

**PERIPHERAL NERVE DECLINE IMPACTS LOWER EXTREMITY MUSCLE  
FUNCTION IN OLDER ADULTS**

by

**Rachel E. Ward**

BS, Duke University, 2006

MPH, University of Pittsburgh, 2011

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This dissertation was presented

by

Rachel E. Ward

It was defended on

June 18, 2013

and approved by

Robert M. Boudreau, PhD, Assistant Professor, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

Paolo Caserotti, PhD, Assistant Professor, Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

Jane A. Cauley, DrPH, Professor, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

Bret H. Goodpaster, PhD, Assistant Professor, Department of Health and Physical Education, Graduate School of Public Health, University of Pittsburgh

Anne B. Newman, MD, MPH, Chair and Professor, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

**Dissertation Advisor:** Elsa S. Strotmeyer, PhD, MPH, Assistant Professor, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

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**ABSTRACT**

The prevalence of poor peripheral nerve function increases with age from approximately 8% at ages 40-49 to 35% after age 80 and likely contributes to declines in muscle strength, power, and mobility limitations. However, longitudinal evidence for the association is lacking and the relationship between nerve function and muscle power has not been examined even at a cross-sectional level. This dissertation investigates the role of sensory and motor peripheral nerve function in muscle function decline and incident mobility limitation in older adults using data from two longitudinal cohort studies. Data from the Osteoporotic Fractures in Men Study (MrOS) show that poor motor and sensory nerve function are independently associated with poor muscle power and that light monofilament insensitivity is associated with greater decline in muscle power. Findings from the Health Aging and Body Composition (Health ABC) Study indicate that sensory and motor nerve function are predictive of subsequent strength and concurrent change in strength, although improvement in nerve function may not always lead to improvements in strength. We also found that sex modified the relationship between nerve function and strength, with motor and sensory nerve function being associated with strength in women and only sensory nerve function being associated with strength in men. Additionally in the Health ABC Study, we found that poor initial motor and sensory nerve function and sustained poor motor nerve function over seven years independently predicted incident mobility

limitation. Understanding the role of neuromuscular parameters in the disablement process may help to identify multiple points of intervention. Our findings have important public health implications, suggesting a need for future work to examine early prevention of modifiable risk factors and secondary prevention to slow muscle function declines and prevent mobility limitation. Since our results persisted after adjustment for known risk factors for poor nerve function such as diabetes and vitamin B12 deficiency, novel risk factors should also be explored.

## TABLE OF CONTENTS

<b>PREFACE.....</b>	<b>XIII</b>
<b>1.0 INTRODUCTION.....</b>	<b>1</b>
<b>1.1 THE EPIDEMIOLOGY AND PUBLIC HEALTH CONSEQUENCES OF NEUROMUSCULAR IMPAIRMENT AND DISABILITY IN LATE LIFE.....</b>	<b>1</b>
<b>1.1.1 Incidence and prevalence of impaired peripheral nerve function with age</b>	<b>3</b>
<b>1.1.2 Mobility-related consequences of reduced nerve function with age .....</b>	<b>5</b>
<b>1.2 DENERVATION AND PATHOPHYSIOLOGY OF MUSCLE AGING .....</b>	<b>7</b>
.....	<b>8</b>
<b>1.3 MUSCLE FUNCTION CONSEQUENCES OF NEUROMUSCULAR AGING .....</b>	<b>11</b>
<b>1.3.1 Sex trends in neuromuscular parameters with age .....</b>	<b>16</b>
<b>1.4 SARCOPENIA AND DYNAPENIA .....</b>	<b>17</b>
<b>1.5 MUSCLE POWER VS. MUSCLE STRENGTH.....</b>	<b>20</b>
<b>1.5.1 Measuring muscle power in older adults.....</b>	<b>25</b>
<b>1.6 CONTRIBUTING FACTORS TO DECLINING NEUROMUSCULAR FUNCTION WITH AGE.....</b>	<b>28</b>
<b>1.6.1 Muscle mass and muscle quality .....</b>	<b>29</b>
<b>1.6.2 Effects of muscle structural changes.....</b>	<b>30</b>

1.6.3	Mitochondrial dysfunction.....	32
1.6.4	Excitation contraction uncoupling.....	33
1.6.5	Hormones .....	33
1.6.6	Inflammatory cytokines .....	34
1.6.7	Nutrition .....	35
1.6.8	Disease related risk factors .....	36
1.6.9	Central nervous system.....	38
1.7	STRENGTH AND POWER TRAINING.....	40
1.8	LIMITATIONS IN THE LITERATURE .....	43
1.9	OBJECTIVES AND SPECIFIC AIMS .....	44
2.0	PERIPHERAL NERVE FUNCTION & LOWER EXTREMITY MUSCLE POWER IN OLDER MEN .....	46
2.1	ABSTRACT.....	47
2.2	BACKGROUND .....	48
2.3	METHODS.....	50
2.3.1	Study population.....	50
2.3.2	Lower extremity muscle power.....	51
2.3.3	Peripheral nerve measures .....	52
2.3.4	Additional covariates.....	53
2.3.5	Statistical analysis.....	54
2.4	RESULTS .....	55
2.5	CONCLUSIONS .....	56

<b>3.0</b>	<b>SENSORY AND MOTOR PERIPHERAL NERVE FUNCTION PREDICT LONGITUDINAL LOWER-EXTREMITY QUADRICEPS STRENGTH.....</b>	<b>65</b>
3.1	ABSTRACT.....	66
3.2	BACKGROUND .....	67
3.3	METHODS.....	69
3.3.1	Study participants .....	69
3.3.2	Quadriceps strength .....	70
3.3.3	Sensory and motor peripheral nerve function .....	70
3.3.4	Additional covariates.....	71
3.3.5	Statistics .....	72
3.4	RESULTS .....	74
3.5	DISCUSSION.....	75
<b>4.0</b>	<b>LONGITUDINAL SENSORY AND MOTOR PERIPHERAL NERVE FUNCTION AND INCIDENT MOBILITY LIMITATION .....</b>	<b>85</b>
4.1	ABSTRACT.....	86
4.2	BACKGROUND .....	87
4.3	METHODS.....	88
4.3.1	Study participants .....	88
4.3.2	Mobility limitation.....	89
4.3.3	Peripheral nerve function .....	89
4.3.4	Additional covariates.....	90
4.3.5	Statistics .....	92
4.4	RESULTS.....	93



4.5	DISCUSSION.....	94
5.0	DISCUSSION .....	103
5.1	SUMMARY OF FINDINGS.....	103
5.2	PUBLIC HEALTH SIGNIFICANCE.....	105
	BIBLIOGRAPHY .....	107

## LIST OF TABLES

Table 1.1. Muscle fiber type characteristics (for review see Houmard 2000).....	9
Table 1.2. Nerve conduction (NC) studies and electromyography (EMG) <sup>74</sup> .....	12
Table 1.3. Strength vs. power .....	24
Table 1.4. Advantages of different muscle power methods.....	28
Table 1.5. Strength vs. power training.....	42
Table 2.1. Characteristics of study population by muscle power (watts/kg) tertiles .....	61
Table 2.2 Nerve function by muscle power (watts/kg) tertiles.....	62
Table 2.3 Separate multivariate linear regression models for each measure of nerve function and muscle power (watts/kg).....	63
Table 2.4 Separate multivariate linear regression models for each measure of nerve function and decline in muscle power (watts/kg) .....	63
Table 3.1 Participant characteristics by sex .....	81
Table 3.2 Initial peripheral nerve characteristics by sex.....	82
Table 3.3 Initial nerve function predicts longitudinal quadriceps strength in women.....	83
Table 3.4 Initial nerve function predicts longitudinal quadriceps strength in men .....	83
Table 3.5 Seven-year change in nerve function predicts concurrent longitudinal quadriceps strength.....	84

Table 4.1 Participant characteristics as risk factors for mobility limitation .....	98
Table 4.2 Peripheral nerve characteristics at year 4 .....	99
Table 4.3 Initial (Year 4) nerve function predicts incident mobility limitation .....	99
Table 4.4 Change in nerve function (Year 4 to Year 11) predicts incident mobility limitation..	100

## LIST OF FIGURES

Figure 1.1. Neuromuscular impairment and the disablement pathway .....	3
Figure 1.2. Neuropathic and aging muscle characteristics .....	8
Figure 1.3. Etiology of the age-associated loss of strength (dynapenia)* .....	19
Figure 2.1 Effect size of nerve conduction amplitudes and monofilament insensitivity compared to age.....	64
Figure 3.1 Participants with strength & nerve function.....	80
Figure 3.2 Percent of participants in each nerve change group .....	81
Figure 4.1 Participants in analysis .....	101
Figure 4.2 Bivariate associations between change in nerve function and mobility limitation ...	102

## **PREFACE**

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## **1.0 INTRODUCTION**

### **1.1 THE EPIDEMIOLOGY AND PUBLIC HEALTH CONSEQUENCES OF NEUROMUSCULAR IMPAIRMENT AND DISABILITY IN LATE LIFE**

The U.S. population is getting older, both the number of older adults and the percentage of the population that they make up are increasing at a rapid rate.<sup>3</sup> Due to this population shift, it is imperative that we identify ways to decrease disability and increase independence in late-life. Late-life disability is a major public health issue with severe economic and social consequences. Approximately 20% of older adults suffer chronic disabilities<sup>4</sup> and over one third of the elderly population has some limitation in functional mobility.<sup>5</sup> The health care costs for older disabled persons are, on average, three times that of nondisabled elderly,<sup>6</sup> with the medical expenditures for disabled elders reaching \$135 billion in 2004.<sup>7</sup> In addition, late-life disability has an important impact on mortality, morbidity, quality of life and caregiver burden.<sup>7,8</sup> As the elderly population is expected to double by 2040, comprising one third of the population,<sup>7</sup> understanding the disablement pathway, risk factors for disability, and potential interventions is a major priority.

While a number of risk factors for disability in late-life have been identified, neuromuscular impairment is believed to play a key role. Figure 1.1 depicts a conceptual model for neuromuscular impairment's role in the disablement pathway. This conceptual model has

drawn from and expanded upon previously proposed models,<sup>9-11</sup> to include important disease and lifestyle risk factors such as diabetes, peripheral arterial disease, nutritional deficiencies, and decreased physical activity. These preventable lifestyle and disease-related risk factors play a role in nerve dysfunction and/or sarcopenia, leading to diminished muscle function parameters such as strength and power, which can progress to functional limitations and ultimately lead to disability. Nerve dysfunction may also act through other pathways, some unknown and some proposed, such as reduced proprioception or position sense,<sup>12,13</sup> leading to poor physical function and disability. Some of these relationships have been investigated in the literature at least at a cross-sectional level, indicated by a solid line, while some have not, indicated with a dashed line. This model attempts to address a major limitation of previously proposed models by depicting the circular nature of functional decline, where decreased muscle function can lead to functional limitations, and disability, which can feed back into risk factors such as reduced physical activity. The two way arrow between disability and functional limitations also illustrates the potential for transition into and out of disability that commonly occurs in late-life.<sup>14,15</sup> It is crucial to recognize the potential for recovery from disability, particularly when considering possible interventions for older adults, since a major goal of disability research is to design effective interventions for prevention and recovery from disability. This simplified model focuses on neuromuscular impairment and does not include other sources of disability, such as cognitive function, which also plays an important role in mobility disability.<sup>16-18</sup> While this model recognizes the importance of the central nervous system,<sup>19</sup> its main focus is on declines in the periphery, specifically nerve dysfunction, and decreased muscle function (strength and power), since the lower-extremity functional limitations strongly and independently predict disability.<sup>8</sup>

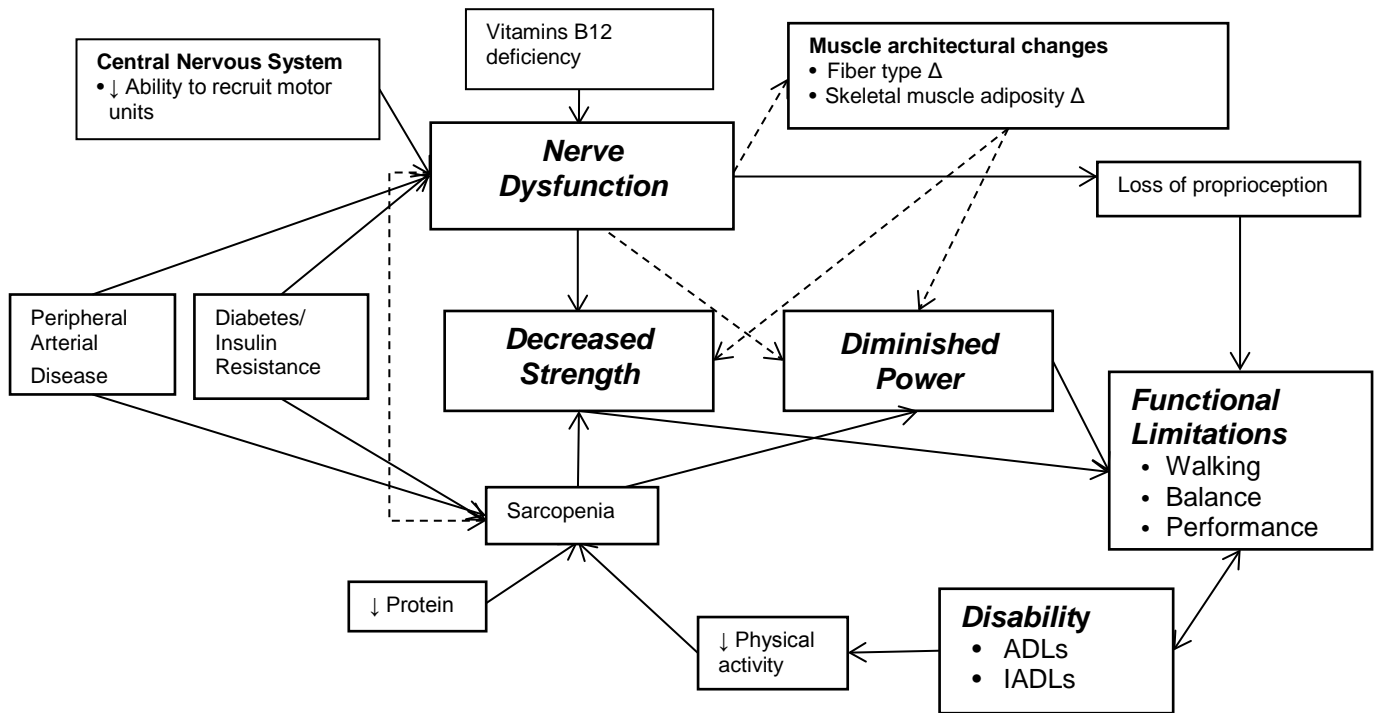


Figure 1.1. Neuromuscular impairment and the disablement pathway

### 1.1.1 Incidence and prevalence of impaired peripheral nerve function with age

An important risk factor within the causal pathway to disability is impaired nerve function, which is associated with diminished lower extremity function in older adults.<sup>20,21</sup> The Italian Longitudinal Study on Aging (ILSA), which used a comprehensive two-phase screening process to identify individuals with distal symmetrical neuropathy (DSN), revealed that DSN is common for both diabetic and nondiabetic older adults.<sup>22</sup> The first phase assessed self-reported symptoms, previous diagnosis, self-reported drugs, and performed a brief neurologic exam. Those who screened positive during the first phase underwent a clinical workup with an extensive neurologic exam, medical history, and a review of medical records to confirm the presence of DSN. Diabetes was similarly assessed with self-report, physician diagnosis, and a fasting glycaemia  $\geq 140\text{mg/dL}$ . Participants with a fasting glycaemia  $\geq 140\text{mg/dL}$ , without a



positive history, were considered positive only if their glycaemia levels were confirmed with a second blood test. The incidence of DSN increased steadily in participants with diabetes, from 13.7 to 48.4 new cases per 1,000 person years, and in those without diabetes, from 4.6 to 8.8 new cases per 1,000 person years, among those 65-79 and 80-84 years of age, respectively. The prevalence of DSN in individuals with diabetes increased with age until the 75-79 age group, whereas the prevalence in individuals without diabetes continued to increase throughout all the age groups. While some of this difference is likely due to a survival effect, it also may suggest that although diabetes is an important risk factors for these neuropathies, age or age-related factors may become increasingly important in all.

Data from the National Health and Nutrition Survey (NHANES) also show a high prevalence of poor sensory nerve function in adults over 40 years of age in the United States among those with and without diabetes at 28.5% and 13.3%, respectively and an increase in prevalence with age from 8.1% at ages 40-49 to 34.7% after age 80.<sup>23</sup> Diabetes was defined as history of physician diagnosis. Due to the use of less sensitive screening measures limited to sensory nerve function (10-g monofilament detection and self-reported symptoms) this is likely an underestimate of nerve dysfunction in the population. Critically, the majority of these participants were asymptomatic, despite the 10-g monofilament's high specificity for detecting neuropathy.<sup>24</sup> Similarly, ILSA found that 85% of DSN cases were undiagnosed.<sup>25</sup> Although not reported, the rate of undiagnosed cases is likely to be even higher in older adults without diabetes, since they are less likely to be screened. These studies demonstrate that poor peripheral nerve function is common in older adults, increases with age and that many may be unaware of their impaired status, even at a level of dysfunction detectable by clinical screening.

The prevalence and incidence of impaired nerve function among different subgroups in old age is understudied. While ILSA found that DSN prevalence did not differ among men and women, the study was limited to a homogenous population of white Italian elderly from one region.<sup>25</sup> Data from NHANES shows that rates of poor nerve function were higher in men compared to women (18.2% vs. 12.6%,  $p < 0.05$ ) and in non-Hispanic blacks and Mexican Americans compared to non-Hispanic whites (21.9% and 19.4% vs. 14.4%,  $p < 0.05$ ); however, since these comparisons were not separated by age, little is known about demographic trends for poor nerve function in older adults. Some of the differences in these groups are likely accounted for by differences in disease-related factors. This will be discussed further in section 1.6.8.

### **1.1.2 Mobility-related consequences of reduced nerve function with age**

Poor peripheral nerve function is associated with key mobility-related outcomes in older adults such as physical function limitations and impairments<sup>26,27</sup> and increased risk of falls.<sup>28-30</sup> Using data from the Women's Health and Aging Study ( $\geq 65$  years of age at baseline), Resnick and colleagues used vibration perception threshold to categorize participants as having mild, moderate and severe peripheral nerve dysfunction. They found that all levels of dysfunction were related to impaired balance and usual and fast-paced walking speeds and that severe dysfunction was related to inability to stand from a chair. They also found that impairments believed to mediate the relationship between nerve dysfunction and physical function, such as strength and position sense, only explained some of the association. Although motor nerve function, which was not measured in this study, may be more mediated by strength, rather than vibration perception threshold, which is a measure of sensory nerve function. In addition, side by side, semi tandem and tandem standing balance was used as a proxy for position sense and they

did not test muscle power as a mediator. The Women's Health and Aging Study includes moderately to severely disabled women at baseline, therefore these findings may not be generalizable to individuals without impairments.

Much of the literature on mobility-related consequences of nerve function has been cross-sectional,<sup>20,27,28,31</sup> with the exception of an analysis in a subsample of participants from the Italian Longitudinal Study of Aging.<sup>32</sup> In 1052 participants (mean age = 71) with normal functioning at baseline, Inzitari and colleagues found that signs and symptoms of DSN predicted decline in performance. While the screening for DSN was quite comprehensive in this study (see section 1.1.1), the adoption of this method by other large epidemiologic studies is unlikely since it is time intensive and requires a physician. Because they limited cases to individuals who were diagnosed with DSN, they were unable to study the effects of subclinical impairments in peripheral nerve function. In addition, consistent with the majority of literature, findings were not presented for motor function. Sensory and motor nerves undoubtedly play distinct roles in mobility. Peripheral sensory nerves likely contribute through proprioceptive feedback,<sup>12</sup> while motor nerves likely affect muscle tissue structure<sup>33,34</sup> and function.<sup>21,35,36</sup> This distinction is supported by findings from Strotmeyer and colleagues that show that motor and sensory nerve function are related to different physical performance measures in the Health ABC Study (ages 70-79 at baseline).<sup>20</sup> Using a gold-standard method of measurement, they were able to quantify impairment in motor nerve function. They also included a subclinical measure of touch sensation (1.4-g monofilament) in addition to a standard measure (10-g monofilament) and a continuous measure of average vibration detection threshold in order to capture various levels of impairment. They found that nerve function is associated with performance, independent of diabetes. This finding has clinical relevance, since older adults without diabetes may be less

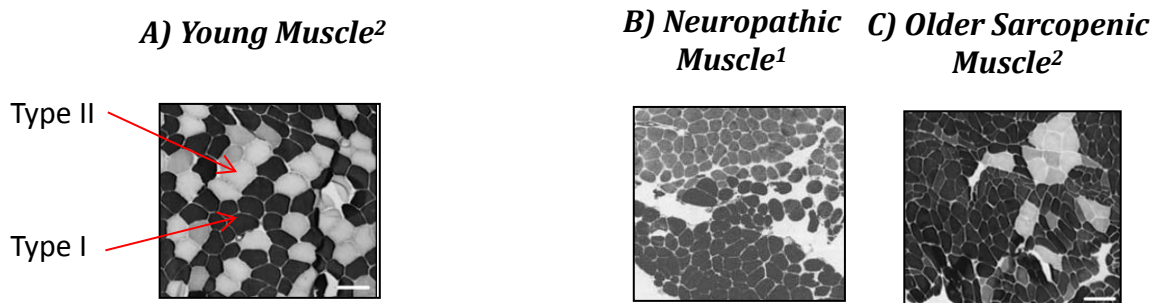
likely to be screened for neuropathy. It also has important implications for future research, indicating that studies should include older adults both with and without diabetes and that both traditional risk factors, such as diabetes, and novel risk factors should be studied in older adults.

## **1.2 DENERVATION AND PATHOPHYSIOLOGY OF MUSCLE AGING**

The number of motor units (or units of single motor neurons and the muscle fibers they innervate) decrease with age.<sup>37</sup> This linear decrease appears to begin around age 60, which is further evidence that neuromuscular impairments may begin to manifest in late-life and are driven by age-related changes. However, the currently available evidence is based on cross-sectional data; therefore while it suggests a decline with age, longitudinal data to confirm this is lacking.

Older adults may exhibit muscle atrophy and fiber type grouping (identified by histochemical staining properties of myosin ATPase)<sup>38</sup> resembling that which occurs in individuals with peripheral neuropathy, albeit to a varied degree.<sup>39,40</sup> With age, a gradual decline in muscle mass is thought to result from a reduction in the size and number of muscle fibers. These reductions preferentially affect type II fast twitch fibers.<sup>41,42</sup> Whereas healthy young muscle fibers are characterized by normal size and an even distribution of type I slow-twitch and type II fast-twitch muscle fibers (see Table 1.1 for fiber type characteristics), both neuropathic and aged muscle fibers are characterized by smaller atrophied fibers and a grouping of type I and type II fibers (see Figure 1.2). This grouping is believed to be a consequence of motor nerve death. When motor nerves die, muscle fibers are denervated, then reinnervated, often switching to the fiber type of adjacent living fibers.<sup>34,43-46</sup> Since fewer motor neurons cannot innervate all

remaining muscle fibers, this denervation may also account for loss in muscle mass<sup>43</sup> and decline in muscle-specific force.<sup>35,36</sup>



**Figure 1.2. Neuropathic and aging muscle characteristics**

**Table 1.1. Muscle fiber type characteristics**

Characteristics	Type I Fibers	Type IIa Fibers	Type IIb or IIx fibers
Contractile properties <sup>38</sup>	Slow-twitch - Produce low tension but have prolonged contraction and relaxation time	Can produce more tension than type I fibers, but also somewhat prone to fatigue	Fast-twitch – Fatigue prone but produce the highest amount of tension
Energy production <sup>38</sup>	Primarily rely on oxidative pathways	Have almost as much oxidative ability as Type I fibers, but also produce substantial energy through the glycolytic pathway	Mostly rely on non-oxidative, glycolytic pathways
Age related changes <sup>47</sup>	Transition to a higher percentage of these with age	Relative contribution to force and power believed to decline with age	
Distribution in the body <sup>38</sup>	Account for approximately 50% of all fibers in the average person  Endurance runners typically greater percentage <sup>38</sup>	Account for approximately 50% of all fibers in the average person  Can account for 80-90% in sprinters <sup>38</sup>  Conditions such as hypothyroidism, <sup>48-50</sup> chronic heart failure, <sup>51</sup> and obesity with non-insulin dependent diabetes <sup>52-55</sup> can lead to an increased expression	Predominant in those sedentary individuals due to inefficient contractile properties <sup>57</sup>  Fewer percentage in trained athletes <sup>55</sup>
		Transition from these to type I fibers is controversial and may take many years of intense training <sup>56</sup>	Transition from these to IIa may take as little as 6-8 weeks of training in healthy younger and older (ages 60-70) men and women <sup>49,55,56</sup>

(for review see Houmard 2000)

To characterize and quantify the relationship between nerve function and declines in muscle with age, objective and reliable assessments of nerve function, such as nerve conduction (NC) studies,<sup>58-61</sup> are needed. NC studies are the most sensitive and specific method to detect peripheral neuropathy non-invasively.<sup>62</sup> They are performed by electrically stimulating a nerve and measuring the response using surface electrodes. NC study measures include compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitude, the size of an evoked response from electrical stimulation of the nerve, and nerve conduction velocity (NCV), the speed at which the response travels down the nerve. Decreases in CMAP amplitude may be indicative of axonal damage, whereas decreases in NCV may indicate damage to the myelin sheath, which insulates the axon.<sup>63</sup> Latency, or the travel time of the signal, is sometimes used in place of NCV. The value of NCV is dependent on the method used to calculate NCV.<sup>64</sup> Nerve conduction velocity is typically calculated by dividing the distance between two stimulation sites by the difference between latencies.<sup>65</sup> Using the difference between two stimulation sites accounts for the variability of travel time that can occur within the neuromuscular junction. In the case that only one latency is available, it can be used on its own or to estimate nerve conduction velocity. Although, NCV takes into account the length of the limb, and thus the distance travelled by the signal, and has established clinical cut points for certain conditions, such as diabetic polyneuropathy,<sup>66</sup> whereas latency does not.

