**PERIPHERAL NERVOUS SYSTEM FUNCTION, PHYSICAL ACTIVITY
AND PHYSICAL FITNESS IN OLDER ADULTS**

by

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ABSTRACT

Peripheral nervous system function (PNS) impairments are often unappreciated as risk factors for major geriatric outcomes. This dissertation aimed to examine the mechanism of these consequences of poor PNS function. The relationships of sensorimotor peripheral nerve function and physical activity (PA), longitudinal physical fitness assessed via endurance walking performance, and the associations with cardiac autonomic function were investigated. Lower-extremity sensorimotor impairments have been linked to poor mobility-related outcomes, while cardiac autonomic impairments are associated with increased risk of cardiovascular outcomes and death. Ultimately, both divisions play important roles in the ability of older adults to be physically active and remain independent. Diabetes-related PNS impairments may present challenges for maintaining PA and endurance, though this work has not been extended to age-related PNS dysfunction. In addition, sensorimotor and autonomic function are rarely examined together, despite being components of the same system.

First, worse sensorimotor peripheral nerve function in older men from the Pittsburgh site of the Osteoporotic Fractures in Men Study was found to be associated with lower levels of self-reported and objectively measured daily PA. In particular, worse amplitude, which indicates axonal degeneration, was associated with lower levels of objectively measured activity. In the Health, Aging and Body Composition Study (Health ABC) sensorimotor peripheral nerve

impairments were related to lower physical fitness, evident through slower endurance walking and greater rate of slowing over six years of follow-up. Those with sensory peripheral nerve impairments completed the long distance corridor walk approximately 15 seconds slower than those without impairments, and these impairments had an additional four seconds of slowing per year. Finally, in Health ABC worse lower extremity sensorimotor function was associated with poorer cardiac autonomic function.

PNS impairments appear to play major roles in the disability pathway in old age and warrant further study. These findings suggest possible novel mechanisms for these associations, including lower PA, fitness and endurance, and cardiac autonomic function. Helping older adults maintain their health and physical function is a major public health priority. Interventions aimed at promoting PA in those with PNS impairments may be beneficial for reducing poor outcomes in older adults.

TABLE OF CONTENTS

LIST OF TABLES

xi

LIST OF FIGURES

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1.0   INTRODUCTION

Declines in aerobic fitness and associated cardiorespiratory changes are hallmarks of the aging process [1-7]. Previous studies have suggested that aerobic fitness peaks in the early to mid-20s and decreases thereafter, with the steepest decline observed after the age of 45 [5,7-11]. Age-related declines in maximal heart rate, forced expiratory volume, and lean body tissue seem to explain much of the observed aerobic fitness deterioration [12-14]. Low aerobic fitness can lead to functional limitations and disability [15], and is associated with increased risk of all-cause mortality [16,17].

Though physical activity and exercise are known to increase physical fitness [18-20], many reasons exist as to why adopting an active lifestyle is difficult—particularly for older adults [21].   Behavioral scientists have played an integral role in developing lifestyle interventions aimed at increasing physical activity (PA) for the prevention and treatment of diabetes [22], obesity [22,23] and other conditions, however, the general population remains primarily inactive [24]. This inactivity is even more pronounced in older adults [25], who are often cited as the least active age group [24,26]. Exploring the impact that conditions associated with aging have on exercise and PA participation, and conversely, the impact that activity can have on these conditions remains a necessary area of investigation.   Inactivity can lead to reduced aerobic fitness, which can then lead to a downward spiral of further inactivity and reduced fitness, making even simple daily activities taxing and fatiguing [27].   Due to the

heterogeneity of older adults in terms of health status and functional ability, strategies to increase activity specific to certain prevalent conditions will be valuable for increasing PA overall in older adults.

Damage to the peripheral nervous system—which encompasses the autonomic and sensorimotor divisions—occurs during the aging process, even in the absence of diabetes [28-30]. Sensorimotor peripheral nerve function is worse in old age, and lower sensorimotor peripheral nerve function in older adults is related to worse lower extremity function [31-34], bone density [35], strength [36] and power [37], as well as an increased risk for falls [38-41]. Age-related impairments in autonomic function negatively impact cardiovascular system function [42]. However, the relationship between exercise and physical activity participation with these impairments has been largely unexplored, despite the potential for exercise and PA participation to influence each of these outcomes. PA could potentially be in the pathway between peripheral nerve function impairments and worse lower-extremity and cardiovascular outcomes. Some work has been done in investigating the influence of nervous system function on PA and physical fitness, but this work has primarily focused on central nervous system function [43-47] or specific neurologic disorders, like Parkinson disease [48,49] and multiple sclerosis [50,51]. The association between the peripheral nervous system and PA or fitness on the other hand, remains a relatively unexplored area. Figure 1 outlines the conceptual model linking physical activity, physical fitness, and the contribution of peripheral nervous system in older adults. The purpose of this dissertation is to identify and address gaps in the literature pertaining to peripheral nervous system function in older adults and its association with physical activity and fitness.

Lower Extremity Sensorimotor Nerve Function Impairments

Gait and muscle function changes

↑ Age

↓ Physical Activity

↑ Sedentary Time

•Metabolic disturbances

•CVD Risk Factors

•↑ Body Fat

•↓ Lean Mass

↓Physical Activity

↓ Aerobic Fitness

↓Endurance

Major Geriatric Outcomes:

•Falls

•Mobility Limitations

•Disability

• Death

Cardiovascular Autonomic Nerve Function Impairments

↓Ability to adapt to stimuli

Figure 1: Conceptual Model for the Relationship between the Peripheral Nervous System, Physical Activity, and Physical Fitness in older Adults

1.1 PERIPHERAL NERVOUS SYSTEM OVERVIEW

The peripheral nervous system (PNS) includes the nerves and ganglia outside of the brain and spinal cord. These nerves control automatic functions of the body and provide information to the central nervous system about the external environment. The PNS is divided into two distinct divisions: the sensorimotor division which provides awareness of and response to

surroundings and the external environment to the through sensory and motor nerves, and the autonomic system which is largely responsible for monitoring and maintaining the internal environment of the body. The autonomic nervous system controls the automatic functions of the body, including regulating heart rate and blood pressure, bronchial dilation and contraction, among other functions of the internal organs. The autonomic nervous system is then further divided to the sympathetic, parasympathetic, and enteric divisions. The sympathetic and parasympathetic divisions are responsible for automatic functions that help the body to either prepare the body to respond to a stimulus or help the body conserve energy. Typically, actions of the sympathetic division are those that are related to the "fight or flight" response while the parasympathetic division is associated with the "rest and digest" state. Both divisions are equally important and exist in a crucial balance. The third portion, the enteric division, is also known as the intrinsic division and exists in the lining of the gastrointestinal system and is the focus of the field of neurogastroenterology.

1.1.1 Diseases Associated with Peripheral Nervous System Dysfunction

While the central nervous system is protected by the spine, cranium, and blood-brain-barrier, the peripheral nervous system does not have these protections and can be vulnerable to chemical and mechanical injuries. A large research focus exists regarding damage to the PNS caused by diabetes, although PNS impairments can arise during the aging process even in the absence of diabetes [29-31,42], and these impairments are often asymptomatic [30]. Other conditions that result in PNS damage include cancer treatment [52], Vitamin B12 deficiency [53,54], long-term alcohol abuse [55], multiple sclerosis [56], Parkinson's disease, spinal cord

injuries, HIV [57-59] and AIDS [60], Guillain Barre Syndrome [61], heavy metal [62,63] and toxic chemical exposure [64], and surgery or injuries involving the nerves.

1.1.1.1 Similarities to Peripheral Arterial Disease

Deficits in sensorimotor nerve function often result in loss of sensation or pain in the extremities, though early and advanced stages of nerve function impairments may be asymptomatic. While peripheral nervous system dysfunction can impact the upper extremities, the lower extremities are the focus when considering outcomes related to mobility. Sensorimotor nerve dysfunction may have parallels to damage that occurs during peripheral arterial disease (PAD). Although PAD impacts the lower extremities through vascular pathways rather than through the nervous system, both PAD [65-68] and sensorimotor nerve function impairments impact lower extremity function [31,34]—a cornerstone for maintaining mobility. Much has been explored regarding the benefits of physical activity and PAD [69,70] and it is recognized that PAD may make physical activity and exercise participation difficult [71]. In particular, pain associated with PAD can lead to the inability to walk long distances, which is also a concern with sensorimotor nerve function impairments.

Since vasculature and nerve impairments are linked conditions [72,73], the associations between PAD and mobility can be can be used as a model for exploring the relationship between peripheral nervous system function and mobility. Work by Ylitalo and colleagues in the National Health and Nutrition Examination Survey (NHANES) indicates that the 2.5% of the U.S. population age 40 and older have both sensorimotor peripheral nerve impairments (defined as 10g monofilament insensitivity) and PAD [74]. Under half (48.8%) of those with both sensorimotor impairment and PAD have diabetes. In this study, those with both conditions were significantly older than those with neither PAD nor peripheral nerve impairment (age 66.4 ± 2.5

vs. 56.2 ± 0.3 years, p<0.001). Exercise induced lower limb ischemia is a common symptom in peripheral arterial disease. Evidence exists that those with this ischemia have worse sensory nerve function, and the sensory nerve abnormalities may be linked to the ischemic pain felt during exercise [75]. Extensive work has been done in examining in the association between PAD and lower extremity difficulties, and this work could serve as a framework for future studies in lower extremity sensorimotor peripheral nerve impairments.

1.1.2   Autonomic Nervous System Function and the Cardiovascular System

In contrast to sensorimotor neuropathies which impact the extremities, autonomic nerve function impairments includes damage to the nerves that carry information from the brain and spinal cord to the heart, bladder, intestines, sweat glands, pupils, and blood vessels. Autonomic nerve function impairments lead several conditions, including digestive system issues (vomiting, constipation, diarrhea, problems swallowing), urinary incontinence, unusually small pupils (usually occurring only in one eye), and heat intolerance, which is related to sweating and blood vessel contraction/dilation and sweating issues [76]. Autonomic nerve function impairments affect many organ systems, but damage to the autonomic nerves in the cardiovascular system is the form that can most greatly affect exercise and physical activity participation. Cardiac autonomic neuropathy is associated with increased mortality [77], sudden cardiac death [78], and silent myocardial infarction [79,80]. Due to the major outcomes associated with cardiac autonomic nerve function impairments, they are often considered to be the most serious form of damage to the autonomic nervous system [81]. Like nerve impairments impacting the sensorimotor nerves, autonomic nerve function impairments are often undiagnosed in older

adults [81]. However, the impact of cardiac autonomic nerve function impairments on geriatric mobility outcomes is largely unknown.

Though sensorimotor and autonomic nerve impairments are seemingly very different, both play crucial roles in the ability for older adults to be physically active and maintain functional independence. Sensorimotor nerve dysfunction may adversely affect the ability to use the lower extremities, while the impairments in autonomic system function may lead to the inability to the cardiovascular system to respond appropriately to exercise.

1.2   SENSORIMOTOR PERIPHAL NERVOUS SYSTEM FUNCTION IN OLDER ADULTS

The sensorimotor division of the peripheral nervous system consists of sensory nerves which detect touch, temperature, pain, vibration, and other sensations, while motor nerves relay signals from the central nervous system (CNS) that allow for voluntary movement. The sensory nerves relay information about the environment to the CNS for integration, which then in turn sends impulses via the motor nerves to lead to motion in response to the environment.

Many methods are used for testing sensorimotor nerve function. Ideally multiple tests should be used together in order to get a complete picture about both the sensory and motor nerves. Sensorimotor peripheral nerve function exists on a continuum, which is important to consider rather than only the presence or absence of clinical neuropathy. From work examining the progression of peripheral nerve function declines in diabetes, we know that intact nervous system function is on the highest end of the continuum, followed by asymptomatic subclinical impairments [82]. Then more pronounced, clinical peripheral nerve function impairments can

occur in the absence of symptoms, or symptoms may manifest without evidence on quantitative tests. The most serious form of nerve function decline is clinical symptomatic peripheral neuropathy. Compared to diabetes, the progression from intact sensorimotor peripheral nervous system functioning to nerve impairments and neuropathy may differ for older adults. Currently, this progression has been inadequately studied in older adults.

1.2.1 Signs and Symptoms of Sensorimotor Peripheral Nerve Function Impairments

Common signs and symptoms of peripheral neuropathy in the lower extremities include prickling, stabbing, burning, or aching pain; feeling of asleep numbness; weakness or heaviness in muscles of the extremities; open, persistent sores; gangrene; foot drop (difficulty in lifting one or both feet) and sensitive skin (more common at night than during the day). Although signs and symptoms are easy to assess via self-report and are specific to the disease, some of these symptoms are not sensitive enough to truly identify those with peripheral neuropathy, peripheral nerve function impairments, or subclinical disease.

Symptoms of neuropathy are often classified as negative or positive symptoms [83], Negative symptoms include: insensitivity to touch, reduced sensitivity to temperature, loss of vibratory sensation, or decreased ability to detect sensation from a pin-prick, and are associated with damage to the large, myelinated sensory fibers. While negative symptoms may be uncomfortable, they are not painful. Positive symptoms, on the other hand, include: ongoing superficial pain, pain from light touch or light pressure or non-painful cold or warm stimulus, tingling, prickling, or burning sensation, itching, pain similar to an electric shock, "pins and needles" sensation, increased response from a painful stimulus, or any sensation of pain from a

stimulus that would not normally cause pain. Positive symptoms are indicative of damage to the thinly myelinated or unmyelinated small fibers.

Neuropathic pain differs from nociceptive pain in several ways. Nociceptive pain serves as a warning for impeding tissue damage and is important for survival. Under circumstances where the nervous system is functioning normally, intense stimuli activate nociceptor primary sensory neurons, these signals are processed in the CNS, and motor neurons illicit a response in order to remove the stimulus. Neuropathic pain, on the other hand, arises from damage to the nerves and provides no survival benefit and can lead to diminished quality of life [84]. Neuropathic pain can arise independently of a stimulus, or from hypersensitivity to a stimulus that would not normally be painful [84].

1.2.2 Epidemiology in the General Population of Older Adults

Sensorimotor peripheral nerve dysfunction is commonly seen in older adults. In particular, absent ankle reflexes and vibration sensation loss have at times been thought of as normal findings in older adults, and have been listed as such in some geriatric text books [85]. However—as in many areas of geriatric research—peripheral nervous system function changes during the aging process are being more closely examined in the context of geriatric outcomes (falls, disability, and death).

Prevalence estimates of peripheral neuropathy and nerve function decline vary greatly depending on population and definitions used. A fundamental aspect of epidemiology is appropriately determining a case definition. Unfortunately, without clear definitions of peripheral neuropathy or nerve dysfunction, describing patterns on the population level is difficult [86]. Currently, no population based studies have examined the patterns of sensory and

motor peripheral nerve function over time in older adults. Even the prevalence of clinical peripheral neuropathy is difficult to assess because not all with symptoms follow up with a health care provider or have treatment [87]. Though nerve conduction testing is useful in clinical settings for identifying damage or impairments in the sensory and motor peripheral nerves, this method is invasive, time consuming, and requires specialized training in order to conduct—ultimately making nerve conduction testing not feasible for many epidemiologic studies. Although symptoms are useful for characterizing severity of disease, an absence of symptoms does not equal an absence of disease [88]. Additionally, since early stages of the disease are often asymptomatic, peripheral nerve function impairments may not be detectable to the participant, although nerve damage may be present. Monofilament testing or vibration detection testing can be incorporated into large epidemiologic studies relatively easily, though these tests only give information on sensory deficits, not motor. Due to the difficulties, comparing prevalence estimates across studies should be done with caution.

Older age is associated with higher incidence of peripheral neuropathy, and this was measured in the Italian Longitudinal Study of Aging (ILSA). Older Italian adults age 65-84 were initially screened for distal symmetrical neuropathy, and then evaluated again after three years of follow-up [29]. A population-based sample from eight different municipalities was followed-up for 3 years, with 100 of the 3,066 participants developing clinical distal symmetrical neuropathy. The initial screening for neuropathy included two stages. The first stage involved self-reported diagnosis, self-reported symptoms and a brief neurologic exam (heel gait, bilateral Achilles tendon reflex, touch and pain sensation). Those who screened positive were then examined by a neurologist and received an extensive neurologic examination in order to determine a clinical neuropathy diagnosis. For the follow-up, cases of peripheral nerve function decline were

10

identified via telephone interview which included questions about self-reported physician diagnosis of neuropathy in the past year.

Age was a significant predictor of developing clinical distal symmetrical neuropathy, with every year of increasing age associated with a relative risk of 1.07 (95% CI: 1.01-1.14) for diabetic participants and 1.05 (95% CI = 1.02-1.09) for the entire study population. Adjusted annual incidence of distal symmetrical neuropathy was 7.9 per 1,000 person years (95% CI = 6.3-9.5) in the entire study population, 5.76 (95% CI: 4.3-7.3) per 1,000 person years for the participants without diabetes, and 32.2 (95% CI: 21.7-42.7) in diabetic participants. Baseline prevalence estimates of distal symmetrical neuropathy were 6.36% in those 70-74 years of age, 9.37 for those 75-79, and 9.32 for those age 80-84 years. A limitation to this study is that cases were initially identified using a clinical diagnosis of peripheral symmetrical neuropathy, while the follow-up involved the self-report diagnosis of peripheral neuropathy. Because many older adults with nerve function impairments may not seek treatment for symptoms or even be aware of their nerve function impairments, these rates may underestimate the true incidence in this population.

To assess prevalence of peripheral nerve function impairments in the general U.S. population, Gregg and colleagues utilized 10-g monofilament touch sensation testing and self-reported neuropathy symptom data from the NHANES 1999-2000 cycle [30]. Peripheral nerve function impairment was defined in this study as having one or more insensate area on the foot using 10g monofilament testing, though this was not a clinical diagnosis. Self-reported symptoms were also collected and included the presence of numbness, loss of feeling, or painful or tingling sensations in the feet in the past three months. Overall, 14.8% of the study population age 40+ years and 26% in the Type 2 diabetic population over 40 years old had peripheral nerve

function impairments. Nearly half of the non-diabetic participants with peripheral nerve function impairment were asymptomatic, while 62% of diabetic participants with peripheral nerve function impairment were asymptomatic. Older age was highly associated with these impairments. For participants age 40-49 years, 8.1% had peripheral nerve function impairment, compared to 28.4% of those age 70-79 and 34.7% of those age 80 and older (p<0.05 for both).

This study filled an important gap in the literature at the time by providing prevalence estimates of peripheral nerve function decline in the general U.S. population as opposed to a clinical population. Additionally, the combination of monofilament testing and symptom reporting provided important insight into the severity of peripheral nerve function impairment in the U.S. Interestingly, most participants with these impairments were asymptomatic. Peripheral nerve function impairments have often been thought of as a condition only occurring with diabetes, but this work in NHANES indicated that this is not the case.

In a study of 759 community dwelling older adults (age 65 and older) recruited from family medicine practices, the prevalence of at least one bilateral sensory deficit was 26% for those age 65-74, 36% in those age 75-84, and 54% in those age 85 years and older [85]. Sensory deficits examined in this study included light touch in the feet, vibration in the medial malleoli, position perception in the great toe and deep tendon ankle reflexes.   Only a portion of those with any sensory deficit reported symptoms of peripheral neuropathy or of impaired physical function: 28% reported numbness of extremities, 48% pain or discomfort, 31% restless legs, 44% trouble walking, and 35% reported trouble with balance, while 29% reported no symptoms. Of those reporting bilateral sensory deficits, only 40% reported having any disease or condition that is known to cause peripheral neuropathy (diabetes, vitamin B12 deficiency, chronic hepatitis, renal failure, autoimmune disease, or reporting a prior diagnosis of peripheral neuropathy). This

supports the thought that peripheral nerve dysfunction in the elderly is typically idiopathic, but using self-report diagnosis is a limitation in this study. Many of these conditions are under diagnosed, and many older adults may have one or more of these conditions without being aware.

1.2.3 Sensorimotor Peripheral Nerve Function Assessment Methods

Numerous methods exist for assessing peripheral nerve function. Methods for assessing motor and sensory function can vary greatly in terms of feasibility for clinical settings or epidemiological studies, cost, participant burden, and experience needed to administer the tests.

1.2.3.1 Nerve Conduction Studies

As mentioned previously, nerve conduction testing is often used in clinical settings to measure sensory and motor nerve function. The usual measurements taken include latency, amplitude, and duration. Latency is the time that it takes for the onset of a negative response after the stimulus; amplitude is defined as the distance between the baseline to negative peak or from the negative peak to positive peak, while the duration is the time from the onset of the negative or positive peak until return to baseline. The distance between two stimulus points and proximal and distal latency to negative peak in milliseconds, are then used to calculate mean conduction velocity (m/s). F-waves can also be studied via nerve conduction testing. In contrast to sensory and motor nerve conduction studies that examine the conduction velocity along a limb segment, F-waves represent the action potential traveling from the simulation site to the spinal cord's ventral horn, and back to the stimulation site. F-wave conduction velocity is

calculated using the distance from the stimulation site to the corresponding spinal segment (this distance is multiplied by two since the action potential must travel back to the stimulated nerve).

In the lower extremity, sensory nerve conduction testing is often done at the sural sensory nerve, while motor nerve conduction testing is done at the peroneal motor nerve or tibial motor nerve. Nerve conduction testing is only able be done for large, myelinated nerve fibers. Motor nerve conduction methods are sensitive, specific, and have moderate to high reproducibility in older adults [89].

Nerve conduction impairments often preclude clinical symptoms and may be the first objective indications of the disease, making them especially important for assessing subclinical disease [82]. However, nerve conduction studies are time consuming in clinical or epidemiologic settings, and the absence of a sural nerve response is common in older adults. Administering these tests also takes a considerable amount of education, training and experience, and inaccuracies in measurement technique may also lead to considerable error in the measurements [90,91]. F-wave analysis is particularly complicated, mostly because several stimuli are required in order to get an accurate measurement. Computerized automated analyses are considered to be feasible and reliable alternatives to analyzing F-wave latencies [92] and other measures of nerve conduction. However, established clinical cut-points of function cannot be used with measurements from automated methods.

1.2.3.2 Quantitative Sensory Testing

Quantitative sensory testing involves using a specific sensory stimulus (touch, temperature, pain, or vibration) to invoke a response from a specific nerve pathway. These testing techniques are considered semi-objective because they rely on a patient's response to the stimulus. This response-dependent testing may be an issue in the oldest-old where cognitive

decline may influence the participant's ability to accurately respond to the stimulus. These tests can be done using a variety of stimuli, a cotton swab, light touch from a finger, or 10-g monofilaments. Although using more than one monofilament, a light (1.4-g) and standard (10-g) monofilament, for example, allows investigators to categorize participants by having light touch sensitivity (1.4g) or standard insensitivity (10g), the use of a single monofilament (typically 10g) is common. The monofilaments are often touched to specific locations on the foot or great toe, and the participant indicates if the touch is detected. However, no standard protocol for monofilament testing exists, particularly in regards to number of touches or location of the foot, which is an issue in research and clinical settings.

Vibration perception threshold tests are also used for sensory nerve function testing, and these tests can be quickly and easily administered in a research or clinical setting. Higher perception threshold values indicate worse sensory nerve function. Quantitative sensory testing is used for evaluating the function of small sensory nerves. Vibration threshold testing can be done using an automated device or with tuning forks. The Vibratron is a device where an individual rests his or her foot on a small platform that has a small post that vibrates under the great toe. The voltage gradually increases and the participant indicates when he or she feels the vibration, and the participant is not told when the vibration will begin. Higher vibration perception threshold indicates worse peripheral nerve function. However, because the participant is instructed to indicate the exact moment when he or she feels the vibration, scores can be influenced by reaction time.

Vibration threshold testing may be done using a tuning fork, and tuning fork tests can either be qualitative or quantitative in nature. For the qualitative method, an examiner taps a 128 Hz tuning fork on a hard surface and then touches the tuning fork to a location on the

participant's body. The perceived vibration of the participant is then compared to examiner. Although this method is easy and is done quickly in a clinical setting, it has not been well validated and is examiner dependent. Questions remain about the reliability, sensitivity, and specificity of this method. The quantitative method, on the other hand, involves using a Rydel-Seiffer 64 Hz tuning fork [93]. This device has two triangles that intersect at different points with different vibration amplitudes from the tuning fork. The intersection point of the triangles moves from 0-8 with decreasing vibration amplitude. The participant indicates when he or she no longer feels the vibration, and the score is the value of where the triangles are intersecting. A sum score of 4 on bilateral toe testing indicates abnormal vibration threshold. The qualitative method takes no additional time compared to qualitative tuning fork method, but has been shown to be better associated with sensory nerve action potential amplitude in a patient population of middle-aged to older adults with Waldenström's macroglobulinemia and non-diseased controls [93].

1.2.4 Risk Factors for Sensorimotor Peripheral Nerve Function Impairments

In general, peripheral nerve function dysfunction or impairments in older adults are idiopathic in nature with no clear cause aside from aging itself. In older adults who are seen in specialty clinics, a specific cause of neuropathy is often determined [94]. However, those who are seen at specialty clinics often have severe symptoms or worse cases of peripheral neuropathy. Likely, a large proportion of older adults are not seen in a primary care setting for their peripheral nerve impairments, much less in a specialty setting [87]. Despite this, several risk factors have been identified in epidemiologic studies related to peripheral nerve impairments and

clinical neuropathy, both in the general population and specifically for populations with diabetes. These risk factors are described in detail in Table 1.

From a demographic standpoint, older age [29,30,95], male sex [30], black race [30], and Hispanic ethnicity [30] are associated with a higher prevalence of peripheral nerve impairment in the general population. Taller height is associated with higher prevalence of peripheral nerve impairment due to neuronal length [96]. Because men are often taller than women, the higher prevalence of peripheral nerve impairment in men compared to women is largely related to height differences. Racial and ethnic differences are often attributed to the higher prevalence of diabetes and other cardiometabolic risk factors in some racial or ethnic minorities compared to whites.

 Cardiovascular risk factors [97], obesity [74,98], coronary heart disease [99], and peripheral artery disease [99] have been found to be associated with worse peripheral nerve function in epidemiologic studies. In some studies, statin use has been associated with worse peripheral nerve function [97,100]. However, the association of statin use and peripheral nerve function impairments has been controversial, with some studies finding a protective effect of statins on the development of peripheral neuropathy [101]. Statins lower cholesterol, a fundamental component of the protective myelin sheath on an axon, which is one of the hypothesized mechanisms by which statin use is associated with worse peripheral nerve function. Statins are among the most commonly used medications by older adults [102], which highlights the importance of determining whether statins cause significant harm to the nervous system, and whether risks of these medications outweigh the cardiovascular benefits.

