Testing and Neuromuscular testing
We will make several measurements intended to provide information regarding how you control your muscle force and timing. To do this, the electrical activity of your muscles will be measured using a procedure called electromyography, also termed EMG. By analyzing the electrical activity generated when you use your muscles or move your limbs, EMG will allow us to develop a better understanding of how your nervous system control your muscles, whether it has been affected with age, and whether this control is affected by exercise. These recordings will be made by placing small sensors on the skin over the muscles on your legs. The sensors are small boxes that will be taped to your skin using non-allergenic tape. There may be slight discomfort associated with shaving the hair from the skin and cleaning the skin with alcohol, and from removing the tape from the surface sensors. Some slight skin irritation is possible, although sensors are removed carefully to reduce the likelihood of this occurrence. If skin irritation does occur, it should disappear in a few days.

We will also study your ability to produce maximal muscle force while pushing your leg against a lever arm. To do this you will be seated in a specifically designed exercise machine and we will stimulate your muscles electrically by means of surface sensors on your legs while you push against the lever as hard as you can. This is done to determine whether you are able to fully use and move your muscles under your own effort. The electrical stimulation can be described as a very concentrated period of muscle tension. While many people find it uncomfortable, the duration of each stimulation is less than a half-second. Slight irritation or redness of the skin may occur due to shaving and cleaning the stimulation site prior to testing.

Computed Tomography (CT scan): You will be asked to lie down on a bed while the CT scan of your non-dominant thigh (opposite of your dominant hand) is done. This will take about 30 minutes. This x-ray technique will be used to obtain a picture of your thigh muscles and will be done at Tufts-New England Medical Center. This measurement will be done once during the study. The total effective radiation dose to your body is approximately the same as the normal background radiation received by an individual in 2.5 weeks, or approximately the same as the amount of radiation you would be exposed to during a twelve hour airplane flight. This is generally regarded as safe.

TIMELINE OF STUDY PROCEDURES

Visit 1: (Screening, 3-hours)

- Complete consent form
- Cognitive screening questionnaire
- Complete a medical history questionnaire
- Medical screening by the study physician
- Resting electrocardiogram (EKG)
- Blood draw
- Short Physical Performance Battery

Visit 2: (Within 1-3 days of visit 1, 4-hours)

- Complete questionnaires:
    - Health
    - Mobility
    - Mood
    - Life satisfaction
    - Ability to perform activities of daily living.
- Gait analysis
- Balance Testing
- Muscle strength and power tests
- 400 meter walk test

Visit 3: (Approximately 7 days after visit 2, 4-hours)

- Muscle strength and power tests
- Neuromuscular testing

Visit 4: (A minimum of 3 days after visit 3, 2-hours)

- CT Scan
- Muscle biopsy of a thigh muscle

If necessary, this schedule will be changed to account for any unforeseen delays or complications

BENEFITS

This research study is not being performed to benefit you directly. The benefits from your participation in this study are that your health and fitness status will be evaluated. The results of the medical screening and fitness evaluations will be made available for you and/or your primary care physician, upon your request. Others may benefit in the future from an improved understanding of the change of an individual's body composition, strength and muscle mass over time.

PAYMENT FOR RESEARCH-RELATED INJURY

Emergency medical treatment will be given to you if you are hurt or get sick as a direct result of this study. You or your insurance carrier will have to pay for any such medical care. Any needed medical care is available at the usual cost. All needed facilities, emergency treatment and professional services are available to you, just as they are to the general public. There are no plans to pay for your treatment if you get hurt or sick as part of this study. The institution has not set aside any money to pay for a research-related injury or illness.

CONTACTS

You have been told that you may reach the Principal Investigator or the study physician at any time of the day or night during the study period if you have any questions or problems related to the study. The telephone numbers are:

Roger Fielding, PhD.	(617) 556-3016	office
	(781) 284-9980	(evenings and weekends)
Edward M. Phillips, M.D.	(617) 573 2222	(Spaulding page operator)
	(617) 556 3042	(Metabolic Research Unit at HNRCA) (evenings/weekends)

If you have any questions about your rights as a research study subject, call the Tufts-New England Medical Center and Tufts University Health Sciences Institutional Review Board (IRB) at (617) 636-7512. The IRB is a group of doctors, nurses, and non-medical people who review human research studies for safety and protection of human subjects.

PAYMENT

You will receive a screening payment of $15 if you are not eligible for the study or do not wish to participate in the study after your initial screening. If you meet the study entry criteria and are willing to participate, you will receive an additional payment of $200 from the Human Nutrition Research Center on Aging at Tufts University at the conclusion of all four sessions of testing. If you do not complete the study, the amount of the payment will be proportional to the time you have spent in the research study (i.e. $15 for the screening test, $60 for completion of each visit 2, 3 and $80 for visit 4).

COSTS

There is no cost to you for participation in this research study.

ALTERNATIVES

Your alternative is not to participate in this research study. You may participate in other exercise programs.

WITHDRAWAL AND STUDY TERMINATION

You may change your mind about being in this study and stop being in this study at any time for any reason. If you decide to withdraw from this research study, you must inform Dr. Roger Fielding, the Principal Investigator.

The investigator or study sponsor may stop your participation in this research study without your permission for any of the following reasons:

- You do not follow the study procedures
- There has been a change in your health
- The study sponsor has ended the study due to new safety information

CONFIDENTIALITY

Medical information produced by this study will not become part of your hospital medical record, unless you request it to be. The information will be stored in the investigator's file and identified by a code number only. Information contained in your research records may not be given to anyone unaffiliated with the HNRCA, in a form that could identify you, without your written consent or as specified by law.

It is possible that your medical and research record, including sensitive information or identifying information, may be inspected and/or copied by the study sponsor (National Institute on Aging), federal or state government agencies such as the Office of Human Research Protection, or hospital accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor or by any of these agencies, the HNRCA will use reasonable efforts to protect your privacy and the confidentiality of your medical information.

All of the information collected on you during the course of the study will remain in a secure location. The coded vials with your muscle biopsy will analyzed at Spaulding Rehabilitation Hospital and the information sent to the Principal Investigator Dr. Roger Fielding at the HNRCA. Information relating to your participation in this study (e.g. such as the results from your exercise testing, completed questionnaires etc.) will be transferred to Boston University School of Public Health where statistical analyses of the data will be performed. Your data will be de-identified, so that your identity will remain unknown and to ensure confidentiality.

The results of this study may be published in a medical book or journal or used for teaching purposes. However, your name and any other identifying information will not be used in any publication or teaching materials.

You will have a research record with the HNRCA. Every effort will be made to maintain the confidentiality of your research records for this study by the investigators.

PARTICIPANT'S STATEMENT

Taking part in this study is totally your choice. Please read all or the following information carefully. Ask Dr. Roger Fielding or his representative, to explain any words, terms, or sections that are unclear to you. You should also ask any questions that you have about this research study. Your questions will be answered in words, or if you prefer, in writing. Do not sign this informed consent form unless you understand the information in it and have had your questions answered to your satisfaction. You should talk about this research study and the information in this informed consent form with whomever you want before you sign it.

I have read this consent form and have discussed with Dr. Fielding, or his representative the procedures described above. I have been given the opportunity to ask questions, which have been answered to my satisfaction. I understand that any questions that I might have will be answered verbally, or if I prefer, with a written statement.

I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to continue to participate. I understand that my participation is voluntary and that I may refuse to participate in this study.

I also understand that if, for any reason, I wish to discontinue my participation in the process at any time, I will be free to do so. I understand that if I discontinue my participation in the study, the amount of the payment will then be proportional to the time I have spent in the study.

Also, the Investigator or the Institution may decide, at any time and for any reason, that my participation in this study may be terminated. In this event, the payment amount will be proportional to the time I have spent in the study.

I understand that in the event I become ill or I am injured as a result of participating in this research study, medical care will be provided to me. However, such medical care will not be provided free of charge, even if the injury or illness is a direct result of this research study. I understand that no funds to provide financial compensation for research-related injury or illness are available.

If I have any questions concerning my rights as a research subject in this study, I may contact the Tufts-New England Medical Center/Tufts University Health Sciences Institutional Review Board at (617) 636-7512.

I have been fully informed of the above-described plan with its possible risks and benefits, and I hereby consent to the procedures set forth above. I will receive a signed copy of this consent form.

I understand that as a participant in this study my identity and my medical records and data relating to this research study will be kept confidential, except as required by law, and except, for inspections by the study sponsor (National Institute on Aging), the Tufts-NEMC Institutional Review Board and the federal Office of Human Research Protections (OHRP).

_____ _____

Date Participant's Signature

I have fully explained to _____ (Participant) the nature and purpose of the above-described procedure and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____

Date Principal Investigator or Representative's Signature

Appendix D

Pre-screening telephone questionnaire

Informed Consent Forms

(Chapter 5)

Project title: "Lower Extremity Muscle Power and Function in the Elderly"

Study 2 - Pre-screening questionnaire:

This questionnaire will be used to determine if you potentially qualify for this study. If you do qualify based on this questionnaire and are interested in participating in this study, you will be invited to participate in additional screens and surveys to further assess your eligibility. By answering these questions, you are under no obligation to participate in this research study.