Decline in peroneal motor amplitude, but not NCV, with age has been independently associated with declines in calf muscle density,<sup>33</sup> a measure of muscle-fat infiltration and intracellular fat content in muscle.<sup>67</sup> Interestingly, these NC parameters were not associated with muscle cross-sectional area, suggesting that the effects of PN on muscle may not be detected as macroscopic changes in muscle mass, but as changes in muscle tissue structure. Moreover, these

relationships may be independent of traditional risk factors, since associations remained when excluding participants with DM and PAD. However, since these associations have only been studied cross-sectionally, longitudinal data is needed to identify temporal relationships and causation.

### **1.3 MUSCLE FUNCTION CONSEQUENCES OF NEUROMUSCULAR AGING**

Age-related changes in muscle structure and nerve function are accompanied by declines in muscle function. Two distinct measures of muscle function are muscle strength, or the maximum force that can be generated during muscle contraction, and muscle power, defined as the product of contractile force and the velocity of movement. Both strength and power decline with age although decline in power is steeper,<sup>68-70</sup> suggesting that power may be an earlier indicator of functional decline.

Decline in muscle function with age is likely due to a number of neuromuscular changes. Loss of muscle mass is closely associated with declines in strength; although, longitudinal decline in strength has been shown to occur three times more steeply with age than mass.<sup>10,71,72</sup> Furthermore, maintaining or gaining muscle mass does not fully prevent the decline in strength that occurs with age.<sup>71</sup> Similarly, training programs may increase strength prior to the occurrence of observable changes in muscle structure (See Gabriel, 2006 for review).<sup>73</sup> Some evidence from physical therapy research suggests that these early increases in strength may result from alterations within motor units and the central nervous system.<sup>73</sup> Strength gains occurring during early phases of training prior to increases in muscle size have been associated with increased amplitude measured using surface electromyography (EMG).<sup>73</sup> This increase in



amplitude has been commonly interpreted as an increase in neural drive, although this measurement technique does not provide an isolated measure of nerve function, but a more global measure of neuromuscular activity (see Table 1.2 comparing EMG and NC studies). An increase in motor unit firing rate during maximal voluntary contraction (MVC) has also been observed in as early as the first 48 hours following training.<sup>73,74</sup>

**Table 1.2. Nerve conduction (NC) studies and electromyography (EMG)<sup>74</sup>**

	Nerve Conduction Studies	Electromyography
Purpose	Used to measure neurodegeneration.  Used clinically as a sensitive and specific method to detect peripheral neuropathy, <sup>62</sup> carpal tunnel, Guillain-Barre syndrome, facioscapulohumeral muscular dystrophy, spinal disc herniation, Guyon Canal syndrome.	Used in the kinesiological analysis of muscle and in biofeedback studies.  Used clinically to study anterior horn cell, nerve root, plexus, peripheral nerve, and primary muscle disorders. Can be used to estimate time since onset and severity of axonal injury. Limited use in purely demyelinating neuropathies, since axons and connections with muscle fibers remain intact. <sup>75</sup>
Methods	Performed by electrically stimulating a nerve and recording the signal at the muscle supplied by that nerve with a surface electrode.	Performed by recording the electrophysiological activity when the motor unit is at rest or during a muscle contraction using either a needle electrode inserted into the leg or a surface electrode.
Measures obtained	The amplitude and speed of an electrical signal transmitted across a stimulated nerve.  Assesses nerve function separately from the muscle.  Records the summated compound potential of many motor units.	Electrical potential generated by muscle cells when the cells are activated by the nerve (either when the motor unit is at rest or during muscle contraction) or an applied electrical stimulation.  Assesses the nerve and muscle fibers that it innervates at the same time (the entire motor unit).  Spontaneous activity and activity from an individual motor unit can be measured within the muscle using needle electrodes.

Measures from NC studies have been associated with muscle strength in older adults. In a cross-sectional analysis of community dwelling older adults from the Health ABC study (ages 70-79 at baseline), Strotmeyer and colleagues found that measures of poor sensorimotor nerve function, including low peroneal motor nerve amplitude, and impaired monofilament and vibration threshold detection, contributed to lower quadriceps and ankle strength.<sup>21</sup> Peroneal motor nerve conduction velocity (NCV), however, was not related to strength. One proposed explanation for this is that a proportion of axons may degenerate in late-life resulting in reduced motor amplitude, while NCV, driven by the axons that remain intact, may stay within normal limits; in this case, even though NCV is normal, decreased amplitude still results in a weaker muscle response.<sup>33,76</sup> These associations were independent of diabetes and lean mass, although they were not adjusted for measures of muscle composition, such as muscle density or intermuscular adipose tissue (IMAT). Previously, these authors found that poor nerve function was related to worse physical performance.<sup>20</sup> Nerve function attenuated the relationship between quadriceps strength and performance battery scores by 13%, suggesting that it may play an important role in the relationship between decline in muscle function and mobility impairments. It is notable that sensory nerve measures (monofilament and vibration threshold detection) were also related to diminished strength. This is not surprising, since the absence afferent (sensory) feedback is related to poor motor nerve performance in patients with severe sensory deficits.<sup>13,77</sup> Additionally, the importance of afferent proprioceptive input on physical function has been previously demonstrated.<sup>78,79</sup> Longitudinal analyses are needed to investigate the role of nerve function in declining strength and physical function in late life. Moreover, similar research examining the connection between muscle power and NC measures are lacking, despite the hypothesized neural contribution to power.

Studies on the link between neuromuscular activation measured using EMG and muscle strength and power in older adults have produced somewhat conflicting findings. Early cross-sectional studies comparing small groups of healthy older (ages 73-91) to healthy younger adults (ages 19-55) have found that older adults experience lower strength, despite being able to fully activate their muscles.<sup>80,81</sup> Similarly, compared to young (ages 19-33)<sup>82</sup> and middle aged (ages 44-57)<sup>83</sup> adults, healthy older adults (ages 59-74<sup>83</sup> and 60-69<sup>82</sup>) had lower muscle power and explosive force without any differences in EMG nerve activity.<sup>82,83</sup> However, mobility limited older adults (ages 70-85) exhibited lower muscle power accompanied by diminished EMG activity when compared to both healthy older (ages 70-85) and younger groups (ages 40-55).<sup>84</sup> This EMG activity was correlated with the velocity component of muscle power across all groups, suggesting that neuromuscular activation plays a key role in muscle contractile velocity. A potential explanation for the discrepancy in these findings is that the progressive loss of motor units with aging may not lead to functional impairments until a critical threshold is reached.<sup>85</sup> Until this threshold is reached, the function of muscle fibers may be maintained through collateral reinnervation in the early stages of motor unit loss. A critical threshold for the tibialis anterior may occur, between 70-80 years of age, when the number of motor units is 50% of that found in younger, healthy adults. Decline in motor units is likely muscle-specific and age-threshold dependent (e.g. increased rate of decline in motor units may occur at an older age for the soleus than for the anterior tibial muscle),<sup>86</sup> which may be related to differences in fiber-type composition or adaptation of muscle activity patterns of movement with age. Therefore, more research is needed to help identify potential critical thresholds in other muscles.

Methodological limitations in these studies need to be addressed. Firstly, they included small sample sizes (n=10-32 per group); therefore, the lack of associations observed could be

due to limited statistical power. They only collected cross-sectional data, providing no evidence for any causal direction of association. Furthermore, a standardized protocol was not used for either power (discussed further in section 1.5.1) or EMG measurement. Different measurement protocols could lead to variation in outcomes and conflicting findings on whether an association exists. In addition, EMG provides an overall measure of the whole motor unit rather than an isolated measure of nerve function (See Table 1.2 for EMG characteristics).

To what extent neuromuscular structural changes and functional declines are inevitable with age is unclear. While muscle atrophy with age is consistently observed across studies,<sup>38</sup> findings on fiber type conversion are conflicting.<sup>43,87-90</sup> Structural changes in muscle with age may be somewhat sex specific. Whereas both type I and type II fiber area decline with age in women,<sup>91</sup> a preservation of type I fiber area has been observed in men.<sup>43,87-89</sup> Resistance training has been found to be effective for improving muscle function (see section 1.7 on training interventions) and structure in older adults,<sup>92-95</sup> although evidence suggests that it cannot completely reverse the impact of the aging process.<sup>90</sup> Small studies have found that physical activity may improve or reduce loss of peripheral nerve function in diabetic and peripheral neuropathy patients; however no clinical trials have been done to examine the effects on age-related peripheral nerve declines.<sup>96-98</sup> Potential mechanisms by which exercise training could prevent or treat peripheral nerve decline include improvements in glycemic control<sup>99</sup> and vasculature (for review see Tasfaye et al., 2005<sup>100</sup>). It is also possible that exercise could have direct and local effects on peripheral nerves (e.g. improvements in Na/K ATPase activity).<sup>96</sup> In addition, specificity of training could potentially lead to physical function improvements that allow those with peripheral nerve impairments to compensate through improved strength, power, and/or balance. More research is needed on the extent to which specificity, intensity, and volume

of training can prevent or mitigate structural and functional neuromuscular declines that occur with age. One important area to investigate is the relative benefits of short term specific training exercises vs. general sustained activity, since this could have important consequences for designing interventions to preserve physical function in older adults.

### **1.3.1 Sex trends in neuromuscular parameters with age**

Compared to men, women have higher rates of disability<sup>101-103</sup> and falls in old age.<sup>104,105</sup> Differences in neuromuscular parameters may play a key role in these late-life disparities. Although muscle strength and quality declines more steeply with age in men,<sup>106</sup> they tend to have significantly more muscle mass, strength, power, and velocity<sup>70,107-109</sup> than women throughout life. During a maximal counter-movement jump, the difference in muscle power was most pronounced during the end of the concentric phase.<sup>108</sup> The majority of this difference in power was attributed to the velocity component during this phase of the jump. This discrepancy could contribute to women being more prone to falls in old age. Recovery of balance from a potential fall requires rapid movement. A small study of younger (ages 21-29) and older (ages 67-81) men and women showed that older women were less likely to recover balance from a fall by taking a single rapid step.<sup>110</sup> In addition, power may explain more of the variance in performance measures, such as chair rises, stair climbing and walking in women than in men.<sup>109</sup>

Reasons for these differences between men and women are not fully understood, although the additional muscle mass and preservation of type I fiber area with age in men<sup>43,87-89</sup> may play a role. Differences in nerve parameters may also occur by sex. Men tend to have slower nerve conduction velocity, which is primarily due to greater height;<sup>111</sup> although estrogen may have some neuroprotective effects,<sup>112</sup> at least at the level of the brain. Men also have

reduced neural activation,<sup>113</sup> commonly defined as the recruitment and rate coding of motor units to generate force through muscle contraction and is measured using EMG.<sup>114</sup> The direction of this difference in nerve parameters may seem counterintuitive, but reduced neural drive has been associated with lower eccentric/concentric ratios, which is a proposed mechanism for injury prevention during activities where muscle fiber tension is high (for review see Stauber et al., 1989).<sup>115</sup> Single muscle fiber quality measures, including fiber size, maximal isometric and specific force, maximal unloaded shortening velocity, power, and specific power, are likely not contributing factors since they have not been found to differ by sex.<sup>107</sup> Research on these gender disparities in neuromuscular parameters, are not only crucial due to their potential consequences for function, disability, and maintaining independence in old age, but may also provide insight into potential kinematic and physiologic mechanisms for these key outcomes.

#### **1.4 SARCOPENIA AND DYNAPENIA**

Sarcopenia, defined as loss of muscle mass with age,<sup>116,117</sup> is associated with functional impairment,<sup>118,119</sup> disability,<sup>120,121</sup> falls,<sup>122</sup> and loss of independence.<sup>123</sup> More recent definitions of sarcopenia have included loss of strength,<sup>124-127</sup> likely due to its association with poor outcomes, independent of lean mass.<sup>9</sup> In 2001, it was estimated to contribute to \$18.2 billion in healthcare costs.<sup>128</sup> Potential risk factors for sarcopenia include nutritional deficiencies, chronic disease, insulin resistance, inflammation, change in endocrine function, and inactivity,<sup>125</sup> although age-related declines in muscle mass can even be observed in fit, athletic older adults.<sup>129</sup> One major proposed mechanism for this age-related decline in muscle mass is a withdrawal of

anabolic stimuli to skeletal muscle, such as the continuous activity of motor neurons, leaving catabolic processes unopposed.<sup>33</sup>

The prevalence<sup>130</sup> of sarcopenia increases with age, however, estimations depend on the definition and method of measurement used. Loss of muscle mass is most precisely quantified using advanced imaging techniques such as dual-energy x-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI).<sup>126,131-134</sup> In the absence of advanced imaging technology, lower-tech substitutions such as calf and mid arm circumference<sup>135</sup> and bioelectrical impedance<sup>136</sup> can be used, albeit with less accurate and reliable results. Once a measure of lean mass is obtained, it is used to produce an index, taking into account height, weight, BMI, or fat mass.<sup>137-139</sup> The Health, Aging, and Body Composition (Health ABC) Study directly demonstrated the effects of using different methodologies for estimating the prevalence of sarcopenia in a single study population of adults ages 70 to 79 years.<sup>138,139</sup> The first method used appendicular lean mass measured by DXA and divided it by height-squared ( $LM/ht^2$ ). For the second method, they adjusted their measure of lean mass by height and fat mass (the residual method). Using both the residual and the  $LM/ht^2$  methods, baseline rates for an age range of 70-79 years were highest in white women (30.5% and 31.4%), followed by white men (27.1% and 25.2%), then black men (8.2% and 11.8%) and finally black women (8.1% and 6.8%). However, the residual method resulted in higher rates for obese men and women (11.5 and 21.0% vs. 0% for both using the  $LM/ht^2$  method)<sup>138</sup> and was more strongly related to poor lower extremity function.<sup>138,139</sup>

While some definitions of sarcopenia include declines in strength, Manini and Clark proposed using a separate term, dynapenia, to describe loss of muscle function, since factors other than muscle mass also contribute to this decline.<sup>9,10</sup> Figure 1.3 shows their theoretical

model illustrating potential neuromuscular parameters as mechanisms for the occurrence of dynapenia with age. The top of the model shows spinal characteristics and the neuropathic processes leading to changes in motor unit recruitment and discharge rate. At the bottom, pathophysiologic parameters, such as excitation-contraction uncoupling, fiber type transformation and architectural changes, may lead to a decline in contractile quality. It also includes lifestyle factors such as a decrease in protein intake and decline in physical activity that can lead to sarcopenia. Factors that act on both the nervous system and muscular system sides, such as hormonal and immunologic changes, peripheral input, and neuropathic processes that can lead to structural changes in the muscle are also included. Major limitations of this model include that it does not include disease-related risk factors or recognize the unique contributions of muscle power.

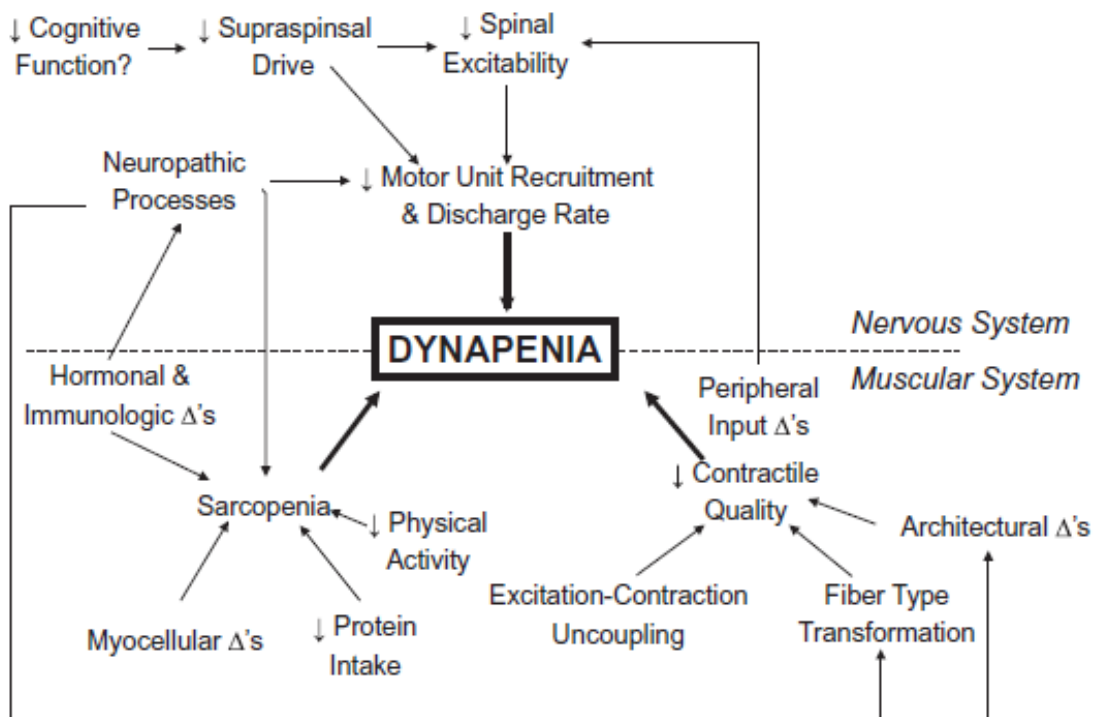


Figure 1.3. Etiology of the age-associated loss of strength (dynapenia)\*

\*Reproduced from Clark and Manini, 2012<sup>10</sup>



## 1.5 MUSCLE POWER VS. MUSCLE STRENGTH

The relationship between nerve function and muscle power may be distinct from the relationship between nerve function and muscle strength. Table 1.3 outlines some important differences between strength and power. Power declines more steeply with age than strength<sup>69,70</sup> and is more strongly related to certain measures of physical function.<sup>140-143</sup> The distinct relationship between physical function and declines in power is likely due to the diminishment of contractile velocity, the distinguishing component of power, which is also associated with physical function impairments.<sup>144</sup> While it has been suggested that decline in power and its unique relationship with mobility may be in part due to loss of type II (fast twitch) muscle fibers and decline in peripheral nerve function,<sup>2,41,74,144-146</sup> more work is needed to elucidate the mechanisms responsible for the decline in muscle contractile velocity with age. Recruitment and discharge rate of motor neurons are also likely to play an important role.

Strength and power distinctly contribute to poor physical function with age,<sup>140-142,147-150</sup> although few studies have been able to fully distinguish the independent roles that strength and power play in different measures of physical function. Table 1.3 integrates the findings from a number of studies in an attempt to summarize these relationships. A major limitation of the literature is that few studies have statistically compared the relationship of strength vs. power with physical function measures. However, based on magnitude of  $R^2$  and correlation coefficients, power may be more strongly related to measures of physical function such as the 6-minute walk,<sup>147,151</sup> the 400m walk,<sup>142</sup> time to stand from a chair 10 times,<sup>140,147-149</sup> stair climb time,<sup>140,141,147-149</sup> the tandem walk,<sup>140</sup> balance scores,<sup>141</sup> the Short Physical Performance Battery (SPPB) score,<sup>140,141</sup> and timed up and go;<sup>147</sup> whereas, strength may be equally or more influential on maximal gait speed,<sup>140,149</sup> time to stand from a chair one time,<sup>147</sup> and the one-leg stand.<sup>147</sup>

There have been conflicting findings in the literature on whether strength or power is more influential on habitual gait speed<sup>140,141,148,149</sup> and time to stand from a chair five times.<sup>141,150</sup> Given the additional component of velocity of movement that is captured in measures of muscle power, it may be expected that power would be more related to performance measures that require speed.

While much of this work has focused on women<sup>143,144,148,149</sup> and those with mild to moderate functional limitations,<sup>140,143,148,149,151,152</sup> few have looked at the oldest old,<sup>68</sup> racially diverse populations,<sup>152,153</sup> or populations of older adults with a wide range of functional abilities. Importantly, various methods of measuring muscle power were used in these studies and whether the method of power measurement has an effect on its relationship to physical function is unknown. For instance, a pneumatic leg press machine such as the Keiser (Fresno, CA) allows power to be measured at varied percentages of the participant's one repetition maximum (1 RM, or the maximum amount of resistance that they can push before failure). As opposed to strength, which has a linear relationship with resistance, muscle power has a J-shaped relationship with resistance.<sup>154</sup> At very low resistances, the force component of power is minimized, resulting in low power. Conversely, very high resistances result in low velocity and therefore low power. Power peaks when resistance is high enough generate a large force, yet low enough to allow for fast velocity of movement. Different physical function tasks may be associated with muscle power production at varying force-velocity ratios.<sup>141</sup> Moreover, task-based measures of muscle power, which use the participant's own body weight as resistance, could potentially be more related to certain measures of physical function since they may mimic everyday tasks such as rising from a sitting position or climbing stairs, although this has not been assessed.

Strength and power cut points for mobility limitations have also been examined. Using data from the Health ABC study (ages 70-79), Manini and colleagues identified strength cut points by dividing strength into sex-specific deciles and using Cox proportional hazard regression to compare change in risk of developing severe persistent mobility limitations, defined as two consecutive reports of a lot of difficulty or inability to walk ¼ mile or climb 10 steps.<sup>155</sup> They found that strength < 1.13 Nm/kg (the first decile) for men and < 1.01 Nm/kg (the third decile) for women were associated with high risk of developing mobility limitation. Cut points for low, moderate, and high risk significantly predicted mobility limitation, gait speed <1.22 m/s, and death. However, given that these cut points were identified in an initially healthy population with no mobility disability at baseline, they may not be generalizable to other populations of older adults. In addition, they did not assess whether strength loss predicted disability.

Similarly, using data from the InCHIANTI study (ages 65-102), Hicks and colleagues identified sex-specific cut points for strength and power for predicting mobility limitation.<sup>156</sup> Men with knee extension strength <19.2 kg and grip strength <39.0 kg had clinically meaningful decline in gait speed<sup>157</sup> of 0.24 m/s over three years. While they did not present these results in quantiles to compare across different ranges of magnitude, these correspond to 3.2 and 3.8 standard deviations (SD) of strength, respectively. Men with power <105 W (1.7 SD) (unilaterally on power rig) were nine times more likely to develop incident mobility disability, defined as being unable to walk 1 km or climb a flight of stairs. In women knee extension strength <18.0 kg (4.3 SD) was associated with minimal gait speed decline of 0.06 m/s, suggesting that strength may be a better predictor for mobility disability in men than in women. Women with leg power <64 W (1.8 SD) were three times more likely to develop incident

mobility disability. Mobility and disability outcomes were not consistently defined for strength and power, since they used the classification and regression tree (CART) method, which identifies predictors and cutpoints that have the strongest relationship with outcomes; therefore, the authors were unable to compare the effects of strength vs. power directly. They also neglected to adjust for potentially important confounders such as body size and comorbid conditions. Three year change in strength and power did not predict incident mobility disability. However, they did not examine the role of baseline measures in the change model, which is important since some individuals may not have experienced much change in strength or power because they started out with low levels and had little room for decline. More research is needed to investigate whether strength and power decline over a longer time period predict incident mobility disability. It may also be possible that strength or power may decline concurrently with physical function; however this has not been examined.