In addition to conditions related to the cardiovascular system, knee osteoarthritis is another common condition in older adults that is associated with potentially worse peripheral

nerve function [103]. Pain arising from osteoarthritis has traditionally been considered to be nociceptive, however, recent evidence has suggested a contributing role of sensory nerve fiber damage in osteoarthritis. In a cohort of patients with knee osteoarthritis (n=92, age 70.3 ± 8.0 years), knee pain was evaluated in order to determine whether the pain was neuropathic in nature (determined by using painDETECT, a peripheral neuropathy questionnaire) [104]. In this cohort 5.4% were classified as having neuropathic pain in their osteoarthritic knee, with an additional 15.2% as having probably neuropathic pain. Presence of neuropathic pain was associated with later stages of osteoarthritis.

From a nutritional standpoint, low vitamin B12 [53] and high homocysteine [54] have been shown to be associated with poorer peripheral nerve function in older adults. Excessive alcohol use [105], which is often linked to poor nutrition and dietary habits, also can lead to nerve damage [106]. Currently, it is unclear whether alcohol has an independent effect on nerve function or whether damage occurs through nutritional pathways [106].

Table 1: Risk Factors for Sensorimotor Peripheral Nerve Function Impairments Identified in Epidemiologic Studies

Risk Factor	Study Population	Outcome Definition	Magnitude of Relationship
Age	Older Italians (Age 65-84)	At baseline, peripheral neuropathy was clinically diagnosed. Follow-up cases were ascertained via self-report diagnosis.	Each year of older age associated with a RR of 1.07 (95% CI =1.01-1.14) in diabetic participants for developing neuropathy and 1.05 (95% CI= 1.02-1.09) in the entire study population of older Italians [29].
	NHANES (Age 40+)	Peripheral nerve function impairment: 1 or more insensate area on monofilament testing using a 10-g monofilament at a total of six sites on the foot.	Prevalence of peripheral neuropathy was higher in older age groups. Prevalence of peripheral neuropathy was 8.1% in those 40-49 years, and 34.7% in those 80+ years [30].
	Women's Health and Aging Study participants (n=894, Age 65+)	Vibration perception threshold measured using the Vibatron II. Nerve function values defined as: Normal = <3.43 units; Mild dysfunction = 3.43 to <4.87; Moderate dysfunction 4.87 to <6.31; Severe dysfunction ≥6.31 units	Women who were age 85 and older were at a 6.5, 7.5, and 13.3 times greater odds of mild, moderate, and severe dysfunction compared to women who were age 65-74 years [95].
Sex	NHANES (Age 40+)	Peripheral nerve function impairment: 1 or more insensate area on monofilament testing using a 10-g monofilament at a total of six sites.	Men had a higher prevalence of peripheral nerve function impairment compared to women (18.2% vs. 12.6%, p<0.05) [30].
Race/Ethnicity	NHANES (Age 40+)	Peripheral nerve function impairment: 1 or more insensate area on monofilament testing using a 10-g monofilament at a total of six sites.	The prevalence of impairment varied across racial groups. Prevalence was 14.4% in non-Hispanic whites, 19.4% in Hispanic participants, and 21.9% in non-Hispanic black participants (p<0.05 compared to whites) [30].
Diabetes	NHANES (Age 40+)	Peripheral nerve function impairment: 1 or more insensate area on monofilament testing using a 10-g monofilament at a total of six sites.	Prevalence of peripheral nerve function impairment in diabetic participants was approximately twice that of the prevalence of the general population of U.S. adults age 40+ (28.5% vs. 14.8%, p<0.001) [30].

Table 1 Continued

Diabetes in Old Age	Women's Health and Aging Study participants (n=894, Age 65+)	Vibration perception threshold measured using Vibatron II. Nerve function values defined as: Normal = <3.43 units, Mild dysfunction = 3.43 to <4.87 Moderate dysfunction 4.87 to <6.31, Severe dysfunction ≥6.31 units	Women with diabetes were at 1.8, 2.4, and 1.6 times greater odds of mild, moderate, or severe dysfunction compared to those without diabetes [95]. (Diabetes was self-reported)
	Italians age 55 years and older (n=4191)	Those with 2 or more symptoms or polyneuropathy underwent clinical examination to confirm neuropathy. Probable polyneuropathy definition: impairment of at least 2 nerve functions (sensation, strength, tendon reflexes) in the extremities with symmetrical distribution	In the study population, the prevalence of probable polyneuropathy was 2.2% in non-diabetic participants compared to 19.0% in diabetic participants [107].
Diabetes Duration	Italians age 55 years and older (n=4191)	Those with 2 or more symptoms or polyneuropathy underwent clinical examination to confirm neuropathy. Probable polyneuropathy definition: impairment of at least 2 nerve functions (sensation, strength, tendon reflexes) in the extremities with symmetrical distribution	Longer diabetes duration was significantly associated with probable polyneuropathy among those with diabetes (p<0.001). The duration of diabetes for those without polyneuropathy was 10.0 years, compared to duration of 12.7 years for those with neuropathy. (p<0.02) [107].
Worse Glycemic Control in those with Diabetes	Diabetic veterans from an outpatient clinic (n=775, Age 65-84)	Peripheral nerve function impairment: insensitivity to 10-g monofilament at any of 9 sites on the foot.	Each 1% increase in glycohemoglobin was associated with 1.06 (p=0.031) greater odds of peripheral nerve impairment [105].
	Italians age 55 years and older (n=4191)	Probable polyneuropathy definition: impairment of at least 2 nerve functions (sensation, strength, tendon reflexes) in the extremities with symmetrical distribution (clinical diagnosis).	Among diabetic participants in this study, those with polyneuropathy had higher mean fasting blood glucose compared to those without polyneuropathy (187.1 vs. 149.0 g/dl, p<0.001) and higher mean post parandial glucose 206.2 vs. 165.4 g/dl, p=0.01) [107].

Table 1 Continued

Cardiovascular Risk Factors	NHANES (Age 40+)	Peripheral nerve function impairment: 1 or more insensate area on monofilament testing using a 10-g monofilament at a total of six sites.	Those with peripheral nerve impairment had higher triglycerides (187.0 vs. 158.5, p=0.05), larger waist circumference (105.5cm vs. 98.4cm, p<0.001) and a larger percentage had hypertension 66.9 vs. 55.3%, p=0.007) compared to those without impairment [97].
Coronary Heart Disease	Non-diabetic, elderly Italians from ILSA (n=2,512, age 74.3±5.7)	At baseline, peripheral neuropathy was clinically diagnosed. Follow-up cases were ascertained via self-report diagnosis. Clinically diagnosed peripheral neuropathy was further classified according to etiology.	A larger proportion of older adults who developed clinical idiopathic distal symmetric neuropathy had a history of coronary heart disease compared to participants who did not develop neuropathy over the 3 year follow up (25.5% vs 12.0%, p=0.04) [99].
Obesity	NHANES (Age 40+)	Peripheral nerve function impairment: 1 or more insensate area on monofilament testing using a 10-g monofilament at a total of six sites.	Obese participants (BMI ≥30) were 2.20 times more likely to have peripheral nerve function impairment compared to non-obese participants [74].
	Women age 42-52 from the Michigan site of the Study of Women Across the Nation neuropathy sub-study (n=396)	Peripheral nerve dysfunction was defined as ≤80% correct responses on 10-gram monofilament testing (10 repetitions on big toe) or ≥4 signs or symptoms on the Michigan Neuropathy Screening Instrument [108].	Each 5 unit increase in baseline BMI was associated with a 1.24 greater odds of peripheral nerve dysfunction by year 12 in the study [98].
Statin Use	NHANES (Age 40+)	Peripheral nerve function impairment: 1 or more insensate area on monofilament testing using a 10-g monofilament at a total of six sites.	Statin use was significantly associated with peripheral neuropathy in adjusted multivariate logistic regression: OR=1.3 (95% CI = 1.1-1.6) compared to those who did not use statins [97].
Low Vitamin B12	Older adults in Health ABC (n=2279, age 72-83)	Peroneal motor nerve conduction amplitude and velocity and 1.4 and 10-g monofilament testing were used to measure peripheral nerve function.	Vitamin B12 deficiency (serum B12 < 260pmol/L) was associated with a 1.50 greater odds off insensitivity to the light monofilament compared to those with normal Vitamin B12. Vitamin B12 deficiency was also associated with worse nerve conduction velocity compared to those with normal Vitamin B12, 42.3 vs. 43.5 m/sec, respectively, p=0.01 [53].

Table 1 Continued

High Homocysteine	Italian older adults in the InCHIANTI Study (n=678, age 60+)	Motor nerve conduction testing, 10-g monofilament testing.	High homocysteine was associated with worse compound motor action potential. Those with initially normal but transitioned to high homocysteine had 5.4 greater odds of not feeling the monofilament compared to those with normal homocysteine [54].
Height	NHANES (n=5,229, age 40+)	Peripheral nerve function impairment: 1 or more insensate area on monofilament testing using a 10-g monofilament at a total of six sites.	Those taller than 175.5 centimeters were at a 2.3 greater adjusted odds of peripheral neuropathy compared to those 175.5 centimeters or shorter [96].
Excessive Alcohol Use	Diabetic veterans (n=775, age 65-84)	Peripheral nerve function impairment: 1 or more insensate area on monofilament testing using a 10-g monofilament at a total of six sites.	A CAGE Alcohol score of 4 (highest possible score) was associated with an increased odds of 6.96 (0.008) of peripheral neuropathy compared to a CAGE score of 0 (lowest possible score) [105].
Peripheral Artery Disease	Non-diabetic, elderly Italians from ILSA (n=2,512, age 74.3±5.7)	Peripheral neuropathy was clinically diagnosed at baseline. Follow-up cases were ascertained via self-report diagnosis. Clinically diagnosed peripheral neuropathy was further classified according to etiology.	Peripheral artery disease was an independent predictor of clinical idiopathic distal symmetric neuropathy (HR = 2.45, 95% CI: 1.01-5.91) [99].
Renal Failure	Participants (n=135) undergoing hemodialysis	Participants underwent clinical nerve function using twenty neurophysiological parameters.	The prevalence of having an abnormal value on any of the neurophysiological tests was 84.4%, with 63% of the study population having two or more abnormal values [109].
Knee Osteoarthritis	Adults (age 53-81) with knee osteoarthritis (n=92) being seen at an outpatient clinic for knee pain.	The PainDETECT questionnaire (possible scores 0-38) was used to assess the possibility of peripheral neuropathic pain. Participants were categorized as likely having neuropathic pain (score ≥19), possibly having neuropathic pain (score 13-18) and as unlikely to having neuropathic pain (score ≤12)	In this cohort, 5.4% of participants were classified as likely having neuropathic pain, and 15.2% as possibly having neuropathic pain. Pain score was positively correlated with Kellgren-Lawrence grade, indicating that neuropathic pain may be associated with later stages of knee osteoarthritis [104].

1.2.4.1 Peripheral Neuropathy in Diabetes

Although peripheral nerve impairments arise during aging, most of the research regarding nerve impairments has been focused on nerve dysfunction that occurs with the progression of diabetes. Diabetic peripheral neuropathy (DPN) has been defined by the Toronto Diabetic Neuropathy Expert Group as "a symmetrical, length-dependent sensorimotor poly neuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemic exposure (diabetes) and cardiovascular risk covariates" [82]. Hyperglycemia is a major factor in the development of neuropathy in diabetes.[110] DPN is the one of the most frequent complication related to diabetes and poor diabetic control, with some estimates of upwards of 50% of peripheral neuropathy in older diabetic populations [88]. Neuropathic pain in diabetes has been defined as "pain arising as a direct consequences of abnormalities in the peripheral sensorimotor system" [111] and symmetrical decreased or loss of distal sensation is also common in DPN [82]. Advanced DPN is often preventable, with podiatric care, patient education, glycemic control, and cardiovascular risk factor reduction being the main targets for prevention [88].

Candrilli and colleagues utilized combined NHANES data from the 1999-2000 and 2001-2002 cycles, to describe the prevalence and burden of peripheral nerve function decline symptoms among adults with self-reported diabetes age 40 and older [112]. Using self-reported symptoms of peripheral neuropathy, the estimated prevalence of symptoms of peripheral neuropathy among this sample was 32.7% [112]. Symptoms of peripheral neuropathy were most prevalent in the 60-69 year age group among diabetic adults (34.4%), and this may have been due to a survival or participation effect. Symptoms were more prevalent in women compared to men (34.4% vs. 31.0%) and in non-Hispanic blacks (38.4%) compared to other race/ethnicity

groups (p<0.05 for all). Symptoms of peripheral neuropathy among diabetic adults were associated with an increased odds of being unable to work due to physical limitations (OR=3.32, 95% CI=1.60-6.52), and having four or more health care visits in the past year (OR=2.25, 95% CI=1.32-3.83) compared to those without symptoms. Although the ability to work may be less relevant to those past retirement age, physical limitations can threaten older adults' independence, which is a major concern in this age group.

Metabolic disorders are also associated with peripheral nerve dysfunction. In particular, diabetes is a major risk factor for peripheral nerve dysfunction in older adults [30,29,95], with longer diabetes duration [29] and worse glycemic control [105,107] being associated with worse peripheral nerve function in those with diabetes. Renal failure and poor kidney function can also adversely affect peripheral nervous system function. Uremic polyneuropathy is commonly seen in patients with chronic renal failure, and may potentially stabilize or improve with chronic dialysis treatment or renal transplantation [113]. Uremic neurotoxin accumulation is the primary mechanism of nerve damage in renal failure.

Though work in diabetes gives insights about damage that occurs to the peripheral nervous system with age, many gaps remain in the literature about the age-related nerve impairments that occur during independently of diabetes. The combined increase of the aging population and rise in diabetes prevalence may lead to much higher rates of peripheral nerve function decline in the coming years. From a public health perspective, urgency exists to understand these nerve function impairments and develop strategies to minimize them in the population.

1.2.4.2 Disease-Related Peripheral Neuropathy

Without question, diabetes is the single largest cause of disease-related peripheral neuropathy, however, other factors are known causes of peripheral neuropathy. These causes fall under a few main categories, including physical injury, systemic disease, toxic exposures, infectious and autoimmune disorders, and inherited conditions [106]. Specific diseases, conditions and the explanations of their effects on peripheral nerve function are listed in Table 2. The specific diseases and conditions that may be most relevant for older adults include kidney disorders, vascular diseases, repetitive injuries, cancer treatments and Shingles.

Table 2: Causes of Clinical Peripheral Neuropathy

General Cause	Specific Cause	Explanation
Physical Injury	Traumatic Injury	Traumatic injury can lead to nerves being severed, crushed, compressed, or stretched. In severe cases, these forces can partially or fully detach the nerve from the spinal cord.
	Repetitive Stress on Joints	Repetitive stress on joints can lead to entrapment neuropathy. The repetitive flexing of joints can damage and inflame ligaments, tendons, and muscles, thus narrowing nerve passageways.
Systemic Disease	Diabetes	Chronic hyperglycemia damages nerve tissue and is a common cause of peripheral neuropathy [82].
	Kidney Disorders	Kidneys are responsible for eliminating toxic substances in the blood. If not functioning properly, toxic substances that damage nerve tissue can accumulate.
	Vascular Diseases	Vascular damage with blood flow can deprive nerve tissue of oxygen and lead to damage.
	Vitamin Deficiencies	Certain vitamins, namely E, B1, B6, B12, thiamine and niacin play essential roles in promoting nerve function. Deficiencies of these vitamins can then in turn lead to nerve tissue damage.
	Chronic Inflammation	Inflammation of the tissue surrounding nerves can spread to the nerve itself. Additionally, chronic inflammation with swelling can lead to nerve entrapment.
	Alcoholism	Alcoholism is often associated with poor nutrition and nutritional deficiencies, with thiamine deficiency being common in alcoholism. Additionally, alcohol itself may directly damage the nerves, but this is not yet clear in the literature.
Toxic Exposures	Anticancer Drugs	Some chemotherapy drugs are neurotoxins, and damage to nerves is dependent on the cumulative dose of the drugs. Recovery from chemotherapy induced neuropathy can take a long period of time in order for nerve regeneration to occur [52].
	Heavy Metals	Arsenic, lead, mercury, cadmium are neurotoxins and can lead to neuropathy. In some cases, the neuropathy reverses when the exposure is taken away, but damage may also be permanent [62].
	Industrial Chemicals	Many solvents and volatile substances are neurotoxins, and exposure is typically seen in industrial workers.[114] These substances may also have synergistic effects when exposure and alcohol abuse occur together [64].

Table 2 Continued

Infectious and Autoimmune Disorders	Shingles, Epstein-Barr Virus, Cytomegalovirus, and Herpes Simplex Virus	This group of viruses target nerve tissue and often lead to damage to the sensory nerves.
	HIV	Neuropathic symptoms are common in HIV, and different forms of neuropathy may develop during different stages of HIV.
	Charcot-Marie-Tooth Disease	Charcot-Marie-Tooth is a condition where the genes responsible for making neurons or the myelin sheath flawed.
	Genetic Mutations	Other genetic mutations may lead to heredity neuropathies. Inherited neuropathies that present in childhood are typically severe, while those that present in early adulthood are less severe.
	Guillain-Barré	This syndrome results in inflammatory neuropathies due to the immune system attacking the nervous system.
Inherited Conditions	Charcot-Marie-Tooth disease	This disease is the most common cause of genetic-related peripheral neuropathy and is characterized by mutations in the genes responsible for the structure or function of the axon or myelin sheath [106].
	General inherited conditions	Other genetic mutations can lead to peripheral nerve dysfunction. Typically more severe mutations result in severe dysfunction that presents in childhood while less severe mutations may not present with any impairment and are typically evident in adulthood, if at all.

1.2.5 Biomechanical Impact of Sensorimotor Peripheral Nerve Impairments

Although much of the work investigating the biomechanical effects of peripheral nerve function decline has been done in diabetic populations, considerable evidence exists that peripheral nerve function impairments result in altered gait mechanics [115-120], and the adoption of inefficient and less stable gait patterns. These gait alterations include shorter and wider steps, and spent more time in the double support and stance phases, and utilize a "hip strategy" while walking by pulling the legs forward using hip flexor muscles, rather than an "ankle strategy" of pushing the legs forward using plantar-flexor muscles [116]. Many of these

27

gait abnormalities may result from the reduced range of motion at the ankle, reduced motor control, loss of sensation, and thickening of soft   tissues [115,117,118,121]. Because of the associations of gait alterations and injuries and falls [117,122-124], these biomechanical factors are likely in the pathway between peripheral nerve function impairments and reduced physical function.

1.2.6   Sensorimotor Peripheral Nerve Function and Walking Endurance

Studies examining sensorimotor peripheral nerve function and gait have typically utilized short walking courses, and little work has been done examining sensorimotor peripheral nerve function on longer courses. Walking endurance—the ability to walk for a sustained time or distance—is important for remaining active in the community. Özdirenç and colleagues compared walking endurance from a 6-minute walk test between diabetic adults (age 59.3±7.8 years) and healthy non-diabetic adults and found that the diabetic adults had significantly worse walking endurance [125]. Though the differences between diabetic and non-diabetic adults may be in part due to peripheral nerve function, this study did not include any measure of peripheral nerve function, which prevented the investigators from fully exploring the potentially reasons for the differences in endurance walking. In addition, although the 6-minute walk test is considered a valid measure of physical fitness, it has been shown that older adults are more likely to work closer to their maximal effort on the Long Distance Corridor Walk (LDCW)—an endurance walking test that was developed in the Health ABC Study [126]. In general, walking in daily activities is performed over a specific distance rather than for a specific time, making walking tests like the LDCW potentially more relevant for daily living in terms of endurance walking.

In the InCHIANTI study, faster motor nerve conduction velocity (indicating better peripheral nerve function) was associated with faster completion of a 400m endurance walking test. Though nerve conduction velocity testing allows for the examination of a range of motor nerve function, this single measure only gives a partial picture. Ideally, studies should include more than one measure, including the presence of symptoms, sensory nerve tests, and touch sensation examinations [82].

1.3 AUTONOMIC PERIPHERAL NERVOUS SYSTEM FUNCTION IN OLDER ADULTS

Autonomic nerve function impairments can affect various involuntary processes in the body, but these impairments are often overlooked in clinical settings. Compared to sensorimotor peripheral nerve impairments and neuropathy, autonomic peripheral nerve impairments are less understood and studied. However, like sensorimotor peripheral nerve function dysfunction, when autonomic nerve function dysfunction acknowledged, it is often in the context of diabetes, although changes occur in the autonomic nervous system with aging [42].

1.3.1 Cardiovascular Autonomic Neuropathy

Cardiovascular autonomic neuropathy (CAN) is a condition that arises due to damage to the autonomic nerve fibers that innervate the heart and blood vessels, which leads to the inability cardiovascular system to properly regulate heart rate, blood pressure, and vascular dynamics.

Autonomic balance is necessary for cardiovascular system regulation, the ability of the cardiovascular system to respond to stimuli, and the maintenance of homeostasis.

Autonomic balance involves the complex interaction between the parasympathetic and sympathetic nervous system and other physiologic mechanisms that keep heart rate and blood pressure functioning normally [80]. CAN results in a higher risk for cardiac arrhythmias, silent myocardial infarction and sudden cardiac death [80]. Signs and symptoms of CAN include resting tachycardia, orthostatic hypotension, and silent myocardial ischemia [127] resulting from cardiac injury from increased mitochondrial oxidative stress and calcium dependent apoptosis [128]. Exercise intolerance is also common in CAN due to the inability of the cardiovascular system to respond appropriately to stimuli. Exercise intolerance is the lack of ability to exercise for a duration or intensity that would be expected for an individual's age and condition, and may result in severe fatigue from exercise, unusual breathlessness, and muscle weakness or pain.

1.3.2 Cardiac Autonomic Function Assessment Methods

Several methods exist for assessing cardiac autonomic function. These methods vary widely in their clinical utility, feasibility, and cost.

1.3.2.1 Heart Rate Variability

Heart rate variability is the most commonly used method for assessing CAN, and decreased heart rate variability is the earliest clinical indicator of CAN [128]. Heart rate variability is defined as "the variation over time of the period between consecutive heartbeats" [129] and reflects abnormalities in parasympathetic and sympathetic function. Imbalances between the sympathetic and parasympathetic nervous system lead to changes in heart rate, with

low sympathetic and/or high parasympathetic activity leading to cardio-deceleration, while high sympathetic and/or low parasympathetic activity leading to cardio acceleration [129]. Reduced heart rate variability may be indicative of poor cardiovascular health, and is predictive of adverse cardiovascular outcomes, such as hypertension, coronary artery disease, chronic heart failure, and myocardial infarction [130].

In the collection of heart rate variability, a participant wears a standard Holter monitor, which includes an electrocardiogram (ECG). Collection periods vary, with durations short durations of 5-7 minutes to free-living data collection of 24 hours being common in the literature [82]. The ECG readings are analyzed using specialized software, with various techniques available for characterizing the data. A number of complex indices related to cardiac electrophysiology and autonomic function can be obtained through HRV measurements, depending on the analysis technique used. These methods include time-domain, geometric, frequency-domain, non-linear methods, and long term correlation, although the time-domain and frequency-domain methods are the most common. The time-domain method is based upon the intervals from beat to beat, while the frequency-domain method utilizes bands of frequency, and then the beats within each band are summed. Common time-domain indices include the standard deviation of all normal to normal intervals (SDNN), the root mean square of successive differences between normal to normal intervals (rMSSD), and the standard deviation of normal to normal intervals in a given short-term time frame (SDNN-index). Generally, higher values are considered to reflect healthier HRV, though exceptions exist.

High frequency signals are indicative of parasympathetic activity (0.15-0.40 Hz) while low frequency signals indicate sympathetic activity (0.04-0.14 Hz) [129]. In general, recordings

of shorter duration (i.e. 5-7 minutes) should be analyzed using the time-domain analysis, where longer recordings (i.e. 24 hours) should be analyzed with the frequency-domain analysis method.

Though higher heart rate variability measures are considered to reflect better cardiac functioning, in some instances this is not the case. For example, in a study of older adults from the Cardiovascular Health Study, abnormal heart rate patterns were found to be associated with elevated time and frequency domain heart rate variability indices [131]. In particular, higher rMSSD values usually reflect higher parasympathetic input, though in older adults higher values can also reflect the presence of erratic heart rhythms. Non-linear heart rate variability measures, however, can detect abnormal heart rate variability indices resulting from underlying cardiac control or function abnormalities. Poincare ratios are often used for the characterizing the degree of erratic rhythms. However, non-linear heart rate variability analysis is often much more time consuming than time or frequency domain analysis. Many older adults may have abnormal heart rate patterns, which add to the complexity of utilizing these measures in older adults.

1.3.2.2 Bedside Autonomic Function Batteries

Although heart rate variability is largely considered the gold standard for assessing cardiac autonomic function, other tests involving blood pressure or heart rate measurement can be easily utilized in the clinical setting [132]. First, orthostatic hypotension is a common indicator of CAN. As a patient transitions from sitting to standing, blood pressure drops significantly with common cut points being >20mmHg for systolic or >10mmHG drop for diastolic blood pressure [132]. Often times this can lead to dizziness, lightheadedness, or syncope, but orthostatic hypotension is commonly asymptomatic. Other measures include: measuring blood pressure during the Valsalva maneuver; heart rate during deep breathing; blood pressure response to a hand grip test, where a patient holds 30% of their maximal hand grip on a

dynamometer for 3-4 minutes; and the 30:15 ratio, where heart rate is measured 30 seconds prior to and 60 seconds after going from supine to standing. In the 30:15 ratio, heart rate should be highest at 15 seconds after standing, while 30 seconds after standing the heart rate should be close to the supine heart rate [132].

1.3.2.3 Resting Heart Rate

Resting heart rate (HR) alone is an easy performed measure used to estimate cardiac autonomic function [132]. Though resting HR can be influenced by several factors, resting HR is indicative of vagus nerve function and parasympathetic function. Elevated resting heart rate has been shown to be associated with an increased risk of cardiovascular morbidity and mortality [133-135]. Elevated resting heart rate has been shown to be associated with an increased risk of cardiovascular morbidity and mortality in numerous studies, even after adjusting for common cardiovascular risk factors. Change in resting heart rate has also been shown to predict ischemic heart disease deaths [136]. In a large prospective cohort study of 13,499 men and 15,826 women without cardiovascular disease in Norway, resting heart rate was measured at baseline and then 10 years later, with mortality follow up continuing for approximately 13 years after the second measure. After a mean follow-up of 12 ± 2 years, there were 3038 deaths, with 388 of the deaths being caused by ischemic heart disease. A change in resting heart rate of greater than 25 beats from the first to the second measure was associated with a 1.80 (95% CI 1.10-3.10) increased risk of death compared to those with a resting heart rate change of ± 5 beats.

Elevated resting heart rate is associated with poor outcomes, though the association between resting heart rate and disease is not necessarily linear. In a meta-analysis including data from three population-based cohorts of middle aged and older adults (including the Health Aging and Body Composition Study, Cardiovascular Health Study [137], and Kuopio

Ischemic Heart Disease Study), a non-linear association was found between resting heart rate and risk of heart failure [138]. Risk for heart failure was higher for those with higher heart rate, but those with very low heart rate (< 60 beats per minute) also had a higher risk of heart failure.