I would like to describe the study and the time commitment it would involve on your part. You are being asked to participate in a research study for approximately 20 weeks, designed to evaluate the effects of an exercise program for your lower body. During the first 2 weeks of the study, you will undergo a series of baseline evaluations. If you fulfill the inclusion criteria you will then be asked to participate in an exercise program consisting of muscle strengthening exercises for your lower body. You will exercise 2 times per week for 16 weeks under the supervision of our research staff. At the end of the study, you will undergo another series of evaluations over a 2 week period.. The stipend for participation in this study is $700

Date: _____

Subject name: _____ Sex: M___ F___

Address:_____
_____

Telephone number:_____

Where did you hear about this study? direct mailing _____ poster_____

advertisement_____ (please specify e.g. newspaper, radio, internet) _____
other_____

Please answer the following questions:

1. What is your age? _____ D.O.B? _____

Only interviewees aged between 70-85 yrs will be invited to participate in the study. If outside these ranges, STOP pre-screening and refer to note B

2. What is your bodyweight: _____ lbs _____ kg

What is your height: ___ feet _____inches _____ meters (_____ m^2)

calculate BMI: _____ kg/m^2 (convert lbs to kg: 1 lb = 0.454 kg, convert inches to meters: 1 inch = 0.0254 meters)

Interviewees with a BMI < 19 kg/m^2 or > 32 kg/m^2 will be excluded from the study. If BMI is outside this range, STOP pre-screening and refer to note B.

3. Do you have health insurance? Yes ____ No ____ **If no, STOP pre-screening and refer to note B.**

4. Are you taking any prescribed medication? Yes ____ No ____

_____

_____

5. Do you currently exercise regularly or participate in a structured exercise program? Yes ___ No ___ If yes, describe activities:

_____

(If interviewee currently performs, or has during the previous 6 months, any regular endurance or resistance training exercise > 3 times/week, STOP pre-screening and refer to note B.

6-12: If interviewee answers 'yes' to any of these questions, STOP pre-screening and refer to note B.

6. Have you had any broken bones within the past 6 months? Yes ___ No ___ If yes, please explain:

_____

7. Have you had a heart attack/myocardial infarction within the last 6 months? Yes ___ No When?

_____

8. Do you have uncontrolled hypertension (BP > 150/90 mm Hg) ? Yes ____ No ____

_____

9. Have you ever been diagnosed with or do you currently suffer from symptomatic coronary heart disease?
Yes ____ No _____

10. Do you currently suffer from any neuromuscular disease (such as muscular dystrophy, ALS/motor neuron disease)? Yes ____ No _____

11. Are you currently receiving hormone replacement therapy? Yes ____ No ____

12. **Females Only**: Are you currently receiving estrogen therapy? Yes ____ No ____

13. Do you have any difficulty:

a. Walking a quarter of a mile or more? Yes _____ No _____
b. Climbing a flight of stairs? Yes _____ No _____
c. Standing up from a chair? Yes _____ No _____
d. Lifting and carrying an object weighing 10 lbs? Yes _____ No _____

(If interviewee answers 'no' to a,b,c and d: STOP pre-screening and refer to note B)

15. Do you currently suffer from any other illnesses? Yes ___ No ____
If yes, please explain:
_____

16. Are you currently participating in any other research studies? Yes ____ No _____ If yes, please explain:
_____

17. Can you get transportation to HNRCA, located at 711 Washington Street. The subway orange line stops one block away from the HNRCA. Yes _____ No _____

18. Are you still interested in participating in this study? Yes_____ No _____

19. Do you have any questions about anything we discussed today?
_____

Notes
A: If interviewee qualifies: Our enrollment coordinator will be contacting you shortly to schedule your screening visit.
B: If interviewee does not qualify: I am sorry, but you do not qualify for this study because _____. Thank you very much for your time and interest in this study. May we keep your name on file and contact you in the future for other research projects?

JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER ON AGING TUFTS UNIVERSITY

PREADMISSION SCREENING CONSENT FORM

Title: Lower Extremity Power and Function in the Elderly: Study 2

Principal Investigator: Roger Fielding, Ph.D.

Physician: Edward Phillips, M.D.

Study Coordinator: Kieran Reid, M.Sc.

You have been invited to participate in a research study at the Human Nutrition Research Center on Aging (HNRCA) at Tufts University. In order to assess your eligibility to participate in this research study, you must go through a preadmission screening process.

You will be invited to the HNRCA for a preadmission screening visit. This visit will occur at the start of a 20-week study period. If you successfully complete this screening visit, you will be accepted into the study and you will be required to attend the laboratory for 2 additional assessment visits within a two-week period and complete a 16-week exercise training program. After completing the exercise program, you will again be required to complete 2 follow-up visits within a two-week period. The study procedures will be performed in the Nutrition Exercise Physiology and Sarcopenia (NEPS) Laboratory at the HNRCA.

At the first pre-entry screening visit:

You will be asked to provide information about all medications (prescription and over-the-counter) that you currently take.

You will be asked to fill out a questionnaire about your health and exercise habits. A licensed physician or nurse practitioner will conduct a brief general physical examination to best assure your fitness to participate in the strength testing,and exercise training parts of the study.

You will also be asked to undergo a Short Performance Physical Performance Evaluation Test. This test has three parts: You will be asked: 1.) to walk about 13 feet. 2) to stand up from a chair five times without using your arms. 3) to stand in different positions while keeping your balance. The examiner will demonstrate what to do and will be nearby to steady you if you need it. The test takes about 5 minutes to complete. A resting electrocardiogram (EKG) will also be performed. To do this, your chest will be rubbed clean with isopropyl alcohol and a set of 10 adhesive (sticky) electrodes (plastic discs) will be placed on the skin.

In addition, you will have 0.5 oz. (3 tsps) of blood drawn from your vein for various routine blood measurements (e.g. complete blood count). We will also ask you to provide us with a small urine sample for urinalysis.

A brief test of your memory and mental function will be administered by the physician, nurse practitioner or other staff to determine your ability to follow directions during the study and provide consent.

The potential risks of this screening visit are related to the EKG, blood draw, and the Short Physical Performance Evaluation Test.

- EKG: There are no risks to this procedure other than occasional skin irritation from the adhesive electrodes.

- Blood Draw: There may be a slight discomfort during blood drawing and there is the possibility of a small bruise forming at the puncture site. There is also the remote possibility of a superficial inflammation (phlebitis) of the vein. There is no risk to the urine sampling.

- Short physical performance evaluation: The only risk expected to be associated with these tests is a risk of losing your balance. The examiner will remain close to help you if you are unsteady.

While this screening procedure may be of no direct benefit to you, you may receive some benefit since the results of this medical testing (physical examination and laboratory results) may be made available to you and/or your physician for follow-up, upon your request. If any abnormalities are discovered as a result of the physical examination and laboratory results, you will be notified and referred to your doctor. The results of this screening procedure may or may not qualify you to be admitted into the research study.

If you have any questions concerning this screening, you can call Dr. Roger Fielding at 617-556-3016 or Dr Eddie Phillips at 617-573-2222.

You understand that you are being screened to participate in the above research study. If for some unforeseen reason the research study does not commence, the HNRCA is not obligated to provide you with financial compensation for the research study. In such a case, the HNRCA staff will attempt to identify an alternative research study for which you qualify and approve.

VOLUNTEER STATEMENT

I understand that the screening process may be discontinued at any time by the staff of the HNRCA. I also understand that, if for any reason I refuse to participate or discontinue my participation in this process at any time, I will be free to do so and this will have no effect upon continuation of any care or treatment I may be receiving from physicians at the Tufts-New England Medical Center.

I understand the importance of correct medical and psychosocial information in the determination of my eligibility for participation, for my own safety and benefit. I, therefore, agree to answer all questions put forth to me during this screening process accurately and to the best of my knowledge.

I understand that my medical records and data will be kept confidential, except as required by law.

I understand that, in the event I become ill or injured as a result of participating in this screening process, medical care will be provided to me. However, such medical care will not be provided free of charge even if the injury or illness is a direct result of this research study. I understand that no funds to provide financial compensation for research-related injury or illness are available.

I understand that I will be paid a stipend of $15.00 for the screening visit. This stipend is provided to defray my travel/parking costs.

I have been fully informed of the above-described plan with its possible risks and benefits and I hereby consent to the plan set forth above. I will receive a copy of this consent form.

I have explained to_____the nature and purpose of the

Participant's Name

screening process and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____

Date Participant's Signature

_____ _____

Date Principal Investigator or Representative's Signature

JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER ON AGING TUFTS UNIVERSITY

INFORMED CONSENT FORM For Research Participation

Title: Lower Extremity Power and Function in the Elderly: Study 2

Principal Investigator: Roger Fielding, Ph.D.