In a post-hoc analysis of data from a 16-week intervention designed to increase muscle function and improve mobility in older adults (mean age 75.2), changes in power predicted clinically meaningful changes in mobility (1 unit in SPPB score and 0.1 m/s in gait speed), while changes in strength did not.<sup>158</sup> Power remained a significant predictor when strength was added into the same model, showing that the association with power was independent of strength. This suggests that power is distinctly important for mobility in older adults.

**Table 1.3. Strength vs. power**

	Muscle Strength	Muscle Power
Definitions	Force  Maximum capacity to generate force	Force x Velocity  Integration of force and velocity of movement  Maximum rate of work production
Age trend	Declines with age beginning around age 40 <sup>159</sup>	Declines with age beginning around age 40 <sup>159</sup>  Declines more steeply than strength (3.5% vs. 1-2% per year <sup>70,68-70,160</sup> )
Relationship with muscle mass	Most of variance is explained by muscle mass, but yearly declines are 3x greater for strength (Goodpaster et al., 2006 JGMS)	
Relationship with resistance	Linear	J-shaped <sup>154</sup>  Low power at very high resistances due to low velocity of movement  Low power at very low resistances due to low force
Relationship with physical function	↓ Strength may result in: functional impairment, disability, falls and loss of independence  Compared to power, strength may be more strongly related to max gait speed, <sup>140</sup> chair stand 1x, and one leg stand	↓ Power may result in: functional impairment, disability, falls and loss of independence  Compared to strength, power may be more strongly related to 400m walk time, <sup>142</sup> 6-minute walk distance, <sup>151</sup> SPPB score, <sup>140,141</sup> chair stand 10x, <sup>140</sup> tandem walk, <sup>140</sup> balance score, <sup>141</sup> get up and go, and stair climb <sup>140,141,148</sup>  Velocity component of power may be more strongly related to physical function measures than force component <sup>144</sup>
Potential mechanism for peripheral nerve involvement	Motor unit recruitment  Muscle atrophy	Motor unit recruitment <i>and</i> discharge rate  Muscle atrophy  Decreased contribution of type II ‘fast-twitch’ fibers to force and power generation
Methods of measurement	Isometric maximal voluntary contraction (MVC) – does not require movement  Dynamic 1 repetition maximum (1 RM) – can be measured isotonically (constant resistance) or isokinetically (constant velocity)	Isokinetic (constant velocity) dynamometer  Fixed load power rig  Pneumatic resistance equipment  Task-based measures using a force plate or scale  Rate of stair climbing (body weight and stair height can be used to estimate power) <sup>149,152,161</sup>

### 1.5.1 Measuring muscle power in older adults

Currently, no gold standard method of measuring muscle power in older adults has been identified. Methods vary by equipment, time, and intensity of activity. Table 1.4 outlines some key advantages for certain measures. Each method likely has various strengths and limitations. However, few studies have systematically compared more than a few power measures in a single study population or assessed feasibility of different power measures for older adults. This has important implications characterizing the feasibility of methods in large epidemiologic studies of older adults, for designing and evaluating training interventions, and for better understanding muscle power's role in the disablement pathway.

Power can be measured using specialized equipment, in which the participant is generally seated and performs a leg press or knee extension. An example of this is the Keiser pneumatic resistance machine, which uses air pressure to provide a constant resistance during the movement. The Keiser has been previously validated against various laboratory and field tests designed to assess power such as the leg extensor power rig, the Wingate anaerobic power test, and the vertical jump test,<sup>162</sup> and is considered to be a reliable and reproducible ( $r = 0.90$ ,  $ICC = 0.85-0.88$ ) measure of lower extremity muscle power.<sup>143,148,162-164</sup> First, the participant's one repetitions maximum (1 RM), or the maximum resistance a participant can displace before failure, must be established. Following a brief rest, power is then measured at different percentages of the 1 RM (generally 40-70%) to find peak power. During the power test, the participant is instructed to press or extend one or both legs as fast as possible through full range of motion. This method provides a separate measure of velocity. Since this equipment allows power to be measured at varying resistances, it may more accurately capture peak power than equipment that uses a fixed resistance. Limitations may include relatively long test duration and

somewhat high participant burden, since a 1 RM must be established before power can be measured. This is disadvantageous for a large epidemiologic study of older adults that must collect multiple measures and may have limited time before the participant fatigues.

A fixed load machine such as the Nottingham power rig can also measure leg press power and has high reproducibility (coefficient of variation = 9.4%) and validity when compared to power measured by an isokinetic dynamometer and two-legged jumps on a force plate ( $\rho=0.73$ ,  $p<0.001$ ;  $\rho=0.86$ ,  $p<0.001$ , respectively).<sup>165</sup> Similarly, the participant is instructed to push one or both pedals as quickly as possible through full range of motion. However, unlike pneumatic resistance equipment, a 1 RM does not need to be established. This may be advantages for time and participant burden; however, it does not allow power measurement at varying resistances. This could potentially cause ceiling or floor effects. The participant is asked to perform until their power plateaus or up to 5-10 trials. Compared to other equipment used to measure muscle power, such as the Keiser, which provides additional components such as velocity and force, and force plates (discussed in the next paragraph), which provide these components as well as additional biomechanical components (e.g. center of mass displacement), power is the only measure provided. This allows for easy, yet limited data collection and management. This equipment uses a flywheel that is low to the ground and must be manually adjusted, which may be difficult for some clinic staff to operate, as experienced by the staff at the University of Pittsburgh (unpublished observation, Dr. Jane Cauley).

One limitation for the above described measures is that they are not portable and only allow measures to be collected in a clinic setting. Novel task-based methods may overcome this limitation. In addition, task-based methods, which use the participant's own body weight as resistance, may more closely mimic older adults' ability to perform tasks essential to

independent daily living. These measures often use a mat or a plate to collect the force component of power and calculate the velocity as the vertical acceleration of the center of mass over time. An example of a task-based method is rising from a chair as quickly as possible on top of a force plate. Jumping (counter movement or squat jumps) on top of a force plate may also be used. Generally, the participant is instructed to jump as high as possible and power is measured from the “push off” phase of the jump. It has been suggested that functional measures of leg power may be able to identify decline in muscle function earlier than physical performance measures<sup>166</sup> and detect greater variability in a high functioning population of older adults,<sup>167</sup> although this has not been investigated. In addition, the force plate collects a number of data parameters in addition to force and velocity that can more fully characterize the task-based movement. Some functionally-based measures of leg power have been validated in the elderly. Chair rise and jumping power have shown high test-retest reliability ( $r = 0.95$  and  $r = 0.99$ , respectively) in older adults.<sup>152,166</sup> Chair rise power has correlated moderately high with the Nottingham power rig ( $r = 0.6$ )<sup>167</sup> in older adults. Jumping power was highly correlated with the Nottingham power rig ( $r = 0.67$ <sup>168</sup> and  $0.86$ <sup>165</sup>) and moderately correlated with chair stand power (women:  $r = 0.58$ , men:  $r = 0.61$ <sup>169</sup>). Jumping power declined consistently more with age than chair rise power.<sup>169</sup> Stair climb power is another example of task-based power, which does not require a force plate. The participant is asked to climb a flight of stairs as quickly as possible (using handrails if necessary). Power is then calculated using the following equation: force times velocity, where force is calculated as body mass times the acceleration of gravity and velocity is calculated as the height of the stairs divided by the time to complete the stair climb.<sup>152</sup> High test-retest reliability in community dwelling older adults with mild-moderate mobility limitations has been found for this measure ( $R=0.99$ ).<sup>152</sup> This method requires little equipment, just a well-lit



stairwell and stopwatch. However, since these are relatively new methods of measuring muscle power, the feasibility and safety in different populations of older adults must be evaluated and appropriate data management and analytic methods established.

**Table 1.4. Advantages of different muscle power methods**

<b>Power measurement</b>	<b>Rate of force development (RFD)</b>	<b>Velocity</b>	<b>Body weight bearing</b>	<b>Reproducible</b>
Nottingham power rig				X <sup>164</sup>
Keiser pneumatic resistance		X		X <sup>161</sup>
Countermovement jump	X	X	X	X <sup>166</sup>
Chair rise	X	X	X	X <sup>165</sup>
Stair climb		X	X	X <sup>152</sup>

## **1.6 CONTRIBUTING FACTORS TO DECLINING NEUROMUSCULAR FUNCTION WITH AGE**

Due to the potential effects of neuromuscular decline on mobility related outcomes, understanding established and novel risk factors for increased neuromuscular decline with age is crucial. A longitudinal cohort study using 22 years of follow up data from the Mini-Finland Health Examination Survey examined a number of potential lifestyle and disease-related risk factor for decline in hand grip strength.<sup>170</sup> Both strenuous work-related physical activity in midlife and becoming sedentary were associated with longitudinal decline in grip strength.

Being overweight or obese and smoking were related to greater decline in grip strength as were incident chronic conditions such as coronary heart disease, other cardiovascular disease, diabetes mellitus, chronic bronchitis, and chronic back syndrome, and persistent conditions including cardiovascular disease, hypertension, and asthma. The greatest observed effect was weight loss that exceeded 10% of body weight. A limitation of this is that they only assessed grip strength when lower extremity strength may be more important for mobility. Findings should be confirmed in more ethnically and culturally diverse populations. Moreover, identifying risk factors for lower-extremity strength and power is crucial given their established relationships with function and disability.<sup>155,156,158</sup>

### **1.6.1 Muscle mass and muscle quality**

Loss of muscle mass with age and its association with strength decline has been clearly demonstrated, although strength declines independent of muscle mass,<sup>71,72</sup> indicating the presence of additional contributing factors. Muscle contractile quality, which is also called muscle quality, specific torque, or specific force, is a measure of strength per unit of muscle mass<sup>71,72</sup> or force per single fiber. As a measure of force per fiber, it can be adjusted by the cross-sectional area of the fiber.<sup>171</sup> Muscle quality, particularly strength per unit of mass, which also declines with age, may account for much of the component of strength decline that is not explained by loss of lean mass.<sup>71,172</sup> Effects of nerve function on measures of muscle quality have yet to be explored.

## 1.6.2 Effects of muscle structural changes

In addition to decreasing mass, a number of structural changes occur within the muscle with age and likely contribute to decline in muscle quality and function. Age-related changes in muscle fiber type composition<sup>41,42</sup> (see section 1.2 on the pathophysiology of muscle aging) are thought to play a key role in declining muscle strength and power. As mentioned previously, aging muscle is characterized by a grouping of type I (slow twitch) and type II (fast twitch) fibers and disproportionate reduction of type II.<sup>41,42</sup> Individually, type II fibers can generate four times the power output of type I fibers.<sup>43</sup> Moreover, type II fiber area may be more strongly associated with strength than type I fiber area.<sup>41,173</sup> However, limited evidence exists that changes in fiber type distribution in late-life directly contribute to declines in muscle function. One study did find that while the percent of type II fibers measured in human muscle biopsy samples was not correlated with strength, a greater percent of type IIB fibers was correlated with greater speed of movement.<sup>41</sup> The relationship between fiber type percentages and power were not studied. However, this finding suggests that type IIB fiber distribution could be related to power, since velocity is the component of power that distinguishes it from strength. In addition, resistance training in older adults, resulting in increased strength (and likely power, although this was not assessed), may also lead to increases in the area and amount of type II fibers, while the area and amount of type I fibers remain unchanged.<sup>174,175</sup> Although, whether fiber type distribution in a small biopsy sample adequately reflects overall distribution in vivo is unclear.

Myosteatosis, defined as fat infiltration in skeletal muscle, increases with age<sup>72</sup> and is associated with changes in muscle function in late-life. Fat depots within skeletal muscle can be characterized as three types: 1) intermuscular adipose tissue; 2) intramyocellular fat; and 3) extramyocellular fat (for a review see Miljkovic and Zmuda, 2010<sup>67</sup>). Intermuscular adipose

tissue (IMAT) is located within the fascia surrounding muscle. Using computed tomography (CT) or magnetic resonance imaging (MRI), this fat depot can be seen as marbling between muscle tissue. CT can also be used to quantify muscle density<sup>33</sup> or muscle attenuation,<sup>133</sup> for which low values reflect greater IMAT. Using data from the Health ABC study, Goodpaster and colleagues computed skeletal muscle attenuation coefficients, where higher values indicated less fat content within the muscle.<sup>133</sup> Higher attenuation coefficient was associated with greater muscle quality, or specific force production, independent of muscle mass. Longitudinal analysis of data from the same study, showed that lower attenuation, reflecting greater fat infiltration, was associated with both decreased strength and increased risk of incident mobility limitations, assessed using self-reported difficulty walking a quarter or a mile and climbing 10 steps without resting.<sup>176</sup> CT, however, cannot distinguish intramyocellular fat, which occurs within muscle fibers, or extramyocellular fat, which occurs as small quantities of lipid droplets surrounding the muscle fiber. These muscle depots can be quantified using magnetic resonance spectroscopy (MRS) or by examining biopsied muscle tissue. Intramyocellular fat also increases with age.<sup>177</sup> Given its positive association with insulin resistance and diabetes, many early cross-sectional studies focused on the metabolic properties of intramyocellular fat. However, this association is not present in endurance trained athletes who tend to have greater intramyocellular fat. This has been termed the “athlete’s paradox”,<sup>178</sup> although later studies have found exercise-induced increases in intramyocellular fat in both inactive healthy and insulin-resistant older adults.<sup>179,180</sup> Moreover, these increases in intramyocellular fat were associated with improvements in insulin sensitivity in overweight and obese participants.<sup>180</sup> Despite the demonstrated effects of exercise on intramyocellular fat, the relationship between intramyocellular fat and physical and muscle function has not been investigated. In addition, fat infiltration is known to occur in those with

severe clinical neuropathy.<sup>181</sup> In a population-based study of European white older adults, low motor amplitude less than <4mV, suggesting axonal degeneration was associated with lower calf muscle density.<sup>33</sup> Early work by Strotmeyer and colleagues shows that poor sensory and motor nerve function is associated with higher IMAT in older men.<sup>182</sup> Future work should examine whether these structural changes could mediate the relationship between nerve and muscle function.

### **1.6.3 Mitochondrial dysfunction**

Mitochondrial dysfunction, which is thought to be a consequence of damage to muscle mitochondrial DNA that accumulates with age,<sup>126</sup> may result in decreased metabolic rate of protein synthesis, ATP synthesis, increased muscle cell apoptosis, and loss of muscle mass, as described in the mitochondrial theory of aging.<sup>183,184</sup> However, whether this is primarily due to lower physical activity in older adults is somewhat controversial. Some evidence suggests that age-related declines in mitochondrial function can be reversed through exercise training.<sup>185-187</sup> Others suggest that impairment in mitochondrial function with age is only partially attenuated with exercise.<sup>188</sup> Additional research is needed to determine whether these improvements in mitochondrial function translate into improvements in muscle function. Research on the association between mitochondrial function and peripheral nerve function is lacking, although Lin and Beal hypothesize that mitochondrial dysfunction plays a major role in neurodegenerative disease through generation of reactive oxygen species and regulation of apoptosis.<sup>189</sup> In addition, down regulation of mitochondrial function has been implicated in type II diabetes, a major risk factor for neuropathy, through genetic linkage and mouse model studies (for review see Wallace, 2005).<sup>190</sup>

#### **1.6.4 Excitation contraction uncoupling**

Animal studies show evidence of excitation-contraction uncoupling with age. Excitation-contraction coupling is the process whereby electrical signaling from the neuron (the action potential) is converted into a mechanical response (muscle contraction). Age-related uncoupling is thought to result from a detaching (or uncoupling) of the ryanodine receptors, which are responsible for releasing the Ca<sup>2+</sup> ion, from the voltage-sensing dihydropyridine receptor units. This results in a reduction in the release of the calcium ion and diminished contractile force.<sup>191</sup> Much of the research in this has been limited mice and rats;<sup>191-193</sup> however, there has been some work confirming the presence of uncoupling in single in vitro human muscle fibers from a small sample of healthy older adults.<sup>194</sup> To what extent this occurs in mobility-limited older adults is unknown and evidence is limited on the direct relationship between excitation contraction uncoupling and muscle function in humans (for review see Jimenez Moreno, et al., 2006<sup>195</sup>).

#### **1.6.5 Hormones**

Age-related changes in hormones also likely play a role in neuromuscular impairments in late life. Declines Insulin-like growth factor-I (IGF-I) may contribute to sarcopenia and declines in nerve function. IGF-I is important for growth, differentiation, and repair of both muscle<sup>196,197</sup> and nerve cells<sup>198,199</sup> and for nerve cell apoptosis. In animal models, overexpression of IGF-I can lead to increased reinnervation of skeletal muscle after injury,<sup>200</sup> prevention of age-related loss of skeletal muscle mass<sup>201</sup> and excitation-contraction uncoupling,<sup>202</sup> and maintenance of muscle fiber-specific force.<sup>203</sup> A recent study of older adult, showed that the IGF-I CA-repeat polymorphism does not influence changes in peak muscle power with strength training.<sup>204</sup>

Testosterone levels also decrease with age and have been shown to contribute to loss of muscle mass<sup>205</sup> although evidence of its effects on muscle function is somewhat conflicting.<sup>205,206</sup> While some evidence suggests that testosterone administered to older adults with low levels may increase muscle mass, strength, and protein synthesis,<sup>207-211</sup> findings are still inconclusive as to whether testosterone therapy improves muscle strength and function in community-dwelling elderly.<sup>212</sup>

### **1.6.6 Inflammatory cytokines**

Aging is associated with an increase in pro-inflammatory cytokines that may be associated with catabolic effects on muscle; however, evidence is conflicting on whether these cytokines predict sarcopenia in older adults. IL-6 has both pro- and anti-inflammatory effects in relation to skeletal muscle. As a pro-inflammatory cytokine, it may mediate the catabolic effects of wasting diseases and sarcopenia in the elderly. Yet, it has also been implicated in metabolic control pathways during exercise and some suggest that it may play an anti-inflammatory role as an inhibitor of the production of inflammatory mediator TNF- $\alpha$ . In addition, IL-6 may interfere with growth hormone (GH) and insulin-like growth factor (IGF)-I, which are essential mediators of skeletal muscle growth. Evidence from mice studies indicates that IL-6 may induce changes in growth factor-related signaling and catabolism and that downregulation of growth factor-mediated intracellular signaling may act as a mechanism for IL-6 induced muscle atrophy.<sup>213</sup> Data from the Health ABC Study shows that high serum levels and soluble receptors of inflammation markers, such as IL-6 and TNF- $\alpha$ , are associated with a greater decline in muscle mass and strength over five years.<sup>214</sup> Some of these associations were attenuated by adjustment

for change in weight, suggesting that that there may be a weight-associated pathway for inflammation in sarcopenia.

### **1.6.7 Nutrition**

Various nutritional deficiencies, such as inadequate protein intake, vitamin D deficiency, and low vitamin B12 have been implicated in neuromuscular decline and particularly decline in lean mass with age (for reviews see Morley et al.,<sup>215</sup> Forbes et al.<sup>216</sup>, and Robinson et al.<sup>217</sup>). Not only do older adults tend to intake less than the recommended daily allowance (RDA) of dietary protein, but their muscles may also produce less protein due to metabolic changes that occur with age.<sup>218</sup> The Health, Aging, and Body Composition Study found that older adults in the highest quintile of protein intake had 40% less decline in appendicular lean mass when compared to those in the lowest quintile.<sup>219</sup> While it is generally accepted that adequate levels of protein are needed to maintain muscle mass in old age,<sup>215-217,220</sup> evidence that increasing protein intake alone can prevent or even reduce the risk of sarcopenia is limited. Trials comparing the combination of strength training and protein supplementation to strength training alone have produced conflicting finding of its efficacy for promoting gains in muscle mass.<sup>221-224</sup> The effect of protein intake on muscle function in the elderly is largely understudied. Existing evidence suggests that protein intake may only be associated with change in muscle strength in older adults with high levels of inflammatory markers.<sup>225</sup> The optimal amount of protein intake in late life is also unknown, however, it has been suggested that older adults may require more than the current RDA of 0.8 g/kg/day.<sup>215</sup> Studies on the supplementation of amino acids necessary for protein synthesis, such as Leucine, have also yielded conflicting findings.<sup>226-228</sup> Clearly, more research is needed in this area.



Vitamin D deficiency is common in the elderly<sup>229-232</sup> and has been associated with low muscle strength<sup>233,234</sup> and impaired nerve function.<sup>235-238</sup> Very low levels of vitamin D can lead to osteomalacia, which is a clinical syndrome involving under-mineralization of bone and is associated with muscle weakness.<sup>239</sup> A recent meta-analysis demonstrated that daily vitamin D supplementation between 800 and 1,000 IU had a beneficial effect on strength and balance in older adults.<sup>240</sup> However, it is unknown to what extent this improvement in function is due to changes in nerve function, lean mass, or other mechanisms. In addition, the Institute of Medicine's review of randomized controlled trials and observational studies indicates lack of sufficiently strong evidence supporting the effect of vitamin D supplementation on physical function and falls. This was due, in part to lack of high quality observational evidence and varied significance in randomized controlled trials.<sup>239</sup>

Deficient levels of the vitamin B12 also have negative neuromuscular consequences. Deficiency can cause nerve demyelination and has been associated with neuropathy,<sup>241-243</sup> lower extremity weakness,<sup>244</sup> decline in physical performance,<sup>245</sup> loss of position sense,<sup>246</sup> bone loss, and fracture.<sup>247,248</sup> Moreover, subclinically low levels of B12 have been related to low sensory (monofilament detection) and motor (nerve conduction velocity) peripheral nerve function in older adults.<sup>249,250</sup> There have been no clinical trials in older adult assessing whether vitamin B12 supplementation influenced muscle function or physical performance.