Although resting heart rate can give some insight on cardiovascular autonomic function, it may also be influenced by other factors, including acute illness, emotional stress, caffeine intake, and certain medications, among others. In particular, beta blockers, calcium channel blockers, and tricyclic antidepressants [139] can influence heart rate. In addition, very low heart rate in young, healthy populations is often indicative of very high fitness levels rather than autonomic imbalance. Because of this, interpreting heart rate as a measure of pure autonomic function should be done with caution.

1.3.2.4 Heart Rate during Exercise Testing

Heart rate should be variable and responsive to various situations (i.e. accelerate during exercise, and then return to normal post-exercise). Thus, measuring heart rate during exercise testing is also be useful for identifying cardiovascular autonomic function impairments [140]. Typically, to evaluate heart rate response, resting heart rate is subtracted from peak heart rate from an exercise test. Though heart rate response is often calculated from maximal graded treadmill tests, these measures can also be examined from submaximal exercise tests. To evaluate heart rate recovery, the difference between peak heart rate and heart rate after a specified rest period after testing (typically one or two minutes post-test). A delay in heart rate returning to normal after exercise has been associated with increased risk of mortality in those with CAN and diabetes [141], though heart rate changes during exercise are also associated with increased risk of cardiovascular outcomes and sudden death in healthy individuals [142].

In healthy, working men between the ages of 42 and 53 years, an increase of heart rate less than 89 beats per minute during a peak exercise test was associated with an increased risk of sudden death (relative risk = 6.18, 95% CI: 2.31-16.11) during 23 years of follow-up. Additionally, a decrease in heart rate post exercise of less than 25 beats per minute (difference between peak heart rate and heart rate measured 1-minute post-test) was associated with an increased risk of sudden death (Relative Risk= 2.20, 95% CI: 1.02-4.74). Likely, the best measures of autonomic function to consider for epidemiologic studies are resting heart rate and heart rate response and heart rate recovery during a submaximal exercise test because of their relative ease to collect and analyze without extensive equipment.

1.3.3   Risk Factors for Cardiac Autonomic Neuropathy

Presently, few studies have examined cardiac autonomic function in the general population of non-diabetic older adults. Much of the work in this area has been focused on populations with diabetes, although risk factors for decreasing heart rate variability have been identified through epidemiologic studies. In particular, older age, male sex, diabetes (fasting glucose $\geq$126 mg/dL), and the presence of other cardiovascular risk factors are associated worse measures of heart rate variability [42,143].

Stein and colleagues were among the first to analyze heart rate variability in a large epidemiologic study of older adults. In the Cardiovascular Health Study, older adults (n=585, age >65 years) had two 24-hour Holter recordings, 5 years apart to examine the change in heart rate variability. When examining the changes, it was found that autonomic cardiac function decreased the most between the ages of 65-75, with function leveling out at 75 and beyond, although overall changes were small. These changes were independent of cardiovascular risk

[42]. However, because participants had to have two visits in order for change to be analyzed, likely the healthiest older participants were able to return for a second visit. In essence, participants who were not unable to return for the visit may also have experienced larger changes in autonomic function, biasing the results towards the null.

When examining differences in heart rate variability by cardiovascular disease risk, those at higher risk for cardiovascular disease at baseline had worse heart rate variability measures after adjusting for covariates compared to those at lower risk. (Low risk for cardiovascular disease was defined as having SBP ≤140 mmHg, DBP ≤90 mmHg, no beta blockers or anti-hypertensive medications, BMI ≤ 30, no history of MI, stroke, known coronary heart disease or congestive heart failure, fasting glucose <110 mg/dl, and no hypoglycemic medication use.) Higher risk participants had lower heart rate overall, and the authors hypothesized that this was likely due to lower physical activity in the higher risk group. Because physical activity was not measured in conjunction with HRV, no confirmation was provided for this hypothesis and it remains to be tested.

In the Atherosclerosis Risk in Communities (ARIC) study [143], Schroeder and others examined the effect of diabetes on 9-year change in heart rate variability using 2- and 6-minute beat-to-beat heart rate recordings. Participants in this study were younger (45-64 years) than those in CHS, and the study sample was also larger (n=6,245 individuals with 9 year follow up data, and n=9,940 with baseline data). Diabetic participants (defined as those with fasting glucose ≥7.0mmol/L, non-fasting glucose ≥11.1mmol/L, self-reported physician diagnosis, or use of pharmacologic hypoglycemic treatment) had lower heart rate variability at baseline (R-R interval 852.69, 95% CI: 844.45-860.94, for diabetic participants vs. 916.99, 95% CI: 913.54-920.43, for participants with normal fasting glucose, p<0.05). (Normal fasting glucose defined

as <5.6mmol/L.) In those with diabetes, the adjusted mean annual change in R-R intervals was 3.88 milliseconds/year (95% CI: 2.72-5.04), compared to 6.74 (95% CI: 6.33-7.16) in participants with normal fasting glucose (p<0.05). Though these epidemiologic studies were useful for identifying changes in autonomic function, more work is needed in order to determine how changes in autonomic function over time are related to geriatric outcomes.

1.3.4 Autonomic Nervous System Function in Diabetes

Diabetes has a major impact on the autonomic nervous system. Changes in cardiac autonomic function can be detected though exercise-based CAN assessments and these abnormalities are even present in middle-aged diabetic individuals who have no evidence of autonomic neuropathy otherwise [144]. In a study of 18 middle age diabetic participants (age 55 ± 2 years) and 20 healthy controls (age 51 ± 1 years) participants underwent two 16-minute submaximal bicycle exercise tests followed by a 45 minute recovery autonomic nervous system function was measured during exercise and recovery. During the second exercise test, atropine was administered at peak exercise in order for the final two minutes of exercise and the recovery period to occur under parasympathetic blockade. Participants underwent standard CAN testing (heart rate response to deep breathing, standing, and Valsalva maneuver, and blood pressure response to standing and during sustained hand grip) to determine whether exercise based testing could uncover cardiac autonomic dysfunction in those with normal standard CAN assessments. In the early recovery period after submaximal exercise, diabetic participants had a delay in heart rate recovery compared to the controls (heart rate recovery one minute post exercise: 18.5 ± 1.9 bpm for diabetic participants compared to 27.6 ± 1.5 bpm for controls, p<0.001). Diabetic participants also had a suppressed parasympathetic effect on the RR interval during recovery

compared to controls (RR interval during recovery: 154 ± 16 milliseconds for diabetic participants vs. 211 ± 15 milliseconds for controls p = 0.004).

The diabetic participants in this study had well-controlled type 2 diabetes and had good scores on the standard CAN assessments. The fact that diabetic participants have autonomic abnormalities on exercise-based assessments but not high scores on typical CAN measures highlights the importance of measuring subclinical autonomic function. However, a limitation of this study is that the techniques used to capture reduced autonomic function (two separate submaximal exercise tests, one with parasympathetic blockade) are not feasible to use in population studies and may be inappropriate for older adults with chronic conditions (particularly cardiovascular disease risk factors) that may make this testing unsafe. Early detection of dysfunctions using techniques that are feasible for older adult populations will be important for future work in this area.

Currently, it is unclear whether tight glucose control has a long-term impact on protecting against the development of autonomic neuropathy in diabetes [80]. In the Veteran's Affairs Diabetes Trial, no microvascular benefits of intensive glucose therapy over standard therapy for veterans with type 2 diabetes, and there was a slight trend of an increase in incidence of autonomic neuropathy existed in the intensive therapy group [145]. However, the participants in this study were a relatively homogeneous group in that they were all veterans, predominantly men (97%) had a relatively long duration of diabetes (mean 11.5 years since diagnosis), and many (40%) already had a cardiovascular event. Long term studies with representative populations of older adults or those with diabetes would be needed to help address this question. The results of this study were in contrast to studies of Type 1 diabetes where better glucose control was related to a lower incidence of CAN in the Diabetes Control and Complications Trial

and Follow-up Study from baseline to study year 13/14 [146]. These contradictory results are possibly due to the "metabolic memory" effect of hyperglycemia, and that historical glucose levels may be most important factor in predicting CAN [147].

1.4   PHYSICAL ACTIVITY AND PERIPHERAL NERVOUS SYSTEM FUNCTION

The benefits of physical activity on metabolic and cardiovascular risk factors are well established and supported by leading professional organizations [26,148-150]. Physical activity may also be beneficial for peripheral nervous system function for older adults. Muscle contraction has an insulin-like effect on the body by increasing the cell membrane ability to absorb glucose from the blood [151], therefore physical activity may be an important part of reducing the damaging effects of hyperglycemia have on the peripheral nervous system. Additionally, physical activity can improve vascular and endothelial function in the lower extremities [152-154], and higher levels of physical activity participation are associated with lower levels of inflammatory markers [155,156], both of which could potentially influence peripheral nerve function.

1.4.1   Evidence of Physical Activity Improving Sensorimotor Peripheral Nerve Function

Worse peripheral nerve function may be associated with lower levels of physical activity, and in turn, low levels of physical activity could potentially lead to worse peripheral nerve function. Despite the potential for these bidirectional effects, little has been done to explore the relationship between physical activity and sensorimotor peripheral nerve function. The

relationship between sensorimotor peripheral nerve function and physical activity has not been examined in epidemiologic studies of older non-diabetic participants. Additionally, only small studies have been performed in humans examining the effects of PA or exercise training on peripheral nerve function, and these studies have been primarily conducted in populations of middle-aged diabetic populations rather than populations of older adults.

One study examining peripheral neuropathy and walking in older adults indicated that older adults with peripheral neuropathy take fewer steps per day compared to older adults without peripheral neuropathy [157]. However, from prior epidemiologic studies it is known that worse sensorimotor peripheral nerve function is associated with worse lower extremity physical functioning even without progressing to the point of clinical peripheral neuropathy [31], making it important to study a full range of peripheral nerve function. In addition, although pedometers can be useful for promoting activity in an intervention setting, pedometers only count ambulatory activity and may not accurately reflect an individual's total daily activity.

In an analysis of diabetic participants in NHANES, no direct relationship was found between peripheral neuropathy and the number of minutes spent in moderate to vigorous physical activity (MVPA) per day [158]. Nevertheless, those with better diabetic control (as measured by HbA1c) and higher levels of activity were less likely to have peripheral neuropathy compared to what would be expected from the individual effects of PA and diabetes control. In this study, the mean number of minutes of MVPA was only 11.7 minutes, which could be an explanation for the lack of association between PA and peripheral neuropathy. Though the use of accelerometer in NHANES may help provide a more accurate representation of participants' total daily activity, only MVPA was considered. Examining objectively measured physical activity at a wide range of intensities (including light intensity activity) may beneficial for

clarifying the relationship between peripheral nerve function and PA in older adults—particularly since older adults spend very little time in MVPA [25,159].

In regards to intervention studies examining change in peripheral nerve function with physical activity, Kluding and colleagues conducted a pre-test post-test design study with middle aged participants (n=19, age 58.4 ± 5.98 years) with diabetes (duration 12.4 ± 12.2 years) to determine the effects of an exercise intervention on neuropathic symptoms and nerve function [160]. The exercise program lasted for 10 weeks and included 2 days per week of aerobic exercise and 2 days of resistance training. After the training program, participants reported less pain compared to baseline on the Michigan Neuropathy Screening Instrument symptom questionnaire (5.2 points vs. 4 points, p=0.01). No differences existed after training in nerve conduction or on quantitative sensory tests. A major limitation to this study is that no control group was studied and the sample size was very small. Additionally the training program may not have been long enough to elicit positive changes in quantitative tests of motor and sensory nerve function. Despite the limitations, this study does provide important insight into the relief of neuropathy pain that could result from an exercise program. However, a controlled trial is needed before making definitive conclusions about these improvements.

A clinical trial in Italy examined the effects of a long-term exercise training program in the prevention of the development of peripheral neuropathy in type 1 and type 2 diabetic participants (n=78) without signs or symptoms of neuropathy [161]. The intervention group (n=31, age 49 ± 15.5 years) participated in a 4 hour per week treadmill-based brisk walking program for a total of 4 years. Control participants did not receive any intervention. After the 4 year trial, 8 control participants (17.0%) but zero intervention participants developed motor neuropathy (p<0.05), and 14 (29.8%) control and 2 (6.4%) intervention participants developed

sensory neuropathy. Although this is a promising result, the authors did not define sensory or motor neuropathy, limiting the interpretability of the results. However, continuous measures of nerve function were included, and peroneal motor nerve conduction improved in the intervention group (1.8 ± 2.7 m/s), while a slight decrease in motor nerve conduction (-0.6 ± 3.3 m/s) was observed in the control group ($p<0.001$ for between group differences). Similarly, there was a slight increase in sural sensory nerve conduction velocity for the intervention group (0.4 ± 3.3 m/s) while there was a decrease in sensory nerve conduction velocity for the control group (-2.7 ± 2.8, $p<0.001$ for difference between groups).

Importantly, this study was much longer than the typical exercise trial (four years total), and required a large commitment from the intervention participants (four one-hour supervised exercise sessions per week). The authors reported that all participants in both arms completed the study, and the attendance rate for the intervention was greater than 90%--adherence that is rarely seen in any kind of clinical trial. The participants in this trial were likely very highly motivated and concerned about their health in order to achieve this sort of attendance—and differed from the general population with diabetes, limiting the generalizability of this study. In addition, the participants in this study had only mild hyperglycemia, and are not representative of those with more serious disease.

Alternative modes of aerobic exercise aside from walking have been proposed as potentially beneficial for those with peripheral neuropathy. These recommendations have been acknowledged in diabetes literature, and the American College of Sports Medicine and American Diabetes Association have recommended that those with peripheral neuropathy engage in non-weight bearing activity [162]. These recommendations may be relevant to older adults with peripheral nerve impairments. In particular, non-weight bearing activity may be a safer

alternative to walking for older adults with sensory impairments or symptoms of numbness or pain in the lower extremities.

In a small (n=29) randomized clinical trial, a walking program was compared to a non-weight-bearing (NWB) exercise program for improving walking capacity (6-minute walking distance) and daily step counts (measured via pedometer) in adults with diabetic peripheral neuropathy (mean age 64.5 ± 12.5 years) [163]. The walking intervention consisted of 1-hour group sessions, 3 times a week, for 12 weeks where participants were instructed to walk to achieve specific step counts, based upon their baseline activity. Step counts were increased every two weeks. Sessions also included balance exercises and body weight resistance exercises. Participants were also instructed to walk outside of the center-based sessions. The NWB group also participated in 1-hour group sessions, 3 times a week for 12 weeks, but used performed all exercises while either lying or sitting. Participants used elastic bands for resistance exercises, and used either a stationary upright or recumbent cycle ergometer for their aerobic exercise.

After the 12-week intervention, the walking group experienced greater increases in walking endurance compared to baseline (27 more meters during the 6-minute walking test for the walking group compared to two fewer meters for the NWB group compared to baseline, p=0.014). Also, the walking group increased their daily step count by an average of 685 steps from baseline, compared to the NWB group who on average walked 493 steps fewer compared to baseline (p=0.026 comparing group differences). Although the walking group improved walking endurance and in daily step counts, the NWB group had greater improvements in HbA1c, (-0.4% compared to baseline) compared to the walking group (-0.2% compared to baseline, p=0.037 comparing group differences). The improvements in glucose control could potentially help peripheral nerve function. Additionally, during exercise, those in the NWB

group had fewer lower extremity musculoskeletal pain complaints compared to the walking group.

It is not particularly surprising that a group in a walking intervention will walk more than a group in an intervention that promotes other modes of exercise. Comparing activity of the two intervention groups using other tools (i.e. an accelerometer or questionnaire) may have given a more accurate comparison of activity between the two groups. This was a small study not powered to detect differences in secondary outcomes, and also did not measure peripheral nerve function, which are limitations to this study. However, this study provides evidence that exercise, whether through walking or NWB activity can be beneficial for those with diabetic peripheral neuropathy, although the benefits may be different for the different exercise modes. Exploring whether walking or NWB exercise is more beneficial for pain and peripheral nerve function outcomes in older adults would be an important next step considering the results of this study.

1.4.1.1 Physical Activity and Sensorimotor Peripheral Nerve Function: Animal Models

Animal models have been utilized in exploring nerve impairments and the physiologic changes that occur after exercise training. Animal work has suggested that aerobic exercise training is beneficial in reducing myelin loss in the sciatic nerves of type 1 diabetic rats (diabetes induced with streptozotocin) with neuropathy after 56 days of aerobic training [164]. In the rats that developed neuropathy, the exercise training was successful in improving motor nerve function compared to the rats with neuropathy that did not undergo the training program. Additionally, treadmill training in wild-type C57BL6 mice with injured peripheral nerves enhanced motor axon regeneration after two weeks of training [165]. These adult mice had surgical induced peripheral nerve injury, where the sciatic nerve was severed and then repaired.

Similar results were found in a study of adult Sprague-Dawley rats that had their sciatic nerve severed and repaired, comparing passive (bicycle) and active (treadmill) exercise in nerve regeneration after transaction and repair at the sciatic nerve [166]. After two months of training, both modes of training led to slight improvements in muscle reinnervation, and there was an increase in the number of regenerated axons in the distal nerve compared to the control animals. These animal studies provide evidence that exercise is beneficial for nerve and motor axon regeneration in a laboratory setting—important precursor work for examining relationships between regeneration of human nerves via exercise training.

Some evidence exists from animal studies that weight bearing aerobic exercise can potentially increase Schwann cell apoptosis in distal peripheral nerves [167]. This work was done in diabetic rats, in which rats were randomly assigned to one of three groups: an aquatic exercise group, a treadmill exercise group, and control. After 12 weeks of exercise, sural and sciatic nerves were assessed, and it was determined that the treadmill based exercise lead to the increased Schwann cell apoptosis in the sural nerves. However, no evidence exists in humans that different aerobic exercise modes differentially affect mechanical loading on peripheral nerves, although this may be an area worthy of investigation in determining ideal modes of exercise for those with peripheral nerve dysfunction.

1.4.2   Evidence of Physical Activity Improving Cardiac Autonomic Function

Physical activity and aerobic exercise are beneficial for overall cardiovascular health, and may help improve heart rate variability by improving vagal tone and decreasing sympathetic activity in the heart [130]. During aerobic activity, the heart rate accelerates in response to increased sympathetic activity and reduced vagal modulation of heart rate. After long term

aerobic training, the balance between sympathetic and parasympathetic activity shifts towards a parasympathetic predominance due to increased vagal modulation of the heart rate and in response to reduced sympathetic activity [168]. The primary autonomic nervous system adaptation with exercise training is a decrease in resting heart rate and lower heart rate at submaximal exercise [128]. Exercise training also improves heart rate variability due to increased compliance of large arteries, which leads to a higher load on barorecepter nerves, which can improve parasympathetic tone [128]. Aerobic exercise may improve vagal tone and decrease sympathetic activity [130], and also increase cortical blood flow, which improves sympathetic, parasympathetic, and central cholinergic activity [169].

Compared to evidence for exercise improving sensorimotor function, more evidence exists to support the benefit of PA and fitness to the cardiac autonomic nervous system. In general, a variety of exercise programs have been shown to improve heart rate variability—particularly in patient populations with diabetes, chronic heart failure, prior myocardial infarction, or those that undergo coronary artery bypass grafting [130]. These prior studies generally involved small sample sizes (n<50) with exercise programs ranging in duration from 2 to 52 weeks.

In one study focusing on older adults, an intensive, 14-week interval cycling training program was found to increase heart rate variability in a small sample of older men (n=11, age 73.5 ± 4.2 years) [170]. However, these older men were former trained cyclists free of any known cardiac abnormalities, and are not representative of the population of older adults. Although the intensity of this program may not be suitable for all older adults, this study supports cycling as an exercise to improve autonomic nerve function. Because cycling is a non-

weight bearing activity, this form of exercise could be beneficial for older adults who have difficulty walking.

The Diabetes Prevention Program (DPP) was a landmark phase III randomized clinical trial which compared a lifestyle intervention (PA + diet), Metformin treatment, and control for the development of diabetes in pre-diabetic adults (age 50.4 ± 10.6 years). Heart rate variability was measured at baseline and annually throughout the four year trial using a ten second 12-lead ECG segment [171]. Mean heart rate, standard deviation of all normal-to-normal R-R intervals (SDNN), and the root mean square of successive differences between all normal-to-normal R-R intervals (rMSSD) were generated for examining cardiac autonomic function. These measures did not vary between treatment groups at baseline; however, the lifestyle intervention group saw the greatest improvements in these measures over the mean follow up of 3.2 years ($p<0.05$ for all). Heart rate decreased by 4.74 beats per minute (95% CI: -5.21 to -4.27) for the lifestyle group, compared to a decline 1.88 beats per minute for the Metformin group (95% CI: -2.39 to -1.37), and a decline of 2.12 beats per minute (95% CI: -2.57 to -1.67) in the control group. For SDNN, the lifestyle group experienced an increase of 1.32 (95% CI: 0.32 to 2.34) ms, while there was no significant change for the Metformin group, and the control group experienced a decline in this measure of 1.21 ms (95% CI: -2.03 to -0.39). The lifestyle group also saw improvements in rMSSD over the follow-up period (change of 2.98 ms, 95% CI: 1.71-4.25) while there were no significant changes for either the Metformin or control groups. Although physical activity was a main component to the lifestyle intervention in the DPP, weight loss through dietary modifications was also an important part of the study. Physical activity could very well have played a major role in the heart rate variability improvements seen by the lifestyle intervention group, but weight loss and dietary changes may have also contributed.

This study was important in that it focused on heart rate variability in a population free of disease at baseline, and the fact that the PA program focused on moderate-intensity activities that could easily be adopted by older adults. Additionally, the large, multicenter design of this study improved generalizability. Though the lifestyle intervention was most effective in the prevention of diabetes in participants age 60-85 [172], the results for this study were not stratified by age, so we cannot conclude whether the improvements in heart rate variability in the lifestyle group were different across age groups.

In the Look AHEAD study, overweight adults with type 2 diabetes (n= 5145 participants from 16 study centers, age 45-75 years) were randomized to participate either in an intensive lifestyle intervention (weight loss via physical activity and dietary changes) or diabetes support and education (general recommendations about healthful eating and physical activity in type 2 diabetes) [173]. The primary purpose of the Look AHEAD trial was to assess whether the intensive lifestyle intervention was successful in reducing cardiovascular morbidity and mortality long-term.

Several measures of cardiovascular function were collected in this study, and in a paper by Ribisl and colleagues, change in heart rate recovery from baseline to 1-Year follow-up were assessed [174]. At baseline, participants underwent a graded exercise treadmill test in order to assess maximal cardiorespiratory fitness. Fitness testing was repeated at the 1-Year follow-up, though this test was submaximal. Because of the potential for certain medications, namely beta-blockers, to influence heart rate response during exercise, participants taking these medications were analyzed separately. Heart rate recovery was used in this study as a measure of autonomic function.

At baseline, no differences existed between the intensive lifestyle group vs. the diabetes education group in any measure of heart rate (resting heart rate, peak exercise heart rate, heart rate range, heart rate at 2-minutes post-test, and heart rate recovery), stratified by beta blocker use. After one year of follow-up, the intensive lifestyle intervention group not taking beta-blockers had significantly lower resting heart rate, higher heart rate range, lower heart rate at 2-minutes post-test, and better heart rate recovery compared to those not taking beta blockers in the diabetes support and education group. These relationships were also observed between the intensive lifestyle intervention group and diabetes support and education group in those taking beta-blocker, though the associations were not as strong. Though the effects of weight loss, dietary changes, and physical activity cannot be teased apart in this study in terms of which had the largest effect on autonomic improvement, this study provides evidence that cardiac autonomic function can be improved via an intensive lifestyle intervention for those with type 2 diabetes. Physical activity interventions appear to be promising for improving cardiac autonomic function, though more work is needed to determine the effect for older adults.

1.5   PHYSICAL ACTIVITY AND OLDER ADULTS

Throughout history—with the exception of the past few decades—humans had little choice but to live active lifestyles in order to survive. Although modern life is astronomically different from that of our Stone Age ancestors, in a biologic and metabolic sense we are still programmed for their way of life. From an evolutionary standpoint, optimization of aerobic metabolic pathways was advantageous in order to conserve energy and prepare for food shortages [175]. Today, food shortages are uncommon in most developed nations and

overconsumption of calories is a cause for concern. Physical inactivity leads to decreased skeletal muscle insulin sensitivity and increased abdominal fat storage, both of which play roles in promoting metabolic dysfunction [175]. Some exercise physiologists assert that rather than studying the effects of physical activity, we are actually studying "the effect of reintroducing exercise into an unhealthy sedentary population that is genetically programmed to expect physical activity" [176]. Physical activity across the lifespan is associated with lower levels of fat mass in women in early old age, and in higher appendicular lean mass in both older men and women [177].

1.5.1 Physical Activity Definitions and Recommendations

Physical activity has been defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" [178], while exercise "is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness" [178]. The 2008 Physical Activity Guidelines for Americans recommends that older adults follow the guideline of performing at least 150 minutes per week of moderate intensity activities, 75 minutes of vigorous intensity activities, or a combination of both, which is consistent with the guidelines for healthy adults [179]. Activities should be performed in bouts of at least 10 minutes, and for optimal health benefits, it is recommended to gradually work up to accumulating 300 minutes per week of moderate activities or 150 minutes per week of vigorous activities. Ideally, this activity should be spread throughout the week. In addition, strength training exercises should be performed at least two days per week at a moderate to high intensity, while working all major muscle groups.

Although these guidelines may be appropriate for older adults without major disease, it has been acknowledged that older adults who are very unfit or have chronic conditions may not be able to achieve these recommendations. Instead, these older adults should be as active as their conditions allow, and any amount of physical activity is better than none. For older adults, the recommendations include performing balance exercises, particularly if they are at risk for falling, although the guidelines do not describe those who may be at fall risk. Balance exercise examples may include backwards walking, standing on one foot, toe stands, and heel or toe walking. These exercises should be progressive, working towards more difficult skills once beginning balance exercises are mastered. Three days of balance exercises are recommended from a balance program designed to reduce the risk of falls in older adults. Flexibility exercises are also important for older adults in order to maintain the range of motion necessary for activities of daily living and physical activities. Flexibility exercises should not take the place of aerobic or strength training activities, and are not known to confer any specific health benefit. Due to the lack of clear evidence of the ideal frequency or duration of flexibility exercises for older adults, no specific flexibility training guidelines exist. All of the above recommendations are consisted with the guidelines set in the ACSM position stand for exercise and older adults [26].

Health and functional status can play major roles in the ability for older adults to adopt a physically active lifestyle [180]. Physical activity could potentially play a role in improving health, but those with health issues may need additional guidance and support from fitness and health care professionals on becoming active. In fact, pain and poor health are the two most common reasons older adults cite as their reason for not being physically active [181]. Also, acute illnesses, which are common in older adults, can quickly lead to loss of muscle tissue and

strength and can delay recovery and the return to prior functional status [182]. Each consecutive illness can lead to inactivity, strength and aerobic capacity declines, and make it harder to return to prior functional capacity. Continuation of this cycle can be extremely detrimental and put older adults at much higher risk for disability [182].