Study Physician: Edward Phillips, M.D.

Study Coordinator: Kieran Reid, M.Sc.

INTRODUCTION

You are being invited to participate in a research study. The purpose of the research is to evaluate the effects of an exercise program for your lower body. You are being invited to take part in this research study because you meet the study entry eligibility criteria set by the study investigators. The entire study will take approximately 20 weeks to complete. Seventy subjects are being recruited to join this study. The research is supported by a grant from the National Institute on Aging.

The study will take place at the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University. The study will involve you undergoing various tests that will be conducted over a two-week period, before and after a 16-week training program.

You have previously had preadmission screening for the research study – *Lower Extremity Power and Function in the Elderly: Study 2.* This form describes the study in further detail.

STUDY PROCEDURES

You will complete the following procedures over the course of a two-week period, before and after the 16-week exercise training program.

Questionnaires

You will be asked to fill out a series of questionnaires related to your health, mobility, memory, emotional disposition, life satisfaction, and ability to perform daily functions such as stair climbing and rising from a chair. You will be given instructions and plenty of time to complete these forms and you can choose not to answer any questions for any reason. These forms will take approximately 60 minutes to fill out.

Muscle Strength Testing

You will have tests of muscle strength conducted at the HNRCA. You will be asked to exercise different muscles of your legs in a specially designed chair that resists movements of the joints. You will be asked to apply as much force as possible against a lever arm that controls the speed of your muscle contraction. You control the intensity of the force that is applied. At the end of the test your muscles will be fatigued. During the study, this measurement will be done eight times. This test will take approximately 30 minutes.

Muscle Power Testing

The maximal amount of power you have in your legs will be determined using weight training equipment. You will be asked to lift a series of increasingly heavier weights by pressing out your legs while your feet are resting on a footplate. You will then be asked to quickly and forcefully give one push to a pedal attached to a machine to measure leg power. You may be asked to repeat this push up to 5 times with rest periods in between, at three different levels of work. This test will take approximately 30 minutes.

Functional Measures

The following tests will take approximately 40 minutes to complete:

Gait Speed Testing

You will be observed and timed as you walk at your usual pace for 20 feet. The risk to these procedures is the chance that you could slip and fall.

Chair stand Test

You will be asked to stand up from a chair ten times with your arms placed across your chest.

400 meter walk (¼ mile)

You will be instructed to walk at your normal pace until you complete a ¼ mile, or can no longer continue. Rest periods are permitted while standing for up to 60 seconds, if necessary. If you cannot continue after 60 seconds rest, or if you need to sit down, the test will be terminated.

Stair Climb/Descend

You will be observed and timed as you climb and descend a flight of 10 stairs at as fast as you possibly can.

Weighted Stair Climb/Descend

You will be observed and timed as you climb and descend a flight of stairs while carrying 20% of your body weight (30 lbs for a person weighing 150 lbs) in two canvas shopping bags as fast as you possibly can.

Activity Monitoring

You will be asked to wear a small electronic device that will record your activity level. This device is about the same size as a watch face. This device will be attached to your belt using velcro and you will be asked to wear the device for 7 days in a row. The device will not be worn during sleeping or bathing.

Surface EMG Testing and Neuromuscular Testing
We will make several measurements intended to provide information regarding how easy it is to move your muscles. To do this, the electrical activity of your muscles will be measured using a procedure called electromyography, also termed EMG. By analyzing the electrical activity generated when you use your muscles or move your limbs, EMG will allow us to develop a better understanding of how your nerves control your muscles, whether they have been affected with age, and whether this control is affected by exercise training. These recordings will be made by placing small sensors on the skin over the muscles on your legs. The sensors are small boxes that will be taped to your skin using non-allergenic tape.

We will also study your ability to push your leg against a lever arm. To do this you will be seated in a specifically designed exercise machine and we will stimulate your muscles electrically by means of surface sensors on your legs while you push against the lever as hard as you can. This is done to determine whether you are able to fully use and move your muscles under your own effort.

Computed Tomography (CT – Scan)

You will be asked to lie down on a bed while the CT scan of your non-dominant thigh (opposite of your dominant hand) is done. This will take about 30 minutes. This x-ray technique will be used to obtain a picture of your thigh muscles and will be done at Tufts-New England Medical Center. This measurement will be preformed twice during the study.

16-WEEK EXERCISE TRAINING PROGRAM

You will be randomly assigned to participate in a supervised exercise program two times per week for 16 weeks at the HNRCA. Ideally, you will have at least 1 day of rest between each visit. You will perform muscle strengthening activities for the lower body, 2 days per week with a trained exercise physiologist. The muscle strengthening exercises will include 15 minutes of warm-up and stretching followed by lifting weights with your legs for approximately 45 minutes at each session. The weight used will be slowly progressed to 80% of the maximal amount of weight you can lift. This is known as the one repetition maximum (1-RM). To help us determine your strength change we will use a numbered subjective rating scale that will tell us how hard or heavy the weight feels to you. Because you are likely to get stronger, we will re-assess your 1-RM bi-weekly. You cannot start any new exercise or rehabilitation program during the study.

STUDY TIMELINE
Visit 1: (Screening, 4-hours)

- Complete consent form
- Cognitive screening questionnaire
- Complete a medical history questionnaire
- Medical screening by the study physician
- Resting electrocardiogram (EKG)
- Blood and urine sample
- Short Physical Performance Battery

Visit 2: (Within 1-3 days of visit 1, 4-hours)
- Complete questionnaires:
  - Health
  - Mobility
  - Mood
  - Life satisfaction
  - Ability to perform activities of daily living
- Functional Testing:
  - Gait analysis
  - Chair stand test
  - 400 meter walk test
  - Stair Climb/Descend
  - Weighted Stair Climb/Descend
- Muscle strength and power tests
- Begin activity monitoring

Visit 3: (Approximately 7 days after visit 2, 4-hours)
- End activity monitoring
- Repeat muscle strength and power tests
- Neuromuscular testing
- CT Scan

Exercise Training:
- Lower body strengthening
- Approximately 60 minutes 2 times per week for 16 weeks

Week 4 Neuromuscular Testing:
After Week 4 of training, you will be required to undergo another assessment of muscle strength, power, surface EMG and neuromuscular testing.

Repeat Testing
You will be required to repeat procedures conducted during visits 2 and 3 within 7 days after the completion of the 16 week exercise training

If necessary, this schedule will be changed to account for any unforeseen delays or complications

POTENTIAL RISKS

Muscle Strength and Power Testing, Surface EMG Testing, and Neuromuscular Testing

The risks of include muscle tightness, soreness and fatigue, and rarely pulled muscles. The potential risks of the EMG procedure are minimal and include possible pain and discomfort and minor skin irritation. There may be slight discomfort associated with shaving the hair from the skin and cleaning

the skin with alcohol, and from removing the tape from the surface sensors. Some slight skin irritation is possible, although sensors are removed carefully to reduce the likelihood of this occurrence. If skin irritation does occur, it should disappear in a few days. The electrical stimulation can be described as a very concentrated period of muscle tension. While many people find it uncomfortable, the duration of each stimulation is less than a half-second. Slight irritation or redness of the skin may occur due to shaving and cleaning the stimulation site prior to testing.

Functional Testing

The risk to these procedures is the chance that you could slip and fall. The examiner will be close to your side as you perform these tests so that you can be steadied if necessary.

Activity Monitoring

There are no risks to this procedure as you will be asked not to change your normal physical activity habits.

Computed Tomography (CT-Scan)

The total effective radiation dose to your body from the CT-scan is approximately the same as the normal background radiation received by an individual in 2.5 weeks.

Exercise Training

There is a chance that these exercise sessions may result in muscle soreness, increased joint pain and injury. You may have an irregularity of your heartbeat, symptoms of chest pain, or abnormality of your blood pressure during exercise sessions. In the event of an emergency, we have a standard emergency procedure (SOP) for the lab. All exercise and testing areas have telephones that are readily accessible and available when emergency assistance is needed. All research staff performing exercise testing and assessments are trained in CPR. At all times there will be at least two CPR trained exercise physiologists and/or research staff members in the lab to assist you. A doctor will be available either at the Metabolic Research Unit at the HNRCA or on-call. Additionally, emergency medical care will be obtained through Tufts-NEMC by dialing 911. You may stop the exercise session at any time, at which point the exercise session may be terminated by the doctor or investigator(s).

BENEFITS

This research study is not being performed to benefit you directly. The benefits from your participation in this study are that your health and fitness status will be evaluated. The results of the medical screening and fitness evaluations will be made available for you and/or your primary care physician, upon your request. Others may benefit in the future from an improved understanding of the change of an individual's body composition, strength and muscle mass over time.

PAYMENT FOR RESEARCH-RELATED INJURY

Emergency medical treatment will be given to you if you are hurt or get sick as a direct result of this study. You or your insurance carrier will have to pay for any such medical care. Any needed medical care is available at the usual cost. All needed facilities, emergency treatment and professional services are available to you, just as they are to the general public. There are no plans to pay for your treatment if you get hurt or sick as part of this study. The institution has not set aside any money to pay for a research-related injury or illness.