### **1.6.8 Disease related risk factors**

One limitation of many studies of strength and power decline with age is that they do not address any disease related risk factors. Diabetes mellitus is a major risk factor for clinical neuropathy and has been implicated as an important risk factor for decline in neuromuscular function. Older

adults with type 2 diabetes have worse muscle strength (4% lower) and quality (7-8% lower).<sup>251</sup> They also show greater declines in strength and quality (33% greater declines for both).<sup>252</sup> While there has been little work on the effects of diabetes on muscle power, a small study found that older adults with concurrent diabetes, peripheral neuropathy, and obesity had lower muscle strength power.<sup>253</sup> In this study, the independent effects of diabetes could not be assessed. In early work using data from the Health ABC study, we have shown that adjustment for diabetes attenuated associations between power and self-reported physical function, explaining a portion of the association.<sup>254</sup> Associated neuropathy is likely an important mechanism in the relationship between diabetes and poor muscle function since the severity of neuropathy and the fiber density and amplitude of motor units was associated with strength. However, in the Health ABC study (ages 70-79 at baseline), Strotmeyer and colleagues found that diabetes predicted lower extremity function independent of peripheral nerve function.<sup>20,21</sup> Increased inflammatory cytokines, such as TNF- $\alpha$  and IL-6 may also play an important role, since they are associated with impaired muscle mass, strength and physical performance and partially attenuate the relationship between diabetes and loss of strength and muscle quality. Insulin resistance also leads to impaired mitochondrial function which likely contributes to neuromuscular health. Those with diabetes also tend to experience a greater amount of intermuscular adipose tissue, termed myosteatosis,<sup>71,133</sup> which has been linked to decreased strength and a higher incidence of mobility limitations.<sup>133,176</sup>

Peripheral Arterial Disease (PAD) is also an important risk factor for neuromuscular decline.<sup>255,256</sup> PAD is defined often subclinically in older adults as ankle brachial index (ABI) < 0.9. PAD is associated with poor sensorimotor nerve conduction, lower calf muscle area and density and a higher percentage of calf muscle fat, which may lead to worse physical

performance.<sup>255,256</sup> Muscle power may attenuate the relationship between PAD and poor physical performance in older adults.<sup>255,257</sup> Both cross-sectional muscle area and nerve conduction velocity (NCV) did not attenuate this relationship; however, NCV was only measured in the right leg, even if the left leg had lower ABI. Muscle strength has not been examined as a mediator. The role of PAD in neuromuscular decline is likely due to ischemia (decline in blood flow) to distal nerve and muscle tissue resulting in denervation, muscle atrophy, and reduced perception, diminished oxygen for muscle fibers to use.<sup>38</sup> Occlusion of vessels leading to decreased blood flow and insufficient oxygen can result in an impaired capacity to replenish ATP and creatine phosphate. This can inhibit cross-bridge interaction between actin and myosin, leading to fatigue.<sup>258-260</sup> Ischemia prevents adequate oxygen delivery which can delay ATP and creatine phosphate resynthesis.<sup>38</sup> This can contribute to fatigue during muscle contractions,<sup>259,260</sup> potentially leading to decreased muscle strength and power.<sup>261</sup> An additional mechanism between PAD and impaired physical function that has been proposed is that those with PAD may reduce their walking speed to avoid ischemic leg symptoms.<sup>257</sup> Over time, this could result in detrimental changes to muscle, further contributing to worse lower extremity function.<sup>257</sup> Alternatively, asymptomatic participants with PAD may experience primary insult to lower extremity nerves (maybe related to ischemia) potentially inducing denervation atrophy of muscles and reduced perception of lower extremity ischemic symptoms.<sup>257</sup>

### **1.6.9 Central nervous system**

With older age, a reduced evoked potential of neurons within the motor cortex of the brain and the spinal cord have been observed using transcranial magnetic stimuli.<sup>262</sup> These corticospinal

neurons and their increased activation (termed central activation) are linked to increased force of contraction, and therefore their decreased activation is believed to be linked to a decrease in force. Imaging has also demonstrated age-related atrophy and changes in and around the motor cortex,<sup>263-266</sup> however, if and how these changes are directly related to loss of muscle function is not known. A higher intensity stimulus is required to achieve maximal motor evoked potentials with older age.<sup>267</sup> This is suggestive of the role of the central nervous system in submaximal activation during maximal voluntary contractions (MVC) with age, necessary for strength and power output.<sup>19</sup> However, some limitations to the methodology available exist for assessing the involvement of the central nervous system in MVC with age. Involvement of the cortex, spinal cord, and neuromuscular junction is typically measured through voluntary activation of muscle fibers<sup>268</sup> using the interpolated twitch technique. The interpolated twitch technique entails supramaximally stimulating motor axons of contracting muscles during MVC. This additional stimuli is thought to recruit muscle fibers that have not been activated through voluntary effort, allowing for their quantification.<sup>19</sup> A notable limitation of this technique that has been suggested is that it may overestimate voluntary activation when using single or paired stimulation and has reduced sensitivity for detecting activation failure above 90% of MVC.<sup>188,189</sup> Single or paired stimulation is more easily tolerated than repetitive “train” stimulation, although it does not allow for summation of forces, and may therefore only represent a small fraction of the torque production during MVC. Moreover, findings on whether central voluntary activation decreases with age have been conflicting and dependent on the muscle studied<sup>19,269</sup> and on the age of the participants.<sup>270</sup> For instance, a decrease in central activation has been observed for the knee extensors and elbow flexors, particularly in older adults greater than 70 years of age, but this

decrease in activation has not been observed in the dorsiflexors.<sup>10,19</sup> Moreover, longitudinal data to look at age-related changes is severely lacking.

## 1.7 STRENGTH AND POWER TRAINING

Until recently, exercise interventions for older adults designed to increase muscle function mostly focused on resistance training with only modest gains in muscle power.<sup>11,271</sup> More recently, some focus has shifted to improving muscle power in older adults with specificity training. Many of these interventions have used some form of high velocity resistance training, in which the concentric phase is performed as quickly as possible, aimed at increasing muscle power and physical function. Table 1.5 summarizes findings from these studies. A number of these studies tested comparative effectiveness with more traditional strength training. Compared to traditional strength training, high velocity power training lead to greater improvements in power, but similar improvements in strength. Both strength and power training generally lead to improvements in physical function, such as the short physical performance battery (SPPB),<sup>161,272,273</sup> stair climb time,<sup>161,274</sup> chair rise time,<sup>274,275</sup> gait speed,<sup>161,274,276</sup> the timed up and go,<sup>275</sup> the Continuous Scale Physical Functional Performance,<sup>277</sup> counter movement jump height,<sup>160</sup> and self-reported function.<sup>272</sup> In some cases power training lead to greater improvements in physical function than strength training, but in other cases, improvements in physical function were not significantly different between training groups. In all cases, strength and power training was well tolerated in older adults, even among those with self-reported disability.<sup>278</sup> Explosive training with heavy loads (80% of 1RM) have been found to be more effective than lighter loads (50% and 20% of 1RM) at improving muscle strength, whereas both

heavy and light loads may be equally effective at improving power.<sup>279</sup> While explosive training with heavy loads may be safe in healthy older adults,<sup>160</sup> evidence is lacking in those with mobility limitations and in individuals susceptible to pain. These studies have been limited by small sample sizes and short-training durations (3-24 weeks). More research is needed diverse populations of older adults with varying physical abilities.

**Table 1.5. Strength vs. power training**

Study	Population	Training Group	↑ Power	↑ Strength	↑ Physical function
Fielding, 2002 <sup>278</sup>	<ul style="list-style-type: none"> <li>N=30</li> <li>Mean age 73 ± 1</li> <li>Women with self-reported disability</li> </ul>	PT	↑↑	↑	--
		ST	↑	↑	--
Miszko, 2003 <sup>277</sup>	<ul style="list-style-type: none"> <li>N=39</li> <li>Mean age 72.5 ± 6.3</li> <li>Leg extensor power &lt;140W (women), 210W (men)</li> </ul>	PT	↑	↑	↑
		ST	↑	↑	0
Henwood, 2008 <sup>274</sup>	<ul style="list-style-type: none"> <li>N=67</li> <li>Mean ages 70.7 ± 5.5, 70.2 ± 5.0, 69.3 ± 4.1, 69.1 ± 3.6</li> <li>Community dwelling older adults</li> </ul>	PT	--	↑	↑
		ST	--	↑	0
Bottaro, 2007 <sup>275</sup>	<ul style="list-style-type: none"> <li>N=24</li> <li>Mean age 66.4 ± 5</li> <li>Healthy, inactive men</li> </ul>	PT	↑↑	↑	↑↑
		ST	↑	↑	0
Caserotti, 2008 <sup>160</sup>	<ul style="list-style-type: none"> <li>N=56</li> <li>Mean ages 62.7 ± 2.2 and 81.8 ± 2.7</li> <li>Community dwelling women</li> </ul>	PT	↑	↑	↑
		ST	--	--	--
Reid, 2008 <sup>280</sup>	<ul style="list-style-type: none"> <li>N=57</li> <li>Mean age 74.2 ± 1.4</li> <li>Mobility limited (mean SPPB 7.7±1.4)</li> </ul>	PT	↑↑	↑	--
		ST	↑	↑	--
Marsh, 2009 <sup>281</sup>	<ul style="list-style-type: none"> <li>N=45</li> <li>Mean age 75.8 ± 5.7</li> <li>ADL difficulty</li> </ul>	PT	↑↑	↑	--
		ST		↑	--
Bean, 2009 <sup>272</sup>	<ul style="list-style-type: none"> <li>N=138</li> <li>Mean age 75 ± 6.8</li> <li>Mobility limited (mean SPPB 7.7±1.4)</li> </ul>	PT	↑↑	↑	↑
		ST	↑	↑	↑
Holsgaard-Larsen, 2011 <sup>282</sup>	<ul style="list-style-type: none"> <li>N=19</li> <li>Mean age 69.7 ± 3.4</li> <li>Women</li> </ul>	PT	--	--	↑
		ST	--	--	--
Drey, 2011 <sup>273</sup>	<ul style="list-style-type: none"> <li>N=69</li> <li>Mean ages 76 (70-82), 78 (73-84), 77 (72-80)</li> <li>Prefrail (Freed definition)</li> </ul>	PT	0	0	↑
		ST	0	0	↑

↑ = Increased with training

↑↑ = Increased significantly more than comparative training group

0 = No effect

-- = Not assessed

## 1.8 LIMITATIONS IN THE LITERATURE

A number of important limitations in the literature need to be addressed. First, many individuals with neuropathy may go undiagnosed<sup>22</sup> and remain asymptomatic,<sup>23</sup> particularly in those without diabetes, therefore subclinical measures of poor nerve function should be included in studies of older adults. The prevalence and incidence of poor nerve function in subgroups of older populations is unknown and should be assessed, particularly given the health disparities of disease related risk factors for neuropathy. The effects of diabetes on muscle power should be studied and mechanisms for its relationship with strength should continue to be uncovered. In addition, while diabetes remains an important risk factor for neuropathy, neuropathy remains quite prevalent in older adults without diabetes<sup>23</sup> and diabetes does not fully account for the relationship between neuropathy and poor mobility outcomes,<sup>20,21</sup> therefore other known and novel risk factors should continue to be explored, particularly using longitudinal data. There is limited longitudinal data on nerve function in older adults. Specifically, data from longitudinal cohort studies are needed to confirm age-related physiologic and functional declines and to assess relationships between nerve function, muscle structure and function, and physical function. The relationship between muscle power and clinical measures of nerve function, such as those from nerve conduction studies and monofilament testing should be investigated. Direct comparison of the relationship of strength vs. power with nerve function and physical function are lacking. Since there are a number of methods currently used to measure muscle function, and particularly muscle power, optimal methods of measurement in older adults need to be evaluated for feasibility and validity in relation to key outcomes and predictors, such as physical function outcomes, nerve function, and muscle characteristics like mass, quality, fiber type composition and mitochondrial function. More research is needed on interventions for neuromuscular decline.



This includes research on training interventions with longer durations, larger sample sizes, and more functionally diverse populations, investigating the specificity, intensity, and volume of training needed to prevent or slow declines in neuromuscular and physical function.

## **1.9 OBJECTIVES AND SPECIFIC AIMS**

This dissertation will address limitations in the literature by using prospective data to investigate the relationships between peripheral nerve function and muscle power, strength, and mobility limitation in older adults. Our objectives include assessing whether cross-sectional and change in sensory and motor peripheral nerve function are associated with lower extremity muscle power in community dwelling older men from the Osteoporotic Fractures in Men Study (MrOS). We will investigate the relationship between motor and sensory peripheral nerve function and longitudinal quadriceps strength in a large cohort of community dwelling older men and women from the Health Aging and Body Composition (Health ABC) Study. Finally, using data from the Health ABC Study we will assess the relationship between sensory and motor nerve function over seven years and incident mobility limitation. The specific aims and hypothesis of this dissertation are listed below. With these objectives, this dissertation will help characterize the role of neuromuscular impairment in the disablement pathway.

Aim 1. To assess the cross-sectional and longitudinal relationship between sensory and motor nerve function and lower extremity muscle power.

Hypothesis 1a. Poorer nerve function will be associated with diminished lower extremity muscle power.

Hypothesis 1b. Poorer nerve function will independently predict decline in muscle power.

Hypothesis 1c. Decline in nerve function will predict concurrent decline in muscle power.

Aim 2. To assess the relationship between baseline and longitudinal change in sensory and motor nerve function to longitudinal change in lower extremity quadriceps strength.

Hypothesis 2a. Poorer baseline nerve function will independently predict decline in quadriceps strength.

Hypothesis 2b. Seven-year decline in nerve function will be associated with concurrent decline in quadriceps strength.

Aim 3. To investigate whether poor baseline and longitudinal change in sensory and motor peripheral nerve function predict incident mobility limitation.

Hypothesis 3a. Worse baseline sensory and motor nerve function will be associated shorter time to incident disability.

Hypothesis 3b. Greater decline in nerve function will be associated with shorter time to incident disability.

## **2.0 PERIPHERAL NERVE FUNCTION & LOWER EXTREMITY MUSCLE POWER IN OLDER MEN**

Rachel E. Ward,<sup>1</sup> Paolo Caserotti,<sup>2</sup> Kimberly Faulkner,<sup>3</sup> Robert M. Boudreau,<sup>1</sup> Sasa Zivkovic,<sup>4</sup> Christine Lee,<sup>5</sup> Bret H. Goodpaster,<sup>4</sup> Peggy M. Cawthon,<sup>6</sup> Anne B. Newman,<sup>1</sup> Jane A. Cauley,<sup>1</sup> Elsa S. Strotmeyer<sup>1</sup>

<sup>1</sup>Department of Epidemiology and <sup>4</sup>Department of Medicine, University of Pittsburgh, Pittsburgh, PA, United States; <sup>2</sup>Laboratory of Epidemiology, Biometry, and Demography, National Institute on Aging, NIH, Bethesda, MD, United States; <sup>3</sup>National Institute for Occupational Safety and Health, CDC, Pittsburgh, PA, United States; <sup>5</sup>Department of Medicine, University of California, San Francisco, CA, United States; <sup>6</sup>California Pacific Medical Center Research Institute, San Francisco, CA, United States

Corresponding Author:  
Elsa S. Strotmeyer, PhD, MPH  
University of Pittsburgh  
Department of Epidemiology  
130 N Bellefield Ave, Rm 515  
Pittsburgh, PA 15213  
412-383-1293  
fax: 412-383-1308  
StrotmeyerE@edc.pitt.edu

(PN Function & Muscle Power in Older Men)

## 2.1 ABSTRACT

**Objective:** To assess whether cross-sectional and change in sensorimotor peripheral nerve function are associated with lower extremity muscle power in a cohort of community dwelling older men.

**Design:** Longitudinal cohort study.

**Setting:** One U.S. clinical site.

**Participants:** Three hundred seventy-two participants from the Osteoporotic Fractures in Men (MrOS) Study (age =  $77.2 \pm 5.1$  years, 99.5% white, BMI =  $27.9 \pm 3.7$  kg/m<sup>2</sup>, power =  $1.88 \pm 0.6$  watts/kg).

**Measurements:** Measurements were collected during a nerve function ancillary study performed  $4.6 \pm 0.4$  years after baseline and a follow up visit that occurred  $2.3 \pm 0.3$  years after the first visit. Muscle power was measured in each leg using the Nottingham Power Rig. Motor nerve conduction amplitude, distal motor latency, and mean f-wave latency were measured at the deep peroneal nerve. Sensory nerve function was assessed using 10-g and 1.4-g monofilaments and sensory nerve conduction amplitude and distal sensory latency were measured at the sural nerve. Symptoms at the leg and feet (numbness or tingling; sudden stabbing, burning, pain or aches; and open or persistent sores) were assessed by self-report. Adjusted models include age, height, total body lean and fat mass or calf muscle volume and muscle density in place of lean and fat mass, Physical Activity Score for the Elderly (PASE), diabetes, ankle-brachial index, hypertension, hip pain, stroke, congestive heart failure, and Teng Modified Mini-Mental State Exam (3MSE) score.

**Results:** After adjusting for age, height, total body lean and total body fat mass, one standard deviation lower motor and sensory amplitude ( $\beta = -0.07$ ,  $\beta = -0.09$ , respectively; both  $p < 0.05$ ) and 1.4-g and 10-g monofilament insensitivity ( $\beta = -0.11$  and  $\beta = -0.17$ , respectively; both  $p < 0.05$ ) were associated with lower muscle power/kg in separate linear regression models. Compared to the effect of age on

muscle power ( $\beta$  per year = -0.05 ,  $p < 0.0001$ ), this was equivalent to aging 1.4 years for motor amplitude, 1.8 years for sensory amplitude, 2.2 years for 1.4-g monofilament detection, and 3.4 years for 10-g detection. Baseline 1.4-g monofilament detection predicted greater decline in power/kg. Short-term change in nerve function was not associated with concurrent short-term change in power/kg.

Conclusion: Motor and sensory nerve conduction amplitude and monofilament sensitivity were associated with lower power/kg. Sensory and motor nerve function may play an important role in impaired muscle function in older men. Simple screening for monofilament detection may potentially identify muscle function decline in late-life, which has implications for disability in older adults.

## 2.2 BACKGROUND

Lower extremity muscle power is an important determinant of late-life physical function mobility.<sup>153,158</sup> While muscle strength is a measure of the ability to produce force, muscle power is a measure of both force and contractile speed. Loss of muscle power in older adults has been linked to risk of falls<sup>283</sup> and loss of mobility as measured by physical performance tests such as walking, chair stands, or stair climbing<sup>70,140-142,149,151,152,166</sup> and self-reported functional status.<sup>143,153</sup> Studies suggest that, compared to strength, muscle power declines more steeply with age<sup>69,70</sup> and may be more strongly associated with certain measures of mobility.<sup>140,141,142 ,143</sup> Moreover, training programs designed to improve muscle power and velocity of movement may be more effective at improving physical performance than those that solely incorporate basic resistance training.<sup>160,278,284</sup>

Although the exact etiology remains somewhat unclear, poor muscle power in late-life and its unique relationship with mobility may be, at least in part, due to impairments in peripheral nerve (PN) function.<sup>2,41,74,144-146</sup> Force and velocity production (the two components

of muscle power) are likely dependent on the number and firing rate of motor units, consisting of neurons and their associated muscle fibers.<sup>84</sup> In addition, afferent input from impaired sensory nerves may play an important role in muscle and physical function through loss of proprioception.<sup>12,13</sup> Like muscle power, PN function has been found to decline with age.<sup>22,23,26,285,286</sup> The 1999-2000 National Health and Nutrition Examination Survey (NHANES) showed that 35% of adults aged 80 years and older had impaired nerve function measured using simple screening for reduced sensation at the foot.<sup>23</sup> Decreased PN function in old age has similarly been linked with physical function limitations and impairments<sup>26,27</sup> and increased risk of falls.<sup>28-30</sup> Additionally, poor sensory and motor PN function has been related to reduced lower extremity quadriceps strength in the Health Aging and Body Composition Study.<sup>21</sup>

Despite the importance of muscle power and nerve function for mobility-related outcomes and the assumed etiologic relationship between them, the relationship of power with motor and sensory PN measures commonly used in clinical evaluations and neurologic studies has not been quantified. In a longitudinal cohort study of older men, we evaluated the whether sensory and motor PN function is related to lower extremity muscle power cross-sectionally and longitudinally with the hypothesis that worse and declining nerve function is associated with poor and declining muscle power.

## 2.3 METHODS

### 2.3.1 Study population

We used data from a nerve function ancillary study in which 372 participants had nerve function and power measured during the first visit and 242 participants had these repeated during a second visit. The ancillary study was performed at the Monongahela Valley site and occurred  $4.6 \pm 0.4$  years after baseline visits, which occurred between 2000 and 2002. The second visit to the ancillary study occurred  $2.3 \pm 0.3$  years after the first. This ancillary study was part of the Osteoporotic Fractures in men study (MrOS), which is a cohort of community dwelling, ambulatory men ( $N = 5994$ ) aged 65 years and older enrolled between March 2000 and April 2002 at six U.S. clinic sites (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA;  $n=1005$  in Pittsburgh at baseline). Eligibility for the main study included ability to walk without assistance of another person or an aide, ability to provide self-reported data, ability to understand and sign an informed consent, absence of bilateral hip replacements, absence of a medical condition that would result in imminent death, and residence near a clinic site for the duration of the study period. The primary recruitment strategy was mailing invitations to men living in the surrounding communities of the clinic sites. Supplementary strategies included community and senior newspaper advertisements and presentations to community groups. The study protocol was approved the University of Pittsburgh institutional review board and written informed consent was obtained from all participants prior to testing. Out of the 662 men with nerve function measured during the first visit of the ancillary study, 372 had muscle power and were included in cross-sectional the analyses. Reasons for missing muscle power included a temporary equipment failure ( $n = 205$ ),

refusal (n = 11), and unable due to physical limitation (n = 74). Participants with missing cross-sectional muscle power data did not differ by age, but had slightly higher BMI (28.6 vs. 27.9 kg/m<sup>2</sup>, p = 0.03) and a higher prevalence of diabetes (27.9% vs. 17.0%, p < 0.001). Out of the participants included in the cross-sectional analysis, 297 returned for a second follow-up visit of the nerve function ancillary. The change analysis included data from 242 participants with complete nerve function and muscle power data from the first and second visits of the ancillary study. During the second visit, 1 participant refused muscle power testing and 53 participants were unable due to physical limitations. Participants with missing data for the change analysis were older (78.8 vs. 76.3 years, p < 0.0001), but had similar BMI and rates of diabetes.

### **2.3.2 Lower extremity muscle power**

Muscle power was measured using an unloaded single leg extension (Nottingham Leg Extensor Power rig, Nottingham, U.K.).<sup>165</sup> Participants were seated with their arms crossed over their chest and instructed to push down on a pedal with one foot as hard and as fast as possible through full range of motion. Pushing the pedal transmits energy through a lever and chain to accelerate a flywheel. The velocity of the flywheel is measured with an optoswitch and used to calculate the power output. Peak power was measured in watts as the maximum power output from five trials. Both sides were tested unless the participant had a hip replacement on one side. The ratio of power to body weight in kg was chosen as the outcome of interest since it may better reflect ability to move one's body weight during normal daily functioning.

To correspond with sensory nerve conduction measures, muscle power data on the non-dominant side was used in the analysis unless prohibited by missing data because of inability due to physical limitation. In the case that no sensory nerve conduction data were available, muscle



power data was matched to the side in which motor nerve conduction and/or monofilament testing were performed. The number of participants with discordant sides analyzed due to missing data was minimal ( $n = 5$  for motor nerve conduction and  $n = 1$  for monofilament testing).

### **2.3.3 Peripheral nerve measures**

Nerve conduction was measured bilaterally on the deep peroneal motor and sural sensory nerves using an automated nerve conduction study device (NC-stat®, NeuroMetrix, Inc., Waltham, MA).<sup>287</sup> This device has been previously validated in healthy older adults with gold standard nerve conduction studies (correlation coefficient  $> 95\%$ ).<sup>288</sup> If participants' feet were less than  $30^{\circ}$  C, they were warmed to at least  $30^{\circ}$  C prior to testing. The parameters recorded from the peroneal motor nerve included the compound muscle action potential (CMAP) motor amplitude in millivolts (mV), measured from baseline to the negative peak of the CMAP waveform, the distal motor latency (DML) in milliseconds (ms), the time from the stimulus to the onset of motor activity, and mean F-wave latency (FWL) in ms, the mean value of the time from stimulus to the onset of F-wave activity. Sural sensory nerve measures included the sural nerve action potential (SNAP) sensory amplitude in microvolts ( $\mu$ V), the difference between negative and positive peak of the SNAP waveform and the distal sensory latency (DSL) in ms, the time from the stimulus to the negative peak of the SNAP. Light (1.4-g) and standard (10-g) monofilament sensitivity were defined as ability to detect three out of four touches at the dorsum of the both great toes. Insensitivity was defined as inability to detect three touches. The standard monofilament was performed only if the participant could not feel the light monofilament. Sensory nerve conduction was performed on the non-dominant side. Motor nerve conduction

and monofilament testing were performed on both sides unless technical difficulty occurred. Participants were asked whether they experienced neuropathic symptoms within the past 12 months. These included having: (1) numbness or tingling, (2) sudden stabbing, burning, pain or aches, and (3) an open or persistent sore, or gangrene on either feet or leg. A count of symptoms was calculated from 0-3. All measures were repeated at the follow-up visit.

#### **2.3.4 Additional covariates**

All models were adjusted for age and height, measured using a stadiometer. Weight was measured with a calibrated balance beam scale but was not included as a covariate since power/kg of body weight was the outcome. Since one potential characteristic of overt neuropathy is atrophy of muscle fibers,<sup>34</sup> lean mass was included as a potential mediator of the relationship between nerve function and power. Fat mass, was included due to its important metabolic and functional consequences.<sup>289,290</sup> Lean and fat mass were measured using dual-energy X-ray absorptiometry (DXA; Hologic 4500A, Hologic, Inc., Bedford, MA). To ensure reproducibility of DXA measurements, standardized measurement and quality-control procedures were used and operators were certified. More localized measures of calf muscle density, which has been positively associated peroneal motor amplitude,<sup>33</sup> and muscle volume, were added in place of lean and fat mass as potential mediators. Muscle density in  $\text{mg}/\text{cm}^3$ , a measure of intermuscular fat, and muscle volume ( $\text{mm}^2$ ) were measured at 66% of the calf length using peripheral quantitative computed tomography (pQCT - Stratec XCT-2000 scanner, Pforzheim, Germany) as previously described.<sup>291</sup> Each of the following covariates was added to the model since they were significantly related to muscle power or one of the nerve function predictors at an alpha level of 0.1. Diabetes was defined by self-report, use of hypoglycemic medications or having a

baseline fasting glucose  $\geq 126$  mg/dl.<sup>292</sup> Other chronic health conditions included self-reported hypertension, congestive heart failure, myocardial infarction, stroke, osteoarthritis, hip pain and Parkinson's disease. Participants self-reported if a doctor or other healthcare provider had ever told them that they had the condition. Ankle-brachial index less than 0.9 was used to define peripheral vascular disease and greater than 1.3 was used to define arterial stiffening. Cognitive function was assessed using the Teng Modified Mini-Mental State Exam (3MSE).<sup>293</sup> Lifestyle factors included smoking status (both past and current), alcohol use (>1 drink/week) and physical activity measured using the Physical Activity Scale for the Elderly (PASE).<sup>294</sup> Variance inflation factors (VIF) were calculated to assess collinearity. No VIF exceeded 3.