1.5.2   Physical Activity Epidemiology in Older Adults

Despite the numerous health benefits associated with physical activity, older adults are the most physically inactive age group in the U.S. [24], with only roughly 10% of adults age 70+ reaching national physical activity guidelines [183]. Over the past 50 years, physical activity has been declining in the population, and these declines can be attributed to changes in occupations, land use, and transportation, and increase in sedentary behaviors like television watching and computer use [184]. NHANES data from 2005-2006 have indicated that the mean minutes of moderate activities declines with age, with 20-29 year old individuals achieving an average of approximately 58 minutes per week, in contrast to those who are age 70 and older, who achieve only approximately 20 minutes of moderate activity per week [183]. Physical activity was measured via hip-worn accelerometry. Though the average number of minutes of moderate activity declines with age, on average, even younger adults do not reach the minimal recommendations of 150 minutes per week.

Prior studies incorporating objective measures of physical activity have shown that most of the activity energy expenditure in older adults comes from sedentary or light activity, like housework or sitting activities [25]. Because light and sedentary activities are difficult to recall using subjective measures, objective tools (like accelerometers and other physical activity monitors) are needed to capture the full range of activity. Also, recent work has shown that

separate health risks from sedentary behaviors exist, independent of physical activity [185,186].

Objective physical activity measures can allow investigators to examine both sedentary activities and physical activities; however, this is a more recent area of focus, and many studies still focus on moderate or vigorous physical activity, which may not be common in populations of older adults.

1.5.3   Methodological Issues in Measuring Physical Activity in Older Adults

Accurately assessing physical activity is challenging in all populations, though there are some methodological issues unique to assessing activity in older populations. Table 3 describes common tools used to measure physical activity, and the strengths and limitations of these tools. Unfortunately, no single tool is perfect, and strengths and limitations must be considered when designing a study.

When choosing a tool for measuring physical activity, several factors must be considered. First, cost is often a barrier, particularly for large scale epidemiologic studies. Although the cost of many physical activity monitors has dropped substantially as technology has improved, the cost of purchasing hundreds of monitors and the needed software for data processing can be prohibitively expensive. Second, an appropriate assessment tool should be appropriate for measuring the types of activities the population actually does. Common domains of activity include occupational activity, transportation, household and care taking, and sports and leisure [187]. In the context of older adults, a questionnaire focusing on occupational activities, sports participation, or activities that older adults are unlikely to do would be inappropriate and likely lead to an underestimation of physical activity. Questionnaires specifically developed for and validated in older adult populations, such as the Physical Activity Scale for the Elderly (PASE)

[188] or CHAMPS [189] would be important to consider. Because light intensity activities make up a large proportion of energy expenditure by older adults, and these light activities can be difficult to recall, physical activity monitors can help to capture the full spectrum of activity intensity. In general, subjective methods are appropriate for assessing moderate and higher intensity activities, while objective measures are more accurate in assessing a range of physical activities [187]. Similarly, the tool of choice should accurately measure the exposure (type of activity) of interest. For example, if light activity is of interest, an objective measure may better capture the exposure rather than a questionnaire. However, a limitation of accelerometry and other activity monitors is that although they can give information about physical activity participation on a full spectrum of intensity, they do not give information about specific activities. For example, resistance training and weight-bearing activity are important for bone density [190], though in general, many activity monitors cannot currently distinguish these from other activities. Though limitations exist with monitors, this is a quickly growing field and the conjunction of physical activity researchers with computer scientists has driven the development of novel analysis techniques and algorithms which can aid in the recognition of specific activities and patterns.

Intensity is an important aspect of classifying types of physical activity, though intensity is a relative term. Activity that one individual may consider "moderate" for one individual may be "very intense" for another individual who has very low aerobic capacity or functional ability. Physical activity monitors can help classify intensity though objective definitions, however, many definitions of intensity were developed from work in young, healthy populations. Comparing activity between younger and older adults even using objective measures should be done with caution. Though older age is associated with lower levels of physical activity, making

absolute comparisons between older and younger adults may be inappropriate using cut-points. Some groups have begun utilizing alternative measures from acceleromtery data rather than counts using cut-points to determine intensity. These measures include minute-by-minute activity counts to examine patterns of activity throughout the day; cumulative activity counts to determine total activity for a day [191]. The field of computer science has also begun to intersect with physical activity epidemiology, and techniques using raw acceleromtery to identify specific activities have also been developed [192,193]. However, currently these techniques require considerable training in computer science and biostatistics to use, though these developments will ultimately help shape physical activity assessment in the future and hopefully help to improve current measurement methods.

Unfortunately, physical activity is not just a public health issue in the United States, but the issue is prevalent in other westernized nations, and is increasingly becoming a problem in developing nations as well [194]. Worldwide, older age is associated with lower levels of physical inactivity, which could lead to a major global public health burden in conjunction with the aging population becoming the fastest growing demographic [195]. Direct comparisons of physical activity levels between countries are difficult due to inconsistent methods used to measure activity, and the lack of reliable data from many low income countries [196]. Expectations about the aging process can influence whether older adults remain or become physically active or participate in other healthy behaviors [197,198]. Norms and expectations regarding aging can vary widely between cultures [199], adding to the complexity of promoting physical activity on a global scale.

Table 3: Common Tools Used to Measure Physical Activity

Measurement Tool	Description	Advantages	Disadvantages
Physical Activity Scale for the Elderly (PASE)	The PASE assesses physical activity from the past seven days. Participants indicate how often and for how long they participated in activities in each intensity category. Participants also indicate whether they participated in household, gardening, occupational, or care giving activities [200]	The questionnaire refers to the past seven days, a period where recall should not be difficult. The questionnaire can be administered in less than 15 minutes, and it is easy to score, making it feasible to incorporate into large studies.	Activity from the past seven days may not be representative of an individual's usual activity habits, which may be more relevant to health outcomes. In a validation study, the correlation between PASE score and doubly labeled water was 0.28 [201].
Modified Minnesota Questionnaire used in the Health Aging and Body Composition Study (Health ABC)	Measures leisure activity, housework, care giving, walking, and stair climbing. Participants first indicate whether they have done each specific activity at least 10 times in the past year. If yes, participants are then questioned about the number of times per week and the duration [202]. Time spent in the activity is multiplied by its metabolic equivalent [203] to obtain weekly energy expenditure.	This questionnaire is easy and quick to administer. Although modified from its original form in order to be appropriate for Health ABC, energy expenditure from this questionnaire is associated with functional outcomes important in studies of older adults [204].	Because this is a modified questionnaire, validation data does not exist specifically for this questionnaire. Energy expenditure values resulting from scoring the total energy expenditure from the original Minnesota Leisure Time Questionnaire (MLTQ) is weakly correlated with total energy expenditure measured by doubly labeled water (r=0.23) . MLTQ energy expenditure (from the original or modified version) may not accurately represent true energy expenditure. Rather, energy expenditure values should be used to rank or group participants. Additionally, participants may have difficulty recalling whether they participated in an

Table 3 Continued

			activity at least 10 times in the past year. Detailed questions are only asked about activity in the past seven days, which may not be representative of usual activity habits.
CHAMPS	Participants indicate the number of days per week and number of hours per session of various physical activities that older adults commonly do. The time frame used in this questionnaire is a "typical week in the past four weeks" [189].	Participants are instructed to think about a typical week in the past four weeks, which may better represent usual activities. In addition to questions about physical activities, this questionnaire also contains questions about other activities that older adults may do (i.e. play cards, visit with friends, etc), to minimize socially desirable responding. The questionnaire can be administered quickly in about 10-15 minutes.	Participants may have difficulty quantifying activity from a "usual week" of the past month.
Physical Activity Diary	Participants record all of their physical activities for a specified duration (i.e. seven days). Typically the specific activity, duration, and intensity are recorded.	Participants can indicate all activities rather than choosing from a specific list of activities. In theory, since participants are recording the activities as they do them, there should be fewer recall issues.	This method requires considerable participant burden. Participants may stop recording their activity if they feel the diary is burdensome. Additionally, calculating and processing data from a physical activity diary is difficult and time consuming for study staff.

Table 3 Continued

Accelerometer	Accelerometers have the capability to capture movement and quantify that movement for the assessment of activity intensity, duration, and frequency.	Accelerometers objectively measure physical activity and are able to capture the full range of physical activity: sedentary, light, moderate, and vigorous.	Specialized software is needed to process accelerometry counts. Several cut-points have been identified for distinguishing the intensity of various activities. However, many cut-points have been established using younger adults and may not be appropriate for older adult populations [205]. Additionally, accelerometers may underestimate step counts for individuals who walk very slowly [206].
ActivPAL Inclinometer	This physical activity monitor is attached to the right upper thigh and records body posture. This monitor can identify lying, sitting, and standing positions, as well as transitions and steps.	This monitor provides accurate and valid estimations of time spent lying, sitting, and standing upright, which is useful for studies examining sedentary time.	Step counting may be less accurate for older adults with impaired physical function and slow gait speed [207]. This monitor is to be used for identifying time spent in various postures, and should not be used in a study where the aim is to measure physical activity.
Pedometer	Pedometers are small devices used for counting steps and are typically worn on the waist band.	Pedometers are inexpensive and can be easily incorporated into an epidemiologic study or clinical trial. Recording step counts is relatively easy and has a low participant burden.	Pedometers may underestimate step counts for those with very slow gait speed [206]. Accuracy of pedometers can vary widely between various piezoelectric and spring levered devices [208]. Positioning on the body is very important. If the device is not positioned properly, it may not be able to detect steps. Additionally, since pedometers only count steps, any activity that does not involve walking or running (i.e. biking, swimming, and weight lifting) would not be counted.

Table 3 Continued

Body Media SenseWear Armband	This physical activity monitor is worn on the upper arm and uses body temperature, heat flux, galvanic skin response, and a tri-axial accelerometer to calculate energy expenditure and track physical activity and sleep [209].	This activity monitor has been validated to provide estimates of energy expenditure in older adults [210].	There have been some reports of minor discomfort while wearing the device [211]. Those with low shoulder mobility may have difficulty putting the monitor on and taking it off.
Doubly Labeled Water	This method involves the ingestion of a measured amount of water labeled with isotopes of oxygen and hydrogen that can be traced as they break down and leave the body, and this rate is used to calculate energy expenditure using calorimetric equations [212].	This method is considered to be the gold standard for assessing free-living energy expenditure. Energy expenditure can be assessed over periods of several days or several weeks, and this method has relatively low participant burden.	Although this method gives information about energy expenditure, the types of activities a participant engages in cannot be assessed. Also, the required isotopes and equipment needed for doubly labeled water analysis is cost prohibitive for large epidemiologic studies.

1.5.3.1 Sensorimotor Peripheral Nerve Function Impairments and Exercise Prescription

On a national scale, brisk walking is encouraged as a primary mode of aerobic exercise. Although walking is important for the maintenance of independence, situations exist where walking is not the most appropriate mode of exercise. For example, many symptoms that develop in the lower extremities during peripheral nerve function decline, including numbness in the feet can make weight bearing exercises like walking—difficult and painful. In the ACSM and American Diabetes Association (ADA) joint position statement on exercise and type 2 diabetes, this difficulty has been acknowledged, and non-weight bearing activities (e.g. swimming or biking) are recommended for those who have symptoms in the feet and lower extremities. If a walking exercise program is deemed appropriate for a patient, foot care is highlighted as a vital component of the program in order to prevent open sores or ulcers [162]. Translating this recommendation to older adults without diabetes but with peripheral nerve function impairments is important since these symptoms can occur in the absence of diabetes.

1.5.3.2 Cardiac Autonomic Function Impairments and Exercise Prescription

Cardiovascular autonomic neuropathy and nerve function decline brings its own set of challenges when prescribing exercise for older adults. Pre-participation screening by a physician is an important step before beginning an exercise program for individuals with cardiovascular risk factors, metabolic disease, or for older adults aiming to exercise at a high intensity [148]. Due to the risk of adverse cardiac events with CAN, a physician should evaluate those with CAN before beginning an exercise program. Screening should be performed in order to detect cardiovascular abnormalities [162].

Because those with autonomic neuropathy often have resting tachycardia but reduced maximal heart rate, the estimated maximal heart rate calculation of 220 minus age may not be suitable for assessing exercise intensity [213]. Alternatively, having participants indicate their rating of perceived exertion (RPE) is appropriate, providing that the scale has been fully explained. Because cardiac autonomic nerve function impairments are associated with low exercise tolerance, physical activity programs should start with short bouts, with gradual increases in duration and intensity. It may take a considerable amount of time before a participant with low exercise tolerance can work up to achieving the recommended dose of physical activity consistent with national guidelines.

1.6   SPECIFIC AIMS

1.6.1   Sensorimotor Peripheral Nerve Function and Physical Activity

A major gap in knowledge exists for the descriptive relationship between physical activity and peripheral nerve function in older adults. The work by Loprinzi [158] and colleagues examining objectively measured physical activity and peripheral neuropathy in diabetic participants from NHANES disregarded the importance of light activities and only focused on MVPA, though it is known that levels of MVPA may be low in the general population, particularly in the general population of older adults. This study also only focused on those with diabetes, and peripheral nerve function was not measured, rather peripheral neuropathy was used as the outcome. In MrOS, peripheral nerve function measures were collected at Visit 3, along with objectively measured physical activity. Although this study only

includes older men, the large sample size, variety of sensorimotor peripheral nerve function measures, and objectively measured physical activity data make this study an excellent opportunity for determining the descriptive relationship between physical activity and peripheral nerve function.

Specific Aim 1: To determine whether better peripheral nerve function is associated with higher levels of physical activity participation and fewer minutes of sedentary time in older men.

Hypothesis: Men with better sensorimotor peripheral nerve function will participate in more minutes of physical activity (light, moderate, and vigorous activity) and fewer minutes of sedentary behaviors per day compared to older men with worse sensorimotor peripheral nerve function.

1.6.2   Sensorimotor Peripheral Nerve Function and Endurance Walking Performance

Second, we do not know how sensorimotor peripheral nerve function impacts endurance walking.   In the Health, Aging, and Body Composition (Health ABC) study sensorimotor peripheral nerve function measures were collected the 2000/01 clinic visit. Additionally, the long distance corridor walk (LDCW)—a validated measure of walking endurance in older adults [214] was administered at the 2000/01 clinic visit, and every other year thereafter through the 10th year of the study (2006/07 clinic visit).   Currently the relationship between walking endurance and sensorimotor peripheral nerve function has not been explored in a longitudinal matter, making this a novel analysis.

Specific Aim 2:   To determine whether worse sensorimotor peripheral nerve function associated with worse performance over time on an endurance walking test, the long distance corridor walk (LDCW).

Hypothesis: Participants with worse sensorimotor peripheral nerve function will be more likely to be ineligible or unable to complete the LDCW, will have slower initial completion times, and experience greater slowing over time compared to those with better sensorimotor peripheral nerve function.

1.6.3 Sensorimotor Peripheral Nerve Function and Indicators of Cardiac Autonomic Function

Finally, sensorimotor peripheral nerve function and cardiovascular autonomic function are often studied separately, though function in both divisions is worse in older age. Cardiovascular autonomic function can be assessed using heart rate and blood pressure measures from fitness tests, like the Long Distance Corridor Walk in Health ABC. Because of the common risk factors associated with sensorimotor and autonomic peripheral nerve impairments (particularly cardiovascular risk factors), it is plausible that those with worse sensorimotor peripheral nerve function also have worse cardiac autonomic peripheral nerve function. Using sensorimotor peripheral nerve function measures and information on heart rate measured during the LDCW from Health ABC 2000/01 clinic visit (resting heart rate, heart rate response to the LDCW, and heart rate recovery after the LDCW), we can assess the associations between these two divisions.

Specific Aim 3: To determine whether **sensorimotor peripheral nerve function is associated with cardiac autonomic function in older adults.**

Hypothesis: Older adults with better sensorimotor peripheral nerve function will also have better cardiac autonomic function.

2.0   SENSORIMOTOR PERIPHERAL NERVE FUNCTION AND PHYSICAL ACTIVITY IN OLDER MEN

ABSTRACT

Sensorimotor peripheral nerve (PN) impairments are common in older adults and negatively impact mobility. The purpose of this study was to determine whether worse PN function is associated with lower levels of PA in older men. In 2007-09, participants at the Pittsburgh, PA, site of the Osteoporotic Fractures in Men Study (age 78.9 ± 4.7 years) underwent nerve conduction testing of the peroneal motor and sural sensory nerves to assess amplitude, latency, and f-wave latency. Sensory PN function was also assessed using 1.4g and 10g monofilaments. Symptoms of peripheral neuropathy were collected via self-report. Self-report PA was assessed using the Physical Activity Scale for the Elderly (PASE). PA was assessed objectively using a multisensor armband to determine minutes per day spent in sedentary (<1.6 METS, excluding sleep), light (1.6 to <3.0 METS), moderate (3.0 to <6.0 METS) and vigorous (6.0+ METS) activity. Continuous measures of PN function were split into worse function (lowest tertile) and better function (highest two tertiles) to approximate clinical thresholds of PN function. We compared adjusted mean PASE scores between PN function groups using ANOVA. Multivariate linear regression modeled the association between PN function and minutes per day of each level of activity.

Participants (n=341) spent a median of 832.4, 63.8, 69.2, and 8.80 minutes per day in sedentary, light, moderate, and vigorous activities, respectively. Higher mean PASE scores (adjusted for age, BMI, self-reported health, diabetes, peripheral arterial disease, and arterial stiffening) were found for those with better distal motor compared to those with worse distal motor latency (PASE score 160.6 vs 138.3, $p<0.01$). Participants reporting any neuropathic symptoms had lower mean PASE scores compared to those with no symptoms (131.9 vs. 155.8, $p<0.05$). In unadjusted models, men with better motor amplitude participated in 17.9%, 19.4 and 41.5% more minutes of light, moderate and vigorous activity per day, and 3.9% fewer minutes in sedentary time compared to those with worse motor amplitude ($p<0.05$ for all). Participants with better sensory amplitude participated in 19.6%, 24.1, and 41.4% more minutes of light, moderate, and vigorous activity compared to those with worse sensory amplitude, though sedentary time did not differ. Adjusting for age, BMI, self-reported health, diabetes, peripheral arterial disease, and arterial stiffening attenuated many relationships with light, moderate, and sedentary time to non-significance, though those with better amplitude participated in more vigorous activity then men with worse amplitude. No relationships were found with other nerve function measures. Worse sensory and motor PN function is associated with less PA in older men, indicating a potential pathway for disability that warrants further investigation.

2.1   INTRODUCTION

Sensorimotor peripheral nerve (PN) dysfunction negatively impacts mobility in older adults—a cornerstone for maintaining independence. Worse sensorimotor PN function in older

adults is associated with poorer lower extremity function [31-34,66], strength [36,215], and power [37], as well as an increased risk for falls [38-41] and mobility disability [216]. Deficits in sensorimotor nerve function may result in pain or loss of sensation in the extremities, which could greatly influence the ability to be physically active.

Currently, few studies have examined the association between clinical peripheral neuropathy and physical activity (PA), and existing studies have focused on adults with diabetes [157,158] rather than community-dwelling older adults. Though diabetes is a common contributor to PN impairments, PN dysfunction occurs with aging even in the absence of diabetes [29]. Worse PN function is associated with worse lower extremity outcomes in older adults even without diagnosed clinical peripheral neuropathy [31], highlighting the importance of examining a full range of PN function.

A major gap in the literature exists regarding the descriptive relationship between PN function and PA in older adults. Examining objectively measured physical activity across a wide range of intensities (including light activity) may be beneficial for clarifying the relationship between PN function and PA in older adults—particularly since older adults spend very little time in moderate or vigorous PA [25,159]. Despite the potential for lower extremity function to influence the ability to be physically active, the relationship between PN function and PA participation has not been explored in community dwelling older adults. Whether worse PN function is related to lower levels of PA is unclear, though PA could potentially be in the pathway from PN impairments to mobility disability. The aim of this study was to determine whether better PN function is associated with higher levels of participation in PA in older men.

2.2   METHODS

2.2.1   Participants

Participants at the Monongahela Valley, PA (near Pittsburgh, PA), site of the Osteoporotic Fractures in Men Study (MrOS) underwent peripheral nerve function assessments at the 2007/09 clinic visit.   Briefly, MrOS is a multicenter longitudinal cohort study of healthy aging focusing on the risk factors for fractures in older men (n=5,994; mean age 73.7 ± 5.9 years at baseline) [217].   Ambulatory men age 65 and older were recruited and completed the baseline visit between March 2000 and April 2002 from six U.S. clinical sites [218].   Eligibility criteria for the main study at the baseline visit included the ability to walk without assistance from another person or walking aid, ability to provide self-reported data, capacity to understand and provide informed consent, absence of bilateral hip replacement, absence of any severe disease or condition that would results in imminent death, and anticipated residence near a clinical site for the duration of the study period. In total, 426 men had PN function and PASE questionnaire data the 2007/09 clinic visit, and objective physical activity data was available for 341 participants (Figure 2).   The study protocol was approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent before testing.
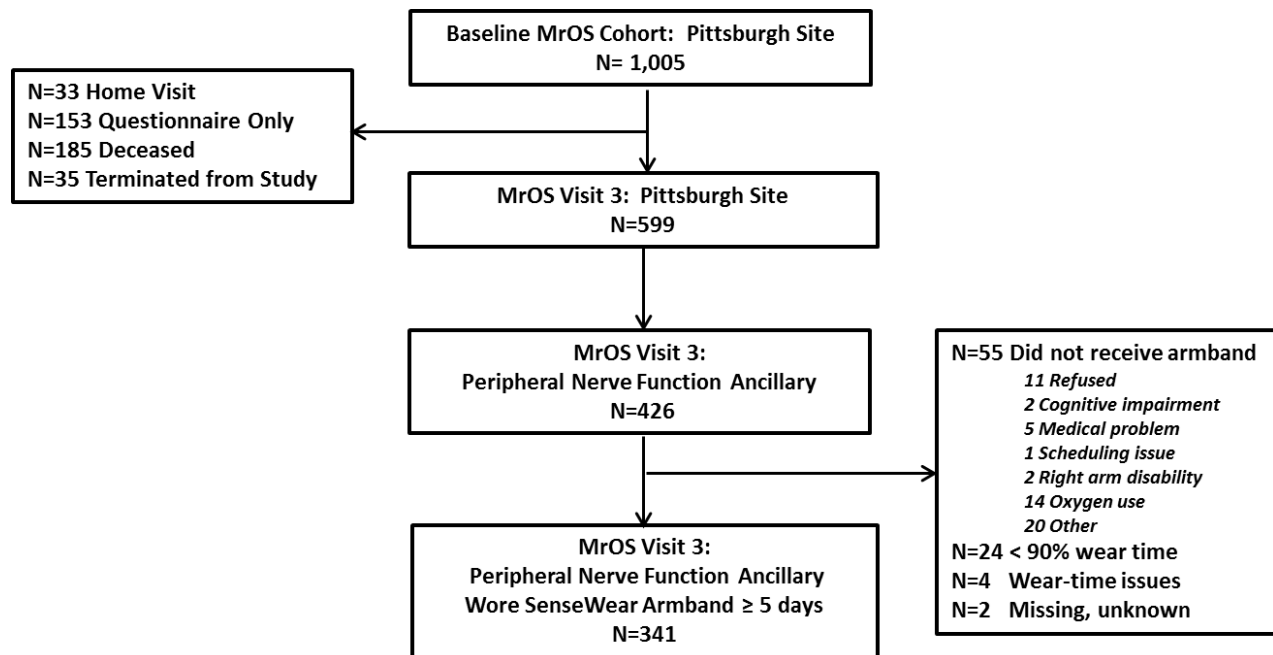
Figure 2: Participant Flow Diagram from the MrOS Pittsburgh Site

2.2.2   Peripheral Nerve Function Examination

Nerve conduction testing was performed bilaterally on the deep peroneal motor nerve and the sural sensory nerve using an automated nerve conduction study device (NC-stat)—a valid and reliable method for assessing nerve function in older adults [92].   Before testing, participants' feet were warmed to 30°C if they were <30°C.   Peroneal motor nerve parameters included: motor amplitude of the compound muscle action potential in millivolts (CMAP); distal motor latency in milliseconds; and mean F-wave latency in milliseconds. Sural sensory nerve measures included sural nerve action potential (SNAP) and sensory amplitude in microvolts and distal sensory latency in milliseconds. Continuous measures of nerve function were split into poor function (lowest tertile) and higher function (middle and highest tertiles) to approximate clinically relevant cut points indicating poor nerve function.

Sensory PN function was also assessed through monofilament testing using light (1.4-g) and standard (10-g) monofilament touches at the dorsum of the left great toe. Light and standard monofilament sensitivity were defined as feeling at least 3 out of 4 touches, while insensitivity was defined as the inability to detect three touches. The standard monofilament was only used if the participant had light monofilament insensitivity. Sensory testing was performed on the non-dominant side while motor testing was performed on both sides except in the case of technical difficulty.

Symptoms of peripheral neuropathy within the past 12 months were assessed via self-report from a modified Michigan Neuropathic Screening Instrument [108] and included (1) numbness or tingling, (2) sudden stabbing, burning, or aches, or (3) an open persistent sore or gangrene on either foot or leg in the past 12 months.

2.2.3   Physical Activity Assessment

Self-report physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) [200]. Briefly, the PASE includes questions about the intensity, frequency, and duration of various physical activities over the past seven days. Activities include walking, strenuous (ex. jogging, swimming, singles tennis), moderate (ex. golf without a cart, doubles tennis) and light activities (ex. golf with a cart, shuffleboard), muscle strengthening exercises, lawn work and gardening, occupational activities that include walking or standing, caring for another person, home repairs, and housework. The frequency and duration of participation in the various categories are multiplied by activity weights based on intensity and summed in order to give a total PASE score. The PASE score is a unitless, relative measure, with higher scores indicating higher levels of physical activity. The PASE has been previously validated against

energy expenditure measured via doubly labeled water [188,201] and objectively measured PA [219,220], and PASE score has been correlated with physiologic and performance characteristics in older adults [221]. The PASE has high test-retest reliability [200,222] and longitudinal changes in PA over approximately five years have been previously described in the MrOS study population [223].