CONTACTS

You have been told that you may reach the Principal Investigator or the study physician at any time of the day or night during the study period if you have any questions or problems related to the study. The telephone numbers are:

Roger Fielding, PhD. (617) 556-3016 office

(781) 284-9980 (evenings and weekends)

Edward M. Phillips, M.D. (617) 573 2222 (Spaulding page operator)

(617) 967 2454 (Anytime)

If you have any questions about your rights as a research study subject, call the Tufts-New England Medical Center and Tufts University Health Sciences Institutional Review Board (IRB) at (617) 636-7512. The IRB is a group of doctors, nurses, and non-medical people who review human research studies for safety and protection of human subjects.

PAYMENT

You will receive a screening payment of $15 if you are found not eligible for the study or do not wish to participate in the study after your initial screening. If you meet the study entry criteria and are willing to participate, you will receive a total stipend of $ 700 if you complete the entire study. Payment will be made at specific intervals during the study – you will receive $100 after visit 3. During the 16-week exercise training period, you will receive a payment of $125 every 4 weeks. After the exercise training, $100 will be paid to you upon completion of the study. In the event that you discontinue your participation in the study, you will be paid an amount proportional to the time you have spent in the study (i.e. $15 for the screening test, $50 for completion of visit 1 etc.)

COSTS
There is no cost to you for participation in this research study.

ALTERNATIVES
Your alternative is not to participate in this research study. You may participate in other exercise programs.

WITHDRAWAL AND STUDY TERMINATION
You may change your mind about being in this study and stop being in this study at any time for any reason. If you decide to withdraw from this research study, you must inform Dr. Roger Fielding, the Principal Investigator.

The investigator or study sponsor may stop your participation in this research study without your permission for any of the following reasons:

- You do not follow the study procedures
- There has been a change in your health
- The study sponsor has ended the study due to new safety information

CONFIDENTIALITY
Medical information produced by this study will not become part of your hospital medical record, unless you request it to be. The information will be stored in the investigator's file and identified by a code number only. Information contained in your research records may not be given to anyone unaffiliated with the HNRCA, in a form that could identify you, without your written consent or as specified by law.

It is possible that your medical and research record, including sensitive information or identifying information, may be inspected and/or copied by the study sponsor (National Institute on Aging), federal or state government agencies such as the Office of Human Research Protection, or hospital accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor or by any of these agencies, the HNRCA will use reasonable efforts to protect your privacy and the confidentiality of your medical information.

All of the information collected on you during the course of the study will remain in a secure location. Information relating to your participation in this study (e.g. such as the results from your exercise testing, completed questionnaires etc.) will be transferred to Boston University School of Public Health where statistical analyses of the data will be performed. Your data will be de-identified, so that your identity will remain unknown and to ensure confidentiality.

The results of this study may be published in a medical book or journal or used for teaching purposes. However, your name and any other identifying information will not be used in any publication or teaching materials.

You will have a research record with the HNRCA. Every effort will be made to maintain the confidentiality of your research records for this study by the investigators.

PARTICIPANT'S STATEMENT

Taking part in this study is totally your choice. Please read all or the following information carefully. Ask Dr. Roger Fielding or his representative, to explain any words, terms, or sections that are unclear to you. You should also ask any questions that you have about this research study. Your questions will be answered in words, or if you prefer, in writing. Do not sign this informed consent form unless you understand the information in it and have had your questions answered to your satisfaction. You should talk about this research study and the information in this informed consent form with whomever you want before you sign it.

I have read this consent form and have discussed with Dr. Fielding, or his representative the procedures described above. I have been given the opportunity to ask questions, which have been answered to my satisfaction. I understand that any questions that I might have will be answered verbally, or if I prefer, with a written statement.

I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to continue to participate. I understand that my participation is voluntary and that I may refuse to participate in this study.

I also understand that if, for any reason, I wish to discontinue my participation in the process at any time, I will be free to do so. I understand that if I discontinue my participation in the study, the amount of the payment will then be proportional to the time I have spent in the study.

Also, the Investigator or the Institution may decide, at any time and for any reason, that my participation in this study may be terminated. In this event, the payment amount will be proportional to the time I have spent in the study.

I understand that in the event I become ill or I am injured as a result of participating in this research study, medical care will be provided to me. However, such medical care will not be provided free of charge, even if the injury or illness is a direct result of this research study. I understand that no funds to provide financial compensation for research-related injury or illness are available.

If I have any questions concerning my rights as a research subject in this study, I may contact the Tufts-New England Medical Center/Tufts University Health Sciences Institutional Review Board at (617) 636-7512.

I have been fully informed of the above-described plan with its possible risks and benefits, and I hereby consent to the procedures set forth above. I will receive a signed copy of this consent form.

I understand that as a participant in this study my identity and my medical records and data relating to this research study will be kept confidential, except as required by law, and except, for inspections by the study sponsor (National Institute on Aging), the Tufts-NEMC Institutional Review Board and the federal Office of Human Research Protections (OHRP).

_____ _____

Date Participant's Signature

I have fully explained to _____ (Participant) the nature and purpose of the above-described procedure and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____

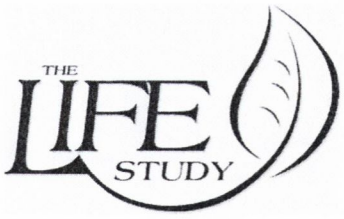
Date Principal Investigator or Representative's Signature

Appendix E

Life Study Analysis Plan Approval Letter

Informed Consent Forms

(Chapter 6)



February 12, 2013

Kieran Reid, M.Sc, MPH

Tufts University

Boston, MA

Re: *Cognitive Function as a Predictor of Physical Activity Adherence*

Dear Dr. Reid:

Congratulations!
The LIFE Publications and Presentations Committee reviewed and voted to approve the above-named publication proposal.

Please review your responsibilities for reporting progress, for gaining prior approval for abstracts and manuscripts outlined in the LIFE Publications and Presentations policy (attached). Note that compliance with the NIH Public Access Policy, which requires that all final peer-reviewed manuscripts arising from NIH funds must be submitted to PubMed Central within 12 months of publication, is also the responsibility of the lead author. Please review the instructions for submitting final manuscripts at http://publicaccess.nih.gov.

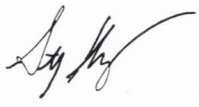
The current members of your writing group are:
Stephen Anton
Robert Axtell
Jeffery Katula
Diana Kerwin
Abby King
Art Kramer
Mike Miller
Valerie Myers
Jack Rejeski
Caterina Rosano
Kaycee Sink
Stephanie Studenski
Joe Verghese
Mike Walkup
Jeff Williamson

Additional members may be identified at the Steering Committee review.

Your DMAQC representative is: Mike Walkup

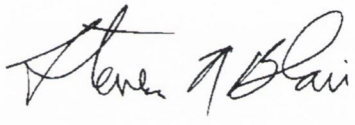
Best wishes and we look forward to working with you on the LIFE study.

Regards,



Stephen Kritchevsky, Ph.D.

Co-Chair, LIFE Publications and Presentations Committee



Steven N. Blair, P.E.D.

Co-Chair, LIFE Publications and Presentations Committee

Marco Pahor, MD

Principal Investigator, The LIFE Study

cc: P&P Committee

Co-Authors

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: The Lifestyle Interventions and Independence for Elders Study (LIFE)

INVESTIGATORS:

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SOURCE OF SUPPORT: National Institute on Aging (NIA) of the National Institutes of Health

Why is this research being done?

This research study will assess 2 different programs that are designed to enhance independence and to improve your health. Measures of health will include functional abilities, physical performance, and, if they occur, fall injuries and other illnesses. The 2 programs being tested are a physical activity program and a Successful Aging health promotion program. Each person will participate in only 1 of the 2 programs. The study will last up to 2 years.

Who is being asked to take part in this study?

If you are between the ages of 70 and 89 and exercise less than 20 minutes per week, you may be eligible to participate. There will be a total of 400 people who will participate in the study. Study sites include Wake Forest University in North Carolina, the University of Pittsburgh in Pennsylvania, Stanford University in California, and The Cooper Institute in Texas. There will be 120 people entered into this study at the University of Pittsburgh.

What procedures will be performed for research purposes?

If you agree to participate in this study you will be asked to complete up to 2 screening visits to see if you qualify for the study. If you qualify, you will be randomly assigned to 1 of 2 groups: a health promotion group or a physical activity group. ***Random assignment means your group assignment is determined by chance, like flipping a coin. You will not be able to choose one group over the other.*** The Successful Aging health promotion group will have up to 40 center -based supervised group sessions over a 2 year period. The physical activity group will have a personal face-to-face visit with the interventionist prior to beginning the program and up to 107 center-based supervised group sessions over a 2 year period. Both groups will receive monthly telephone calls and up to 4 additional clinic assessment visits over the 2 year period. The clinic assessment visits are located at 130 N Bellefield, Pittsburgh, PA 15213. If you need transportation, it will be provided for attending clinic assessment visits. Details about these procedures are provided below.