### **2.3.5 Statistical analysis**

Jonckheere-Terpstra tests and Analysis of Variance (ANOVA) were used to test for trends in participant characteristics across weight-adjusted muscle power tertiles. Pairwise comparisons were made between muscle power tertiles using t-tests and chi-squared statistics. Multivariable linear regression was used to compare: 1) each measure of baseline nerve function to baseline muscle power per kg of body weight; 2) each measure of baseline nerve function to change in muscle power/kg; 3) each measure of change in nerve function to change in muscle power/kg. Significant associations in the change analyses were then compared across tertiles and groups of baseline and nerve function change using least squared means adjusted for age, height, lean and fat mass for ease of interpretation. Separate models for each measure of nerve function were built progressively in order starting with the measure of nerve function. Age and height were added to the first set of minimally adjusted models. Total body lean and fat mass were added to the second set of models. For the third set of models, lean and fat mass were replaced with more

localized measures of calf muscle density. And finally, models were adjusted for lifestyle factors, chronic health conditions and cognition to assess independent associations.

## 2.4 RESULTS

Participant characteristics were compared across muscle power tertiles (Table 2.1). Those in the lowest power tertile were older, shorter in height, and had a higher BMI, greater fat mass, lower lean mass, and were more likely to have a history of hypertension and myocardial infarction. Men in the lowest tertile also had lower motor and sensory amplitude and were less likely to have 1.4-g and 10-g monofilament sensitivity and more likely to report numbness symptoms in the leg or feet (Table 2.2).

One standard deviation lower motor and sensory amplitude and standard touch monofilament insensitivity were associated with lower power/kg when adjusted for age and height (Table 2.3). The associations between power and motor and sensory amplitude remained significant upon further adjustment for lean and fat mass, and confounders including lifestyle factors and chronic conditions (results not shown). When we adjusted for calf muscle density and volume (results not shown) rather than lean and fat mass, the association between monofilament insensitivity and power was attenuated to nonsignificant by muscle density. Muscle density was positively associated with muscle power ( $\beta = 0.03$ ,  $p < 0.001$ ). The association of monofilament sensitivity with power was also attenuated to nonsignificant by low ankle arm index, which was borderline associated with muscle power ( $\beta = -0.11$ ,  $p < 0.07$ ).

We then compared the effect sizes for significant nerve function variables from the 2<sup>nd</sup> Models to the effect size of age on muscle power in standard deviations of power/kg (Figure

2.1). One standard deviation lower motor and sensory amplitude had the effect of aging 1.4 and 1.8 years, respectively and inability to detect 1.4-g and 10-g monofilament had the effect sizes of aging 2.2 and 3.4 years, respectively. Table 2.3 shows that inability to detect 1.4-g monofilament at baseline predicted a greater decline in muscle power/kg (least squared means = -0.08 vs. 0.07 watts/kg,  $p = 0.02$ ) when adjusted for age and height. Results were consistent when adjusted for lean and fat mass or muscle density and volume and additional covariates. Change in nerve function was not associated with a change in power.

## 2.5 CONCLUSIONS

Although muscle power is known to be dependent on both the nervous and musculoskeletal systems, previous research has not evaluated PN function measures commonly used in clinical practice and neurologic studies. Studies have indicated that muscle power declines at an even faster rate with age than strength,<sup>69,70</sup> and our findings show that the potential effects of peripheral nerve function are 1.5 to 3.5 times the effect of age alone. This finding has particularly important consequences, given that neuropathy is a preventable risk factor. Establishing the relationship between muscle power and clinically relevant measures of nerve function in late-life is crucial since older adults experience the highest burden of neuropathy and diminished muscle function and both likely play key roles in the disablement pathway.<sup>23,71</sup> Our findings show that poor sensory and motor peripheral nerve function are independently associated with and may be important risk factors for poor muscle power in old age. Risk factors for poor muscle power are somewhat understudied in epidemiologic studies of older adults, yet

poor muscle power has important consequences in late-life such as impaired mobility,<sup>70,140-143,149,151,152,166</sup> disability,<sup>148,153</sup> and increased risk of falls.<sup>283</sup>

We found that lower amplitude, but not latency, was associated with poor muscle power. Consistent with our study findings, Strotmeyer and colleagues reported that peroneal motor nerve amplitude, but not conduction velocity, was related to lower extremity muscle strength.<sup>21</sup> Latency is the travel time of the response and is measured from the moment of stimulation to the appearance of the action potential. Nerve conduction velocity is typically calculated by dividing the distance between two stimulation sites by the difference between latencies.<sup>65</sup> Diminished amplitude may indicate axonal degeneration and motor nerve death, whereas latency or conduction velocity may be a measure of demyelination of the protective sheath surrounding the nerve.<sup>63</sup> Amplitude may decline in some individuals, while velocity, driven by the motor units that remain intact, remains normal.<sup>33,76</sup> In participants in the lowest muscle power tertile, we observed lower amplitude but no difference in latency, compared to those in higher muscle power tertiles (Table 2.2). However, given that power is a measure of contractile velocity in addition to force, it is reasonable to hypothesize that the travel time, particularly for the motor nerve response, may be related to power. We, however, were not able to assess whether participants had low power due to low force or low velocity, since the power rig does not measure these two components separately.

Sensory nerve function measured by monofilament detection and average vibration perception threshold was associated with muscle strength in the previous study as well.<sup>21</sup> We found that sensory amplitude was also related to muscle power. While motor nerves directly innervate muscle, it is less clear how the sensory nerves are involved. Blocking afferent input in healthy individuals has led to impaired maximal voluntary contractions,<sup>13</sup> which may occur

through loss of proprioceptive feedback.<sup>12</sup> Furthermore, sensory neuropathy has been associated with significant loss of ankle movement perception.<sup>295,296</sup> While an effort was made to collect multiple trials until a plateau in peak power was reached, it is possible that impaired sensory nerve function may have dampened participants' ability to achieve proper foot placement and push at a maximum effort. The fixed load single leg extension requires participants to push with their heel while maintaining contact between the pedal and the entire dorsum of the foot. Multiple trials may be needed for the participant to familiarize themselves with the movement and in some cases up to 9 trials may be need to produce a maximum effort.<sup>165</sup> Assessing the relationship between nerve function and alternative methods of measuring muscle power may be an important future direction. An additional explanation could be that large fiber neuropathies, which are the most common type of neuropathies in older adults,<sup>297</sup> may affect both sensory and motor nerves, with most deficits first presenting as sensory loss. This can progress to reduced position sense, muscle weakness and wasting, and depressed tendon reflexes.<sup>297</sup> Numbness and tingling were the most commonly reported neuropathic symptoms in this study with 30% of the total study population reporting them, supporting this hypothesis. There was also a significant trend across muscle power tertiles, with those in the lowest tertile being most likely to report numbness symptoms.

Muscle density and low ankle arm index attenuated the relationship between monofilament sensitivity and muscle power to nonsignificant. Interestingly, diminished nerve function in older adults has been previously associated with lower muscle density, a measure of intermuscular fat, but not with cross-sectional muscle area,<sup>33</sup> which could suggest that age-related changes in nerve function lead to changes in muscle tissue structure over macroscopic changes in muscle mass. Moreover, peripheral vascular disease measured using ankle arm index

has been associated with reduced leg muscle power and lower motor nerve conduction velocity, although the previous study did not examine sensory monofilament detection.<sup>255</sup>

A major strength of this study is the inclusion of both motor and sensory PN function measures. We also used reproducible sensitive and specific measure of nerve conduction for both motor and sensory nerves.<sup>287,298</sup> Our measure of muscle power has been previously validated and is commonly used.<sup>165</sup> Models were adjusted for a number of potential confounders, including body composition measures, lifestyle factors, and comorbidities. And finally, we were able to examine longitudinal relationships between nerve function and muscle power change, although some of our null findings are likely attributable to the short time period (2.3 years) between measures.

One limitation of this study is that our results may not apply to other populations such as non-whites, women, the “young-old” and institutionalized individuals. Future studies should assess the relationship between muscle power and clinical measures of motor and sensory nerve function in a larger more diverse population with a broader range of function.

We showed that sensory and motor nerve function are independently associated with muscle power, which is associated with poor outcomes in older adults such as falls,<sup>283</sup> impaired mobility,<sup>70,140-143,149,151,152,166</sup> and disability.<sup>148,153</sup> Future work should investigate whether there is a direct relationship between poor nerve function and these poor health outcomes. Since monofilament insensitivity was predictive of greater muscle power decline, future studies should also test whether simple screening for monofilament detection may identify early impairments and predict declines in muscle power. Detecting poor or declining muscle power early on could lead to more effective disability prevention and treatment efforts, such as training programs targeted at increasing muscle power.<sup>160,278,284</sup> Importantly, understanding risk factors in the



disablement pathway such as poor nerve function and impaired muscle power can help identify multiple points of intervention. Future studies should characterize the effects of known and novel risk factors of poor nerve function on muscle power.

**Table 2.1. Characteristics of study population by muscle power (watts/kg) tertiles**

	Lowest tertile ≤1.60 watts/kg (N=122)	Middle tertile >1.60 and ≤2.06 watts/kg (N=129)	Highest tertile >2.06 watts/kg (N=121)	p-value	Total (N=372)
Muscle power (watts/kg), mean (SD)	1.27 (0.2) <sup>a,b</sup>	1.84 (0.1) <sup>c</sup>	2.52 (0.4)	<0.0001	1.88 (0.6)
Age (years), mean (SD)	80.0 (5.1) <sup>a,b</sup>	76.7 (4.9) <sup>c</sup>	75.0 (4.1)	<0.0001	77.2 (5.1)
White race (%)	122 (100)	128 (99.2)	120 (99.2)	0.38	370 (99.5)
<b>Body composition</b>					
Height (m), mean (SD)	171.5 (6.8) <sup>b</sup>	172.0 (6.7) <sup>c</sup>	173.9 (6.3)	0.01	172.5 (6.7)
BMI (kg/m <sup>2</sup> ), mean (SD)	28.1 (3.7)	28.2 (3.6)	27.3 (3.5)	0.13	27.9 (3.7)
Fat mass (kg), mean (SD)	23.2 (6.6) <sup>b</sup>	22.7 (7.1)	21.3 (6.5)	0.09	22.4 (6.8)
Lean mass (kg), mean (SD)	55.6 (6.7) <sup>b</sup>	56.9 (7.5)	57.5 (6.6)	0.09	56.6 (7.0)
Muscle density (mg/cm <sup>3</sup> )	67.9 (4.6) <sup>a,b</sup>	69.4 (3.7)	70.4 (3.8)	<0.0001	69.2 (4.2)
<b>Chronic health conditions</b>					
Diabetes, n (%)	25 (20.5)	20 (15.5)	16 (13.2)	0.25	63 (17.0)
AAI <0.9, n (%)	46 (42.6)	41 (34.2)	36 (30.3)	0.05	123 (35.5)
History of hypertension, n (%)	74 (60.7) <sup>b</sup>	66 (51.2)	50 (41.3)	0.003	190 (51.1)
History of stroke, n (%)	8 (6.7)	6 (4.7)	3 (2.5)	0.13	17 (4.6)
History of MI, n (%)	17 (13.9) <sup>a</sup>	31 (24.0)	18 (14.9)	0.84	66 (17.7)
History of CHF, n (%)	10 (8.2)	9 (7.0)	8 (6.6)	0.63	27 (7.3)
Hip pain, n (%)	19 (15.6)	24 (18.6)	16 (13.2)	0.62	59 (15.9)
<b>Lifestyle characteristics</b>					
History of smoking, n (%)	3 (2.5)	2 (1.6)	5 (4.1)	0.42	10 (2.7)
Physical Activity Score (PASE), mean (SD)	147.4 (65.8)	146.8 (64.6)	162.4 (65.2)	0.11	152.1 (65.4)

SD = standard deviation; m = meters; kg = kilograms; PASE = Physical Activity Scale for the Elderly; <sup>a</sup>p<0.05 for Lowest tertile vs. Middle tertile, <sup>b</sup>p<0.05 for Lowest tertile vs. Highest tertile, <sup>c</sup>p<0.05 for Middle tertile vs. Highest tertile

**Table 2.2 Nerve function by muscle power (watts/kg) tertiles**

	Lowest tertile ≤1.60 watts/kg (N=122)	Middle tertile >1.60 and ≤2.06 watts/kg (N=129)	Highest tertile >2.06 watts/kg (N=121)	p-value	Total (N=372)
<b>Motor nerve conduction</b>					
Motor amplitude (mV), mean (SD)	2.15 (1.4) <sup>b</sup>	2.25 (1.4) <sup>c</sup>	2.84 (1.5)	0.0007	2.42 (1.5)
DML (ms), mean (SD)	4.33 (0.6)	4.42 (0.8)	4.49 (0.9)	0.34	4.41 (0.8)
Mean FWL (ms), mean (SD)	60.8 (6.6)	60.6 (5.8)	60.4 (5.5)	0.89	60.6 (5.9)
<b>Sensory nerve conduction</b>					
Sensory amplitude (μV), mean (SD)	3.07 (3.2) <sup>a,b</sup>	4.01 (3.4)	4.84 (3.7)	0.002	4.01 (3.4)
DSL (ms), mean (SD)	3.07 (2.9)	3.06 (0.2)	3.13 (0.3)	0.17	3.12 (0.4)
<b>Monofilament sensitivity, n (%)</b>					
1.4g sensitivity	51 (42.5) <sup>a,b</sup>	77 (60.2)	73 (60.3)	0.006	201 (54.5)
10g sensitivity	92 (76.7) <sup>a,b</sup>	110 (86.6)	104 (86.7)	0.04	306 (83.4)
<b>Neuropathic symptoms, n (%)</b>					
Numbness	45 (36.9) <sup>a</sup>	37 (28.9)	30 (24.8)	<0.05	112 (30.2)
Pain	26 (21.5)	19 (14.8)	21 (17.5)	0.42	66 (17.9)
Open/persistent sore	4 (3.3)	2 (1.6)	2 (1.7)	0.39	8 (2.2)
One symptom	44 (36.4)	38 (29.9)	37 (31.2)	0.38	118 (32.4)
Two symptoms	15 (12.4)	8 (6.3)	7 (5.9)	0.06	30 (8.2)

SD = standard deviation; m = meters; kg = kilograms; mV = millivolts; DML = distal motor latency; ms = milliseconds; FWL = F-wave latency; DSL = Distal sensory latency; g = grams;

<sup>a</sup>p<0.05 for Lowest tertile vs. Middle tertile, <sup>b</sup>p<0.05 for Lowest tertile vs. Highest tertile,

<sup>c</sup>p<0.05 for Middle tertile vs. Highest tertile

**Table 2.3 Separate multivariate linear regression models for each measure of nerve function and muscle power (watts/kg)**

	1 <sup>st</sup> Models		2 <sup>nd</sup> Models	
	$\beta$ (SE)	$R^2$	$\beta$ (SE)	$R^2$
Motor nerve function per SD lower				
Motor amplitude	-0.10 <sup>†</sup> (0.03)	0.20	-0.07* (0.03)	0.29
Distal motor latency	-0.05 (0.03)	0.17	-0.04 (0.03)	0.27
Mean F-wave latency	0.05 (0.03)	0.18	0.05 (0.03)	0.27
Sensory nerve function per SD lower				
Sensory amplitude	-0.10 <sup>†</sup> (0.04)	0.20	-0.09* (0.04)	0.28
Distal sensory latency	-0.10 (0.34)	0.12	-0.06 (0.32)	0.21
Monofilament insensitivity (yes/no)				
1.4g	-0.10 (0.06)	0.19	-0.11* (0.05)	0.28
10g	-0.16* (0.07)	0.19	-0.17* (0.07)	0.29
Neuropathic symptoms (yes/no)				
Numbness	-0.10 (0.06)	0.20	-0.09 (0.06)	0.28
Pain	0.01 (0.07)		0.04 (0.07)	
Open sore	-0.32 (0.18)		-0.36* (0.18)	

1<sup>st</sup> Models adjusted for age and height.

2<sup>nd</sup> Models adjusted for variables in 1<sup>st</sup> Models plus total body lean and fat mass.

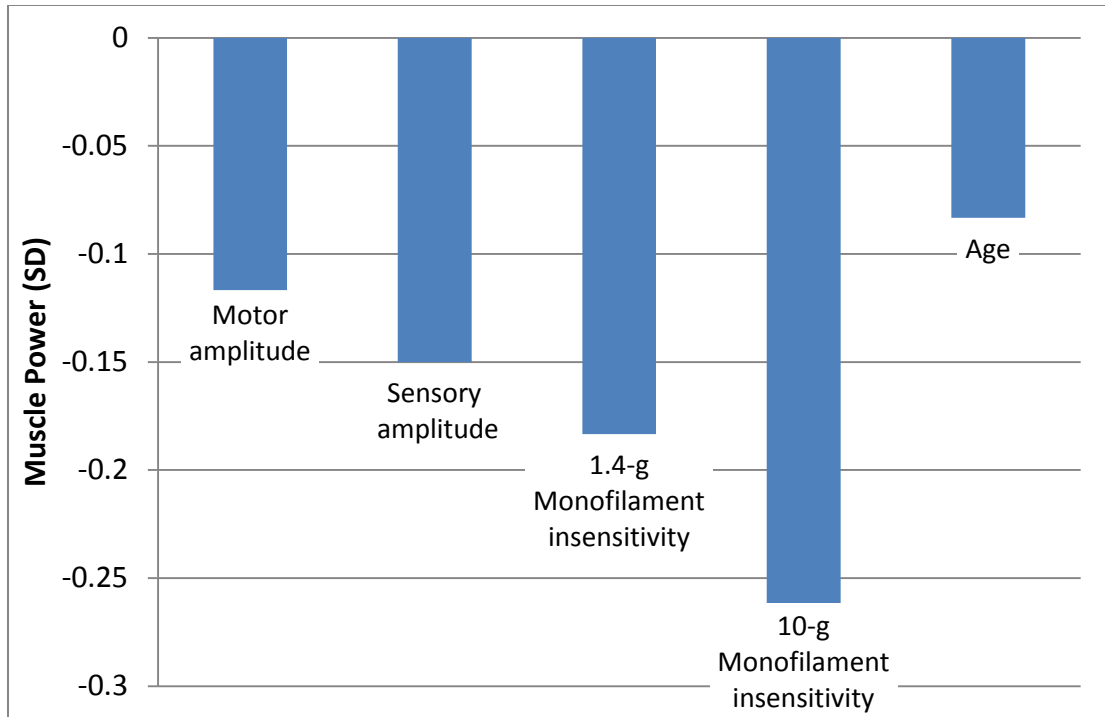
SE = standard error; \*P<0.05; <sup>†</sup>P<0.01; <sup>‡</sup>P<0.001.

**Table 2.4 Separate multivariate linear regression models for each measure of nerve function and decline in muscle power (watts/kg)**

	Models	
	$\beta$ (SE)	$R^2$
Motor nerve function per SD lower		
Motor amplitude	0.001 (0.04)	0.005
Distal motor latency	-0.001 (0.03)	0.003
Mean F-wave latency	0.02 (0.04)	0.01
Sensory nerve function per SD lower		
Sensory amplitude	-0.05 (0.04)	0.01
Distal sensory latency	-0.06 (0.04)	0.03
Monofilament insensitivity (yes/no)		
1.4g	0.15* (0.07)	0.02
10g	0.11 (0.09)	0.01
Neuropathic symptoms (yes/no)		
Numbness	0.11 (0.07)	0.02
Pain	-0.13 (0.09)	
Open sore	0.15 (0.125)	

Models adjusted for age and height.

SE = standard error; \*P<0.05; <sup>†</sup>P<0.01; <sup>‡</sup>P<0.001.



**Figure 2.1 Effect size of nerve conduction amplitudes and monofilament insensitivity compared to age**

Motor and sensory amplitude per standard deviation (SD) lower; 1.4-g and 10-g monofilament insensitivity (yes/no); age per year older; separate models adjusted for age, height, total body lean and fat mass; age adjusted for height, total body lean and fat mass; SD = Standard Deviation.

### **3.0 SENSORY AND MOTOR PERIPHERAL NERVE FUNCTION PREDICT LONGITUDINAL LOWER-EXTREMITY QUADRICEPS STRENGTH**

Rachel E. Ward,<sup>1</sup> Robert M. Boudreau,<sup>1</sup> Paolo Caserotti,<sup>2</sup> Tamara B. Harris,<sup>3</sup> Sasha Zivkovic,<sup>4</sup>  
Bret H. Goodpaster,<sup>4</sup> Suzanne Satterfield,<sup>5</sup> Stephen Kritchevsky,<sup>6</sup> Ann V. Schwartz,<sup>7</sup> Aaron I.  
Vinik,<sup>8</sup> Jane A. Cauley,<sup>1</sup> Anne B. Newman,<sup>1</sup> Elsa S. Strotmeyer<sup>1</sup>

<sup>1</sup>Department of Epidemiology, Graduate School of Public Health, and <sup>4</sup>Department of Medicine,  
School of Medicine, University of Pittsburgh, Pittsburgh, PA, United States; <sup>2</sup>Institute of Sports  
Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark;  
<sup>3</sup>Laboratory of Epidemiology, Biometry, and Demography, National Institute on Aging, NIH,  
Bethesda, MD, United States; <sup>5</sup>Department of Preventive Medicine, University of Tennessee,  
Memphis, TN; <sup>6</sup>Department of Internal Medicine-Gerontology and Geriatric Medicine, Wake  
Forest School of Medicine, Winston-Salem, NC; <sup>7</sup>Department of Epidemiology and Biostatistics,  
University of California, San Francisco, CA, United States; <sup>8</sup>Department of Neurobiology,  
Eastern Virginia Medical School, Norfolk, VA

Corresponding Author:  
Elsa S. Strotmeyer, PhD, MPH  
University of Pittsburgh  
Department of Epidemiology  
130 N Bellefield Ave, Rm 515  
Pittsburgh, PA 15213  
412-383-1293  
fax: 412-383-1308  
StrotmeyerE@edc.pitt.edu  
(Longitudinal Strength & PN Function)

### 3.1 ABSTRACT

**Objective:** To investigate the relationship between motor and sensory peripheral nerve function and longitudinal quadriceps strength in a large cohort of community dwelling older men and women.

**Design:** Longitudinal cohort study.

**Setting:** Two U.S. clinical sites.

**Participants:** Eighteen hundred and thirty participants from the Heath Aging and Body Composition (Health ABC) Study (age =  $76.3 \pm 2.8$  years, 51.0% female, 34.8% black, BMI =  $27.2 \pm 4.6$  kg/m<sup>2</sup>, strength =  $96.1 \pm 36.6$  Nm).

**Measurements:** Our outcome was quadriceps strength measured using an isokinetic dynamometer at Years 4, 6, 8, and 10 of the study. Our predictors were nerve function measured at Year 4 and concurrent change in nerve function from Years 4 to 11 categorized as maintained normal, normal to poor, poor to normal, or sustained poor nerve function. Motor nerve conduction amplitude (poor <1 mV) and velocity (poor < 40 m/s) were measured on the deep peroneal nerve. Sensory nerve function was assessed using 10-g and 1.4-g monofilaments and average vibration perception threshold. Symptoms at the leg and feet (numbness or tingling; sudden stabbing, burning, pain or aches; and open or persistent sores) were assessed by self-report. Adjusted models include age, height, total body lean and fat mass, diabetes, ankle-brachial index, cerebrovascular disease, cardiovascular disease, knee pain, cognition, depression, vitamin B12 status, smoking, alcohol consumption, physical activity, and renal function.