Objective physical activity was measured using the SenseWear Armband (SWA; Body Media, Inc., Pittsburgh, PA). Participants were instructed to wear the monitor at all times for 7-days, removing the monitor only for brief periods for bathing or water activities. The SWA includes heat flux, galvanic skin response, skin temperature, and near body temperature sensors, as well as a two-axis accelerometer. Data were sampled in 1-minute epochs and used to estimate energy expenditure in kilocalories per day [224]. Data collected by the sensors along with age, height, weight, handedness, and smoking status were used in propriety algorithms (Innerview Professional 5.1 software) to estimate energy expenditure, metabolic equivalents (METS), and sleep time. Energy expenditure measured by SWA has been validated using doubly labeled water in older adults [210]. Average minutes per day spent in each level of PA were calculated using MET cut-points, with categories being defined as follows: light/lifestyle activity = 1.6 to <3.0 METS, moderate activity 3.0-<6.0 METS, vigorous activity 6.0+ METS, and sedentary time < 1.6 METS (excluding sleep time). Total time spent in each of these categories during the wearing period was averaged over all days in order to limit variability and reflect usual activity patterns. As described previously by Cawthon and colleagues [225], if a participant wore the monitor < 90% of the time during any 24-hour period, that period was not used in calculating energy expenditure. Only participants with at least five 24-hour periods were included in analyses.

2.2.4   Covariates

We considered several factors potentially related to PA or PN function as covariates. Height and weight were measured using a stadiometer and calibrated balance beam scale, respectively, and were used to calculate body mass index (BMI).   Lean and fat mass were measured using dual-energy x-ray absorptiometry (Hologic 4500A).   Diabetes was defined by fasting glucose measure of ≥126mg/dL [226] at the baseline MrOS clinic visit or self-reported physician diagnosis at the 2007/09 clinic visit.   Peripheral arterial disease was defined as ankle-brachial index (ABI) of <0.9, while arterial stiffening was defined as an ABI of >1.3 [227].   The Teng Modified Mini-Mental State Exam (3MSE) was used to assess cognition [228] and the Geriatric Depression Scale (GDS) measured depressive symptoms [229].   History of cigarette smoking (never, current, former), current alcohol consumption (drinks/week), and health status (excellent, good, fair, poor, very poor) were assessed though self-report. Chronic health conditions included self-report hypertension, congestive heart failure, cerebrovascular disease, and cardiovascular disease.

2.2.5   Statistical Analyses

Descriptive statistics were expressed using mean ± standard deviation for continuous variables or median and interquartile range where appropriate, and frequencies for categorical variables.   Participants were grouped based upon tertile of daily average METS from the SenseWear Armband, and tests of trend were used to assess differences in participant characteristics between the three ordered groups.   PN function measures and minutes spent in the four levels of activity were also compared between MET groups.   ANOVA models compared the

adjusted mean PASE score between PN function groups. Because many measures of PN function were correlated (correlation coefficients ranging from 0.17 for sensory amplitude and latency and 0.34 between motor and sensory amplitude, $p<0.05$ each), each measure of PN function was modeled separately. Multivariate linear regression was used to model the association between PN function and objectively measured PA, which allowed an examination of the effect of PN function on participation in each level of activity (sedentary, light, moderate, and vigorous) in one model. This method makes use of the correlations between the components of the multi-dimensional outcome to better identify differences between the groups. Minutes spent in each level of activity were right skewed to no activity, thus natural logged versions of these variables were used for analysis. Results were back transformed in order to report minutes spent in each level of activity.

All models (ANOVA models for PASE; multivariate regression models for SWA outcomes) were built progressively, with covariates with $p<0.10$ being considered for a multivariable model, though diabetes was forced into the final model regardless of significance. Factors that could influence PA or PN function were considered as covariates until a final, parsimonious model with only factors reaching $p<0.05$ was determined for each PN function predictor and PA level outcome. All data analyses were performed using STATA version 12.1 (StataCorp, College Station, TX).

2.3   RESULTS

Participants (n= 341, age 78.7 ± 4.7 years, BMI 28.1 ± 4.0 kg/m^2) in this cohort of older men spent a median of 832.4, 63.8, 69.2, and 8.80 minutes per day in sedentary, light, moderate,

and vigorous activities, respectively. Those with lower mean daily MET levels were older, consumed fewer drinks per week, had higher BMI, higher fat and lean mass, were more likely to have diabetes, and reported more depressive symptoms compared to those in the higher mean daily MET tertile (Table 4; $p<0.05$ for trend for all). Differences across other chronic conditions and diseases were not significant. Participants with lower daily average MET levels had lower motor amplitude, were more likely to have 1.4 or 10-g monofilament insensitivity, and had a higher burden of neuropathic symptoms—particularly numbness (Table 4). As expected, those with lower daily MET levels had lower scores on the PASE, spent fewer minutes per day in light, moderate, and vigorous activities, and spent more minutes per day being sedentary compared to those with higher daily MET levels (Table 5; $p<0.001$ for all).

Table 4: Participant Characteristics by Tertile of Average Daily METS

	Tertile 1 (n=114) Average Daily METS: 0.79 – 1.11	Tertile 2 (n= 114) Average Daily METS: 1.11 -- 1.29	Tertile 3 (n= 113) Average Daily METS: 1.30 – 2.11	P for Trend
Age, Mean ± SD	80.0 ± 5.2	78.6 ± 4.6	77.6 ± 4.1	<0.001
Health Habits				
Drinks per week	2.4 ± 1.2	2.5 ± 1.2	2.9 ± 1.2	0.013
Current Smoker, N (%)	4 (3.5)	3 (2.6)	2 (1.8)	0.963
Former Smoker	64 (56.1)	73 (64.0)	67 (59.3)	
Body Composition				
Height, cm	171.8 ± 6.1	173.1 ± 6.1	171.9 ± 6.4	0.754
BMI, kg/m^2	30.3 ± 4.0	27.9 ± 3.3	26.1 ± 3.4	<0.001
Fat Mass, kg	27.5 ± 7.0	22.7 ± 5.8	19.0 ± 6.1	<0.001
Lean Mass, kg	58.3 ± 7.5	57.0 ± 6.5	54.5 ± 7.0	<0.001
Chronic Health Conditions				
Diabetes, N (%)	35 (33.3)	20 (18.9)	17 (16.2)	0.003
Hypertension	72 (63.2)	59 (51.8)	60 (53.1)	0.127
Heart Attack	22 (19.3)	9 (7.9)	13 (11.5)	0.079
Stroke	7 (6.1)	3 (2.6)	7 (6.2)	0.988
Congestive Heart Failure	8 (7.0)	3 (2.6)	3 (2.7)	0.098
Peripheral Arterial Disease	14 (13.6)	13 (12.0)	8 (7.6)	0.210
Arterial Stiffening	18 17.5)	26 (24.1)	31 (29.3)	
Cognition and Mental Health				
3MSE Score	92.8±5.3	94.3 ± 4.7	92.6 ± 6.3	0.554
GDS Score	2.0 ± 2.0	1.5 ± 1.6	1.5 ± 1.6	0.034

**Table 5: Peripheral Nerve Function and Physical Activity by Tertile of Average Daily METS**

	Tertile 1 (n=114) Average Daily METS: 0.79 – 1.11	Tertile 2 (n= 114) Average Daily METS: 1.11 -- 1.29	Tertile 3 (n= 113) Average Daily METS: 1.30 – 2.11	P for Trend
Motor Nerve Function				
Motor Amplitude (CMAP), mV	1.9 ± 1.4	2.2 ± 1.6	2.6 ± 1.6	<0.001
Distal Motor Latency, ms	4.6 ± 0.9	4.6 ± 0.7	4.5 ± 0.8	0.757
Mean F-Wave Latency, ms	61.2 ± 4.5	61.6 ± 5.5	61.0 ± 5.5	0.924
Sensory Nerve Function				
Sensory Amplitude (SNAP), mV	2.2± 2.6	3.4 ± 3.0	4.0 ± 3.1	<0.001
Distal Sensory Latency, ms	3.2 ± 0.2	3.2 ± 0.2	3.2± 0.3	0.311
1.4-g Monofilament Insensitivity	25 (26.6)	31 (35.6)	17 (18.5)	0.012
10-g Monofilament Insensitivity	21 (22.3)	5 (5.8)	12 (13.0)	
Neuropathic Symptoms				
Numbness	36 (38.7)	25 (28.7)	19 (20.7)	0.007
Stabbing Pain	15 (16.0)	11 (12.6)	11 (12.0)	0.425
Open Sore	1 (1.1)	2 (2.3)	0 (0.0)	0.492
Any symptoms	43 (45.7)	30 (34.5)	25 (27.2)	0.008
One Symptom	33 (35.5)	23 (26.4)	20 (21.7)	0.012
Two Symptoms	9 (9.7)	6 (6.9)	5 (5.4)	
Three Symptoms	0 (0.00)	1 (1.2)	0 (0.0)	
PASE Score	118.6 ± 65.8	152.9± 57.3	172.6 ± 70.5	<0.001
Daily Minutes of Activity from SenseWear Armband, Median (Interquartile Range)				
Sedentary, <1.6 METS	894.8 (830.4-953.8)	846.4 (806.0-908.4)	742.4 (693.7-808.0)	<0.001
Light, 1.6 to <3.0 METS	38.5 (28.4-54.4)	63.7 (50.0-81.8)	89.4 (74.6-111.4)	<0.001
Moderate, 3.0-<6.0 METS	37.5 (21.8-52.8)	71.1 (51.0-88.8)	134.0 (102.0-163.8)	<0.001
Vigorous, ≥6.0 METS	4.7 (2.0-8.5)	8.6 (5.6-13.0)	17.8 (10.0-28.2)	<0.001

Figure 3 displays the differences in adjusted mean PASE score (adjusting for age, BMI, self-reported health, diabetes, peripheral arterial disease, and arterial stiffening) by PN function. Those with better distal motor latency had significantly higher total PASE scores compared to those with worse distal motor latency (160.6 ± 9.7 vs 138.3 ± 13.5, p=0.009). Those without symptoms of peripheral neuropathy had higher PASE scores compared to those reporting one or two or more symptoms (155.8 ± 10.3 vs 131.9 ± 13.3, p=0.007). Specifically, those without numbness had higher PASE scores compared to those with numbness (153.5 ± 10.4 vs 132.4 ± 15.1, p=0.025). Motor amplitude, f-wave latency, sensory amplitude, distal sensory latency, monofilament detection, stabbing pain, and presence of open sores were not associated with PASE score.
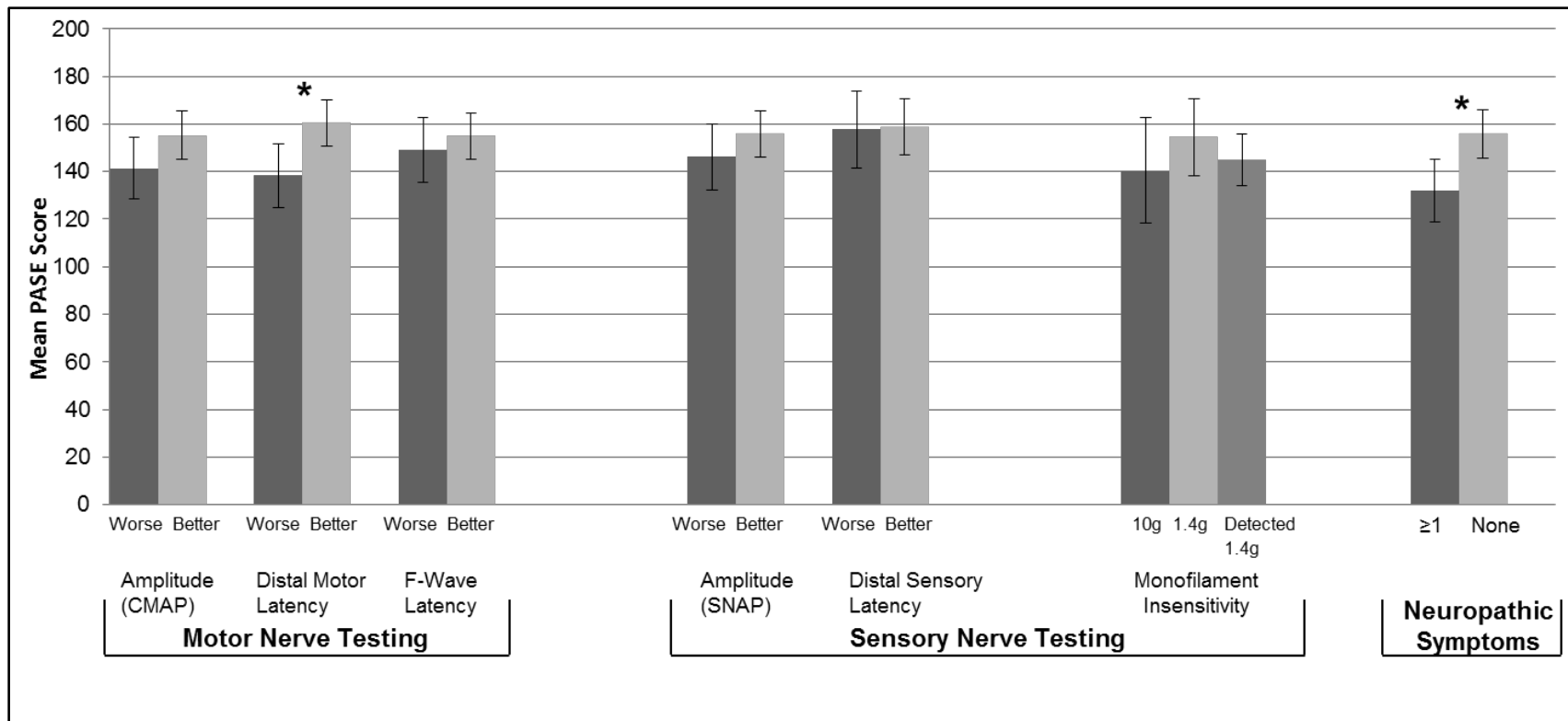
Means adjusted for age, BMI, self-reported health, diabetes, peripheral arterial disease, arterial and stiffening.

Continuous measures of nerve function were split into tertiles and those with worse function (lowest tertile of amplitude, highest tertile of latency) were compared to those with better function (combined highest and middle tertile of amplitude, combined lowest and middle tertile of latency).

*P<0.05 for difference between groups.

Figure 3: Adjusted Means of Total Physical Activity Scale for the Elderly (PASE) Score by Peripheral Nerve Function

In unadjusted multivariate regression models examining minutes spent in objectively measured activity, men with better CMAP participated in 17.9%, 19.4 and 41.5% more minutes of light, moderate and vigorous activity per day, and 3.9% fewer minutes in sedentary time (data not shown) compared to those with worse CMAP (p<0.05 for all). Participants with better sensory amplitude participated in 19.6%, 24.1, and 41.4% more minutes of light, moderate, and vigorous activity compared to those with worse sensory amplitude, though sedentary time did not differ. Adjusting for age, BMI, self-reported health, diabetes, peripheral arterial disease, and arterial stiffening attenuated the relationships with light, moderate, and sedentary time to non-significance. Those with better motor amplitude participated in 27.2% more minutes of vigorous activity compared to those with worse motor amplitude (p=0.015), while those with better sensory amplitude participated in 24.2% more vigorous activity compared to those with worse sensory amplitude (p=0.046) (Figure 4). Distal motor latency, f-wave latency, distal sensory latency, monofilament detection, and symptoms of peripheral neuropathy were not associated with objectively assessed physical activity.
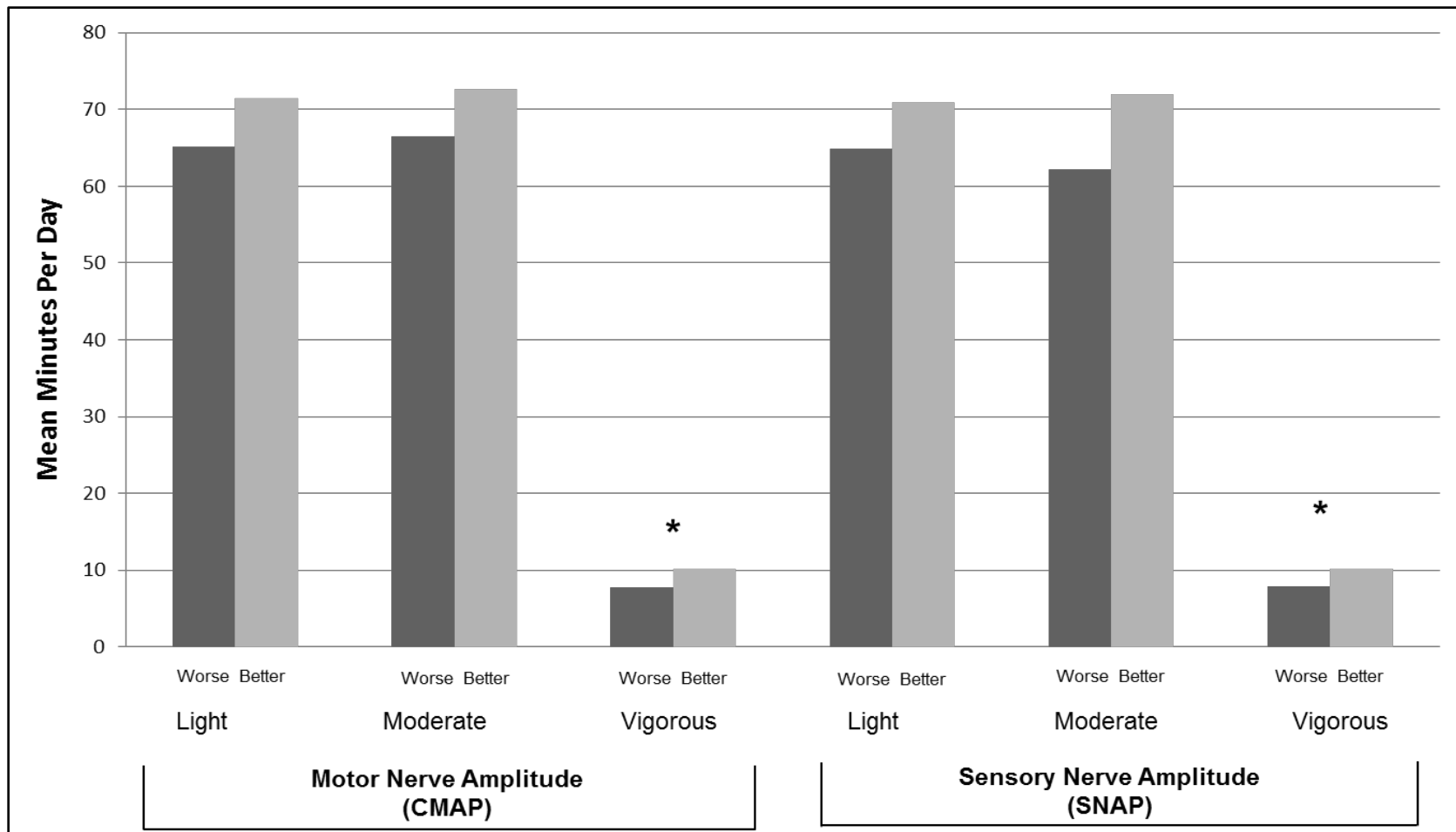
Means adjusted for age, BMI, self-reported health, diabetes, peripheral arterial disease, and arterial stiffening. Activity Definitions; Light: 1.6 to <3.0 METS; Moderate: 3.0 to < 6.0 METS; Vigorous: ≥6 METS. *p<0.05 for difference between worse and better function groups.

Figure 4: Mean Minutes Spent in Light, Moderate, and Vigorous Activity per Day by Motor and Sensory Amplitude

2.4   DISCUSSION

In this cohort of community dwelling older men, better PN function was associated with higher levels of PA. However, not all nerve function measures were associated with PA. We observed relationships of PN function with PA both using both objective and self-report measures of PA. Sensory and motor amplitude were associated with objective PA, while distal motor latency and presence of neuropathic symptoms were associated with self-report PA. We are uncertain as to why these relationships varied, though were consistent in indicating motor nerve function relationships with PA.   Importantly, motor nerve function is rarely measured in studies of PA and older adults, though future studies should consider doing so. This study adds to the growing body of literature that PN function should be evaluated as a factor in the disablement pathway for older adults.

Presently, very little work has been done in investigating the relationship between PN function and PA, and this work has focused on diabetic populations rather than older adults. In diabetic participants in the in 2003-2004 cycle of for the National Health and Nutrition Examination Survey (NHANES), no direct association was found between minutes per day of moderate to vigorous PA and peripheral neuropathy. However, though those with better diabetic control (as measured by HbA1c) and higher PA were less likely to have peripheral neuropathy compared to what would be expected from the individual effects of PA and diabetes control [158]. On average, this population participated in very few minutes of objectively measured PA (measured using hip-worn accelerometers) per day (mean = 11.7 minutes, 95% CI = 9.1-14.4

minutes), which may have limited the ability to examine the relationship between PA and peripheral neuropathy in this population.

Peripheral neuropathy has been acknowledged in the diabetes literature as potentially making PA difficult. Due to the relationship between worse sensory PN function and worse lower extremity outcomes [31-34,36-41,66,215,216], these considerations may be relevant for older adults with PN impairments. The American College of Sports Medicine and American Diabetes Association recommended in a joint position statement that those with peripheral neuropathy can safely participate in weight-bearing exercises as long as they do not have any open sores [162]. Additionally, it was recommended that foot care (examining for potential sores, selecting appropriate footwear) be an important component of any PA program for those with diabetic peripheral neuropathy. However, these recommendations have not been tested for older adults, and clearly more work is needed in this area.

In our study, motor and sensory amplitude were associated with objective PA, though other measures of nerve function were not. Nerve conduction testing may be a more sensitive measure to pick up earlier or subclinical impairments compared to monofilament testing or symptoms. Interestingly, we observed relationships with objective PA and both sensory and motor amplitudes but not latencies. This is consistent with prior work in this cohort by Ward and colleagues who examined the association between PN function and lower extremity muscle power [230]. Amplitude and latency are indicators of different types of PN damage, with worse amplitude being indicative of axonal degeneration, while latency, a component of conduction velocity, is a sign of demyelination [231]. These aspects of PN function do not necessarily decline simultaneously, and the protective myelin sheath may remain intact for remaining motor

units [232]. The effect of reduced axonal degeneration may have a greater impact on PA than latency, though this should be examined further.

In the InCHIANTI study—a population based cohort study of older adults in Italy—higher CMAP measured at the peroneal motor nerve was found to be associated with higher calf-muscle density in older adults [232]. PN impairments, particularly axonal degeneration along with the associated worse muscle quality and function could make activity more difficult, and PA is also known to influence body composition and muscle function. Determining the timing of these neuromuscular changes with PA patterns is worthy of future study in order to develop interventions to reduce the burden of lower extremity outcomes.

A major strength of this study is the inclusion of comprehensive PN function measures, which allowed us to examine a range of PN function and also examine potential specific pathways of PN function. Also, assessing objective PA in addition to self-report PA allowed us to better characterize the activity patterns of these older men than through using a self-report measure alone. This was particularly helpful for assessing participation in light intensity activities and sedentary time. The majority of energy expenditure for older adults comes from sedentary and light activities [25,159], which makes it especially important to measure the lower end of intensity in order to capture the full extent of activity in this population. Light activity and sedentary time are difficult to recall, and PA questionnaires may not be adequate for assessing these intensities [233].

Limitations to this work should be considered. Although the use of an automated neurodiagnostic instrument allowed nerve conduction testing to be done in a non-invasive, efficient manner, clinical cut-points established using traditional methods cannot be applied to measurements from automated instruments. Instead, we approximated clinical thresholds by

comparing those in the worst tertile to those in the middle and best tertiles. Future work is also needed in order to determine whether these results are applicable to other populations, including those with disabilities, women and non-white older adults.

In our analyses examining objective activity, we used MET cut-points to define intensity levels of physical activity. Though these categories allowed us to examine a range of activity intensities, cut-points can have limitations when applied to populations of older adults. Physical activity guidelines include recommendations for specific intensity levels, but relative intensity is important for prescribing physical activity for older adults [26]. Because many studies originally validating cut-points from accelerometer output were conducted in younger, healthy populations, alternate activity count cut-points and novel analysis methods have been suggested for assessing physical activity for older adults using accelerometers [191,234-236]. Many of these suggestions were made for traditional accelerometers, not necessarily for multi-sensor devices which process data using proprietary algorithms.

We considered the cross-sectional relationship between PN function and PA, though a bidirectional relationship between PN function and PA is possible. PN impairments—particularly sensory impairments—may make activity more difficult, while PA may be beneficial for improving PN function. Small studies of participants with diabetes have indicated that exercise training may help reduce symptoms in those with peripheral neuropathy [237], a long-term exercise intervention (4 years) can help reduce the incidence of peripheral neuropathy [161], and short term interventions may produce beneficial changes in gait performance in those with diabetic peripheral neuropathy. Improving functional outcomes via PA is important for helping those with PN impairments to maintain independence.

In conclusion, some measures of better PN function were associated with more PA per day in older men. Lower levels of physical activity may potentially be in the pathway between worse PN function and lower extremity disability. This potential pathway warrants further investigation in diverse populations of older men and women, and also in longitudinal work.

3.0 SENSORIMOTOR PERIPHERAL NERVE FUNCTION AND THE LONGITUDINAL RELATIONSHIP WITH ENDURANCE WALKING IN THE HEALTH, AGING AND BODY COMPOSITION STUDY

ABSTRACT

Sensorimotor peripheral nerve deficits affect gait and may reduce walking endurance in older adults. The purpose of this study was to determine whether lower extremity sensorimotor peripheral nerve deficits are associated with reduced walking endurance in older adults. Community dwelling older adults enrolled in Health, Aging and Body Composition study who participated in the 2000/01 annual clinical examination (n=2393; age 76.5 ± 2.9 years; 48.2% male; 38.2% black) and subset with longitudinal data (n=1,178) underwent sensorimotor peripheral nerve function testing. Nerve conduction amplitude and velocity were measured at the peroneal motor nerve. Sensory nerve function was measured using vibration detection threshold and monofilament testing at the big toe. Symptoms of lower-extremity peripheral neuropathy included numbness or tingling and sudden stabbing, burning, pain, or aches in the feet or legs. The long distance corridor walk (LDCW) was administered in 2000/01 and every two years afterwards for 6 years to assess endurance walking performance over time. In separate fully adjusted linear mixed models poor vibration threshold (>130 microns) 10g and 1.4g monofilament insensitivity were each associated with slower LDCW completion time (16.0, 14.1, and 6.7, seconds slower, respectively, $p<0.05$ for each). Poor motor amplitude (<1mV),

poor vibration perception threshold, and 10-g monofilament insensitivity were related to a greater slowing/year (4.7, 4.3, and 4.3 additional seconds/year, respectively, p<0.05), though poor motor amplitude was not associated with initial completion time. Poorer sensorimotor peripheral nerve function is related to slower endurance walking and greater rate of slowing over time. Interventions for those with poor sensorimotor peripheral nerve functioning should be considered in order for adults to maintain walking endurance.