A. Screening Visits

Clinic Screening Assessment Visit (approximately 2 hours) performed at the clinic located at 130 N. Bellefield, Pittsburgh, PA 15213. At this visit you will be asked to sign this informed consent form if you are interested in participating in the study. We will ask you to bring the containers for all of your prescription and over-the-counter medications, including vitamins and supplements that you

have used over the previous 2 weeks. If you did not have a prior screening visit, you will be asked to complete a number of physical tasks that include:

1) standing up from a seated position in a chair 5 times in a row;
2) standing in 3 positions to assess your balance;
3) walking for a short distance (about 13 feet); and,

If you are eligible after initial screening, you will be asked to complete the next part of the screening visit.

1) Review your medical history and ask you about your ability to get around in your environment.
2) Undergo a physical exam by a study physician/nurse practitioner
3) Walk about ¼ mile (400 meters) at your own pace
4) Measure your blood pressure, heart rate, height, weight and waist circumference
5) Complete an electrocardiogram (ECG), a painless test that measures the electrical activity of your heart.

The tests that you complete will help us determine if you qualify for the study and whether it is safe for you to participate. If you qualify and still wish to participate, we will ask you to keep track of your physical activity and the amount of fruits and vegetables that you eat for 1 week. This is because we'd like to give you an idea of the type of forms that we will be asking you to fill out if you qualify and agree to be a participant in this study. You will also be asked to complete a questionnaire at home about your health and use of healthcare services. This should take 30 minutes to complete. We will ask you to return for a second screening visit.

Randomization Visit (approximately 3 hours):

For this visit, you will be asked to fast for 12 hours before your appointment so that we may take a sample of your blood. We ask that you do not eat anything or drink anything but water. We will also ask you to bring the completed version of the physical activity monitoring form and the questionnaires about your health, the record of how many fruits and vegetables you have eaten, and your use of healthcare services. We will then review this information to determine if you are still qualified.

If you are still qualified, you will have less than 5 tablespoons (less than 70 ml) of blood drawn from a vein. After your blood test is complete, we will give you a snack. Following your snack, we will ask you questions to measure your mood. Your bone density and body fat will be measured while you are lying on an exam table using a DEXA machine (a machine that measures bone density and body fat) that uses a small amount of radiation to take pictures of your body. These tests are painless. We will also perform some other simple tests of daily activities, such as determining your ability to put on and button a shirt and your hand strength using a hand grip dynamometer.

We will ask you to provide written permission to contact your physician/health care provider for a copy of your medical records and/or to discuss any health related concerns that arise during your study participation. We will also ask for your permission to contact someone who is in close contact with you to answer questions about your mobility and ability to get around in your environment. This visit will last about 3 hours.

B. Randomization and the Program Group

Once the screening process is complete and a determination of your eligibility is made, if you still wish to participate, you will be told which of the 2 study groups you will join. We will use a random process to find out what program group you will join. Random assignment means your group is determined by chance, and that you will not be able to choose. A member of the study staff will help you make your first appointment with your assigned study group.

You will be assigned to 1 of 2 groups:

1) ***Successful Aging Health Promotion Group*** – In this group, you will required to attend a series of classes, lectures, discussions and demonstrations that will provide up-to-date information and cover topics relevant for older adults. Potential topics include medication use, foot care, traveling, nutrition, upper body stretching, and communicating with health care professionals. The Successful Aging Workshops will be held in the conference room of the Division of Geriatric Medicine in the Liliane S. Kaufmann Building at 3471 Fifth Avenue, Suite 500, Oakland.

   If you are randomized into the Successful Aging group will receive a 45-minute individualized, face-to-face introductory session, by a health educator, during which time the program is described and questions are answered.

a. Months 1-6 will include lectures, discussion, and demonstrations 1 time each week. The sessions will last for approximately 60-90 minutes. Simple "homework" tasks for each lecture will be offered to reinforce the session content.

b. From Months 7 through the end of your study participation, attendance to 1 event per month will be required. These sessions will last approximately 60-90 minutes. Simple "homework" tasks for each lecture will be offered to reinforce the session content.

c. Beginning in month 7, a phone interview (lasting about 5-10 minutes) will be conducted by a staff member to provide ongoing support and encouragement regarding healthy lifestyle behaviors.

2) ***Physical Activity Group*** – In this group you will receive a fitness program consisting primarily of moderate walking activities (you will receive a pedometer to track your daily walking), lower body strengthening exercises, flexibility, and balance training supervised by an exercise physiologist. Moderate activity level is a level where "you are able to walk and talk at the same time" or somewhat hard. You will be introduced to the exercises in a structured way such that you begin with lighter intensity and gradually increase over the first 2-3 weeks of the program. Medical clearance from your doctor will not be obtained prior to starting the physical activity portion of the study. However, you will undergo a physical exam by a study physician or nurse practitioner. All exercise sessions are conducted and supervised by trained exercise physiologists, who monitor potential adverse experiences and symptoms. Based on the clinic screening visit, interventionists will be alerted if you might be prone to balance or other problems. You will be carefully monitored to identify any abnormal responses to exercise. In the early center-based training sessions, blood pressure, glucose levels, and heart rate will be monitored. You will be instructed to seek your physician's permission before continuing with the exercise program if health problems arise.

During all center-based exercise sessions an automated electronic defibrillator is on-site. On-site staff are trained in CPR and advanced cardiac life support. Also, University of Pittsburgh Medical Center (UPMC) emergency medical services will be activated if needed.

If you are randomized into the exercise group, you will be required to attend a 45-minute individualized, face-to-face introductory session, by an exercise physiologist, during which time the program is described and questions are answered.

a. Pre-intervention

i. Attend center-based exercise sessions 1-3 times per week at your choosing. This period will allow you to become familiar with the exercise procedures, facility and staff. The time for participation in the pre-intervention phase may vary but will not exceed 6 weeks before an exercise group is formed.

b. Months 1-2

i. Group training sessions will occur 3 times per week and last 60-90 minutes. These will be held at our exercise center in the Liliane S. Kaufmann Building at 3471 Fifth Avenue, Suite 1200, Oakland.

ii. A total of 10 group-based problem solving sessions will be held approximately once per week immediately following a scheduled exercise session.

c. Months 3-6

i. Group training sessions at our Kaufmann Building Exercise Center will decrease to 2 times per week.

ii. Home-based physical activity will be required 1 or more times per week.

iii. You will receive a monthly phone call from an exercise staff member to review problems and concerns and to problem solve potential barriers to physical activity.

iv. Additional behavioral sessions lasting 30-45 minutes will be offered at weeks 14 and 20 to ensure your success with home exercise.

d. Months 7 to the end of the study

i. Group training sessions at our Kaufmann Building Exercise Center will be reduced to 1 time per week.

ii. Home based physical activity will be increased to 2 or more times per week.

iii. You will receive a monthly phone call from an exercise staff member to review problems and concerns and to problem solve potential barriers to physical activity.

iv. Behavioral sessions will be offered on an as needed basis (30 minutes).

Your performance in the exercise program will be assessed in several ways. Interventionists will track whether you attend the center-based sessions as well as meet your weekly target of minutes of physical activity. We will also check your performance through completion of your exercise logs, and from the number of steps/day logged on your pedometers.

For both the exercise and Successful Aging health education groups, if you do not attend one or more scheduled sessions, a staff member will call to problem solve reasons why you didn't attend and promote your participation.

C. Follow-up Visits

Three-month follow-up phone interview (5 minutes):

A trained assessment team examiner will contact you by phone for an interview to ask you about how you are doing and to record health problems that you might have experienced since the start of the study.

Six-month clinic assessment follow-up visit (2 hours):

We will ask you to make another appointment for a follow-up visit. For this visit, you will be asked to fast for 12 hours before your appointment. Please do not eat any food or drink anything but water for 12 hours before this appointment. We will ask you to bring the containers for all of your prescription and over-the-counter medications including vitamins and supplements that you have taken over the past two weeks. You will be mailed a questionnaire about your health and use of healthcare services before this appointment and we will ask you to bring this completed questionnaire to this visit. We will record names of the medications you have taken and collect another 5 tablespoons of blood. We will provide a snack. You will also complete a number of tasks including several walking tests, blood pressure, chair stands, balance tests, grip strength and waist circumference, just like you completed during your screening visit. We will also ask about your overall health, quality of life and about any serious health problems you might have experienced. Within 3 days of your clinic visit, an identified close contact will be called to ask about your mobility and ability to get around in your environment.

Nine-month follow-up phone interview (5 minutes):

A trained assessment team examiner will contact you by phone for an interview to ask you about how you are doing in the study and to record any health problems you might have experienced.