**Results:** Poor initial 10-g monofilament detection was associated with 10.48 Nm lower strength ( $p < 0.001$ ) and 1.02 Nm faster strength decline ( $p < 0.05$ ) in women and 7.81 Nm lower strength ( $p < 0.05$ ) in men. In the concurrent change analysis, sustained poor 10-g monofilament

sensitivity over seven years was associated with 15.88 Nm lower strength ( $p < 0.001$ ) and 1.52 Nm faster strength decline ( $p < 0.01$ ). Poor 10-g monofilament sensitivity was associated with 12.41 Nm lower strength, despite improving to normal by the end of seven years ( $p < 0.01$ ). One SD worse initial average vibration detection threshold was associated with 2.81 Nm lower strength in men ( $p < 0.01$ ). In the concurrent change analysis, sustained poor and declining from normal to poor vibration detection threshold over seven years were associated with 16.20 ( $p < 0.01$ ) and 10.29 ( $p < 0.001$ ) Nm lower strength, respectively. One SD worse initial motor amplitude and reporting two peripheral neuropathy symptoms were associated with 1.87 ( $p < 0.01$ ) and 5.97 ( $p < 0.01$ ) Nm lower strength in women. In the concurrent change analysis, poor motor amplitude and symptoms were associated with 14.11 ( $p < 0.05$ ) and 7.45 ( $p < 0.05$ ) Nm lower strength despite improving to normal by the end of seven years.

Conclusion: In this cohort of older adults, poor initial and seven-year peripheral nerve function were associated with lower strength and a faster rate of strength decline, suggesting an important mechanism for late-life disability. Poor initial motor amplitude and symptoms predicted lower strength regardless of improvements by the end of seven years, suggesting that future work should investigate early prevention of modifiable risk factors and timely intervention.

### 3.2 BACKGROUND

Poor strength in late-life contributes to poor physical function,<sup>299,300</sup> mobility disability,<sup>121,176,301</sup> hospitalization,<sup>302,303</sup> and mortality.<sup>303-305</sup> Given its major role in late-life disablement, investigating common risk factors and potential mechanisms for strength decline and disability in



older adults is essential.<sup>20</sup> While sarcopenia, or muscle atrophy that occurs with age, plays a major role in declining strength, maintaining or gaining muscle mass does not guarantee prevention of strength loss with age,<sup>71</sup> suggesting that other physiologic processes must be involved. One important mechanism for strength decline and incident disability that has been proposed is decline in peripheral nerve function.<sup>21</sup> Impaired peripheral nerve function, which is highly prevalent<sup>23</sup> in older adults both with and without diabetes mellitus, is associated with physical performance measures predictive of mobility disability<sup>8</sup> in the Health, Aging and Body Composition (Health ABC) study.

Cross-sectional evidence shows that peripheral nerve function is associated with diminished strength, independent of lean mass.<sup>21,159</sup> Using data from the 2000-2001 (Year 4) visits in the Health ABC study, Strotmeyer and colleagues report that poor sensory and motor peripheral nerve function were related to lower quadriceps and ankle strength.<sup>21</sup> However, the timing of the process is unclear. Using longitudinal data from this study cohort, we propose to further understand the importance of peripheral nerve function in longitudinal strength decline by examining: (1) the relationship between sensorimotor nerve function measured at one time point and subsequent longitudinal decline in lower extremity quadriceps strength over six years and; (2) the relationship between concurrent decline in sensorimotor nerve function and quadriceps strength.

## 3.3 METHODS

### 3.3.1 Study participants

The Health ABC Study is an ongoing prospective cohort study of well-functioning older adults ( $n = 3,075$ ; 48.4% male; 41.6% black, ages 70-79 years at baseline) that was established in 1997-1998 to investigate body composition and disability changes in older age. Participants were recruited through mailings to a random sample of white Medicare beneficiaries and all black community residents eligible by age. Eligibility, determined by phone interview, included having no difficulty walking a quarter of a mile, walking up 10 steps, or performing activities of mobility-related daily living, as well as having no life-threatening cancers with active treatment within the past 3 years, and planning to remain in the study area for at least 3 years. Informed consent, provided prior to examination, was approved by the institutional review boards at the University of Pittsburgh and the University of Tennessee Health Science Center. Figure 3.1 describes the number of participants that had nerve function and quadriceps strength measured at each visit. Compared to participants who returned for peripheral nerve exams seven years after the initial nerve exam, participants with missing data for the concurrent change in nerve function and strength analysis were older (76.8 vs. 76.1 years,  $p < 0.0001$ ), had lower BMI (26.7 vs. 27.5  $\text{kg/m}^2$ ,  $p = 0.0003$ ), less fat mass (25.8 vs. 27.5 kg,  $p < 0.0001$ ), more peripheral arterial disease (18.6% vs. 11.2%,  $p < 0.0001$ ), worse sensory nerve function (monofilament insensitivity: 10.1% vs. 6.8%,  $p = 0.01$ ; vibration perception: 52.7 vs. 48.2  $\mu$ ,  $p < 0.01$ ), and lower strength (92.9 vs. 98.0 Nm,  $p = 0.002$ ). Other factors (sex, race, diabetes prevalence, smoking status, alcohol consumption, knee pain, blood pressure, motor nerve conduction, lean mass, physical activity) were not different.

### **3.3.2 Quadriceps strength**

Quadriceps strength was measured concentrically at 60° per second from 90° to 30° using a Kin-Com isokinetic dynamometer (Harrison, TN) at Years 4, 6, 8, and 10 on the right leg, unless the participant had a knee replacement or knee pain. Following a warm up at submaximal effort, participants performed three to six trials, and the mean maximal torque from the three best trials was calculated. Contraindications for this test included history of brain aneurysm or stroke, bilateral knee replacement, severe bilateral knee pain, systolic blood pressure greater than 199 mmHg and diastolic blood pressure greater than 109 mmHg. Individuals with contraindications are labeled as “excluded” in Figure 3.1.

### **3.3.3 Sensory and motor peripheral nerve function**

Peripheral nerve function was measured at Years 4 and 11 of the Health ABC study as previously described.<sup>65</sup> Each study site (Memphis and Pittsburgh) had a clinic staff examiner trained by a technician experienced in clinical trials using NC measures as outcomes and a board certified neurologist with additional certifications in electrodiagnostic medicine and neuromuscular medicine, qualifications in clinical neurophysiology, and specialization in neuromuscular disorders. After warming the feet to 30°C, measures were performed on the right leg unless contraindicated because of knee replacement, amputation, trauma, ulcer, or surgery. If the right leg was contraindicated, measures were performed on the left leg, unless it too was contraindicated. Peroneal motor nerve conduction amplitude and velocity were measured from the popliteal fossa to the ankle using the NeuroMax 8 (XLTEK, Oakville, Ontario, Canada). Sensory nerve function was measured using average vibration detection threshold on the bottom

of the large toe with a VSA-3000 Vibratory Sensory Analyzer (Medoc, Ramat Yishai, Israel). Monofilament insensitivity, defined as the inability to detect three out of four touches, was measured at the dorsum of the large toe with a 10-g standard monofilament and a 1.4-g light monofilament. Number of self-reported peripheral neuropathy symptoms were collected and coded from 0-3; these include having (1) numbness or tingling, (2) sudden stabbing, burning, pain or aches, and (3) an open or persistent sore, or gangrene on either feet or leg, all in the past 12 months.

For the concurrent change analysis, participants were divided into one of four categories: (1) maintained normal; (2) normal to poor; (3) poor to normal; and (4) sustained poor. Poor nerve function was categorized using clinical cut points of  $<1$  mV for motor amplitude and  $<40$  m/s for motor nerve conduction velocity. Poor nerve function was also defined as 1.4-g and 10-g touch monofilament insensitivity, lack of detection of a maximum vibration perception threshold ( $>131 \mu$ ), and reporting 2 peripheral neuropathy symptoms. Participants who experienced  $<5\%$  of continuous change for amplitude, velocity, or vibration perception threshold were not considered to have transitioned from normal to poor or from poor to normal.

### **3.3.4 Additional covariates**

We considered several factors known or hypothesized to be associated with nerve function and lower extremity strength and function. Height and weight were measured using a stadiometer and a calibrated balance beam scale. Whole body bone-free lean and fat mass were measured using dual-energy X-ray absorptiometry (DXA; Hologic 4500A, Hologic, Inc., Bedford, MA). Diabetes was defined as self-report of physician diagnosis, hypoglycemic medication use, or fasting glucose greater than 126 mg/dL (47.0 mmol/L) and impaired fasting glucose was defined

at 100 mg/dL to <126 mg/dL after an 8-hour or longer fast.<sup>306</sup> Hypertension was assessed by self-report, medication use, and diastolic blood pressure  $\geq 90$  mmHg or systolic blood pressure  $\geq 140$  mmHg. A >1 drink/week cutpoint for alcohol consumption was used. Ankle brachial index cutpoints were used to indicate peripheral arterial disease (<0.9) and arterial stiffening ( $\geq 1.3$ ). Depressive symptoms were measured using an interviewer-administered Center for Epidemiologic Studies Depression Scale.<sup>307</sup> We measured cognitive function using the Modified Mini-Mental State Examination (3MSE), and attention, psychomotor speed, and executive function using the Digit Symbol Substitution Test (DSST).<sup>308</sup> Insufficient renal function was defined as Cystatin-C > 1mg/dL.<sup>309</sup> Self-reported knee pain on most days in the past 12 months was assessed. We defined poor vitamin B12 status as < 260 pmol/L.<sup>249</sup> Prevalent cerebrovascular disease(transient ischemic attack or stroke), cardiovascular disease (bypass or coronary artery bypass graft, carotid endarterectomy, myocardial infarction, angina pectoris, congestive heart failure), knee pain, Cystatin-C, alcohol consumption, and DSST were measured at baseline (1997/1999). Smoking status and 3MSE were measured at Year 3 (1999/2000). All other covariates were measured during the Year 4 nerve exam (2000/2001). Body weight, total lean mass, total fat mass, and weekly physical activity spent walking and climbing stairs (kcal/kg/week) were included as a time varying covariates from Years 4, 6, 8, and 10.

### **3.3.5 Statistics**

Since men and women differ greatly in muscle strength and body composition, means and frequencies of participant characteristics were compared between men and women using t-test and chi-squared statistics. Mixed linear models were used to assess the relationships between initial and concurrent change in nerve function and strength to maximize the use of all available

time points of strength data and to account for the correlation between repeated measures. We included participants that had at least two measures of strength with one measure occurring at Year 4. Most participants had all four strength measures (n=1110), although some only had two (n=349) or three (n=371). Strength was entered as a time varying outcome in the models. The beta value for the main effect of each predictor represents the magnitude of the effect on strength over all available timepoints. The beta value for the interaction between time and each predictor is the magnitude of the effect on rate of decline in strength. Separate models were built for each measure of nerve function since some were moderately correlated (motor amplitude and conduction velocity:  $r=0.33$ ,  $p<0.0001$ ) and each represents a different aspect of peripheral nerve function. The first set of models started with baseline nerve function then were minimally adjusted for age, race, height, weight, study site, and the interaction between each variable and time. Then models were additionally adjusted for lean and fat mass instead of weight, given their relationship with strength and physical function,<sup>71,310</sup> and to assess whether lean mass mediated the relationship between nerve function and strength. Additional variables were added to the final models if they were related to the initial predictor or outcome at an alpha level  $<0.1$ . Fully adjusted models included diabetes, ankle brachial index, cerebrovascular disease, cardiovascular disease, knee pain, cognition, depression, vitamin B12 status, smoking, alcohol consumption, physical activity, and renal function, unless removed due to a p-value  $>0.1$  to prevent collinearity. We also tested interactions between sex and nerve function measures to assess whether sex modified the relationship between nerve function and strength. In addition, due to the known effect of diabetes on peripheral nerve function and muscle strength,<sup>251,252</sup> we ran a sensitivity analysis excluding all cases of diabetes.

### 3.4 RESULTS

Table 3.1 compares characteristics between men and women. Men had greater quadriceps strength, height, lean mass, and fat mass. They were more likely to consume >1 drink/week and had higher physical activity levels. Men also had higher rates of diabetes, impaired fasting glucose, arterial stiffening, cardiovascular disease, and poor vitamin B12 status. Men had worse sensory and motor nerve function, but women reported more peripheral neuropathy symptoms (Table 3.2). Figure 3.1 shows the percentage and number of participants in each nerve change group. Significant and borderline significant interactions between sex and initial average vibration detection threshold ( $p = 0.01$ ) and motor amplitude ( $p = 0.09$ ) were associated with strength; therefore analysis for initial nerve function and strength were performed separately in women (Table 3.3) and men (Table 3.4). The analysis assessing relationships between concurrent change in nerve function and strength were not stratified by sex since there were no significant interactions between nerve function change and sex. All beta values for continuous predictors are standardized.

Initial 1.4-g and 10-g monofilament insensitivity were associated with 2.72 and 10.48 Newton meters (Nm) lower strength in women and 4.94 and 7.81 Nm lower strength in men. In the concurrent change analysis (Table 3.5), maintaining poor 10-g and 1.4-g sensitivity over seven years were associated with 15.88 and 5.31 Nm lower strength, respectively, although the association with 1.4-g sensitivity was attenuated to nonsignificant after further adjustment for comorbid conditions, lifestyle factors, and cognition (results not shown). Poor 10-g monofilament sensitivity was associated with 12.42 Nm lower strength, despite improving to normal by the end of seven years. Initial 10-g monofilament insensitivity was related to increased strength decline in women, as was maintaining poor 10-g monofilament sensitivity in

the concurrent change analysis. In men, worse initial average vibration detection threshold was associated with 2.81 Nm lower strength, but not in women. Declining from normal to poor and sustaining poor average vibration detection threshold over seven years was also associated with 10.29 and 16.20 Nm lower strength, respectively in the concurrent change analysis. In women, lower initial motor amplitude and reporting two peripheral neuropathy symptoms were associated with 1.87 and 5.97 Nm lower strength but not in men. Despite improving to normal over the seven year period, starting with poor motor amplitude and peripheral neuropathy symptoms remained associated with 14.11 and 7.45 Nm lower strength. In women, initially reporting one peripheral neuropathy symptom was associated with greater strength decline, as was transitioning from reporting two to reporting less than two symptoms over the seven year period, but both were attenuated to nonsignificant when adjusting for comorbid conditions, lifestyle factors, and cognition (results not shown). When we excluded participants with diabetes, 1.4-g monofilament insensitivity was no longer a significant predictor of strength in men or in the concurrent change analysis. Also going from reporting less than two to reporting two peripheral neuropathy symptoms (normal to poor) was associated with lower strength, whereas the other symptom groups were not. All other associations remained consistent.

### **3.5 DISCUSSION**

Using prospective data from this large cohort of older men and women, we were able to characterize neuromuscular decline in late-life using multiple clinical measures of peripheral neuropathy. We found that poor peripheral nerve function at one time point and over seven years were associated with low concurrent strength and strength decline. These findings are important



because they confirm key mechanisms for strength decline, which contribute to poor function,<sup>299,300</sup> disability,<sup>121,301</sup> and other major health outcomes<sup>302-305</sup> in older adults. Clearly factors other than decline in lean mass contribute to strength loss,<sup>21,71</sup> yet prior to this, the complex longitudinal relationship between strength and measures of motor and sensory nerve function had not been demonstrated in an aging cohort.

In our study population, Strotmeyer and colleagues<sup>21</sup> found that both sensory and motor nerve function measures were cross-sectionally associated with strength. The mechanisms for sensory and motor nerve involvement are undoubtedly different and our longitudinal data offers some insights. Motor nerves carry signals to the muscles and are responsible for movement, while sensory nerves carry external stimuli to the brain or spinal cord. Afferent (sensory) input may be necessary to achieve proper placement, timing, and movement of the leg during testing, since severe sensory neuropathy has been associated with poor ankle proprioception.<sup>295,296</sup> Moreover, experimentally blocking afferent input in healthy individuals has led to reduced maximal voluntary contractions<sup>13</sup> and suggests a direct relationship with strength. Consistent with findings from our previous work, motor amplitude, but not nerve conduction velocity was related to quadriceps strength. Low motor amplitude indicates axonal degeneration of the nerve, while low nerve conduction velocity indicates demyelination. Our findings implicate axonal degeneration in the pathology of neuromuscular weakness, particularly in women, but do not discount the important role of sensory afferents.

Motor and sensory nerve function at the initial time point predicted six-year muscle strength in women, whereas only sensory nerve function predicted strength in men. In the concurrent change analysis, poor sensory nerve function over time was consistently associated with poor strength. While early poor function seemed critical for motor amplitude and peripheral

neuropathy symptoms, transitioning to poor function seemed to be the key for vibration perception threshold. Given that these measures of nerve function are not highly correlated and each capture distinct physiologic aspects of the peripheral nervous system and the neuropathic process, it is not surprising that these different relationships with muscle strength were observed.

We also investigated the role of lean mass in these relationships. Peripheral neuropathy may include symptoms of weakness and muscle wasting in severe cases.<sup>311</sup> In addition, muscle tissue from individuals with clinical neuropathy can be characterized by smaller atrophied fibers.<sup>34</sup> Although, Lauretani and colleagues found that neither motor amplitude nor nerve conduction velocity were associated with lean mass cross-sectionally.<sup>33</sup> In our study, although lean mass was associated with strength, it did not mediate the relationship between peripheral nerve function and strength. Previous work has found a cross-sectional relationship between muscle density (a measure of intermuscular fat) and motor amplitude; therefore future work should examine muscle density as a potential mediator.

Consistent with our previous findings, we found that, compared to women, men had worse peripheral nerve function for all measures.<sup>21</sup> Slower nerve conduction velocity in men can be attributed to greater height.<sup>111</sup> We also found that men in our study population had higher rates of known risk factors for peripheral neuropathy such as diabetes, impaired fasting glucose, and vitamin B12 deficiency.<sup>249</sup> Additional disparity may be attributable to increased clinical and subclinical cardiovascular disease in men<sup>312</sup> and its effects on peripheral nerve function.<sup>100,313</sup> Although we adjusted for cardiovascular disease, blood pressure, ankle brachial index, and smoking we may not have fully captured all of the subclinical cardiovascular effects on peripheral nerve function. It is somewhat counterintuitive that while women tend to have better nerve function, they experience more late-life disability.<sup>101-103</sup> Since men tend to have

significantly more muscle mass and strength throughout life than women,<sup>58</sup> one hypothesis is that women, lacking this additional strength, are more susceptible to the negative effects of poor nerve function. Future studies are needed to investigate these neuromuscular sex differences, particularly given their likely connection to late-life disability.

This study had a number of strengths. Both sensory and motor nerve function were assessed using clinical methodology. Our measures of motor nerve function are gold standard clinical measures of peripheral neuropathy that have been found to be highly reproducible in a subset of older adults from this study cohort with interclass correlation coefficients (ICCs) of 0.90-0.99 and coefficients of variation of 2.15-4.24.<sup>65</sup> We used multiple years of prospective data from a large, multiethnic, well-characterized cohort of older men and women. We assessed change in nerve function using clinical cutpoints.<sup>314</sup> For categories created from continuous measures (motor amplitude, conduction velocity, and vibration perception) individuals with marginal change (<5%) were not considered to have transitioned from normal to poor or poor to normal, preventing those with minimal changes from biasing our results.

Moreover, our nerve change categories allowed for all directions of change, including improvement. The number of participants with improved nerve function depended on the method of measurement and ranged from n = 13 for motor amplitude to n = 179 for 1.4-g monofilament sensitivity. One potential reason for nerve function improvement may be neuroplasticity of newly mildly impaired nerves, since nerves that experience early mild damage are more likely to regain some function.<sup>315,316</sup> We found that the majority of participants improved on a more sensitive measure of nerve function, supporting this hypothesis. Another potential reason for improvement is better control of diabetes. Twenty percent of participants in this analysis had diabetes at the initial nerve exam of the study. Early intervention for diabetic and prediabetic

individuals can slow the progression of and may even improve peripheral neuropathy.<sup>317-320</sup> An additional reason for improvement of nerve function could be treatment for vitamin B12 deficiency.<sup>249,250</sup> However, our data is limited in that we do not know when these improvements occurred. These findings may be evidence of neuroplasticity of peripheral nerves in older adults, and warrant further study. Our finding that individuals improving to normal motor amplitude and experiencing reduced symptoms had worse strength may be evidence of the negative and lasting effects of early nerve function impairments and suggest the importance of early prevention and intervention, such as better glycemic control or supplementation for a vitamin B12 deficiency.<sup>249,250</sup>

Diabetes may still have independent effects on muscle strength. We found that in men, diabetes remained a significant predictor of poor strength in models with sensory nerve function measured at the initial time point, while impaired fasting glucose remained a significant predictor of strength decline in models with motor amplitude and nerve conduction velocity. In women, diabetes remained a significant predictor of strength decline in models with symptoms and average vibration detection threshold. Our results, however, were mostly consistent when we excluded individuals with diabetes in our sensitivity analysis, suggesting that the relationships we found were not driven by diabetes alone. This is consistent with what we found in our previous cross-sectional study<sup>21</sup> and is likely explained by the high prevalence of impaired nerve function that has been found in older adults without diabetes.<sup>23</sup>

One limitation is that we may have had insufficient statistical power to detect associations between strength and some nerve function change groups due to small numbers of observations in the groups. In addition, these small numbers may have prevented us from detecting sex as a modifier in the relationship between change in nerve function and strength.

Furthermore, participants who returned for follow up clinic visits were somewhat healthier than those without missing data, resulting in some inevitable retention bias.<sup>321</sup>

In conclusion, poor motor and sensory nerve function contribute to poor and declining strength in older adults. Given the high incidence and prevalence of subclinical and overt neuropathy in older adults,<sup>22,23</sup> and the current and projected future diabetes epidemic,<sup>322</sup> identifying associated risks and outcomes of poor nerve function such as muscle weakness and declines in strength is essential. Poor nerve function is likely to play an important role in the pathway to disability and future work should focus on this area. Modifiable risk factors and interventions for neuromuscular decline in late-life and optimal timing for administering these intervention are understudied areas that need to be investigated.