3.1   INTRODUCTION

Sensorimotor   peripheral nerve function deficits are common in older adults; with estimates from the National Health and Nutrition Examination Survey (NHANES) indicating that 28.5% of older adults aged 70-79 and 34.8% of those 80+ have reduced touch sensation on the foot as measured by a simple screening tool [30].   In the Health, Aging and Body Composition (Health ABC) study, recent work has shown that 55% of older adults (N=1,680; age 76.5 ± 2.9 years) without mobility disability at the 2000/01 examination had evidence of lower extremity peripheral nerve impairments [216]. Poor peripheral nerve function in older adults is associated with worse lower extremity function [31-34], quadriceps and ankle dorsiflexion strength [36,215] quadriceps muscle power [37], as well as an increased risk for falls [38-41] and lower extremity limitation [216]. Worse lower extremity sensation and motor control resulting from sensorimotor peripheral nerve dysfunction can lead to altered gait mechanics and the adoption of inefficient and less stable gait patterns [115-120].   In addition, symptoms related to peripheral nerve function impairments—including pain or numbness in the lower extremities—may make weight bearing activities, such as walking, difficult.

Although poorer sensorimotor peripheral nerve function is associated with slower usual gait speed on short walking courses

[31,34,66], the impact of peripheral nerve function on endurance walking in community dwelling older adults is limited in current literature. Walking endurance—the ability to walk quickly for a sustained time or distance—is important for maintaining independence and remaining active in the community. Though aerobic fitness plays a major role in walking endurance, other disease-related factors—such as peripheral nerve function—may influence walking endurance and the maintenance of walking endurance over time, particularly given the associations with lower extremity function.

Poor peripheral nerve function in older adults occurs even in the absence of diabetes [29], though diabetes is a major contributor. However, work has been limited in exploring the association of peripheral nerve dysfunction and walking endurance in either population. Evidence exists that walking endurance is worse in diabetic adults compared to non-diabetic healthy adults [125], Peripheral nerve function may contribute to these differences, though it was not measured in previous studies. Walking endurance is worse in the presence of a greater burden of lower extremity complications resulting from diabetic peripheral neuropathy, including ulcers and amputations [238], however, these are extreme examples of peripheral neuropathy damage. In the InCHIANTI study, motor nerve conduction velocity was cross-sectionally associated with slower completion of a fast-paced 400m walking test for older adults [66]. These studies were limited in their peripheral nerve function assessments by using only peripheral neuropathy diagnoses or one measure of motor nerve function. Ideally, both motor and sensory nerve assessments should be included in addition to the collection of symptoms in order to examine the full range of peripheral nerve function from subclinical to symptomatic [82]

and also investigate the contribution of sensory versus motor function.   Furthermore, no longitudinal studies have examined if peripheral nerve function contributes to decline in endurance walking over time in old age.

The aims of this study were to 1) examine whether sensorimotor peripheral nerve function is related to walking endurance in older adults, and 2) determine whether sensorimotor peripheral nerve function is associated with the rate of change in walking endurance over six years of follow-up in the Health ABC study.

3.2   METHODS

3.2.1   Participants

Participants were from Health ABC, a longitudinal cohort study of community-dwelling older adults (n=3075; age 70-79; 48.4% male; 41.6% black at baseline) from Pittsburgh, PA and Memphis, TN aimed at investigating factors related to the development of functional limitation and disability [126]. Participants were recruited through mailings to a random sample of white Medicare beneficiaries and to all age-eligible black community residents. To be eligible for the study, participants had to self-report no difficulty in walking ¼ mile, climbing 10 steps, or performing any basic activity of daily living; be free of any life-threatening cancers; and plan to remain in the study area for at least three years. Participants completed the baseline visit between April 1997 and June 1998 and provided written informed consent. All protocols associated with the Health ABC study were approved by institutional review boards at the University of Pittsburgh and University of Tennessee Health Science Center.

A total of 2,404 participants had a clinic visit in 2000/01. Of these, 2393 had complete data for nerve function and long distance corridor walk measures. Figure 1 describes the number of participants who completed this visit and had complete nerve function and long distance corridor walk measures.
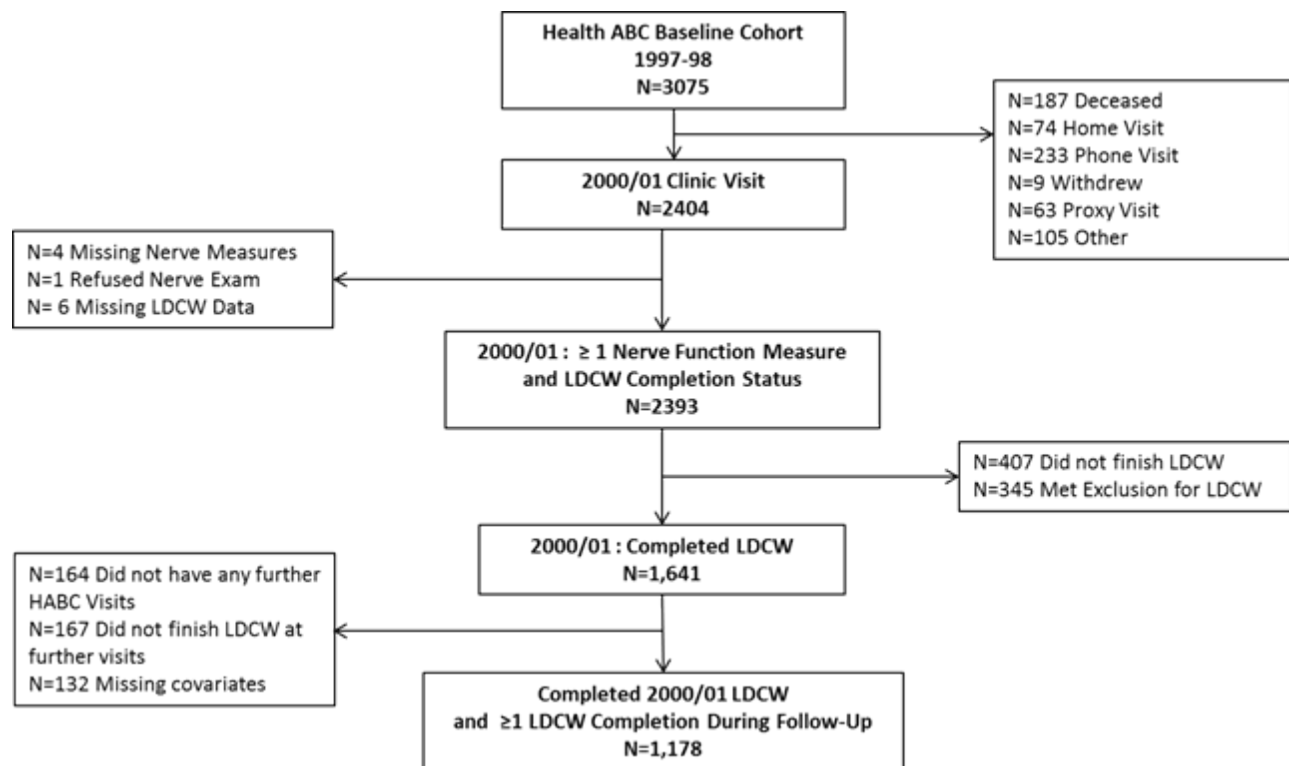
Figure 5: Participant Flow Diagram for the Health ABC Cohort

3.2.2 Endurance Walking Assessment

The long distance corridor walk (LDCW) was administered in 2000/2001 and at follow-up visits in 2002/03, 2004/05 and 2006/07 to assess walking endurance [214]. Exclusion criteria included: systolic blood pressure >200 mmHg, resting pulse of ≥120 beats per minute, presence of an electrocardiogram abnormality, or cardiac surgery, worsening of chest pain or shortness of breath in the prior three months. The test was conducted in a dedicated corridor with two traffic cones spaced 20 meters apart. Participants walked 10 laps around the cones for a total of 400 meters. The distance walked in the two minute warm-up was measured and completion time for the 400m walk was recorded in seconds. This test included a two minute warm-up walk where the participant was instructed to "cover as much ground as possible" followed immediately by the LDCW performed "as quickly as possible at a pace that can be maintained for 400 meters" [239]. Heart rate was recorded for each lap and blood pressure was measured at the end of the test. The test was stopped if heart rate surpassed 135 beats per minute, or for lightheadedness, dizziness, chest pain, shortness of breath or leg pain.

3.2.3 Peripheral Nerve Function Examination

Lower extremity sensory and motor nerve function was assessed in 2001/2002 visit by a trained examiner. Motor nerve function was measured objectively using peroneal motor nerve conduction amplitude in millivolts and peroneal motor nerve conduction velocity in meters per second, as previously described [89]. Stimulation occurred at the popliteal fossa and ankle using the NeuroMax 8 (XLTEK, Oakville, Ontario, Canada). Sensory nerve function was measured using vibration detection threshold and monofilament testing. Vibration detection threshold (in

microns) was measured at the bottom of the great toe with a VSA-3000 Vibratory Sensory Analyzer (Medoc, Durham, NC). Monofilament insensitivity was defined as the inability to detect three out of four touches at the dorsum of the large toe with a standard 10-g monofilament and light touch 1.4-g monofilament (North Coast Medical, Morgan Hill, CA). Feet were warmed to 30°C before all tests. All measures were performed on the right side unless contraindicated due to knee replacement, amputation, trauma, ulcer, or recent surgery, in which case the left side was tested unless also contraindicated.

Symptoms of peripheral neuropathy were collected via self-report in a modified Michigan Neuropathy Screening Instrument questionnaire [108] and included (1) numbness, "asleep feeling," prickly feeling or tingling (2) sudden stabbing, burning, or deep aches, or (3) an open persistent sore or gangrene on either foot or leg in the past 12 months.

Clinically meaningful cut points were used to define motor nerve impairment, with motor amplitude <1 mV and motor nerve conduction velocity <40 m/sec being used to define poor function [240]. For vibration threshold, >130 microns was used to define impairment. These cut-points were previously established by Ward and colleagues and are related to quadriceps strength changes over time [215] and incident mobility limitation [216].

3.2.4 Additional Covariates

Clinical site, baseline age, sex, and race were included as demographic characteristics. Several factors potentially related to poor nerve function or walking endurance were also considered as covariates. These measures were from the 2000/01 clinic visit unless otherwise noted.

91

Smoking history (never, former, current) was reported by questionnaire at 1999/2000. Health status (excellent, very good, good, fair, or poor), current alcohol use (drinks per week), physical activity (kilocalories expended per week in walking and stair climbing) [203] were assessed via questionnaire. Body composition (fat mass and bone-free lean mass) was measured using dual-energy X-ray absorptiometry (DXA; 4500A, Hologic, Inc., Bedford, MA). Body mass index (BMI) was calculated in weight in kilograms per squared height in meters using a standard physician's balance scale and stadiometer, respectively.

Diabetes was defined using self-reported physician's diagnosis, hypoglycemic medication use, or by fasting glucose ≥126 mg/dL (8 hour fast), and impaired fasting glucose was defined as fasting glucose level of 100-125 mg/dL after an 8 hour fast [226]. Arterial stiffening and peripheral arterial disease were assessed using ankle brachial index [227], with values <0.9 being used to indicate peripheral arterial disease and >1.3 for arterial stiffening. Hypertension was defined by self-report, medication use, or measured systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg. Poor vitamin B12 status was defined as <260 pmol/L [53] and insufficient renal function was defined as Cystatin-C >1mg/dL [241]. The Center for Epidemiologic Studies Depression Scale (CES-D) score assessed depressive symptoms [242].

Cognitive function was measured using the Digit Symbol Substitution Test [243] at baseline and the Modified Mini-Mental State Examination [244] in 1999/2000. Prevalent coronary heart disease (bypass/coronary artery bypass graft, carotid endarterectomy, myocardial infarction, angina, or congestive heart failure), cerebrovascular disease (transient ischemic attack or stroke), lung disease (asthma, chronic obstructive pulmonary disease, or emphysema), and osteoarthritis in the knee or hip were assessed at baseline.

3.2.5 Statistical Methods

Participants were grouped based upon initial 2000/01 eligibility and completion. Groups included: being ineligible for the LDCW, starting but not completing the full 400m, completing the full LDCW in >7 minutes, and completing the LDCW in ≤7 minutes. Prior work from the aerobic fitness validation study of the LDCW has indicated that those who require >7 minutes (420 seconds) to complete the LDCW likely have significant functional limitations [214]. Descriptive statistics were expressed using proportions for categorical variables and mean ± standard deviation for continuous variables. Tests of trend were used to assess differences in characteristics between the four ordered groups. We also examined the peripheral nerve function measures between the four initial LDCW eligibility and completion groups. Linear mixed-effects models were used to assess the association between peripheral nerve function and change in LDCW completion time over six years of follow-up. Mixed models were used in order to maximize the available data, though only participants who completed the LDCW in 2000/01 and at least one follow-up could be included in the models (n=1178, Figure 5). We used two-sample t-tests for continuous variables and chi-square tests for categorical variables to compare those who were included in the model or not.

Some peripheral nerve function measures were moderately correlated; therefore each peripheral nerve function measure was modeled separately. The date of each Health ABC visit was used in the models as the time parameter. Interaction terms between each predictor and time indicate rate of change in LDCW completion time over the course of the study contributed by that predictor.   We used time-varying covariates for factors that were updated throughout the study (physical activity, weight, body composition). Models were built progressively using forward stepwise techniques, initially retaining factors reaching a significance of p<0.10. We

93

started with unadjusted models including peripheral nerve function and the interaction term between time and peripheral nerve function. Age, sex, race, site, height, and weight and interaction terms for each of the covariates with time were then added for a minimally adjusted model. We further adjusted for baseline health status, lifestyle habits (smoking, alcohol consumption, and physical activity), prevalent diseases and conditions, and mental health and cognitive function variables as well as the time interactions for each of these covariates. For our final, parsimonious model, we retained only factors reaching a significance of $p<0.05$ in the multivariate model. Because of the strong relationship between diabetes and peripheral nerve function, diabetes was retained in the final model regardless of significance. No factors other than these appreciably attenuated the effect of peripheral nerve predictors. For sensitivity analyses we added an interaction term between diabetes and peripheral nerve function, and we also reran the linear mixed models excluding participants with diabetes. We did not impose any structure on the covariance matrix of the random effects, and all models included a random intercept and a random slope for the visit parameter. All data analyses were performed using STATA version 12.1 (StataCorp, College Station, TX).

3.3   RESULTS

Of the participants with complete data on 2000/01 visit LDCW eligibility and at least one measure of nerve function (n=2393; age 76.5 ± 2.9 years; 48.2% male; 38.2% black), 345 participants (14.4%) were ineligible for the LDCW, 407 participants (17.0%) started the walk but were unable to complete the full 10 laps, 113 participants (4.7%) completed the LDCW in >7 minutes, and 1528 participants (52.0%) completed the LDCW in ≤7 minutes. A significant trend

existed for those who completed the LDCW to be slightly younger, have a lower BMI, be less likely to be female or black, and generally be in better health and have fewer chronic conditions than those who were ineligible or unable to complete the full LDCW (Table 6). Specifically, there were approximately 3.5 times more participants who were ineligible for the LDCW reported fair or poor health compared to those who completed the LDCW in ≤7 minutes. Though trends were significant across groups, similarities existed between those who were ineligible, did not complete the full LDCW, and completed in >7 minutes.

Table 6: Participant Characteristics by Long Distance Corridor Walk (LDCW) Eligibility and Completion in the Health, Aging, and Body Composition Study 2000/01 Clinic Visit

Participant Characteristics	Ineligible for LDCW n=345	Did Not Finish LDCW n=407	Completed LDCW in >7 Minutes n=113	Completed LDCW in ≤7 minutes n=1528	P for Trend
Pittsburgh Site % (n)	55.7 (192)	53.6 (218)	43.4 (49)	49.7 (760)	0.03
Age, Mean ± SD	77.2 ± 2.9	76.8 ± 2.9	76.8 ± 3.0	76.3 ± 2.8	<0.001
Female Sex	57.1 (197)	62.7 (255)	62.8 (71)	46.9 (716)	<0.001
Black Race	55.7 (192)	46.2 (188)	54.0 (61)	31.0 (473)	<0.001
Health Fair or Poor	29.2 (100)	22.7 (92)	22.3 (25)	8.3 (127)	<0.001
Body Composition					
BMI	28.9 ± 5.4	28.6 ± 5.3	28.6 ± 5.8	26.4 ± 4.1	<0.001
Bone-Free Lean Mass (kg)	48.6 ± 9.3	48.6 ± 9.7	47.4 ± 9.5	49.3 ± 10.7	0.24
Fat Mass (kg)	28.5 ± 10.1	28.6 ± 9.5	28.8 ± 10.4	24.9 ± 7.7	<0.001
Lifestyle Habits					
Current Smoker	10.2 (34)	10.4 (42)	11.6 (13)	7.5 (113)	<0.001
Drink >1 Drink/Week	25.2 (84)	23.6 (95)	21.4 (24)	33.6 (509)	<0.001
Physical Activity* (kcal/kg/week)	3.1 ± 6.7	3.6 ± 6.0	3.0 ± 7.4	7.3 ± 20.1	<0.001
Prevalent Diseases and Conditions					
Diabetes	29.9 (103)	28.8 (117)	30.1 (34)	26.3 (263)	<0.001
Impaired Fasting Glucose	15.7 (54)	18.0 (73)	13.3 (15)	15.8 (242)	
Hypertension	77.9 (261)	67.5 (272)	68.8 (77)	54.5 (822)	<0.001
Coronary Heart Disease	21.5 (73)	26.3 (105)	15.2 (17)	14.7 (222)	<0.001
Cerebrovascular Disease	11.5 (38)	9.9 (39)	7.3 (8)	4.8 (72)	<0.001
Lung Disease	24.6 (85)	26.3 (105)	17.7 (20)	15.0 (229)	<0.001
Osteoarthritis (Knee or Hip)	17.1 (59)	14.0 (57)	14.2 (16)	9.0 (138)	<0.001
Peripheral Arterial Disease	28.8 (90)	24.5 (94)	19.4 (21)	11.2 (167)	<0.001
Arterial Stiffening	4.5 (14)	4.4 (17)	8.3 (9)	5.2 (79)	<0.001
Insufficient Renal Function**	41.1 (139)	35.9 (143)	37.6 (41)	22.4 (335)	<0.001
Poor Vitamin B12 (<260 pmol/L)	16.0 (52)	16.7 (65)	17.1 (18)	17.4 (344)	0.51
Shortness of Breath While Walking	44.6 (154)	43.7 (178)	38.1 (43)	22.5 (344)	<0.001
Mental Health and Cognitive Function					
CES-D Score***	8.2 ± 7.7	7.4 ± 7.0	7.6 ± 6.0	5.7 ± 5.8	<0.001
3MSE Score****	87.9 ± 8.9	89.0 ± 8.8	86.9 ± 9.6	91.6 ± 7.3	<0.001
Digit Symbol Substitution Score	31.7 ± 14.4	34.7 ± 14.5	31.6 ± 15.2	28.6 ± 14.2	<0.001

*Physical Activity: Kcals/kilogram body weight spent per week walking and stair climbing

**Cystatin-C >1mg/dL

***CES-D: enter for Epidemiologic Studies Depression Scale [242]

****3MSE: Modified Mini-Mental State Examination [244]

Better peripheral nerve function was associated with being eligible for and having better performance on the LDCW (Table 7). In particular, higher motor amplitude, lower vibration threshold, detection of both monofilaments, and no symptoms of peripheral neuropathy were associated with better LDCW performance (p<0.05 for each). Motor nerve conduction velocity was not associated with LDCW eligibility or completion.

Table 7: Peripheral Nerve Function by LDCW Eligibility/Completion Group

Peripheral Nerve Function Measure	Ineligible for LDCW n=345	Did Not Finish LDCW n=407	Completed LDCW in >7 Minutes n=113	Completed LDCW in ≤7 minutes n=1528	P for trend
Motor Nerve Function					
Motor amplitude, mV, Mean ± SD	3.0 ± 2.1	3.1 ± 2.0	3.1 ± 2.0	3.5 ± 2.0	<0.001
Poor amplitude	19.9 (47)	13.8 (41)	15.0 (12)	8.8 (110)	<0.001
Sensory Nerve Function					
Conduction velocity, m/sec	43.2 ± 5.6	43.3 ± 5.2	44.8 ± 5.7	43.7 ± 5.4	0.33
Poor conduction velocity	21.1 (52)	22.7 (63)	20.3 (15)	21.9 (262)	0.37
Vibration threshold, microns	56.0 ± 39.5	52.5 ± 35.4	55.2 ± 35.8	50.1 ± 34.7	0.03
Poor vibration threshold	9.9 (32)	4.8 (19)	9.2 (10)	5.0 (74)	0.008
1.4 monofilament insensitivity	38.3 (127)	36.7 (35)	42.7 (84)	36.2 (23)	<0.001
10-g monofilament insensitivity	13.0 (43)	10.3 (41)	14.6 (16)	7.1 (107)	
Symptoms of Peripheral Neuropathy					
One symptom	31.0 (105)	31.0 (125)	30.1 (34)	24.9 (379)	<0.001
Two or More Symptoms	19.2 (65)	11.4 (46)	6.2 (7)	7.9 (120)	

In the longitudinal analysis examining change in LDCW completion time over the 6 years of follow-up (n=1178; age 76.2 ± 2.8 years; 52.1% male; 31.2% black), worse motor amplitude (per 1 SD lower), worse vibration threshold (per 1 SD higher) and poor vibration threshold (threshold >131 microns), 10g and 1.4gmonofilament insensitivity were associated with 3.9, 5.2, 19.6, 9.3, and 20.7 seconds slower initial LDCW completion time, respectively, (Table 8) when adjusting for age, sex, race, site, height, and weight (p<0.05 for all). In general, the relationships were slightly attenuated after further adjusting for health habits and health conditions, though the same significant relationships remained with the exception of lower motor amplitude (per SD poorer amplitude). Poor vibration perception threshold (>130 microns) was associated with completing the LDCW 16.0 seconds slower, and an additional 4.3 seconds of slowing per year compared to those with vibration perception threshold ≤130 microns. Standard 10-g monofilament insensitivity was associated with completing the LDCW 14.1 seconds slower and an additional 4.3 seconds of slowing per year. No associations between either motor nerve conduction velocity or presence of symptoms of peripheral neuropathy were found in any of the models. In sensitivity analyses, no significant interaction was found between peripheral nerve function and diabetes, and all results remained consistent when excluding individuals with diabetes.

Compared to those included in the mixed models, those not included in the longitudinal analyses were slightly older (mean age 76.9 ± 2.9 vs. 76.2 ± 2.8 years, p<0.001), more likely to be women (55.8% vs. 52.1%, p<0.001) and more likely to be black (44.9% vs. 32.2%, p<0.001). Those not included in the models also had worse motor nerve amplitude (3.1 ± 1.9 vs. 3.6 ± 2.0 mV, p<0.001), higher vibration perception threshold (53.6 ± 36.4 vs. 49.5 ± 34.6 microns, p=0.005), were more likely to have 10-g (10.7% vs. 7.0%) or 1.4-g (37.6% vs. 36.1%)

monofilament insensitivity (p=0.004), and were more likely to report at least one symptom of peripheral neuropathy (42.3% vs. 31.8%, p<0.001). No difference existed in motor nerve conduction velocity between those excluded and those included in the longitudinal analysis (43.5 ± 5.4 vs. 43.7 ± 5.8 m/sec, p=0.54). The most common reasons for not being included in the mixed models were not finishing the initial LDCW (n=407) and meeting exclusion criteria at the initial LDCW assessment (n=345).

Table 8: Peripheral nerve functioning and longitudinal performance in LDCW from 2000/01 to 2006/07 in the Health, Aging and Body Composition Study

	Model 1		Model 2		Model 3: Final Model	
	Standardized Betas		Standardized Betas		Standardized Betas	
	Main Effect	Time Interaction	Main Effect	Time Interaction	Main Effect	Time Interaction
Motor Nerve Function						
SD lower amplitude, mV	3.9*	0.5	3.7*	0.3	2.2	0.3
Poor amplitude	5.8	4.8**	3.2	4.4**	-0.9	4.7**
SD Slower Conduction Velocity, m/sec	-0.8	-0.1	-0.5	0.3	1.1	0.3
Poor Conduction Velocity	-2.1	-0.04	0.9	-0.3	-3.9	-0.5
Sensory Nerve Function						
SD higher vibration perception threshold, μ	5.2**	1.6**	4.9**	1.7**	3.2*	1.7**
Poor vibration perception threshold	19.6**	4.1*	20.1**	4.9**	16.0*	4.3*
1.4 monofilament insensitivity	9.3**	-0.6	8.6**	-0.6	6.7*	-0.7
10-g monofilament insensitivity	20.7**	4.4**	16.3**	4.5**	14.1**	4.3**

*p<0.05, **p≤0.01. **Model 1:** Adjusted for age, sex, race and site. **Model 2:** Adjusted for Model 1 + health status, physical activity, current cigarette smoking, lean mass and fat mass
Model 3: *Motor amplitude and conduction velocity*: Model 2 + PAD, cerebrovascular disease, diabetes, insufficient renal function, shortness of breath while walking, and DSST score. Cigarette smoking and health status were removed from Model 3.
Model 3: *Sensory nerves function*: Model 2 + PAD, cerebrovascular disease, diabetes, insufficient renal function, DSST score, CES-D and hypertension. Cigarette smoking and health status were removed from Model 3.
Model 3: *Vibration perception threshold*: Model 2 + PAD, cerebrovascular disease, diabetes, insufficient renal function, DSST score, CES-D and hypertension. Health status was removed from Model 3.

3.4   DISCUSSION

In this cohort of community-dwelling older adults, poorer motor and sensory peripheral nerve function was related to worse endurance walking performance and sensory nerve function was associated with greater slowing of endurance walking speed over time. Additionally, peripheral nerve function and presence of symptoms of neuropathy were related to the inability to complete the LDCW. Peripheral nerve dysfunction should be appreciated as a risk factor in the disablement pathway, and these findings add to the growing body of literature indicating that peripheral nerve dysfunction in older adults is related to adverse lower-extremity outcomes. Though peripheral nerve dysfunction is often thought to be primarily a concern for those with diabetes, these results support previous work indicating that peripheral nerve function is an important predictor of mobility related outcomes in older adults independent of diabetes [31,216].

The sensory and motor nerves of the lower extremities play key roles in gait.   Sensory nerves detect touch, vibration, and other sensations regarding the external environment, and motor nerves that relay signals from the central nervous system that allow for voluntary movement. Sensory peripheral nerve function in the lower extremities is crucial for perception of joint position, posture, and balance—all factors that play roles in walking quickly. Vibration perception threshold and standard monofilament insensitivity were strongly associated with the slowing of endurance walking over time. Worse vibration perception threshold has been shown to be associated with worse balance and slower gait in older adults without diabetes or overt peripheral neuropathy [31,34,95,245].

Little work exists relating sensorimotor peripheral nerve function and endurance walking in older adults. McDermott and colleagues found in the InCHIANTI study that motor nerve conduction velocity was associated with slower completion of a fast-paced 400m walking test for older adults [66], though this study did not include measures of motor nerve amplitude, sensory peripheral nerve function or the assessment of symptoms of peripheral neuropathy. The association with conduction velocity is in contrast to our results where we found that sensory peripheral nerve function measures were associated with worse walking endurance and greater slowing over time, while there was no association with motor nerve conduction velocity. Age and racial differences between the InCHIANTI and Health ABC cohorts may have contributed to the differences in findings. Our null findings with nerve conduction velocity are consistent with prior work in this cohort. Worse motor nerve amplitude (a sign of axonal degeneration) but not worse motor nerve conduction velocity (a sign of demyelination) has been shown to be associated with lower extremity physical performance [31] and incident lower extremity limitation [216] in the Health ABC cohort.