Twelve-month clinic assessment follow-up visit (3 hours):

We will ask you to make another appointment for a follow-up visit. For this visit, you will be asked to fast for 12 hours before your appointment. Please do not eat any food or drink anything but water for 12 hours before this appointment. We will ask you to bring the containers for all of your prescription and over-the-counter medications including vitamins and supplements that you have taken over the past two weeks. You will be mailed a questionnaire about your health and use of healthcare services before this appointment and we will ask you to bring this completed questionnaire to this visit. We will record the names of the medications you have taken and collect another 5 tablespoons of blood. We will provide a snack. You will also complete a number of tasks including several walking tests, blood pressure, chair stands, balance tests, grip strength, and waist circumference, just like you completed during your screening visit. In addition you will repeat the DEXA test. We will also ask about your overall health, quality of life and about any serious health problems you might have experienced. Within 3 days of your clinic visit, an identified close contact will be called to ask about your mobility and ability to get around in your environment.

Fifteen-month follow-up phone interview (5 minutes):

A trained assessment team examiner will contact you by phone for an interview to ask you about how you are doing in the study and to find out about any serious health problems you might have experienced. Depending on when you first started the study, for some people, the study will end near the fifteen-month time. If this is true for you, we will ask you to make an appointment for a close-out visit, instead of doing the phone interview.

Eighteen-month clinic assessment follow-up visit (2 hours):

We will ask you to make another appointment for a follow-up visit. For this visit, you will be asked to fast for 12 hours before your appointment. Please do not eat any food or drink anything but water for 12 hours before this appointment. We will ask you to bring the containers for all of your prescription and over-the-counter medications including vitamins and supplements that you have taken over the past two weeks. You will be mailed a questionnaire about your health and use of healthcare services before this appointment and we will ask you to bring this completed questionnaire to this visit. We will record the names of the medications you have taken. You will also complete a number of tasks including

several walking tests, blood pressure, chair stands, balance tests, grip strength, and waist circumference, just like you completed during your screening visit. We will also ask about your overall health, quality of life and about any serious health problems you might have experienced. Within 3 days of your clinic visit, an identified close contact will be called to ask about your mobility and ability to get around in your environment.

Close-out clinic assessment visit (3 hours):

For some people who start in the study at a later time than others, the study will end near the 15-month time. If this is true for you, we will ask you to make an appointment for a visit to the Health Studies Office instead of doing the phone interview.

We will ask you to bring the containers for all of your prescription and over-the-counter medications including vitamins and supplements that you have taken over the past two weeks. You will be mailed a questionnaire about your health and use of healthcare services before this appointment and we will ask you to bring this completed questionnaire to this visit. We will record the names of the medications you have taken. You will also complete a number of tasks including several walking tests, blood pressure, chair stands, balance tests, grip strength, and waist circumference, just like you completed during your screening visit. We will also ask about your overall health, quality of life and about any serious health problems you might have experienced. Within 3 days of your clinic visit, an identified close contact will be called to ask about your mobility and ability to get around in your environment.

Alternative Visits (1 hour):

If you are not able to come for one of the follow-up assessment visits, we will ask your permission to visit you at your home. We will ask you to complete study procedures and questionnaires similar to your clinic visit. Within 3 days of your clinic visit, an identified close contact will be called to ask about your mobility and ability to get around in your environment.

Storage and Use of Blood Samples

As a participant in the LIFE study, you will be asked to donate a blood sample 3 times during the study (at the second screening visit, and at the 6 and 12 month clinic visits). These samples will be stored indefinitely in the laboratory of Dr. Barbara Nicklas (a study co-investigator), at the Biological Specimens Repository at Wake Forest University in Winston-Salem, NC. Each specimen will be labeled with a Biological Specimen ID number with no personal identifiers. Information linking this code number to your identity will be kept in a separate, locked secure location at the Field Center and only accessible to study personnel with a different key from that of all other files. Blood samples may be used by investigators other than the investigators of the current study and will

not include information that identifies you. The use is limited to non-commercial purposes. The samples will be used in the future to better understand how factors we can measure in your blood relate to physical health, mental mood, memory, and attention, and your responses to the group program. Some of these samples will be used to look at your genes. Genes contain information about you that you inherited from your parents, and some of these genes may play a role in your health.

What are the possible risks, side effects, and discomforts of this research study?

There are some potential (possible) discomforts and risks associated with participating in the LIFE Study. There may be some infrequent (1-10 out of 100) discomfort in the beginning of the study from increasing your physical activity. The possibilities include, but are not limited to, some muscle and joint stiffness. This stiffness generally subsides in 1 or 2 days, and is not considered to be serious. You might experience an exercise-related injury such as a strain, sprain, or other injury to your muscles or joints. Procedures to minimize discomfort include warm-up and cool-down activities that include flexibility exercises. Risks associated with exercise training will be minimized as all sessions are conducted and supervised by trained exercise physiologists who monitor potential adverse experiences and symptoms.

There exists the possibility that certain physical changes may occur during your participation in your physical activity. These include abnormal blood pressure, fainting, abnormal heart beats, and, in rare (less than 1 out of 100) instances, heart attack, stroke, and death. Every effort is made to minimize these risks by reviewing information about your health before the activities begin. Emergency equipment and trained personnel are available to deal with unusual situations that may arise.

DEXA bone density measurement of the whole body involves a very small amount of radiation, equal to 2.0 - 3.0 mrem, which is less than 1% of the average amount of natural environmental radiation exposure (300 mrem) that each member of the general public receives per year. This is a small fraction of the maximum annual radiation exposure limit (50,000 mrem) permitted to any single organ of radiation workers allowed by federal regulations. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (cellular abnormalities) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from this study is considered to be low and comparable to other everyday risks.

On infrequent occasions, (1-10 out of 100), you may experience some skin irritation, chafing, or redness from the ECG electrodes.

You may experience temporary pain, or bruising during the blood sample collection process. Only specially-trained staff will be responsible for the collection of blood samples. There is a possibility that if the results of the research studies involving your biologic samples or genetic material were to

become generally known, this information could impact future insurability, employability, or reproduction plans, or have a negative impact on family relationships, and/or result in paternity suits or stigmatization.

Taking part in this research may involve providing information that you consider confidential or private. Efforts such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

As with any research study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious or life threatening.

A committee of health experts (doctors and scientists) who are not connected with the study will be reviewing all study activities at regular intervals to assure that the risks and benefits being described to you are accurate.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?"

You will be promptly notified if any new information develops during the conduct of this research study that may cause you to change your mind about continuing to participate.

What are the possible benefits of taking part in this study?

You will receive health and medical screening examinations and the results will be discussed with you. You will be given the results of the tests of blood pressure and body composition. You and your doctor will be notified by phone and letter if abnormal test results that require immediate attention. You will benefit from increased attention from clinic staff and from health promotion materials supplied. You may have the opportunity to participate in a physical activity program or health promotion program with professional supervision.

Benefits to others: In the future other older adults could benefit from the results of this research. Information gained from this study could lead to improved medical care for them. However, the study staff will not know if there will be benefits to other people until all of the information obtained from this research has been collected and analyzed.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?

Neither you nor your insurance provider will be charged for the costs of any of the procedures performed for the purpose of this research study.

Will I be paid if I take part in this research study?

You will be paid to participate in this study. You will be paid $20 for each clinic assessment visit, up to 6 visits, for a possible total of $120. A check will be mailed to you from the University of Pittsburgh, following your visit. Also, transportation for your clinic assessment visits will be provided free of charge or you will be reimbursed for parking if you drive yourself. You will **not** be paid for any of your group (approximately 40 visits) or individual activity (approximately 107 visits) visits during the health promotion or physical activity programs. We will reimburse you for parking fees associated with your group or individual activity visits. Transportation for your group or individual activity visits will be provided if needed.

Who will pay if I am injured as a result of my taking part in this study?

University of Pittsburgh researchers and their associates who provide services at University of Pittsburgh Medical Center (UPMC), recognize the importance of your voluntary participation in their research studies. These individuals and their staffs will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you are injured as a result of the research procedures being performed, please contact immediately the Principal Investigator or one of the co-investigators listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. You will not receive any monetary payment for, or associated with, any injury that you suffer in relation to this research.

Who will know about my participation in this research study?

Any information about you obtained from this research study will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in locked file cabinets. Your identity on these records will be indicated by a case number rather than your name. Each specimen will be labeled with a Biological Specimen ID number without any information that identifies you. Information linking this code number to your identity will be kept in a separate, locked secure location at the Field Center and only accessible to study personnel with a different key

from that of all other files. You will not be identified by name in any publication of the research results unless you sign a separate form giving your permission (release).

Will this research study involve the use or disclosure of my identifiable medical information ?

This research will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g. physicians office) records. This information that will be recorded will be limited to information concerning your health status and hospitalizations. This information will be used for the purpose of tracking your health status for the duration of the study. No identifiable information will be placed in your medical record unless you specifically request that we send identifiable study results to your health care provider.

Who will have access to my identifiable medical record information related to my participation in this research study?

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to your identifiable medical record information related to your participation in this research study:

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable medical record information for the purpose of monitoring the appropriate conduct of this research study.