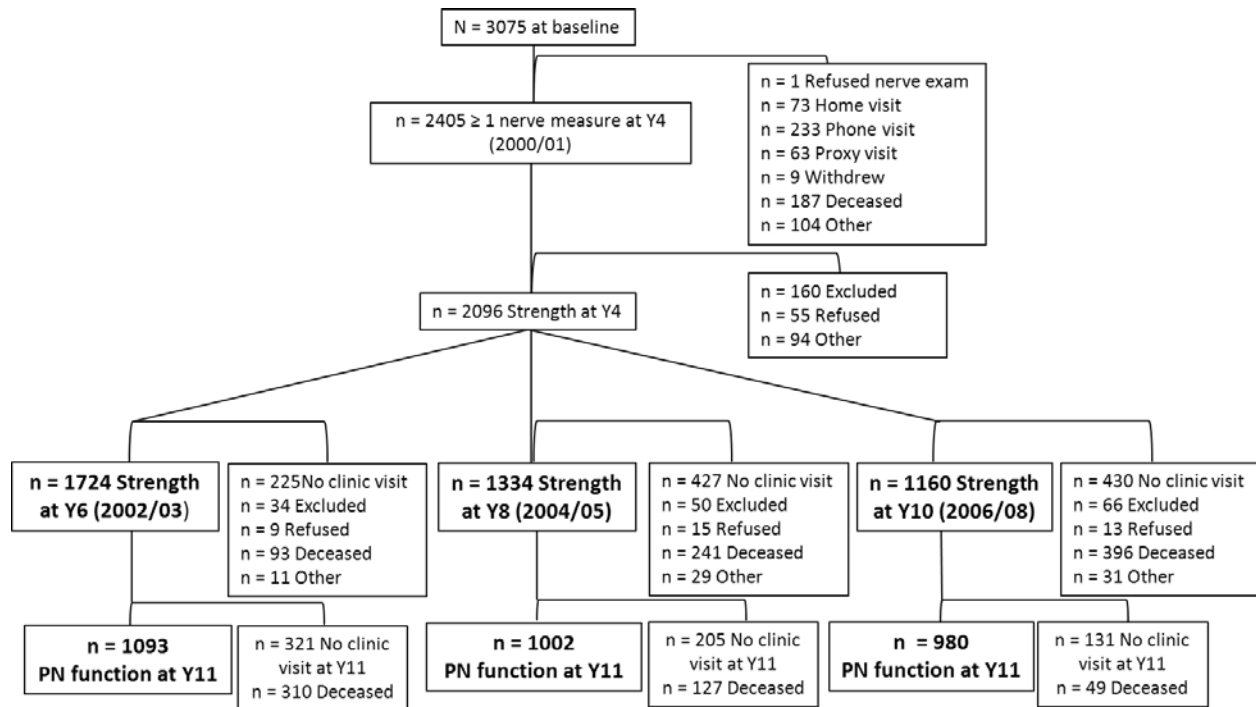
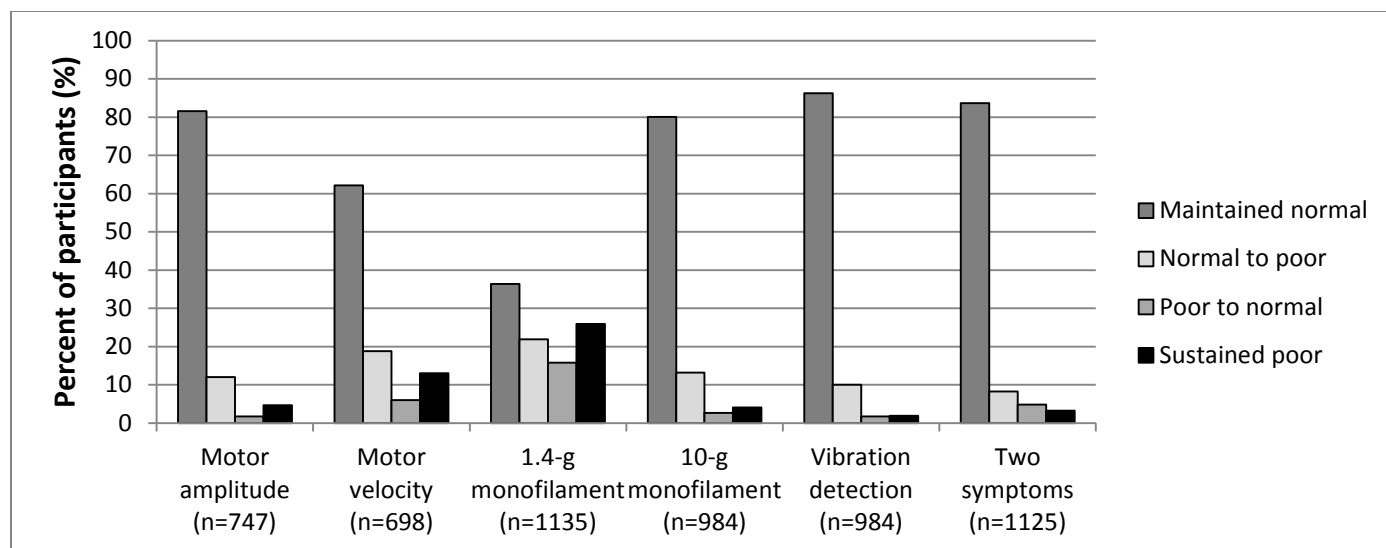


Figure 3.1 Participants with strength & nerve function



**Figure 3.2** Percent of participants in each nerve change group

Poor nerve function defined as <1 mV for motor amplitude, <40 m/s for velocity, lack of detection of 3 out of 4 touches with 1.4-g and 10-g monofilaments, lack of detection of >131  $\mu$  of vibration, reporting 2 or more peripheral neuropathy symptoms.

**Table 3.1** Participant characteristics by sex

Characteristics	Women n = 934	Men n = 896	p-value
Age, years	76.2 (2.8)	76.5 (2.8)	0.005
Black race, n (%)	367 (39.3)	270 (30.1)	<0.0001
Quadriceps strength, Nm	74.0 (21.0)	119.1 (30.8)	<0.0001
Body composition			
Height, cm	158.1 (15.0)	172.8 (8.8)	<0.0001
BMI, kg/m <sup>2</sup>	27.2 (5.3)	27.1 (3.8)	0.56
Lean mass, kg	40.8 (6.1)	56.3 (7.2)	<0.0001
Fat mass, kg	28.7 (9.1)	25.1 (7.2)	<0.0001
Lifestyle characteristics			
Current smoker, n (%)	58 (6.5)	56 (6.5)	0.99
Alcohol consumption > 1/week, n (%)	424 (46.1)	526 (59.7)	<0.0001
Physical activity, kcal/kg/week	5.0 (15.5)	6.9 (13.6)	0.004
Chronic health conditions			
Diabetes, n (%)	161 (17.4)	211 (23.9)	0.0006
Impaired fasting glucose, n (%)	118 (12.8)	174 (19.7)	<0.0001
Ankle-arm index <0.9, n (%)	126 (14.0)	120 (13.8)	0.90
Ankle-arm index >1.3, n (%)	30 (3.3)	63 (7.2)	0.0002
Hypertension, n (%)	745 (80.8)	695 (78.5)	0.23
Cardiovascular disease, n (%)	84 (9.7)	191 (23.0)	<0.0001
Cerebrovascular disease, n (%)	53 (5.8)	45 (5.2)	0.54
Knee pain most days per month, n (%)	153 (16.6)	124 (14.0)	0.13
Poor vitamin B12, n (%)	128 (14.4)	177 (20.3)	0.001

Data are means  $\pm$  SD unless otherwise specified

**Table 3.2 Initial peripheral nerve characteristics by sex**

Peripheral nerve characteristics at Year 4	Women n = 934	Men n = 896	p-value
Motor nerve function			
Amplitude, mV	3.7 (2.0)	3.1 (1.9)	<0.0001
Conduction Velocity, m/s	45.3 (5.3)	41.9 (4.9)	<0.0001
Sensory nerve function			
1.4g monofilament insensitivity, n (%)	348 (37.7)	446 (50.4)	<0.0001
10g monofilament insensitivity, n (%)	49 (5.3)	95 (10.8)	<0.0001
Vibration threshold, $\mu$	42.7 (31.4)	57.4 (36.4)	<0.0001
Peripheral nerve symptoms			
Numbness, n (%)	273 (29.5)	217 (24.3)	0.01
Pain, n (%)	173 (18.7)	106 (11.8)	<0.0001
Two, n (%)	94 (10.1)	55 (6.14)	0.002

**Table 3.3 Initial nerve function predicts longitudinal quadriceps strength in women**

	1 <sup>st</sup> Models		2 <sup>nd</sup> Models		3 <sup>rd</sup> Models	
	Betas		Betas		Betas	
	Main effect	Time interaction	Main effect	Time interaction	Main effect	Time interaction
Motor nerve function						
Amplitude, SD lower	-2.31 <sup>‡</sup>	-0.09	-2.35 <sup>‡</sup>	-0.07	-1.87 <sup>†</sup>	0.11
Velocity, SD lower	-0.29	-0.07	-1.30	-0.04	0.24	-0.11
Sensory nerve function						
1.4-g monofilament insensitivity	-3.03*	0.14	-2.68*	0.05	-2.72*	0.12
10-g monofilament insensitivity	-10.65 <sup>§</sup>	1.14*	-11.61 <sup>§</sup>	1.12*	-10.48 <sup>‡</sup>	1.02*
Vibration perception threshold	-0.03	-0.04	-0.84	0.03	0.45	-0.01
Symptoms						
One	-0.64	0.52*	-0.64	0.46*	0.06	0.35
Two	-6.54 <sup>†</sup>	0.65	-7.05 <sup>‡</sup>	0.64	-5.97 <sup>†</sup>	0.44

SD = standard deviation

\*P<0.05; †P<0.01; ‡P<0.001; §P<0.0001.

1<sup>st</sup> Models – adjusted for age, race, height, weight, site, time interactions

2<sup>nd</sup> Models – 1<sup>st</sup> Models + lean & fat mass instead of weight

3<sup>rd</sup> Models:

**Motor nerve function** – 1<sup>st</sup> Models + low and stiffening AAI, knee pain, DSST, CES-D, smoking, physical activity, renal function

**Sensory nerve function** – 1<sup>st</sup> Models + diabetes, low and stiffening AAI, knee pain, DSST, CES-D, smoking, physical activity, renal function

**Symptoms** – 1<sup>st</sup> Models + low and stiffening AAI, knee pain, DSST, CES-D, smoking, physical activity, renal function

**Table 3.4 Initial nerve function predicts longitudinal quadriceps strength in men**

	1 <sup>st</sup> Models		2 <sup>nd</sup> Models		3 <sup>rd</sup> Models	
	Betas		Betas		Betas	
	Main effect	Time interaction	Main effect	Time interaction	Main effect	Time interaction
Motor nerve function						
Amplitude, SD lower	-1.96	0.28	-1.60	0.30	-1.24	0.26
Velocity, SD lower	0.01	0.27	0.33	0.16	0.69	0.33
Sensory nerve function						
1.4-g monofilament insensitivity	-5.24 <sup>†</sup>	-0.15	-4.73 <sup>†</sup>	-0.35	-4.94 <sup>†</sup>	0.05
10-g monofilament insensitivity	-9.23 <sup>†</sup>	0.31	-8.95 <sup>†</sup>	0.12	-7.81*	0.50
Vibration perception threshold	-3.75 <sup>§</sup>	0.08	-4.41 <sup>§</sup>	0.16	-2.81 <sup>†</sup>	0.01
Symptoms						
One	-1.29	-0.42	-0.26	-0.22	0.44	-0.58
Two	-1.73	0.11	-2.28	0.63	1.48	0.02

SD = standard deviation



\*P<0.05; †P<0.01; ‡P<0.001; §P<0.0001.

1<sup>st</sup> Models – adjusted for age, race, height, weight, site, time interactions

2<sup>nd</sup> Models – 1<sup>st</sup> Models + lean & fat mass instead of weight

3<sup>rd</sup> Models:

**Motor nerve function** – 1<sup>st</sup> Models + low and stiffening AAI, stiffening AAI, cerebrovascular disease, knee pain, poor vitamin B12, DSST, CES-D, renal function

**Sensory nerve function** – 1<sup>st</sup> Models + diabetes, cerebrovascular disease, knee pain, DSST, CES-D, renal function

**Symptoms** – 1<sup>st</sup> Models + diabetes, cerebrovascular disease, knee pain, DSST, CES-D, renal function

**Table 3.5 Seven-year change in nerve function predicts concurrent longitudinal quadriceps strength**

	Maintained normal	Normal to poor		Poor to normal		Sustained poor	
		Betas		Betas		Betas	
		Main effect	Time interaction	Main effect	Time interaction	Main effect	Time interaction
Motor nerve function							
Amplitude	REF	-0.11	-0.25	-14.11*	1.51	-5.46	0.64
NCV	REF	2.59	-0.43	3.24	-0.51	2.84	0.01
Sensory nerve function							
1.4-g monofilament sensitivity	REF	1.34	-0.14	-3.12	-0.01	-5.31 <sup>†</sup>	-0.05
10-g monofilament sensitivity	REF	-1.29	-0.11	-12.42 <sup>†</sup>	0.64	-15.88 <sup>‡</sup>	1.52 <sup>†</sup>
Vibration perception threshold	REF	-10.29 <sup>‡</sup>	0.57	-6.18	0.95	-16.20 <sup>†</sup>	-0.19
Two symptoms	REF	-2.31	0.07	-7.45*	1.04*	-3.78	0.29

Model adjusted for age, race, height, lean and fat mass, site, time interactions;

Poor nerve function defined as <1 mV for motor amplitude, <40 m/s for velocity, lack of detection of 3 out of 4 touches with 1.4-g and 10-g monofilaments, lack of detection of >131 μ of vibration, reporting 2 or more peripheral neuropathy symptoms.

\*P<0.05; †P<0.01; ‡P<0.001; §P<0.0001.

#### 4.0 LONGITUDINAL SENSORY AND MOTOR PERIPHERAL NERVE FUNCTION AND INCIDENT MOBILITY LIMITATION

Rachel E. Ward,<sup>1</sup> Robert M. Boudreau,<sup>1</sup> Paolo Caserotti,<sup>2</sup> Tamara B. Harris,<sup>3</sup> Sasha Zivkovic,<sup>4</sup> Bret H. Goodpaster,<sup>4</sup> Suzanne Satterfield,<sup>5</sup> Stephen Kritchevsky,<sup>6</sup> Ann V. Schwartz,<sup>7</sup> Aaron I. Vinik,<sup>8</sup> Jane A. Cauley,<sup>1</sup> Eleanor M. Simonsick,<sup>9</sup> Anne B. Newman,<sup>1</sup> Elsa S. Strotmeyer<sup>1</sup>

<sup>1</sup>Department of Epidemiology, Graduate School of Public Health and <sup>4</sup>Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, PA, United States; <sup>2</sup>Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark; <sup>3</sup>Laboratory of Epidemiology, Biometry, and Demography, National Institute on Aging, NIH, Bethesda, MD, United States; <sup>5</sup>Department of Preventive Medicine, University of Tennessee, Memphis, TN; <sup>6</sup>Department of Internal Medicine-Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC; <sup>7</sup>Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, United States; <sup>8</sup>Department of Neurobiology, Eastern Virginia Medical School, Norfolk, VA; <sup>9</sup>Clinical Research Branch, National Institute on Aging, NIH, Baltimore, MD, United States

Corresponding Author:  
Elsa S. Strotmeyer, PhD, MPH  
University of Pittsburgh  
Department of Epidemiology  
130 N Bellefield Ave, Rm 515  
Pittsburgh, PA 15213  
412-383-1293  
fax: 412-383-1308  
[StrotmeyerE@edc.pitt.edu](mailto:StrotmeyerE@edc.pitt.edu)

(PN Function & Mobility Limitation)

## 4.1 ABSTRACT

**Importance:** Poor peripheral nerve function, which is highly prevalent in older adults, is associated worse lower extremity function and limitation. Although, longitudinal evidence is needed to elucidate sensory and motor nerve function's role in mobility disability.

**Objective:** To assess the relationship between sensory and motor nerve function over 7 years and incident mobility limitation over of 8.5 years (IQR: 4.5-9.6).

**Design:** Longitudinal analysis in the Health, Aging, and Body Composition (Health ABC) Study, a prospective cohort study designed to assess body composition and its effects on mobility limitation.

**Setting:** Two U.S. clinical sites.

**Participants:** Population-based sample of community-dwelling men and women with no mobility limitation at baseline (N=1680, age=76.5±2.9, BMI=27.1±4.6, 50.2% women, 36.6% black, 10.7% with diabetes; 30% developed limitation).

**Exposures:** Our predictors were nerve function measured at Year 4 and change in nerve function from Years 4 to 11 categorized as maintained normal, normal to poor, poor to normal, or sustained poor nerve function. Motor nerve conduction amplitude (poor <1 mV) and velocity (poor < 40 m/s) were measured on the deep peroneal nerve. Sensory nerve function was measured using 10-g and 1.4-g monofilaments and vibration detection threshold. Self-reported symptoms were assessed at the leg and feet and included numbness or tingling, sudden stabbing, burning, pain or aches, and open or persistent sores.

**Main Outcomes and Measures:** Incident mobility limitation was measured semiannually over 10 years after the initial nerve function exam and was defined as two consecutive self-reports of a lot of difficulty or inability to walk a ¼ of a mile or climb 10 steps.

Models were adjusted for age, sex, race, study site, body composition, diabetes, ankle arm index, cerebrovascular disease, knee and hip pain, osteoporosis, depression, smoking, alcohol consumption, vitamin B12 status, physical activity, and renal function.

**Results:** Initial (HR = 1.26 per SD, 95% CI: 1.12-1.41) and sustained poor motor amplitude over seven years (HR = 3.56, 95% CI: 1.63-7.76) were independently associated with incident mobility limitation. Worse initial sensory nerve function measured using vibration detection threshold (HR = 1.11, 95% CI: 1.01-1.22) and self-reported symptoms (HR = 1.47, 95% CI: 1.09-1.99) also predicted mobility limitation.

**Conclusions and Relevance:** In this cohort of older adults, poor motor and sensory nerve function were independently associated with incident mobility limitation, with the strongest hazard ratio for sustained poor motor amplitude over time. These findings suggest a role in the causal pathway towards mobility disability.

## 4.2 BACKGROUND

Poor motor and sensory peripheral nerve function are associated with measures of lower extremity function,<sup>20,27,28</sup> including gait speed, balance, chair stands, and muscle strength in older adults both with and without diabetes. These measures of physical function are predictive of activities of daily living (ADL) and mobility disability,<sup>8</sup> suggesting that poor nerve function may play a role in the late-life disablement process. Moreover, evidence shows that sensory measures and neurological signs are associated with mobility limitations.<sup>28,31</sup> These findings have critical implications for older adults, since they experience the highest burden of both poor nerve function and disability.<sup>4,22,23</sup>

While the cross-sectional evidence suggests that motor and sensory nerve function may be an important risk factor for disability, quantification of their relationship with incident mobility limitation is lacking. This longitudinal investigation will help elucidate the potential etiologic role of nerve function in the disablement process. We assessed whether initial and change in sensory and motor peripheral nerve function measured at two time points, seven years apart, predicted incident mobility limitation in a cohort of community dwelling older adults.

### **4.3 METHODS**

#### **4.3.1 Study participants**

The Health, Aging, and Body Composition (Health ABC) Study is an ongoing prospective cohort study established in 1997-1998 to study the long-term effects of body composition on disability changes in older adults (n = 3,075; 48.4% male; 41.6% black, ages 70-79 years at baseline). Participants were recruited by mail to a random sample of white Medicare beneficiaries and all black community residents eligible by age. Eligibility was determined by phone interview and included having no difficulty walking a quarter of a mile or walking up 10 steps, having no difficulty performing mobility-related activities of daily living, having no life-threatening cancers with active treatment within the past 3 years, and planning to remain in the study area for the next 3 years. Participants included in the initial nerve (Figure 4.1) had at least one nerve function measure performed at Year 4 (2000/01) of the study and no mobility limitation prior to Year 4 (n = 2148). Participants in the nerve change analysis had nerve function measured at Year 4 and Year 11 and no mobility limitation prior to Year 11 (n = 977).

### **4.3.2 Mobility limitation**

Mobility limitation was assessed semiannually during clinic visits or over the phone by either the participant or an identified proxy. Persistent mobility limitation was defined as two consecutive self-reports of a lot of difficulty or inability to walk a ¼ of a mile or climb 10 steps and will be referred to as mobility limitation for simplicity. For the initial nerve analysis, time to event was calculated as the time from the Year 4 (2000/01) nerve function exam to the first self-report of mobility limitation out of the two consecutive reports. For the nerve change analysis, time to event was calculated as time from the Year 11 (2008/09) nerve function exam to the first report out of two consecutive. Participants who did not experience mobility limitation were censored at their last date of contact or at death. If death was preceded by one or more missed contacts, information from the decedent proxy interview was used to determine any incident mobility limitation. The proxy's estimated date of onset was compared to the visit window for the missed contact and if the reported onset occurred before the end of the visit window, the incident limitation was assigned to that contact.

### **4.3.3 Peripheral nerve function**

Peripheral nerve function was measured at Years 4 (2000/01) and 11 (2008/09) of the Health ABC study by a trained and certified clinic examiner as described previously.<sup>65</sup> After the feet were warmed to 30°C, measures were performed on the right leg unless contraindicated because of knee replacement, amputation, trauma, ulcer, or surgery. If the right leg was contraindicated, measures were performed on the left leg, unless it too was contraindicated. Peroneal motor nerve conduction velocity and amplitude were measured after nerve stimulation at the popliteal fossa,

fibular head and the ankle using the NeuroMax 8 (XLTEK, Oakville, Ontario, Canada). Sensory nerve function was measured using vibration detection threshold on the bottom of the large toe with a VSA-3000 Vibratory Sensory Analyzer (Medoc, Ramat Yishai, Israel). Monofilament insensitivity, defined as the inability to feel three to four touches, was measured at the dorsum of the large toe with a 10-g standard monofilament and a 1.4-g light monofilament. Number of self-reported peripheral neuropathy symptoms were collected and coded from 0-3; these include having (1) numbness or tingling, (2) sudden stabbing, burning, pain or aches, and (3) an open or persistent sore, or gangrene on either feet or leg, all in the past 12 months. For the nerve change analysis participants were divided into one of four categories: (1) maintained normal; (2) normal to poor; (3) poor to normal; and (4) sustained poor. We used clinically meaningful cut points of <1 mV for motor amplitude and <40 m/s for motor nerve conduction velocity (NCV) to define poor nerve function. Poor nerve function was also defined as 1.4-g and 10-g touch monofilament insensitivity, lack of detection of a vibration threshold >131  $\mu$ , and reporting 2 or more peripheral neuropathy symptoms. Participants were only classified as normal to poor or poor to normal if they had >5% for continuous nerve function measures of amplitude, velocity, or vibration detection. For example a participant with a poor Year 11 motor amplitude that was <5% lower than his normal Year 4 motor amplitude would be categorized as maintained normal rather than normal to poor.

#### **4.3.4 Additional covariates**

We considered several factors known or hypothesized to be associated with both poor nerve function and incident mobility disability. All covariates were measured at the initial Year 4 nerve exam (2000/01), unless otherwise noted. We included demographics characteristics of age, sex,

race, and study site. Standing height was measured using a stadiometer and weight was measured using a calibrated balance beam scale at the initial nerve exam. Dual-energy X-ray absorptiometry (DXA; Hologic 4500A, Hologic, Inc., Bedford, MA) was used to measure total body bone-free lean and fat mass. Diabetes was defined as self-reported physician diagnosis, hypoglycemic medication use, or fasting glucose greater than 126 mg/dL [47.0 mmol/L] after an 8-hour or longer fast.<sup>306</sup> Ankle arm index (AAI) <0.9 was used to indicate peripheral arterial disease and >1.3 was used to indicate arterial stiffening. Hypertension was determined by self-report, medication use, and diastolic blood pressure  $\geq$  90 mmHg or systolic blood pressure  $\geq$  140 mmHg. Prevalent cardiovascular disease (bypass/coronary artery bypass graft, carotid endarterectomy, myocardial infarction, angina, or congestive heart failure), cerebrovascular disease (transient ischemic attack or stroke), and osteoporosis were assessed at the 1997/98 visit. Participants were also asked whether they experienced knee or hip pain on most days or for at least one month in the past 12 months (1997/98). The Center for Epidemiologic Studies Depression Scale Depression (CES-D), which was interviewer administered, was used to assess depressive symptoms. Poor vitamin B12 status was defined as < 260 pmol/L.<sup>249</sup> Smoking status (current/past) was measured during the 1999/00 visit and alcohol consumption (<1 drink/week) was measured during the 1997/98 visit. Physical activity was estimated as kcal/kg/week spent walking and stair climbing using a questionnaire. Poor renal function was defined as Cystatin-C > 1mg/dL (1997/98). Cognitive function was measured with the Modified Mini-Mental State Examination (3MSE) (1999/00), and attention, psychomotor speed, and executive function was measured with the Digit Symbol Substitution Test (DSST) (1997/98).<sup>308</sup>

For the nerve function change analysis, time varying covariates were entered into the models. Based on their relationship with mobility, these included weight or lean and fat mass



entered in place of weight,<sup>176,290</sup> weight change,<sup>323</sup> calculated using weight from the previous clinic visit, knee and hip pain,<sup>324</sup> physical activity,<sup>325,326</sup> and psychometric measures such as CES-D,<sup>327</sup> 3MSE,<sup>327,328</sup> and DSST scores.<sup>329</sup> Diabetes, impaired fasting glucose,<sup>330</sup> and AAI,<sup>255</sup> were also entered as time varying, since these variables are closely related to nerve function.

#### **4.3.5 Statistics**

Means and frequencies of baseline characteristics were calculated and assessed as potential risk factors for incident mobility limitation using bivariate Cox proportional hazards regression. Multivariable Cox proportional hazards regression was used to model the relationships between time to mobility limitation and initial and change in nerve function predictors. We will built four sets of models: (1) nerve function predictor adjusting for age, sex, race, study site, height, and weight; (2) Model 1 plus diabetes; (3) Model 2 substituting lean and fat mass for total body weight; (4) Model 3 plus other additional confounders related to either the outcome or the predictors using an alpha level of 0.1. These additional covariates were then removed from Model 4 if they had a p-value >0.1 to prevent collinearity. We also tested the interactions between nerve function variables and sex, which were nonsignificant. As a sensitivity analysis, we excluded participants with diabetes to test its influence on the associations between nerve function and mobility limitation.