The effect size of poor sensory peripheral nerve function was similar in magnitude to those of common risk factors associated with worse walking endurance. For example, current smoking was independently associated with completing the initial LDCW 14.0 seconds slower, and those with cerebrovascular disease completed the initial LDCW 16.1 seconds slower than those without cerebrovascular disease, though neither of these factors were significantly associated with greater slowing over time. This is similar to the effect of poor vibration perception threshold (16.0 seconds slower) and 10g monofilament insensitivity (14.1 seconds) on initial LDCW completion time, and these factors were each related to greater slowing over time (4.3 seconds slower for each). This effect is also approximately equivalent to 5 years of aging.

Peripheral nerve impairments are common in older adults,[30] and improving functional outcomes in those with these impairments may be important on many levels. Work in diabetic populations has shown that deficits in lower extremity peripheral nervous system function are associated with altered gait biomechanics [118-120]. Because of the associations between gait alterations and injuries and falls [117,122-124], these factors may also be in the pathway between peripheral nerve dysfunction and worse lower-extremity function for older adults. Sensory nerve impairments in particular may increase the risk of falling due to the inability to adequately sense the lower extremities. Physical activity can help older adults improve physical function and delay persistent mobility limitations [246], however, whether physical activity interventions can be used to reduce physical functional impairments due to poor peripheral nerve function is currently unknown.

A major strength of this study is that we incorporated several measures of both motor and sensory nerve function as well as symptoms associated with peripheral neuropathy. Including objective and subjective measures is especially important because an absence of symptoms does not necessarily equate to an absence of disease [88], particularly in older adults where nerve function deficits may be asymptomatic [30]. In addition, the large sample size and longitudinal study design allowed an examination of several factors that could potentially influence peripheral nerve function and/or walking endurance over time.

Though the use of mixed models allowed us to maximize our available data, only those who completed the LDCW at the 2000/01 clinic visit and at least one follow-up could be used in the longitudinal analysis. Those who could not complete the LDCW at the 2000/01 clinic visit or at least one follow-up had worse peripheral nerve function compared to those who completed the LDCW, and it is possible that those without a 2000/01 clinic visit or at least one additional

103

follow-up had the worst peripheral nerve function of all. Thus, we may have underestimated the true effect of peripheral nerve function on the worsening of walking endurance. Unfortunately, the retention bias resulting from the fact that participants returning for clinic visits are healthier than those who did not is applicable to most cohort studies of older adults [247]. An additional limitation is that our physical activity assessment measure was restricted to only kilocalories per kilogram body weight spent per week in walking and stair climbing, as these were the only physical activities assessed consistently throughout the selected follow-up period. Some limited evidence exists that adults with well controlled diabetes and higher levels of physical activity are less likely to have peripheral neuropathy [158], though additional work is needed in determining the relationship between physical activity and peripheral nerve function.

In conclusion, poorer sensory and motor peripheral nerve function in older adults is related to slower endurance walking and greater slowing over time. Interventions to reduce the burden of sensorimotor peripheral nerve function impairments should be considered in order to help older adults to maintain walking endurance—which can be crucial for remaining independent in the community.

4.0 SENSORIMOTOR AND CARDIOVASCULAR AUTONOMIC PERIPHERAL NERVE FUNCTION IN OLDER ADULTS IN THE HEALTH, AGING AND BODY COMPOSITION STUDY

ABSTRACT

Age-related peripheral nervous system (PNS) impairments are prevalent, with sensorimotor impairments associated with poor mobility and cardiac autonomic impairments associated with adverse cardiac outcomes. Although sensorimotor and cardiac autonomic impairments have been found associated in persons with diabetes, the nature of the relationship in general community-dwelling populations of older adults is unknown. Health ABC Study participants (n=2393, age=76.5±2.9, 52% women, 38% black) underwent peripheral nerve testing at the 2000/01 clinic visit. Nerve conduction amplitude and velocity were measured at the peroneal motor nerve. Sensory nerve function was measured using vibration detection threshold and monofilament testing at the big toe. Symptoms of lower-extremity peripheral neuropathy included numbness or tingling and sudden stabbing, burning, pain, or aches in the feet or legs. Cardiac autonomic function measures included resting HR (HR), orthostatic hypotension, as well as HR range and recovery to submaximal exercise testing. Poor motor conduction velocity (<40 m/sec) was associated with higher odds of orthostatic hypotension (OR=1.57, p=0.05), while poor motor amplitude (<1 mV) was associated with higher resting HR (β= 2.20, p=0.001). Insensitivity to the 1.4g monofilament was associated with worse HR range (increase in HR from

resting to the end of the submaximal test, adjusting for performance; β=-1.56, p=0.028). Other PNS measures were not related. Associations remained were independent of age, sex, race, diabetes, and health and lifestyle factors known to influence PNS function. Sensorimotor and autonomic function are independently related, and future studies should investigate common underlying processes for the development of multiple PNS impairments in older adults.

4.1   INTRODUCTION

The peripheral nervous system (PNS) consists of two distinct divisions, the sensorimotor and the autonomic nervous systems. Even though both play integral roles in providing information to the central nervous system to appropriately respond to stimuli and in controlling automatic functions of the body, typically they are examined as separate entities. PNS aging is characterized by a phenomenon known as "selective vulnerability" in which locally specific structural and functional changes can occur which vastly affect some groups of neurons while leaving others relatively intact [248]. In particular, long, myelinated axons (like those innervating the lower limbs) and sympathetic neurons are vulnerable to damage. PNS dysfunction is often considered in the context of diabetes or specific neurological conditions, though age-related impairments may occur in either division even in the absence of any pathologic conditions [28].

Sensorimotor peripheral nerve function impairments are common in older adults [29,30], with recent work from Health ABC showing that 55% of older adults (N=1,680; age 76.5 ± 2.9 years) without mobility disability have evidence of lower extremity peripheral nerve impairments [216]. Sensorimotor nerve function impairments in the lower extremities are

associated with poorer lower extremity physical function [31-34], worse lower extremity muscle strength [36,215] and power [37], and an increased risk for falls [38-41] and mobility limitations [216]. In contrast to lower extremity sensorimotor PNS impairments that impact sensory perception and motor control of the lower limbs, cardiac autonomic impairments inhibit the ability of the cardiovascular system to appropriately respond to internal and external stimuli and maintain homeostasis. Autonomic nerve function impairments can affect other bodily systems, though cardiac autonomic nerve impairments are often seen as the most serious given their association with adverse cardiovascular outcomes and death [133,140,142,249,250]. Despite these risks, autonomic impairments are underappreciated as risk factors in epidemiologic studies of older adults. Though under-studied, autonomic impairments are common in older adults. In the Irish Longitudinal Study on Ageing (n=4475, age 50+ years), 6.9% of the study cohort and 18.5% of participants age 80 and older had postural hypotension, an indicator of cardiac autonomic impairment [251].

Although sensorimotor and autonomic nerve impairments seem very different, they may be related. Damage to sensorimotor and autonomic nerve fibers in diabetes has largely been attributed to damage related to hyperglycemia [132,252-254] and poor metabolic control; although advanced glycation end products [255,256], inflammation [257,258], dyslipidemia [259] and other cardiovascular risk factors [73,260-262] appear to play roles as well. Work in populations with diabetes (both Type 1 and Type 2) provides evidence that worse sensorimotor function is associated with an increased risk of cardiovascular events [263,264]. Additionally, cardiac autonomic neuropathy is associated with higher odds of developing diabetic somatic peripheral neuropathy [261], with the severity of cardiac autonomic neuropathy related to a higher prevalence of peripheral neuropathy [265].

Aside from the extensive studies of neuropathy in diabetic populations, the relationship between sensorimotor and cardiac autonomic function is largely unexamined in either diabetes or general populations of older adults. Age-related PNS changes can occur independently of diabetes. Associations between age-related sensorimotor and autonomic impairments have not been explored and may differ from impairments attributed to diabetes. However, because of the common underlying risk factors associated with sensorimotor and autonomic peripheral nerve impairments (particularly cardiovascular risk factors), it is plausible that those with worse sensorimotor function may also have worse cardiac autonomic function. The purpose of this study was to examine the independent association between lower-extremity sensorimotor peripheral nerve function and cardiac autonomic function in older adults.

4.2   METHODS

4.2.1   Participants

Study participants were from the Health, Aging and Body Composition Study (Health ABC) who completed a clinic visit in 2000/01. Briefly, Health ABC is a longitudinal cohort study of black and white, initially well-functioning, community dwelling older men and women from Pittsburgh, PA and Memphis, TN (n=3075; age 70-79; 48.4% male; 41.6% black at baseline). The purpose of Health ABC was to investigate factors related to the development of functional limitations and disability [126]. Participants were recruited via mailings to a random sample of white Medicare beneficiaries and to all age-eligible black community residents. Eligibility criteria for this study included: having no self-reported difficulty in walking ¼ mile,

climbing 10 steps, or performing any basic activity of daily living; no life-threatening cancers; and plans to remain in the study area for at least the next three years. Participants underwent baseline clinic visits between April 1997 and June 1998.