Authorized representatives of the sponsors of this research study, National Institute on Aging (NIA), may review and/or obtain your identifiable medical record information for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data. Authorized representatives of the study sponsor may also be present during your participation in certain research procedures. While the study sponsor understands the importance of maintaining the confidentiality of your identifiable medical record information, the UPMC and University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor.

The investigators involved in the conduct of this research study may receive funding from the sponsor to perform the research procedures and to provide the sponsor with identifiable medical record information related to your participation in the study.

Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to your identifiable medical record information for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2)

addressing correct payment for tests and procedures ordered by the investigators; and (3) for internal hospital operations (i.e. quality assurance).

In unusual cases, the investigators may be required to release your identifiable research information (which may include your identifiable medical record information) in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Taking part in this research may involve providing information that you consider confidential or private. Efforts such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe

May I have access to my medical record information resulting from participation in this research study?

In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider unless otherwise specifically stated below.

May I refuse to provide my authorization (consent) for the use of my identifiable medical record information for the purpose of this research study?

Your authorization (consent) to use and disclose your identifiable medical record information for the purpose of this research study is completely voluntary. However, if you do not provide your written authorization (consent) for the use and disclosure of your identifiable medical record information, you may not be allowed to participate or continue to participate in the research study.

Whether or not you provide your authorization (consent) for the research use and disclosure of your medical record information will have no affect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider. Whether or not you provide this written authorization (consent) will have no affect on your current or future relationship with the University of Pittsburgh.

May I withdraw, at a future date, my authorization (consent) for the use of my identifiable medical record information for the purpose of this research study?

You may withdraw, at any time, your authorization (consent) for the use and disclosure of your identifiable medical record information for the purpose of this research study. However, if you withdraw your authorization (consent) for the use and disclosure of your identifiable medical record

information, you may also be withdrawn from further participation in this research study. Any identifiable medical record information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your authorization may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your authorization (consent) you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form. Should you decide to withdraw from study participation, your specimens will continue to be stored with a linkage code to your identity.

Your decision to withdraw your authorization (consent) for the research use and disclosure of your medical record information will have no affect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider. Your decision to withdraw this authorization will have no affect on your current or future relationship with the University of Pittsburgh.

If I agree to take part in this research study, can I be removed without my consent?

If it is deemed medically unsafe for you to continue in the physical activity intervention, the investigator will limit your participation to clinic assessments and phone calls, however, no participants will be withdrawn.

For how long will the investigators be permitted to use my identifiable medical record information?

The investigators may continue to use and disclose your identifiable medical record information for the purposes described above for an indefinite period of time.

****

VOLUNTARY CONSENT

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions which I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (412-383-1480).

We have set out a specific question for you to consider below. Please initial one of the answers.

" I give my permission to use my biological sample, or genetic material, without personal identifiers, in this research project involving the study of enhancing independence."

YES_____ NO_____

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____ _____

Participant's Signature Date

CERTIFICATION OF INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation.

Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date

CONSENT TO PARTICIPATE IN A RESEARCH STUDY
STANFORD UNIVERSITY

Title: Physical exercise to prevent disability pilot study
(also known as The LIFE Study)

Part A. Specific to Intervention Programs & Measurements

WHAT IS THIS STUDY ABOUT?
This is a research study that will compare a Successful Aging program with a physical activity program. We hope to learn about the impact of both programs in reducing the occurrence of mobility disability in older adults. We plan to enroll up to 100 participants at the Stanford field center. Up to 300 additional participants will be enrolled study-wide (across 3 field centers).

WHY WAS I ASKED TO PARTICIPATE?
You were selected as a possible participant in this study because: (a) you are 70 – 85 years of age; (b) you do not have overt cardiovascular disease; (c) you are not currently meeting the US recommended guidelines for physical activity; and (d) you report an ability to walk 1/4 mile.

WHAT WILL I BE ASKED TO DO?
We must first determine whether you meet all of the eligibility requirements of this study. So, at the beginning of the study you will be asked to complete **2 baseline evaluations.** These evaluations will take place at the **Stanford Prevention Research Center, Stanford University**. Each evaluation will take place between 7:00 am and 5:00 pm and will require approximately **1.5 - 2 hours**. These evaluations will include:

1. Measurement of your resting blood pressure, heart rate and electrocardiogram (i.e., electrodes will be attached on your chest to measure the functioning of your heart). An examination gown will be worn over the electrodes;

2. A medical history and review of the medications that you take;

3. A physical examination by the study physician;

4. A walk of about 1/4 mile **at your own pace**;

5. A test of hand-grip strength where you will be asked to squeeze a hand-held device as hard as possible (similar to performing a "strong handshake"); you will be asked to do this with each hand;

6. Completion of questionnaires regarding your physical activity, medical history, health habits, disability status, and memory/concentration. The questionnaires will be done either by paper-and-pencil, on a computer, or by personal interview with research staff. You have the right to refuse to answer any questions, and refusal will not affect your participation.

7. Provide blood samples after a 12-hour fast. Approximately 67 milliliters (about 4.5 tablespoons) of blood will be collected by venipuncture (entering a vein with a needle through the skin) per clinic visit. In total, approximately 13.5 tablespoons of will be collected over the course of the study (3 clinic visits).

IF I AM ELIGIBLE, BASED ON THIS TEST, WHAT HAPPENS NEXT?

You will be **randomly assigned, like the flipping a coin,** to 1 of 2 programs. You have a 50% chance of being assigned to one of these groups:

(a) Successful Aging Program: If, by chance, you are assigned to this program, you will receive an initial session to review the expectations and content of this program. You will then be asked to attend Successful Aging classes, located at the Stanford Prevention Research Center, once per week for the first 6 months of the study. During the last 6 months of the study, you will be asked to attend the class once per month. The Successful Aging classes will provide up-to-date information and cover topics relevant for older adults including information on medications, foot care, traveling, and nutrition. Beginning with the 7th month of the study to the end, you will receive monthly telephone calls from study staff to provide ongoing support and encouragement regarding healthy lifestyle behaviors. Each Successful Aging class will last approximately 1 hour. Your participation in the Successful Aging Program will last for 12 months.

(b) Physical Activity Program: If, by chance, you are assigned to this program, you will receive an initial session to review the expectations and goals of this program. This session will also serve to individually tailor a physical activity program for you based on your baseline measurements. For the first 2 months of the study, you will be asked to attend 3 supervised exercise classes per week. These exercise sessions will be based at the Stanford Prevention Research Center, or a community facility, using Stanford research staff as trained exercise instructors. These sessions will be used to initiate a walking program and introduce you to strength, stretching, and balance exercises in a safe, progressive manner. Each exercise session will last approximately 40 – 60 minutes. Once per week, the exercise class will be followed by a 30-minute skills training session. These sessions are designed to promote independence, and discuss strategies to overcome barriers and lapses related to physical activity. During months 3 – 6 of the program, you will be asked to attend 2 supervised exercise classes per week. During this period, we will provide instruction on home-based exercises that you can do in a variety of settings. The weekly skills training sessions will continue once per week. During months 7 – 12, you will be asked to attend 1 supervised exercise class per week and continue with home-based exercises. The frequency of the skills training sessions will be reduced to once per month. During the 12-month program you will also receive monthly telephone calls from research staff to review problems, concerns and problem-solve around barriers to physical activity participation. Your participation in the Physical Activity Program will last for 12 months.

Members of both groups (Successful Aging and Physical Activity Programs) will be asked to undergo the same procedures of the **baseline evaluation** again at 6-months, and 12-months. An 18-month visit will only be asked of the first 25-50 participants recruited into the study. The 18-month visit will involve: blood pressure measurement, personal interview covering medical and disability status, and physical functioning measures that were done as a part of the screening process.

24 month visit (if applicable)

We may ask you to come back to our clinic for a visit that will last about 30-45 minutes. At that visit, we will ask you about your health and ask you to walk about 1/4 mile if you are able.

If you are not able to come for one of the follow-up visits, we will ask your permission to visit you at your home. We will ask you to complete study procedures and questionnaires similar to your clinic visits.

Audiotaping or Videotaping: During the initial sessions or the follow-up contacts, you may be asked to consent for such sessions to be audiotaped, or on occasion, videotaped. The purpose of these recordings is to enhance quality control and quality assurance of the research staff, and to ensure that all the groups receive information in a similar manner across all staff. You have the right to refuse to be audio- or videotaped, and such refusal will not prejudice your participation in the study or future encounters with our research staff. You will be informed immediately before any sessions that could be taped, and you will have the opportunity to refuse taping at that time.

Do you agree to be audiotaped? (circle one): Yes No
Do you agree to be videotaped? (circle one): Yes No

BENEFITS

You may experience physical and emotional benefits from the comprehensive health evaluations and participation in a program promoting healthful behaviors. However, WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS STUDY.