## 4.4 RESULTS

After a median follow-up time of 8.5 (Interquartile Range [IQR]: 4.5-9.6) years from the initial nerve exam, 655 (30%) participants developed mobility limitation. Table 4.1 shows the characteristics of our study population. Characteristics that bivariately predicted mobility limitation included older age, female sex, black race, higher BMI and fat mass, current smoking status, diabetes mellitus, cardiovascular disease, cerebrovascular disease, hypertension, low AAI, depressive symptoms, and knee and hip pain. Characteristics that were protective for mobility limitation included participation at the Pittsburgh study site, alcohol consumption >1/week, higher physical activity and better 3MSE and DSST scores. Table 4.2 presents descriptive means and frequencies for initial peripheral nerve measures and their bivariate HR predicting mobility limitation. Figure 4.2 shows bivariate associations between change in nerve function and incident mobility limitation and the number of participants in each nerve change group.

Tables 4.3 and 4.4 show hazard ratios (HR) and 95% confidence intervals (CI) for initial and change in nerve function measures predicting incident mobility limitation. One standard deviation lower initial motor amplitude and sustained poor motor amplitude over seven years were associated incident mobility limitation when adjusting for all covariates. Declining from normal to poor motor amplitude predicted mobility limitation, although was attenuated to nonsignificant by lean and fat mass. One standard deviation worse average vibration detection threshold was also associated with incident limitation. Both sustained poor and declining to poor vibration detection threshold predicted mobility limitation, although they were attenuated to nonsignificant when adjusted for diabetes and lean and fat mass, respectively. Initially reporting one and two symptoms were associated with mobility limitation. Improving from reporting 2 peripheral neuropathy symptoms to reporting < 2 also predicted mobility limitation in the

minimally adjusted model, but was attenuated to nonsignificant by diabetes. Initially poor 1.4-g monofilament sensitivity (10-g sensitivity with 1.4-g insensitivity) was associated with mobility limitation, although the association was borderline significant and attenuated to nonsignificant when adjusted for diabetes.

When we excluded individuals with diabetes in the sensitivity analysis, initial lack of 1.4-g monofilament sensitivity no longer predicted mobility limitation. Initial vibration detection threshold was no longer a significant predictor of mobility limitation in the fully adjusted model. Transitioning from normal to poor motor amplitude and vibration detection threshold were nonsignificant in the minimally adjusted model. All other associations remained consistent with the original analysis.

## **4.5 DISCUSSION**

Using longitudinal data from a large cohort of older men and women, we quantified the relationship between sensory and motor nerve function and incident mobility limitation. Sensory and motor nerve function measured at one time point and motor nerve function measured over seven years were independent predictors of mobility limitation. Peripheral nerve function is understudied in older adults, particularly in those without diabetes, yet our sensitivity analysis shows that it is an important predictor of mobility limitation independent of diabetes status. These findings have important implications for preventing and delaying mobility disability in older adults. More research is needed on developing interventions to target modifiable risk factors related to peripheral nerve function and their effect on reducing disability. Secondary

prevention of disability in those who have already developed poor nerve function should also be investigated.

One limitation of previous studies is that they have often relied on only one measure of peripheral nerve function, usually a sensory measure.<sup>27,31</sup> Sensory and motor nerves undoubtedly play distinct roles in mobility limitation. Since overt peripheral neuropathy is partially characterized through symptoms of weakness and in extreme cases muscle wasting,<sup>311</sup> one potential mechanism for the relationship between motor nerve function and disability is the denervation of muscle fibers. Microscopic examination of muscle tissue in cases of overt neuropathy shows smaller atrophied muscle fibers and a shifting from type I slow twitch to type II fast twitch fibers due to denervation and reinnervation of muscle fibers.<sup>34</sup> These changes potentially could lead to decreased muscle strength and power.<sup>41</sup> Sensory nerve function measures such as monofilament detection and vibration detection threshold, which are also cross-sectionally associated with impaired balance, gait, and lower extremity performance,<sup>20,331</sup> may contribute to mobility limitation through loss of proprioceptive feedback.<sup>12</sup>

Initial and sustained poor motor amplitude over seven years predicted mobility limitation, while motor nerve conduction velocity did not. Previously, we showed that motor amplitude but not nerve conduction velocity was cross-sectionally related to poor physical performance and quadriceps muscle strength in this same cohort of older adults.<sup>21</sup> Low motor amplitude is indicative of axonal degeneration and impaired synchronicity of nerve firing, while low nerve conduction velocity signifies nerve demyelination.<sup>63</sup> These two measures of nerve function may not decline simultaneously, since low amplitude may result from axonal damage to a proportion of nerves, while normal nerve conduction velocity may persist, driven by the nerves that remain intact.<sup>33,76</sup> Moreover, the association between mobility limitation and motor nerve amplitude

remained the most consistent finding following adjustment for potential confounders. This finding suggests that degeneration of the motor axon likely plays a key role in the development of mobility limitation.

Sensory deficits also predicted mobility limitation even though the associations were not as robust as those seen with motor function. Associations between mobility limitation and two sensory measures, 10-g monofilament sensitivity and vibration detection threshold, were attenuated when adjusting for diabetes and nonsignificant in our sensitivity analysis that excluded participants with diabetes. This could indicate that poor sensory nerve function is particularly important for mobility limitation in individuals with diabetes. Post-hoc analysis showed that the interactions between diabetes and vibration detection threshold (HR for interaction = 1.23, 95% CI: 1.10-1.38) and diabetes and 10-g monofilament sensitivity (HR for interaction = 1.83, 95% CI: 1.32-2.55) were significant predictors of incident mobility limitation, indicating greater harmful effects of worse sensory nerve function by diabetes status.

Strengths of our analysis include that we used multiple measures of sensory and motor nerve function, including a gold standard measure of nerve conduction that we found to be highly reproducible in a sample of participants from this aging cohort.<sup>65</sup> One unique strength is that our outcome of incident mobility limitation was assessed semiannually over 10 years following the initial measurement of our predictor. Our analysis used prospective data from a large well-characterized cohort of older men and women. We assessed nerve function change by creating categories from clinically meaningful cut points that allowed for all directions of change, including sustained poor function over the seven years and improvement from poor to normal. In order to prevent minimal change from biasing our results, individuals with marginal

change (< 5%) for continuous measures were not categorized in transitional nerve function groups (poor to normal and normal to poor).

Some groups in the nerve function change analysis did have small numbers, such as the poor to normal motor amplitude (n=13) and vibration detection threshold groups (n=17) and the sustained poor vibration threshold group (n=13). Low statistical power may have accounted for lack of association and attenuation in these groups. Another potential limitation of our study is that our participants may have been somewhat healthier than the general population, given that they had no mobility limitation at the initial nerve exam. Despite this, we found that 30% of participants in the analysis of initial nerve function measures developed mobility limitation. This finding illustrates the high incidence of mobility limitation in older adults, and suggests that this rate could be even higher in less healthy populations.

Our findings confirm that peripheral nerve function plays an important role in the development of mobility limitation in late-life. The importance of our findings are highlighted by the high incidence of mobility limitation that we found in this community-dwelling population of older adults and the high prevalence of poor nerve function in older adults.<sup>23</sup> It is essential for future work to focus on the prevention of nerve function decline and subsequent disability in those with poor nerve function through known and novel risk factors.

**Table 4.1 Participant characteristics as risk factors for mobility limitation**

Characteristics	Value	HR (95% CI) for mobility limitation	P-value
Age, years	76.5 (2.9)	1.15 (1.07-1.25)	0.0002
Women, n (%)	1079 (50.2)	1.18 (1.01-1.37)	0.04
Black race, n (%)	785 (36.6)	1.25 (1.07-1.46)	0.005
Pittsburgh site, n (%)	1090 (50.7)	0.64 (0.55-0.75)	<0.0001
<b>Body Composition</b>			
BMI, kg/m <sup>2</sup>	27.1 (4.6)	1.29 (1.20-1.39)	<0.0001
Lean mass, kg	48.3 (10.2)	1.07 (0.99-1.16)	0.07
Fat mass, kg	26.5 (8.4)	1.28 (1.19-1.38)	<0.0001
<b>Lifestyle characteristics</b>			
Current smoker, n (%)	176 (8.3)	1.56 (1.21-2.02)	0.0006
Past smoker, n (%)	974 (46.2)	1.05 (0.90-1.23)	0.51
Alcohol consumption > 1/week (%)	1103 (52.4)	0.73 (0.63-0.86)	<0.0001
Physical activity, kcal/kg/week	6.3 (17.5)	0.27 (0.20-0.36)	<0.0001
<b>Chronic conditions</b>			
Diabetes, n (%)	437 (10.7)	1.63 (1.37-1.96)	<0.0001
Impaired fasting glucose, n (%)	348 (16.5)	1.02 (0.83-1.25)	0.87
Cardiovascular disease, n (%)	344 (17.4)	1.42 (1.16-1.73)	0.0006
Cerebrovascular disease, n (%)	126 (6.1)	1.87 (1.42-2.46)	<0.0001
Hypertension, n (%)	1707 (80.9)	1.66 (1.33-2.08)	<0.0001
AAI <0.9, n (%)	315 (15.3)	1.60 (1.31-1.96)	<0.0001
AAI >1.3, n (%)	105 (5.1)	1.32 (0.95-1.84)	0.09
Depression, CES-D score	5.4 (5.5)	1.30 (1.22-1.39)	<0.0001
Osteoporosis, n (%)	76 (3.6)	1.67 (1.18-2.35)	0.004
Knee or hip pain, n (%)	445 (21.0)	1.77 (1.50-2.09)	<0.0001
Low vitamin B12, n (%)	345 (16.8)	1.07 (0.88-1.33)	0.48
<b>Cognition</b>			
3MSE score	90.7 (8.0)	0.86 (0.80-0.93)	<0.0001
DSST score	37.2 (14.5)	0.83 (0.77-0.89)	<0.0001

Data are means ± SD unless otherwise specified; HR are per SD for continuous variables

**Table 4.2 Peripheral nerve characteristics at year 4**

Peripheral nerve characteristics at Year 4	Value	HR (95% CI) for mobility limitation	P-value
Motor nerve function			
Amplitude, mV	3.4 (2.0)	1.30 (1.18-1.42)	<0.0001
NCV, m/s	43.7 (5.3)	1.09 (1.00-1.19)	0.06
Sensory nerve function			
Vibration detection threshold	51.2 (35.4)	1.24 (1.15-1.34)	<0.0001
Monofilament sensitivity			
10-g, n (%)	1930 (91.6)	0.71 (0.54-0.92)	0.01
1.4-g, n (%)	1159 (54.5)	0.81 (0.70-0.95)	<0.01
PN symptoms			
Pain, n (%)	315 (14.8)	1.92 (1.60-2.31)	<0.0001
Numbness, n (%)	568 (26.6)	1.58 (1.34-1.86)	<0.0001
Sores, n (%)	34 (1.6)	1.36 (0.79-2.36)	0.27
One, n (%)	735 (34.5)	1.74 (1.49-2.03)	<0.0001
Two, n (%)	174 (8.1)	2.08 (1.66-2.60)	<0.0001

Data are means ± SD unless otherwise specified; HR are per SD for continuous variables

**Table 4.3 Initial (Year 4) nerve function predicts incident mobility limitation**

	HR (95% CI)			
	1 <sup>st</sup> Models	2 <sup>nd</sup> Models	3 <sup>rd</sup> Models	4 <sup>th</sup> Models
Motor nerve function				
Amplitude per SD lower	1.29 (1.17-1.42) <sup>§</sup>	1.29 (1.17-1.42) <sup>§</sup>	1.30 (1.17-1.44) <sup>§</sup>	1.28 (1.16-1.43) <sup>§</sup>
NCV per SD lower	1.10 (0.99-1.22)	1.10 (0.99-1.22)	1.10 (0.99-1.23)	1.11 (0.99-1.24)
Sensory nerve function				
Vibration per SD higher	1.21 (1.11-1.31) <sup>§</sup>	1.18 (1.09-1.29) <sup>§</sup>	1.20 (1.11-1.31) <sup>§</sup>	1.13 (1.03-1.23)*
Monofilament sensitivity				
None	1.27 (0.96-1.68)	1.24 (0.93-1.65)	1.31 (0.98-1.75)	1.20 (0.86-1.68)
10g	1.19 (1.00-1.40)*	1.18 (0.99-1.39)	1.20 (1.01-1.43)*	1.18 (0.98-1.41)
1.4g	Reference	Reference	Reference	Reference
Symptoms				
None	Reference	Reference	Reference	Reference
One	1.44 (1.21-1.71) <sup>§</sup>	1.42 (1.19-1.70) <sup>§</sup>	1.44 (1.20-1.73) <sup>§</sup>	1.34 (1.10-1.63) <sup>†</sup>
Two	1.44 (1.11-1.86) <sup>†</sup>	1.41 (1.09-1.82) <sup>†</sup>	1.44 (1.10-1.87) <sup>†</sup>	1.42 (1.07-1.88)*

\*P<0.05; †P<0.01; ‡P<0.001; §P<0.0001.

1<sup>st</sup> Models – adjusted for age, race, height, weight, site

2<sup>nd</sup> Models – 1<sup>st</sup> Models + diabetes

3<sup>rd</sup> Models – 2<sup>nd</sup> Models + lean & fat mass instead of weight

4<sup>th</sup> Models:

**Motor nerve function** – 3<sup>rd</sup> Models + arterial stiffening, knee and hip pain, CES-D, smoking, alcohol consumption, physical activity, renal function

**Sensory nerve function** – 3<sup>rd</sup> Models + low ankle arm index, cerebrovascular disease, knee and hip pain, osteoporosis, CES-D, smoking, physical activity, renal function



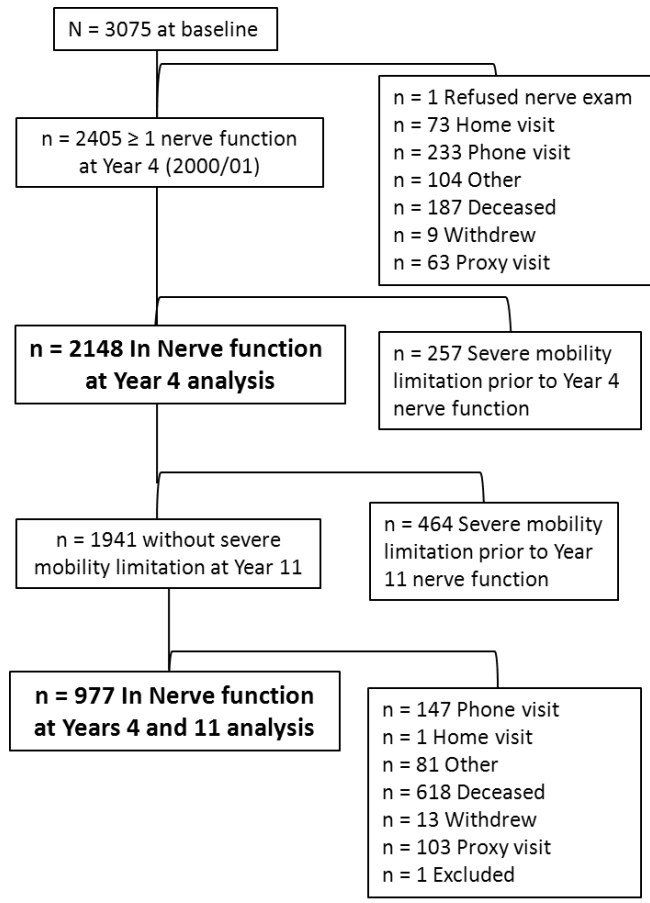
**Symptoms** – 3<sup>rd</sup> Models + low ankle arm index, arterial stiffening, cerebrovascular disease, knee and hip pain, CES-D, vitamin B12 status, smoking, alcohol consumption, physical activity, renal function

**Table 4.4 Change in nerve function (Year 4 to Year 11) predicts incident mobility limitation**

	Maintained Normal	Normal to Poor		Poor to Normal		Sustained Poor	
		HR	95% CI	HR	95% CI	HR	95% CI
Motor nerve function							
Amplitude	REF	2.02*	1.06-3.88	1.94	0.46-8.19	3.56 <sup>†</sup>	1.63-7.76
NCV	REF	1.75	0.90-3.40	1.73	0.72-4.17	1.97	0.94-4.16
Sensory nerve function							
1.4g monofilament sensitivity	REF	1.06	0.64-1.75	1.40	0.86-2.29	1.17	0.73-1.89
10g monofilament sensitivity	REF	1.52	0.94-2.44	1.07	0.39-2.94	0.56	0.17-1.80
Vibration threshold	REF	1.99*	1.11-3.59	2.45	0.96-6.25	2.90*	1.16-7.24
2 Symptoms	REF	1.94*	1.13-2.77	1.13	0.46-2.77	1.15	0.42-3.13

Model adjusted for age, sex, race, site, height, weight, and weight change;

Poor nerve function defined as <1 mV for motor amplitude, <40 m/s for velocity, lack of detection of 3 out of 4 touches with 1.4-g and 10-g monofilaments, lack of detection of >131  $\mu$  of vibration, reporting 2 or more peripheral neuropathy symptoms.



**Figure 4.1 Participants in analysis**

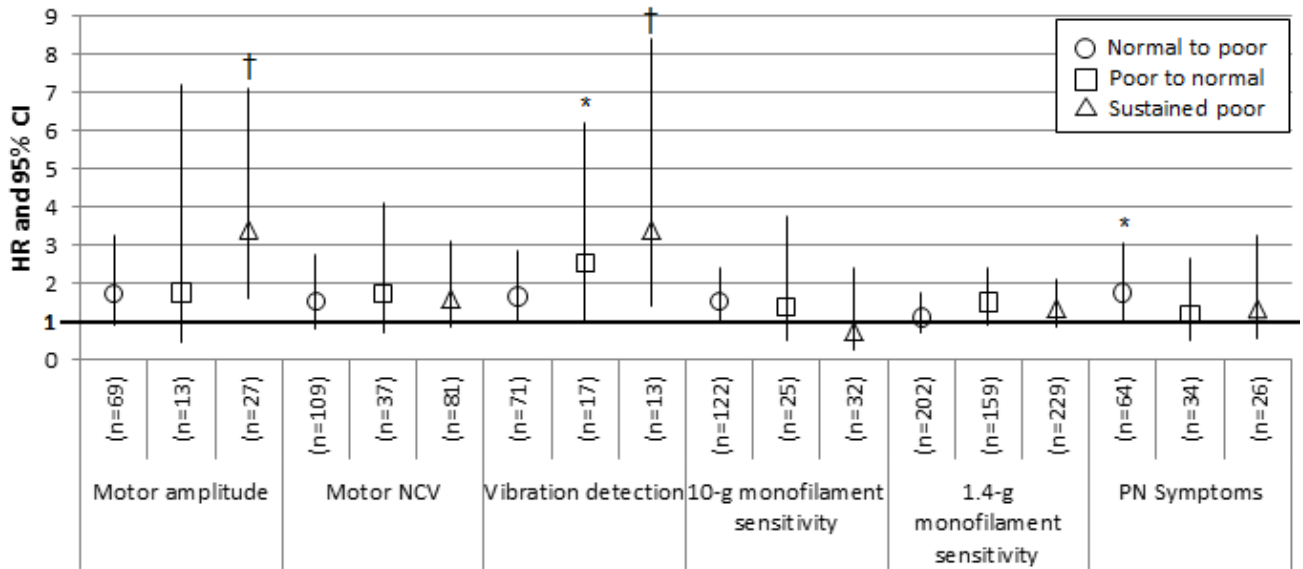


Figure 4.2 Bivariate associations between change in nerve function and mobility limitation

\*P<0.05; †P<0.01; ‡P<0.001; §P<0.0001;

Poor nerve function defined as <1 mV for motor amplitude, <40 m/s for velocity, lack of detection of 3 out of 4 touches with 1.4-g and 10-g monofilaments, lack of detection of >131  $\mu$  of vibration, reporting 2 or more peripheral neuropathy symptoms.

## 5.0 DISCUSSION

### 5.1 SUMMARY OF FINDINGS

The results of our analyses show that sensory and motor peripheral nerve function are associated with muscle power, longitudinal quadriceps strength, and mobility limitation in older adults. Findings from the MrOS study indicate that, in men, poor motor and sensory nerve function are independently associated with lower muscle power and that light monofilament insensitivity is associated with greater decline in muscle power. This was the first study to examine the cross-sectional and longitudinal associations between nerve function measures commonly used in clinical evaluations and neurologic studies and muscle power. Prior to this, it was generally accepted that decline in power was at least partly due to loss of peripheral nerve function with age, although the association between these two measures had not been tested even at a cross-sectional level. In addition, we presented the effect sizes of our nerve function predictors in terms of the effect of age and found that they were 1.5 to 3.5 times higher than one year of age. These findings contextualize the relationship between nerve function and power, since muscle power is known to decline with age at an even faster rate than strength,<sup>69,70</sup> though strength has been more widely studied in aging research. Since our study was limited to mostly white men, future studies should examine these relationships in more diverse study populations of men and women. Our follow-up time for our longitudinal analysis was only 2.3 years, therefore the

longitudinal relationships between nerve function and muscle power over a longer time period should be investigated. In addition, other methods of measuring power should be assessed since they vary by intensity of activity, availability of data, and the force-velocity ratio that comprises power.

Using prospective data from the Health ABC Study, we found that, in women, poor motor and sensory nerve function predicted lower subsequent strength and that poor sensory nerve function predicted greater strength decline. In men, however, only poor sensory nerve function predicted lower subsequent strength. When assessing concurrent change, sustained poor sensory nerve function, initial poor motor nerve function and monofilament sensitivity, and transitioning to poor vibration perception threshold were associated with lower longitudinal strength. This work is important because this was the first study to use prospective data to show that sensory and motor nerve function are predictive of subsequent strength and concurrent change in strength, indicating that poor nerve function may be an important mechanism for poor and declining strength in older adults. Because we used data from a large cohort of men and women, we were also able to identify sex as a modifier in the relationship between nerve function and longitudinal strength. These sex differences are important because they could shed light on differences in risk factors and disability outcomes between men and women. Moreover, they could suggest a need for interventions for specific impairments targeted towards each sex. Future work should further investigate these sex differences. Because we had small numbers in groups for the nerve function change analysis, these results should be confirmed in a larger population. In addition, we only measured nerve function change at two time points, seven years apart. Future studies should examine multiple time points to better characterize the timing of

peripheral nerve function and strength decline and the effect of the duration of poor nerve function.

Once again, we used prospective data from the Health ABC study, this time with the goal of assessing the relationship between sensory and motor peripheral nerve function and mobility limitation. We found that 30% of our study population had incident mobility limitation. This is a staggering proportion and likely underestimates the rate experienced by the general population given that these participants were healthy at baseline and had to visit the clinic for a nerve exam during the 2000/01 study year. Poor initial motor and sensory nerve function and sustained poor motor nerve function over seven years independently predicted incident mobility limitation. This was the first study to use multiple measures of nerve function to examine the longitudinal relationship between motor nerve function and incident mobility limitation in cohort of both men and women. In addition, the majority of research had been cross-sectional and focused on performance measures<sup>20,27</sup> or was limited to moderately to severely disabled women.<sup>27,31</sup> These findings are significant since they suggest that future work targeting modifiable risk factors for peripheral nerve function may be important for disability prevention. Secondary prevention of disability in those who already have poor nerve function is also an important future direction. Moreover, we found that these associations persisted when adjusting for known risk factors such as diabetes mellitus and poor vitamin B12, suggesting that novel risk factors should be explored.

## **5.2 PUBLIC HEALTH SIGNIFICANCE**

There is a high incidence and prevalence of poor nerve function and overt neuropathy in older adults both with and without diabetes mellitus.<sup>22,23</sup> Many adults experiencing poor nerve function

may be asymptomatic and unaware of persisting pathology. Our findings indicate that poor initial motor and sensory nerve function may lead to lower strength, power, and greater incidence of mobility limitation anywhere from two to seven years later. We found evidence of improvement from poor to normal nerve function, yet this was not always accompanied by better muscle function; this suggests that although nerve function improvement is possible, the effect on muscle function and disability may persist. Therefore, future work should not only focus on interventions for modifiable risk factors of neuromuscular impairment, but also on administering those interventions early enough to have an effect. Light (1.4-g) monofilament insensitivity was predictive of greater muscle power decline. Future works should examine whether this simple test can be used as a screener to identify those who may be at risk for muscle power decline and whether it should be included as part of routine geriatric assessment. In addition, understanding the role of neuromuscular parameters in the disablement process may help to identify multiple points of intervention. The effects of known risk factors for poor nerve function such as diabetes and vitamin B12 deficiency and novel risk factors should be studied on muscle function and ultimately on mobility disability. In addition, interventions targeted at increasing muscle strength and power should be investigated in individuals with poor and at risk for poor peripheral nerve function, with the goal of preventing subsequent disability.

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