Of the original cohort, 2404 participants completed the 2000/01 clinic visit (187 participants were deceased, 74 had a home visit, 233 phone visit, 9 proxy visit, 9 withdrew from study, and 105 were missing for other reasons). A total of 2393 participants underwent sensorimotor peripheral nerve function testing and were considered for this analysis (1 refused nerve exam, 4 were missing nerve measures, 6 had other missing data). All of the 2393 participants included for this analysis had at least one measure of cardiac autonomic function. Figure 6 shows the participant flow chart of the analytic samples for this study. All participants provided written informed consent before participating in the study. All study protocols were approved by institutional review boards at the University of Pittsburgh and University of Tennessee Health Science Center.
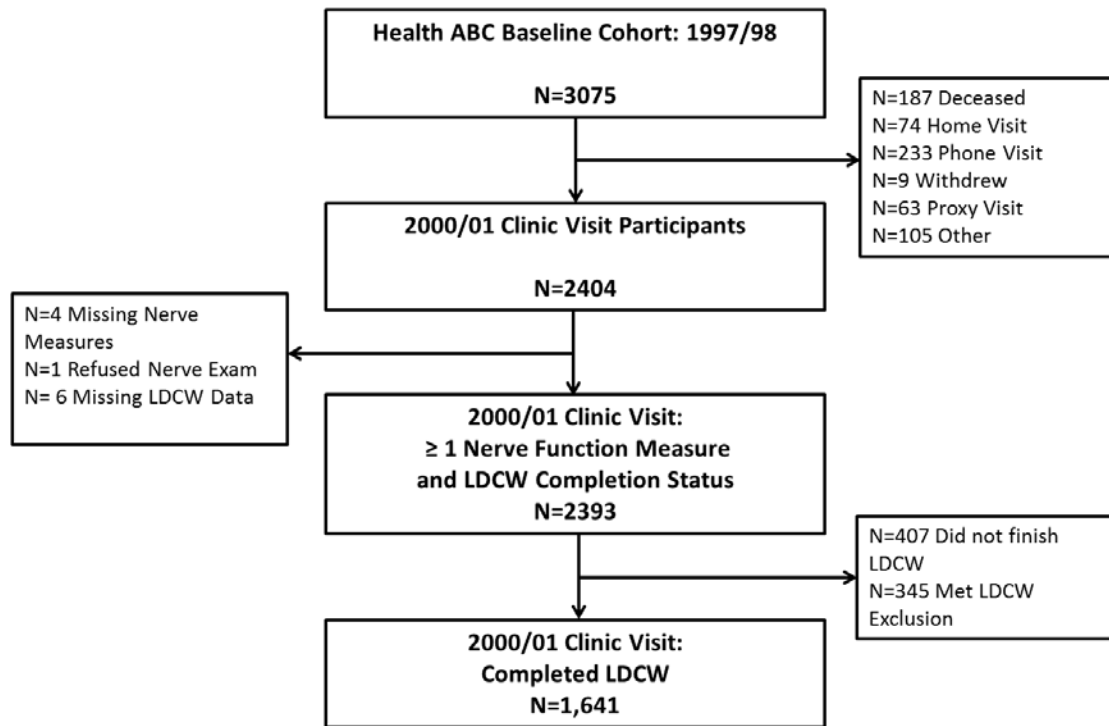
```
Health ABC Baseline Cohort: 1997/98
N=3075
                                          N=187 Deceased
                                          N=74 Home Visit
                                          N=233 Phone Visit
                                          N=9 Withdrew
                                          N=63 Proxy Visit
                                          N=105 Other

2000/01 Clinic Visit Participants
N=2404

N=4 Missing Nerve
Measures
N=1 Refused Nerve Exam
N= 6 Missing LDCW Data

2000/01 Clinic Visit:
≥ 1 Nerve Function Measure
and LDCW Completion Status
N=2393
                                          N=407 Did not finish
                                          LDCW
                                          N=345 Met LDCW
                                          Exclusion

2000/01 Clinic Visit:
Completed LDCW
N=1,641
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Figure 6: Participant Flow Chart for the 2000/01 Health ABC Clinic Visit

4.2.2   Sensorimotor Peripheral Nerve Function

Lower extremity sensory and motor nerve function testing was performed by a trained examiner. Peroneal motor nerve conduction responses were obtained at the extensor digitorum brevis muscle, with recording of amplitude (in millivolts) and motor nerve conduction velocity (in meters per second), as previously described [89]. Peroneal nerve was stimulated at the popliteal fossa and ankle using the NeuroMax 8 (XLTEK, Oakville, Ontario, Canada). Sensory nerve function was assessed via vibration threshold and light touch detection. Vibration detection threshold (in microns) was measured at the bottom of the great toe with a VSA-3000 Vibratory Sensory Analyzer (Medoc, Durham, NC). Light touch sensitivity testing was performed using a standard 10-g monofilament and light touch 1.4-g monofilament (North Coast

Medical, Morgan Hill, CA). Monofilament insensitivity was defined as the inability to detect at least 3 of 4 touches at the dorsum of the great toe. If needed, feet were warmed to 30°C before nerve testing. All measures were performed on the right side unless contraindicated due to knee replacement, amputation, trauma, ulcer, or recent surgery, in which case testing was performed on the left side. Symptoms of peripheral neuropathy were collected via self-report using a modified version of the Michigan Neuropathy Screening Instrument questionnaire [108]. Presence of symptoms included reporting any of the following on either foot or leg in the past 12 months: (1) numbness, "asleep feeling," prickly feeling or tingling (2) sudden stabbing, burning, or deep aches, or (3) an open persistent sore or gangrene. Clinically meaningful cut-points of motor amplitude of <1 mV and motor nerve conduction velocity <40 m/sec were used to define poor function [240]. For vibration threshold, >130 microns was used to define impairment. These cut-points were previously used by Ward and colleagues, and have been shown to be associated with lower quadriceps strength [215] and worse endurance walking performance [266], as well as incident mobility limitation [216].

4.2.3   Cardiac Autonomic Function

Radial pulse was used for resting heart rate (HR). Postural hypotension was assessed using the difference between blood pressure measurements taken while in a seated position, and one minute after transitioning to a standing position. Diastolic postural hypotension measured in this manner predicted falls in diabetic participants in Health ABC [39]. Postural hypotension was defined as drop of >20 mmHg of systolic or >10mmHg diastolic blood pressure between seated and standing measurements [267].

Cardiac autonomic function was also assessed using the cardiovascular response to the long distance corridor walk (LDCW) [239]. Participants who were ineligible for the LDCW (n=345) or who did not complete the full 10 laps (n=407) were not included in analyses involving HR range or recovery. Briefly, the LDCW is an over ground, submaximal walking test which has been validated to provide an estimate of aerobic fitness in older adults [214]. HR range was defined as the difference between resting HR and HR at the end of the LDCW, while HR recovery was defined as the difference between HR at the end of the LDCW and HR 2 minutes post-test. These methods have been used previously by Newman and colleagues in assessing the association between LDCW performance and incident cardiovascular disease, mortality, and mobility limitation and disability in Health ABC [268]. Because HR parameters measured during submaximal exercise are influenced by exertion, models for HR range and HR recovery were adjusted for LDCW completion time. In Paper 2 we found that participants who had worse peripheral nerve function had slower LDCW completion times were more likely to complete the LDCW in greater than 7 minutes, an indicator of very low aerobic fitness [269]. We tested for interactions between sensorimotor function and completion time on HR range and HR recovery and stratified analyses by completion time (completed in ≤7 minutes vs. >7 minutes) if evidence of a significant interaction existed.

4.2.4 Covariates

Age, sex, race, and clinical site were included as demographic characteristics. In addition, several factors which could potentially influence sensorimotor or cardiovascular function were considered as possible covariates. All factors were measured at the 2000/01 clinic visit unless otherwise stated. Lifestyle factors were assessed via self-report and included:

smoking history (never, former, current; reported in 1999/2000), current drinking frequency (drinks per week), and physical activity (kilocalories expended per week in walking and stair climbing) [203]. Body composition (fat mass and bone-free lean mass) was measured using dual-energy X-ray absorptiometry (DXA; 4500A, Hologic, Inc., Bedford, MA). Body mass index (BMI) was calculated in weight in kilograms per squared height in meters using a standard physician's balance scale and stadiometer, respectively.

Diabetes was defined using self-reported physician's diagnosis, hypoglycemic medication use, or by fasting glucose ≥126 mg/dL (8 hour fast) and impaired fasting glucose was defined as fasting glucose level of 100-125 mg/dL (8 hour fast).[226] Ankle brachial index values of <0.9 indicated peripheral arterial disease and >1.3 for arterial stiffening [227]. Hypertension was defined by self-report, medication use, or systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg measured at the clinic visit. Poor vitamin B12 status was defined as <260 pmol/L [53] and insufficient renal function was defined as Cystatin-C >1mg/dL [241].

Other prevalent diseases or conditions assessed at baseline (1997/98) included cardiovascular disease (bypass/coronary artery bypass graft, carotid endarterectomy, myocardial infarction, angina, or congestive heart failure), Parkinson's disease, cerebrovascular disease (transient ischemic attack or stroke), lung disease (asthma, chronic obstructive pulmonary disease, or emphysema), and osteoarthritis in knee or hip. Self-reported pain in the lower extremities while walking was assessed via questionnaire. Depressive symptoms were collected using the Center for Epidemiologic Studies Depression Scale (CES-D) [242]. Medications known to potentially influence HR, blood pressure, or cholesterol were included from the detailed medication inventory collected at the 1999/2000 visit. These medications included use

of beta blockers, anti-hypertensive medications (based on the Iowa Drug Information Service),
calcium-channel blockers, tricyclic antidepressants [139] and statins. Levels of total cholesterol,
interleukin-6 (IL-6), and C-reactive protein (CRP) were assessed from blood samples collected
by venipuncture after an overnight fast.

4.2.5   Statistical Methods

Descriptive statistics and measures of sensorimotor and autonomic function were
expressed using mean ± standard deviations and proportions for continuous and categorical
variables, respectively.   Means and proportions were compared between men and women
because of the potential sex-differences in PNS function [270,271].   T-tests and chi-squared
tests, respectively, compared descriptive factors unless non-parametric versions of these tests
were more appropriate.   We examined the correlations between sensorimotor and cardiac
autonomic function using Pearson correlation coefficients for continuous measures, and
Spearman correlation coefficients for correlations involving interval measures.

We modeled the effect of sensorimotor function on continuous indicators of cardiac
autonomic function (resting HR, HR range, and HR recovery) using linear regression.   We also
split these continuous outcomes into quintiles, and modeled the effect using ordinal or
multinomial logistic regression when appropriate to account for potential non-linear
relationships.   The effect of sensorimotor peripheral nerve function and odds of postural
hypotension were modeled using logistic regression.

We began with minimally adjusted models, and progressively added covariates using
manual stepwise regression techniques.   Covariates reaching a significance level of $p<0.10$ were
considered for a multivariable model.   Only factors reaching a significance of $p<0.05$ in the

114

multivariable model were included in the final, parsimonious model, though age, sex, race, site, and diabetes were forced into final models regardless of significance. Because measures of sensorimotor function are moderately correlated (r=0.32, p<0.001 between motor amplitude and conduction velocity), separate models were built for each. Models were sex stratified if interactions were observed between sex and sensorimotor function in predicting autonomic function. We also ran sensitivity analyses using age tertiles rather than continuous age in order to determine whether associations between sensorimotor and autonomic function differed by age group or the effect of age was not linear. Final sensitivity analyses were run removing participants taking any medication that could potentially influence heart rate (beta blockers tricyclic antidepressants, and calcium channel blockers).

4.3   RESULTS

Women and men in this study differed on many lifestyle and health factors (Table 9). The prevalence of select diseases and conditions varied by sex, with women being less likely to have diabetes or impaired fasting glucose, coronary heart disease, arterial stiffening, insufficient renal function, or poor vitamin B12 status, though women were more likely to have hypertension and osteoarthritis, and reported more depressive symptoms. Women had higher levels of CRP and total fasting cholesterol, while men had slightly higher values of IL-6. Women were more likely to take hypertensive, calcium channel blockers, and tricyclic antidepressants.

Table 9: Health ABC 2000/01 Clinic Visit Participant Characteristics by Sex

Participant Characteristics	Men N= 1154	Women N=1239	P-Value
Pittsburgh Site % (n)	51.2 (591)	50.7 (628)	0.80
Age, Mean ± SD	76.7 ± 2.9	76.4 ± 2.9	0.01
Black Race	33.5 (386)	42.6 (528)	<0.001
Health Fair or Poor	13.4 (154)	15.4 (190)	0.17
Anthropomorphic Characteristics and Body Composition			
Body Mass Index	27.1 ± 4.0	27.4 ± 5.4	0.057
Height, meters	1.7 ± 0.7	1.6 ± 0.6	<0.001
Weight (kg)	81.0 ± 13.4	69.9 ± 14.6	<0.001
Bone-Free Lean Mass (kg)	57.0 ± 7.3	41.5 ± 6.2	<0.001
Fat Mass (kg)	23.9 ± 7.4	28.4 ± 9.2	<0.001
Lifestyle Habits			
Current Smoker	8.9 (101)	8.3 (101)	<0.001
Drink >1 Drink/Week	39.0 (442)	21.9 (267)	<0.001
Physical Activity* (kcal/kg/week)	7.1 ± 18.2	4.7 ± 15.0	<0.001
Prevalent Diseases and Conditions			
Diabetes	25.0 (289)	18.4 (228)	<0.001
Impaired Fasting Glucose	20.0 (231)	12.4 (153)	
Hypertension	57.8 (658)	63.4 (774)	0.01
Parkinson's Disease	0.7 (8)	0.5 (6)	0.50
Coronary Heart Disease	24.8 (269)	13.3 (155)	<0.001
Cerebrovascular Disease	6.4 (72)	7.1 (85)	0.54
Lung Disease	16.2 (187)	19.6 (243)	0.03
Osteoarthritis (Knee or Hip)	10.4 (120)	16.1 (200)	<0.001
Peripheral Arterial Disease	16.2 (180)	16.2 (192)	<0.001
Arterial Stiffening	7.2 (80)	3.2 (38)	
Insufficient Renal Function**	33.1 (376)	23.5 (282)	<0.001
Poor Vitamin B12 (<260 pmol/L)	19.9 (221)	14.4 (169)	<0.001
Depressive Symptoms	5.6 ± 5.9	7.2 ± 6.8	<0.001
Pain in Legs While Walking	23.0 (264)	24.9 (307)	0.48
Laboratory Measures			
CRP, mg/L	4.4 ± 9.6	5.3 ± 7.3	0.014
IL-6, pg/mL	3.8 ± 3.7	3.5 ± 3.8	0.048
Total Fasting Cholesterol, mg/dL	180.6 ± 32.8	202.1 ± 38.4	<0.001
Medication Use			
Statins	20.7 (232)	18.8 (228)	0.26
Beta Blockers	17.5 (199)	16.9 (208)	0.71
Calcium Channel Blockers	21.3 (242)	25.2 (310)	0.02
Anti-hypertensive Medications	56.2 (640)	61.6 (758)	0.008
Tricyclic Antidepressants	1.3 (15)	3.3 (40)	0.002

*Physical Activity: Kilocalories/kilogram body weight spent per week in walking and stair climbing; **Cystatin-C >1mg/dL; ***CES-D: Center for Epidemiologic Studies Depression Scale

Several significant differences in sensorimotor and autonomic function were observed by sex (Table 10). Women had better motor and sensory peripheral nerve function, but were more likely to report symptoms of peripheral neuropathy. Women had slightly higher resting HR, but were less likely to have postural hypotension and also had a better HR range and recovery to the LDCW compared to men.

Table 10: Sensorimotor and Cardiac Autonomic Function by Sex

Peripheral Nervous System Function Measure	Men N=1154	Women N=1239	P-Value
Motor Nerve Function			
Motor amplitude, mV, Mean ± SD	3.0 ± 1.9	3.6 ± 2.0	<0.001
Poor amplitude, %(n)	15.7 (137)	7.4 (73)	<0.001
Conduction velocity, m/sec	41.7 ± 4.8	45.3 ± 5.3	<0.001
Poor conduction velocity	33.2 (272)	12.9 (120)	<0.001
Sensory Nerve Function			
Vibration threshold, microns	59.8 ± 37.1	44.1 ± 32.5	<0.001
Poor vibration threshold	8.7 (96)	3.2 (39)	<0.001
1.4 monofilament insensitivity	40.9 (463)	33.2 (404)	<0.001
10-g monofilament insensitivity	12.3 (139)	5.6 (68)	
Symptoms of Peripheral Neuropathy			
One symptom	25.7 (296)	28.3 (347)	0.005
Two or More Symptoms	8.2 (94)	11.8 (144)	
Autonomic Nervous System Function			
Resting HR, BPM, Mean ± SD	62.3 ± 10.8	63.6 ± 10.0	0.002
Postural Hypotension	7.2 (83)	6.1 (76)	0.30
HR Range*	43.4 ± 14.3	44.6 ± 15.1	0.087
HR Recovery	17.8 ± 10.5	18.9 ± 10.5	0.029

*HR at End of LDCW – Resting HR, BPM, Mean ± SD

**HR at End of LDCW – HR 2 Min Post Test, BPM, Mean ± SD

Despite the differences in participant characteristics and PNS function by sex, no significant interactions by sex existed, and thus the following results were not sex-stratified. Several of the motor and sensory nerve measures were significantly correlated with the indicators of cardiac autonomic function, although no associations were observed with symptoms of peripheral neuropathy (Table 11).

Table 11: Correlation* Matrix of Continuous Sensorimotor and Autonomic Function Measures

	Resting HR	**Orthostatic Hypotension**	**HR Range**	**HR Recovery**
Motor Nerve Amplitude	**-0.052** **(0.026)**	0.014 (0.547)	0.037 (0.179)	0.019 (0.481)
Motor Nerve Conduction Velocity	0.027 (0.226)	**-0.090** **(<0.001)**	**0.097** **(<0.001)**	**0.057** **(0.044)**
Vibration Threshold	0.005 (0.830)	**0.046** **(0.029)**	**-0.047** **(0.002)**	-0.022 (0.378)
Monofilament Insensitivity	-0.010 (0.650)	-0.005 (0.806)	**-0.051** **(0.041)**	0.008 (0.738)
Presence of Neuropathy Symptoms	0.013 (0.547)	0.025 (0.224)	0.018 (0.474)	0.022 (0.0372)

*Pearson correlation coefficients shown for correlations of continuous measures, and Spearman correlation coefficients shown for correlations involving interval measures. Partial correlation coefficients are shown for HR Range and HR Recovery to account for long distance corridor walk completion time.

Figure 7 displays the mean unadjusted resting heart rate by sensorimotor function. After adjusting for age, study site, race, diabetes, beta blocker use, CRP and total fasting cholesterol, each standard deviation of lower motor nerve amplitude was associated with a resting HR of 1.03 higher beats per minute, and having poor motor amplitude ($< 1mV$) was associated with higher resting HR of 2.20 beats per minute ($p=0.005$). After removing participants taking medications that could influence heart rate ($n=876$), poor amplitude was associated with a higher resting heart rate of 2.48 beats per minute ($p=0.011$). The relationship between amplitude and resting heart rate was attenuated when removing participants taking any medication that could influence resting heart rate, though results remained statistically significant.
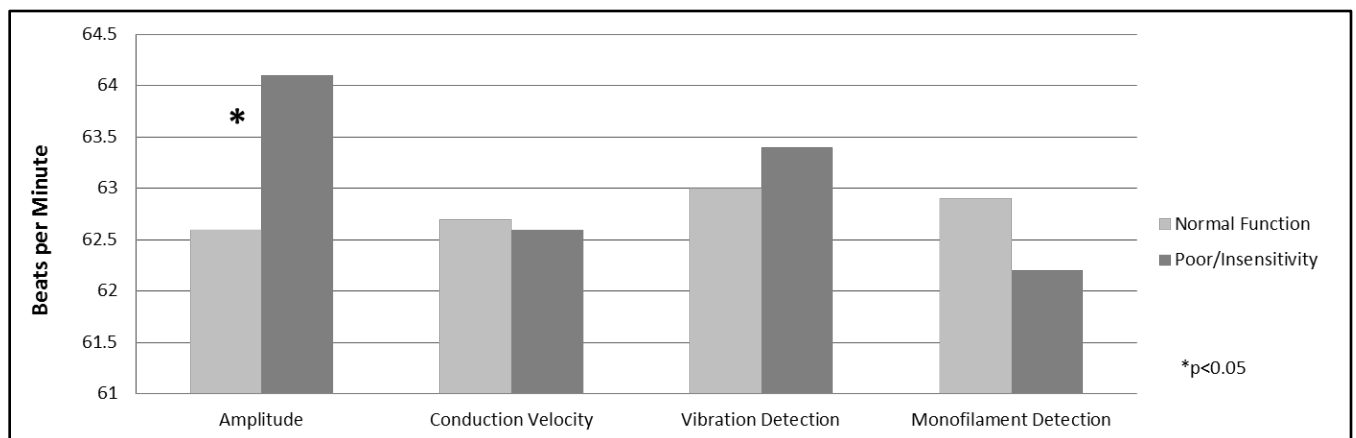

Figure 7: Mean Unadjusted Resting Heart Rate by Sensorimotor Function

Unadjusted odds of orthostatic hypotension by sensorimotor function are displayed in Figure 8. In adjusted models, only conduction velocity remained associated with odds of orthostatic hypotension. Each standard deviation of slower motor nerve conduction velocity was associated with 1.37 higher odds of orthostatic hypotension (p=0.005) after adjusting for age, sex, race, site, diabetes, poor health, and IL-6. Poor conduction velocity (< 40m/sec) was associated with 1.57 higher odds of orthostatic hypotension (p=0.05). Finally, those with 1.4g monofilament insensitivity had an average HR range of 1.43 beats per minute lower compared to those who were able to detect the 1.4g monofilament (p=0.036). No associations remained with HR recovery after adjusting for common covariates.
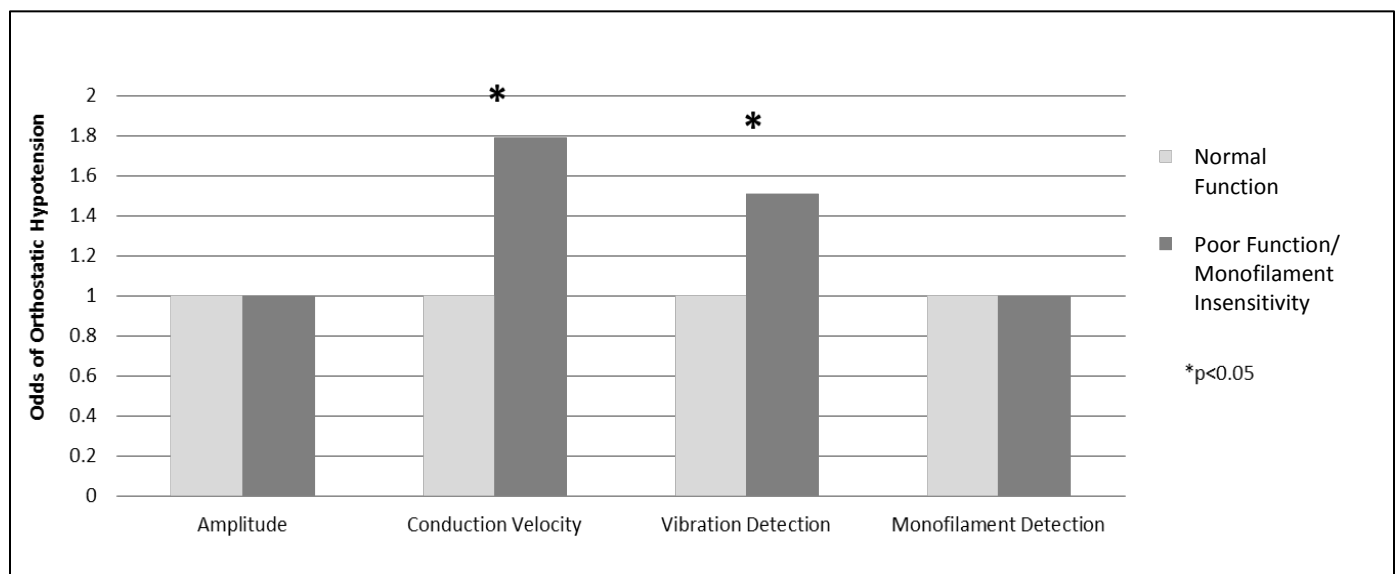

Figure 8: Unadjusted Odds of Orthostatic Hypotension by Sensorimotor Function

HR range and recovery were negatively correlated with LDCW completion time (r = -0.309 and r = -0.328, respectively, p<0.001 for each.) In adjusted models, associations between monofilament detection (1.4g and 10g insensitivity combined for statistical power) and HR range remained. A significant interaction existed between completion time and monofilament detection on HR range, and thus models for monofilament detection and HR range were stratified by completion time (completed in ≤7 minutes vs. >7 minutes). In separate fully adjusted models (adjusted for age, sex, race, site, diabetes, height, fat mass, lean mass, beta blocker use, and calcium channel blocker use), monofilament insensitivity was associated with a HR range of 1.8 beats per minute lower in participants who completed the LDCW in 7 minutes or less, while monofilament insensitivity was not significantly associated with HR range in those who competed the LDCW in greater than 7 minutes (Figure 9). When removing participants taking any medication that could influence heart rate (n=534), monofilament insensitivity was associated with a heart rate range of 1.66 beats per minute lower (p=0.035) compared to those who detected the monofilaments.

Heart Rate Range by Monofilament Detection, Stratified by Completion Time
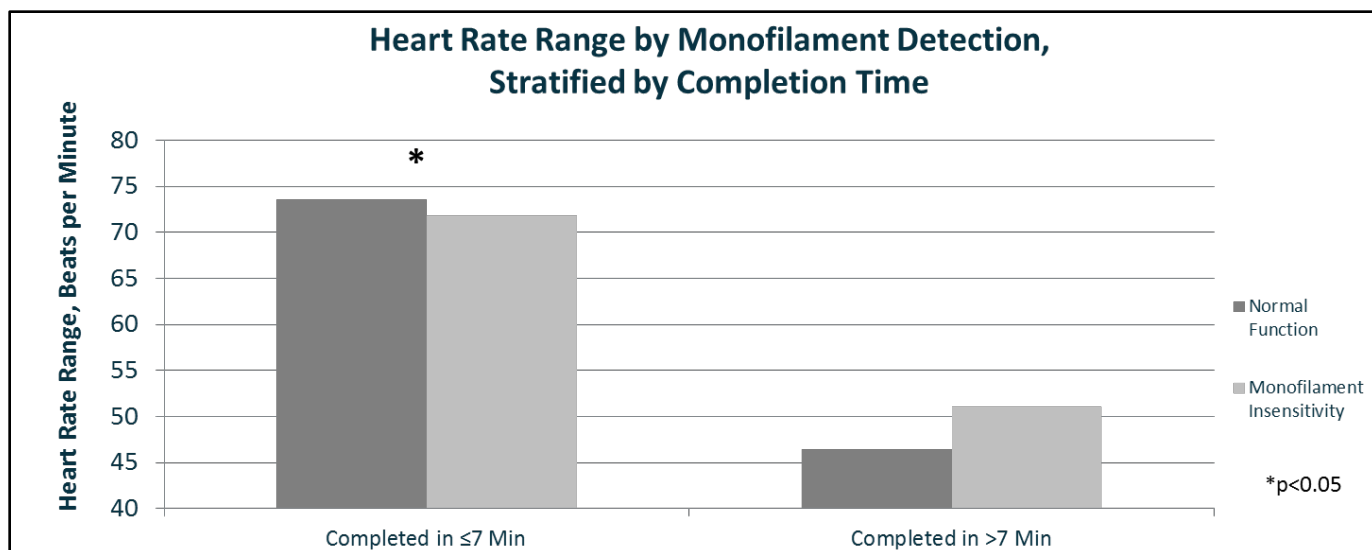
Adjusted for age, sex, race, site, diabetes, fat mass, lean body mass, height, beta blocker use, and calcium channel blocker use.

Figure 9: Adjusted Heart Rate Range During the LDCW By Monofilament Detection

4.4   DISCUSSION

Some indicators of worse sensorimotor peripheral function were independently associated with worse cardiac autonomic function for some, but not all measures. Motor nerve function was associated with cardiac autonomic function measures of resting heart rate and orthostatic hypotension. Monofilament insensitivity was associated with lower HR range in participants who completed the LDCW in seven minutes or less, while monofilament insensitivity was associated with higher HR range in those who took greater than 7 minutes complete the LDCW. To our knowledge, this is the first study examining the association between these PNS divisions in a population of community dwelling older adults. Generally, the

122

sensorimotor and autonomic divisions of the PNS are not examined simultaneously. Though PNS function is often considered in the context of diabetes, age-related PNS changes are not as well understood.

The PNS is comprised of large and small fibers, each responsible for distinct aspects of neurotransmission. Within the sensorimotor division, large myelinated fibers (Aα, Aβ) mediate motor control as well as touch, vibration, and position perception. Small, thinly myelinated (Aδ) or unmyelinated (C fibers) of the sensorimotor division provide information about pain in addition to cold and warm perception, respectively. The autonomic division is made up of thinly myelinated and unmyelinated fibers, and mediates HR, blood pressure, sweating, gastrointestinal and genitourinary function. The most consistent significant associations observed in this analysis were between motor nerve function and HR and orthostatic hypotension, which are highly influenced by vagal nerve function. Though these relationships were between different fiber types, this observation is consistent with the notion of selective vulnerability, where the long nerve fibers (like the vagus and peroneal nerves) are particularly prone to damage.

Damage to the peripheral nervous system in the context of diabetes is often attributed to long-term metabolic disturbances and hyperglycemia, [88,110,260] though our observed associations were not explained by factors largely thought of as influencing nerve function. In particular, these associations were independent of age, sex, race, diabetes, and prevalent diseases. In the model building process, very few covariates were significantly associated with sensorimotor and indicators of cardiac autonomic function, and multivariable models included few parameters beyond age, sex, race, study site and diabetes—which were included in all models regardless of significance, suggesting a primary association between the PNS components. However, the effect sizes of the observed relationships were small. For example,

poor motor amplitude was associated with a resting heart rate of 2.20 beats per minute higher compared to those with normal amplitude. In a longitudinal study by Jensen and colleagues examining the risk of mortality by resting heart rate in middle aged men, the risk of mortality increased by about 16% per every 10 beats per minute higher. The heart rate differences observed in our study were much smaller, and may not be as clinically relevant. Additionally, even though some measures of sensorimotor peripheral nerve function were independently associated with the indicators of cardiac autonomic function, the overall R^2 values for these models were low (results not shown). This may indicate potential underlying mechanisms common to the pathogenesis of sensorimotor and autonomic dysfunction that were not captured by the included covariates, or it may simply indicate small associations.

We expected age to explain a large portion of the association between sensorimotor and cardiac autonomic function. Sensorimotor impairments are highly prevalent in this cohort of older adults; however, age was weakly associated with orthostatic hypotension and HR recovery, and was not associated with resting HR or HR range (results not shown). Age did not significantly attenuate any of the observed associations between sensorimotor and autonomic function. This supports an independent relationship between sensorimotor and autonomic function, and that the relationships we observed were not simply due to simultaneous age related declines in sensorimotor and autonomic function, but rather a direct relationship between the two.

Monofilament insensitivity was differentially associated with HR range in this cohort, with the relationship differing between those who completed the LDCW in ≤7 compared to those who completed in >7 minutes. In those who completed the LDCW in ≤7, monofilament insensitivity was associated with lower HR range when adjusting for continuous completion

time, indicating worse cardiac autonomic function. However, in those who completed in >7 minutes, monofilament insensitivity was not significantly associated with larger HR range. Work validating the LDCW against maximal treadmill testing indicated that requiring >7 minutes (420 seconds) to complete the LDCW is approximately equivalent to an aerobic capacity level of <12 mL O_2 per kilogram of body weight per minute [269], which is a critical threshold of fitness where independence and community living may be severely compromised [272].

A major strength of this study is the inclusion of many diverse factors known to influence sensorimotor or autonomic function. In addition, sensorimotor peripheral nerve function was assessed through the use of objective and subjective measures in addition to self-reported symptoms—an important consideration since impairments in older adults are commonly asymptomatic [30]. Examining motor and sensory nerve function separately allowed us to investigate specific pathways in which sensorimotor and autonomic function may be related. The measures of autonomic function are clinically relevant and could feasibly be administered in a variety of settings. A limitation is that we could only assess heart rate range and heart rate recovery in participants who completed the full LDCW. In Paper 2 we demonstrated that participants with sensorimotor impairments are less likely to complete the full LDCW compared to those with better sensorimotor function. Thus, the participants who were included in the heart rate range and heart rate recovery portion of the analysis had better sensorimotor function overall compared the full analytic sample, potentially biasing these results towards the null.

Though we were able to include a variety of measures of cardiac autonomic function, other measures often utilized in clinical settings—for example, expiratory-inspiratory ratio, HR variability, and tilt-table testing—were not assessed in Health ABC. These measures are rarely included in epidemiologic studies, and HR variability in particular can be computationally

125

challenging to analyze and also difficult to interpret. The measures we used are surrogates of autonomic function, and could be influenced by current acute physiologic and health status, potentially resulting in residual confounding. This is a first step in an area which needs much more investigation, including detailed assessments of cardiac autonomic function. Future work should include comprehensive examinations of each aspect of sensorimotor and autonomic function. Including HR variability and other sensitive measures of autonomic function may aid in clarifying this association. Though it has limitations, HR variability analyzed using frequency domain methods may be useful for separating the effects of sympathetic and parasympathetic modulation. Consideration of other organ systems controlled largely by the autonomic nervous system (gastrointestinal, genitourinary) may also be useful. A final limitation is that though we had access to a detailed medication inventory, these medications were assessed in the 1999/2000 clinic visit and thus may not reflect the participants' medication regimen one year later when PNS function was measured.

This study demonstrated that some aspects of worse sensorimotor peripheral nerve function are independently associated with worse indicators of cardiovascular autonomic function in community-dwelling older adults. Both play roles in the ability of older adults to be physically active and remain independent. Given the poor outcomes associated with PNS impairments, future epidemiologic studies should consider assessing these often underappreciated risk factors in order to gain insight into the contribution of PNS function to health in old age.

5.0   DISSERTATION DISCUSSION

5.1   SUMMARY OF FINDINGS

The overall objective of this dissertation was to examine age-related peripheral nerve function impairments in the context of PA, fitness, and autonomic function in older adults. Prior work has indicated the association between poor sensorimotor peripheral nerve function impairments and mobility-related outcomes in older adults. PA, fitness, endurance, and autonomic function may be in the pathway between sensorimotor impairments and geriatric outcomes. This work is critical as it provides potential mechanisms with ay underlie the relationships between poor peripheral nerve impairment and lower extremity outcomes in old age.

One factor which may account for the relationships of poor peripheral nerve impairment and lower extremity outcomes of older age is reduced PA. Lower extremity sensorimotor impairments were found to be cross-sectionally associated with lower levels of PA in older men from the MrOS study. In particular, worse distal motor latency and the presence of neuropathic symptoms were associated with lower self-reported PA, while worse motor and sensory amplitude were associated with fewer minutes per day of objectively measured PA. Crude associations between worse motor and sensory amplitude with light and moderate activity were attenuated by age, BMI, diabetes, self-reported health, peripheral arterial disease and arterial

stiffening, though significant relationships existed with vigorous activity. Because of the cross-sectional nature of this study, it is unclear whether higher levels of activity (particular vigorous activity) are protective against age-related peripheral nerve function impairments, or whether those with intact peripheral nerve function are able to maintain high activity levels because of their better nerve function. However, this was the first study to examine the relationship between peripheral nerve impairments and PA in older adults and supports the need for longitudinal studies for clarifying the direction of these relationships and the intensity of PA that is most beneficial.

Declines in physical fitness and endurance in old age can lead to mobility impairments/disability [15,273] and even death [16,274]. PA can influence physical fitness and endurance in older adults [5,19,20], though declines in physical fitness and endurance may be fundamental aspects of the aging process [4,2,8,275]. Maintaining fitness and endurance above critical thresholds is pertinent for preventing mobility disability. In addition to reduced PA, declines in fitness and endurance could also be in the pathway between sensorimotor impairments and adverse mobility outcomes. Poor sensorimotor function was associated with worse walking endurance performance, with sensory impairments being associated with a greater rate of slowing over time in older black and white men and women in Health ABC. Those with sensory peripheral nerve impairments completed the long distance corridor walk approximately 15 seconds slower and experienced an additional slowing of four seconds per year compared to those without these impairments. Interestingly, motor impairments were not related to longitudinal decline. These findings were independent of diabetes and other health and behavioral factors known to influence sensorimotor function. Sensory nerve impairments (poor vibration perception threshold and 1.4/10g monofilament insensitivity) had the largest effect on

endurance walking performance over time, indicating the major impact that reduced sensation has on mobility. Maintaining walking endurance is critical for remaining independent in the community. Interventions aimed at reducing the burden of sensory impairments, or maintaining endurance in spite of impairments should be considered.

An additional component of the PNS, the autonomic division, supports the ability to be physically active, particularly via cardiovascular response to exercise. The capacity of the cardiovascular system to adequately respond to and recover from activity is a major focus in exercise physiology, and is largely controlled by the autonomic nervous system. Poor cardiac autonomic function is associated with exercise intolerance and can ultimately lead to cardiac outcomes, disability, and death. Work in populations with diabetes has suggested an association between cardiac autonomic neuropathy and the development of sensorimotor peripheral neuropathy [261]. Greater severity of cardiac autonomic neuropathy has also been associated with a higher prevalence of peripheral neuropathy [276].

Despite being components of the same system, sensorimotor function and autonomic function are rarely examined together, and the association has not been previously examined or defined for older adults. Cardiac autonomic impairments could potentially also be within the pathway between sensorimotor impairments and geriatric outcomes. In Health ABC, we found that poor conduction velocity was associated with higher odds of orthostatic hypotension, suggesting an association between demyelination and the inability for the cardiac autonomic system to adequately respond to postural changes. Additionally, poor motor amplitude was associated with higher resting HR. Insensitivity to the 1.4g monofilament was associated with a lower heart rate range during the submaximal exercise test, after adjusting for performance on the test. Sensorimotor and autonomic function remained independently related after adjusting

for age, sex, race, diabetes, and health and lifestyle factors known to influence PNS function, and these factors did not attenuate findings substantially. Therefore, this work suggests a primary association between function in the two divisions of the PNS. Future studies should investigate common underlying processes for the development of multiple PNS impairments.

5.2   PUBLIC HEALTH SIGNIFICANCE

Traditionally, studies examining PNS function were concentrated in the area of diabetes or other disease-related dysfunction and impairment. Despite the important work from populations with diabetes, age-related peripheral nerve impairments may differ from those in diabetes and should be examined for their impact on geriatric conditions and outcomes. Though diabetes-related peripheral nerve impairments can give insight and drive hypotheses regarding age-related changes, is important to study these impairments in broader populations of older adults—particularly given the tremendous expected increase in number and proportion of this population in the coming years. Gaining a better understanding of the peripheral nervous system in older adults can ultimately help drive prevention efforts including the development of interventions to help reduce the poor outcomes associated with age-related impairments. Work from this dissertation suggests PA interventions which focus on PNS impairments may be beneficial for older adults. Alternative PA recommendations for those with reduced sensation in the lower extremities may be warranted, though further work is needed in this area.

Ultimately, PA is likely in the pathway between PNS impairments and major geriatric outcomes like falls, disability, and death. Older adults tend to become less active over time [277], and PNS impairments may be a contributing factor to these declines in activity. No

130

longitudinal studies have examined changes in physical activity by peripheral nerve impairments. However, peripheral nerve impairments are associated with a higher risk of mobility disability [216], an indicator that physical activity is likely decreasing as well.

My prior work in Health ABC has indicated that higher levels of PA are associated with better long distance corridor walk performance [275]. Additionally, higher levels of PA are associated with better cardiac autonomic function in older adults [278], and PA interventions can also improve cardiac autonomic function [171,174]. It is unclear whether PA interventions lead to improvements in sensorimotor peripheral nerve function in older adults; though improving outcomes for those with sensorimotor impairments via PA is a worthy of study, particularly given the high prevalence of these impairments in community-dwelling older adults [29,30,216].

PA can play a key role in improving health, reducing chronic conditions, and promoting independence throughout the aging process [279]. Given the drastic demographic shift occurring in the U.S. as the "baby boomer" generation ages, keeping older adults healthy and independent for as long as possible is a major public health priority. By the year 2030, it is expected that the population of U.S. adults age 65+ will double, with this age group making up 20% of the population [280]. Because many older adults have at least one chronic health condition, nearly 66% of national health care expenditures are for this age group [280].

Per Olaf Astrand, a notable exercise physiologist may have best stated the major cost of physical inactivity and reduced aerobic fitness in older adults: "As a consequence of diminished exercise tolerance, a large and increasing number of elderly people will be living below, at, or just above "thresholds" of physical ability, needing only a minor intercurrent illness to render them completely dependent" [19]. Unfortunately little has changed regarding the PA status of older adults since he made this comment nearly 20 years ago.

131

Sensorimotor and autonomic peripheral nerve function impairments have been underappreciated as risk factors for disability in older adults, despite their potential to significantly impact lower extremity and cardiovascular function. Although national PA guidelines acknowledge that older adults may have difficulty achieving the recommended levels of PA due to chronic conditions, these recommendations are generally not tailored to these specific chronic conditions. For example, reduced sensation in the lower extremities due to PNS impairments may make walking difficult, whereas other forms of physical activity may be more appropriate. Acknowledging specific conditions like PNS impairments and providing PA recommendations based upon those conditions may make PA more feasible for older adults.

5.3   FUTURE DIRECTIONS

Both sensorimotor and cardiac autonomic peripheral nerve function play roles in the ability for older adults to be physically active. Peripheral nerve impairments should be integrated into future work examining the impact of PA on functional outcomes in older adults.

Worse sensorimotor peripheral nerve function was found to be associated with lower levels of PA in a primarily white, community-dwelling population of older men. An obvious future direction of this work is to examine this association in women and in ethnically diverse populations. The field of PA epidemiology has advanced significantly with the development of activity monitors, though the use of traditional summary measures of activity (i.e. total minutes spent in various intensities of activity) has its limitations. More recently, novel techniques for analyzing raw PA signals has allowed for researchers to examine patterns of activity accumulation [191], duration of activity bouts, and even the identification of specific activities

[192,193]. Though some of these methods need further validation in free-living environments, they bring exciting possibilities for future work. Examining whether sensorimotor peripheral nerve function impairments are not only associated with lower levels but also different activity patterns could help drive the development of successful PA interventions. Considering the high prevalence of sedentary behaviors in older adults, work examining patterns of sedentary time and breaks in sedentary behaviors are warranted. Simply avoiding sedentary behavior confers its own health benefits [185], which are important even for those who are active [186].

Currently, many traditional algorithms used for analyzing objectively measured physical activity data do not distinguish between aerobic and resistance training activities. However, novel analysis techniques are constantly being developed which may allow for even more detailed analyses of activity than are currently available. Given the association between sensorimotor impairments with worse lower extremity strength [36,215] and power [230], resistance training activities are of particular interest in examining the association between PA and sensorimotor impairments and for developing future interventions to reduce mobility limitations. Though overground walking may be difficult for those with reduced lower extremity sensation, weight bearing activities for the purpose of developing muscle strength and power may be beneficial for improving functional outcomes.

Aspects of cardiac autonomic function are often assessed in exercise physiology studies, including heart rate range and heart rate recovery to exercise testing. Autonomic function can impact the ability to be active, and is a potential mechanism in which PNS impairments lead to geriatric outcomes and conditions. The association between sensorimotor and cardiac autonomic function is a particularly novel finding, and provides valuable insight into PNS aging. This work suggests a primary association between cardiac autonomic and lower extremity sensorimotor

function.　　　Traditionally, effects of aging on specific bodily systems have been examined separately, though aging does not affect single system components in isolation.　Work is needed to further investigate the development of multiple PNS impairments during the aging process. The inclusion of comprehensive sensorimotor and cardiac autonomic assessment methods (i.e. nerve conduction and heart rate variability, among others) into one single study could help further clarify this relationship. Using a holistic approach to study PNS impairments may also be more efficient for developing interventions for improving overall PNS function and related lower-extremity outcomes for older adults.

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