RISKS

Potential risks of participation in this study are of several kinds, all of which are rare, when the procedures are conducted by trained personnel under medical supervision:

(a) Cardiovascular, orthopedic (i.e., foot or leg problems), or bone and joint problems can occur during exercise training, but serious complications are rare if a properly designed exercise regimen is followed. Temporary muscle and joint soreness can be expected quite frequently upon starting an exercise program, but these effects are temporary.

Unless there is damage due to a previous injury, serious orthopedic complications are uncommon as a result of the exercise being recommended. Heart attack is a rare risk of exercise in middle-aged and older men and women. Studies of this risk indicate that a fatal heart attack occurs approximately once in 80,000 hours of exercise training.

(c) There is a remote risk that persons completing questionnaires or interviews focused on psychological issues may become distressed. There is no evidence that any permanent dysfunction has resulted from such testing.

(d) It is possible that, based on information gained from this study, the investigators may have serious concerns (relating to matters such as severe depression, suicide, etc.) about your health and/or safety; in such a case, the investigators may contact you and provide a referral for your care.

(e) There is a risk of losing your balance and falling associated with the physical performance-based testing (e.g, the 1/4 mile walk, balance tests, rising from a chair). We will minimize this risk by: (1) safely escorting you chairs located along the walking course should you become unsteady; (2) following you at a close distance; and, (3) will be at your side should you need assistance.

In addition, there may be risks associated with treatments or procedures in this study that are currently unforeseeable.

COSTS/COMPENSATION

- There is **no cost to you** to participate in this study. All costs for the study will be supported by the research grant from the National Institutes of Health (NIH)

- You will receive $30 upon completion of each clinical visit. Legally, you can be paid only if you are a US citizen, a legal resident alien (i.e., possess a "green" card), or have a work eligible visa sponsored by the paying institution

- You or your insurance company will be responsible for costs of medical management during or after the study period

FUNDING SOURCE

- The funding source for this study is the National Institutes of Health. The Principal Investigator has other research grants sponsored by the National Institutes of Health.

Part B. General Consent Form Requirements

PARTICIPATION IN OTHER STUDIES

While participating in this study, you should not take part in any other research project without the informed approval of investigators from each separate project. This is to protect you from possible injury arising from situations such as extra blood drawing, interaction of research drugs, or similar hazards.

Are you participating in any other research studies, or, do you have plans to participate in other research studies that will overlap with the duration of this study?

(Check one): _____ yes _____no

RIGHT TO REFUSE OR WITHDRAW

Your participation in this study is entirely voluntary. The alternative to participating is not to participate. Your decision whether or not to participate will not prejudice you or your medical care. If you wish to participate in this study, you must sign this form. If you decide to participate, you are **free to withdraw** your consent, including your authorization regarding the use and disclosure of your health information, and to discontinue participation at any time without prejudice to you or effect on your medical care. If you decide to terminate your participation in this study, you should notify the Project Director, Dr. Leslie Pruitt, at (650) 725-5318. There are no anticipated consequences to withdrawal from this study.

If you do decide to withdraw from this study, you will be contacted by a member of the research staff in order to answer any questions you may have, and to facilitate to process of providing you with any information about the study outcome, or your personal results pertaining to the study. Please note that some results may not be available until all participants have completed the study.

You may be withdrawn from this study for the following reasons: 1) failure to follow instructions, 2) the investigator decides that continuation could be harmful to you, 3) you need treatment not allowed in the study, 4) the study is canceled, or 5) other administrative reasons. At the discretion of the protocol director, **subjects may be taken out of this study** due to unanticipated circumstances.

YOU WILL BE INFORMED SHOULD NEW INFORMATION BE LEARNED

You will be told if **any new information** is learned which may affect your condition or influence your willingness to continue participation in this study.

COMPLICATIONS

- All forms of medical diagnosis and treatment -- whether routine or experimental -- involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the

researchers will assist you in obtaining appropriate medical treatment but this study does not provide financial assistance for additional medical or other costs. You do not waive any liability rights for personal injury by signing this form. For further information, please call (650) 723-5244 or write the Administrative Panel on Human Subjects in Medical Research, Administrative Panels Office, Stanford University, Stanford, CA 94305-5401. In addition, if you are not satisfied with the manner in which this study is being conducted or if you have any questions concerning your rights as a study participant, please contact the Human Subjects Office at the same address and telephone number.

- If you think you have experienced a **research related injury** call Karen Bolen at (650) 723-9835.

QUESTIONS

- If you have any questions, we expect you to ask us. If you have any additional questions later, Dr. Abby King, Principal Investigator, at (650) 723-6255, or Dr. Leslie Pruitt, Project Director at (650) 725-5318 will be happy to answer them.

CONFIDENTIALITY

- Any data that may be published in scientific journals will not reveal your identity. Patient information may be provided to Federal and regulatory agencies as required. The Food and Drug Administration, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

- If your interviews or phone contacts suggest that you may be severely depressed, the research staff will provide you with information on how and where you could receive treatment. During this time, a research staff member will also provide you with a list of resources. If your answers suggest that you may be at risk to harm yourself or someone else, a research staff member will speak with you and appropriate steps will be taken to ensure your safety (e.g., going to an emergency room).

INFORMATION ABOUT BLOOD COLLECTION AND STORAGE

Your blood contains chemical information (biomarkers, DNA) that may provide important information related to aging and physical activity. We are collecting and storing your samples so that we may measure such chemical information. There are several things you should know before allowing your samples to be studied:

- Your samples will be linked to your unique research identification number (ID number) and will be stored under your ID number;

- Your name or other public identifiers will not be included with any samples shared with other investigators;
- Whenever measures relating to genetics (DNA) are performed, there are questions raised that are related to informing you of any results. Possible risks of knowing results include: anxiety, other psychological distress, and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. Sometimes participants have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. Donation of your samples for this study is not genetic testing. (However, if you are interested in such clinical testing or genetic counseling, you should contact your physician);
- You will be told of the results from baseline, 6-month, and 12-month samples, but not of other possible tests performed in the future. Please be aware that all samples are "batched" (or saved to be measured at a single time), so results from baseline, 6-month, and/or 12-month samples may not be available until all participants have completed the study;
- You have the right to refuse to allow your samples to be studied now or saved for future study. We may retain your identified samples, if they relate to your routine clinical care, but not for additional research;
- Sometimes information from your samples may have importance for your family members. You may determine whether or not you wish to share such information with your family by completing the following:

I (circle one) [consent / withhold consent] for the investigator to provide genetic information about me to my family members.

USE AND DISCLOSURE OF YOUR MEDICAL INFORMATION

By signing this form, you are authorizing the use and disclosure of your health information collected in connection with your participation in this research study. Your information will only be used in accordance with the provisions of this consent form and applicable law. If you decide to terminate your participation in the study, or if you are removed from the study by the protocol director, you may revoke your authorization, *except* to the extent that the law allows us to continue using your information.

What Information Will Be Used or Disclosed?

Your health information related to this study, including, but not limited to, medical history, physical examination, blood/urine samples, and

questionnaire data may be used or disclosed in connection with this research study.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director (Dr. Abby King)
- The Stanford University Administrative Panel on Human Subjects in Medical Research
- The Research Team (Project Director, Evaluation Director, Clinic Coordinator, Staff Physician, data analysts, and research assistants)
- Research staff at collaborating institutions (Wake Forest University School of Medicine, Cooper Clinic [Dallas, TX], University of Pittsburgh)

Who May Receive / Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The National Institutes of Health
- A Medical Safety Committee consisting of non-Stanford scientists
- A Data and Safety Monitoring Board consisting of non-Stanford scientists

Your information may be re-disclosed if the recipients described above are not required by law to protect the privacy of the information.

Expiration

Your authorization for the use and/or disclosure of your health information will continue indefinitely.

When Access to Your Information May Be Limited

We expect that you will have access to all of the information collected in connection with this research project (e.g., functional test results, physical examination results, blood/urine sample results, questionnaire results, etc.) Under special circumstances, you may not be allowed to see or copy certain information in your medical records collected in connection with your participation in this research study while the research is in progress.

YOUR BILL OF RIGHTS

Persons who participate in a research project have certain rights. These rights include but are not limited to the subject's right to:

- Be informed of the nature and purpose of the experiment;
- Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- Be given a description of any attendant discomforts and risks reasonably to be expected;
- Be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- Be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- Be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should rise;
- Be given an opportunity to ask questions concerning the experiment or the procedures involved;
- Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- Be given a copy of the signed and dated consent form, and;
- Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision

YOUR SIGNATURE INDICATES THAT YOU HAVE READ AND UNDERSTAND THE ABOVE INFORMATION, THAT YOU HAVE DISCUSSED THIS STUDY WITH THE PERSON OBTAINING CONSENT, THAT YOU HAVE DECIDED TO PARTICIPATE BASED ON THE INFORMATION PROVIDED, AND THAT A COPY OF THIS FORM HAS BEEN GIVEN TO YOU.

_____ _____

Signature of Participant Date

Person Obtaining Consent

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied – that the participant has been provided with the Experimental Subject's Bill of Rights, if appropriate, that I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

_____ _____

Signature of Person Obtaining Consent Date