CHAPTER 1

Introduction

OVERVIEW

Understanding the determinants of health, disease, and disability are essential to the goal of Healthy People 2020, to create "a society in which all people live long, healthy lives."[1] Persisting knowledge gaps about the causes of disability limit our ability to achieve this goal. Historically, many research studies have estimated the prevalence of disabilities in persons over the age of 65 without appreciating the likelihood of their initiation and progression as limitations in physical functioning in the younger mid-life years. In the last decade, the prevalence of disability has remained relatively unchanged; in 2009, the National Health Interview Survey identified that approximately 20% of mid-life adults aged 45-64 had some functional limitation or disability.[2,3] However, despite the maintained prevalence rate, the shifting age demographic of the United States as our population has aged has caused an increase in the absolute number of persons with disability.[3] Furthermore, at every age group, women are more likely to report disabilities than men.[2,3] Expanding assessments of physical limitations to include

the mid-life years is warranted particularly among women, who are at high risk for future disability and decreased quality of life.

Peripheral neuropathy, defined as any disorder of the peripheral nerves and characterized by loss of sensation with or without pain in the extremities, may be a leading cause of physical limitations and disability. Although neuropathy has been well-described as a complication of diabetes mellitus, it is beginning to attract attention as a health condition relevant in persons without diabetes as well.[4-6] The co-occurrence of peripheral neuropathy with diabetes, obesity, and limitations in physical functioning may help explain why some women experience more substantial age-related declines in physical functioning than other women. Peripheral neuropathy may also explain the high prevalence of disability reported among women in the United States.

Much of the available research on peripheral neuropathy has been performed in clinical populations.[7-12] Prevalence estimates of neuropathy vary considerably, but the degree to which this is a function of the assessment methodology, the sample being investigated, or both have not been suitably addressed.[4] Only recently has neuropathy been appreciated as a condition of the general population occurring in individuals with and without diabetes.[5,6] The prevalence of neuropathy in persons without diabetes and the observation that many individuals have peripheral neuropathy at the time of their diabetes diagnosis[13] suggests disease-causing pathways may be more extensive than diabetes pathogenesis, and/or peripheral neuropathy may be a pre-diabetic

complication preceding the recognition or onset of overt diabetes. In addition, it has also been suggested that there is a relationship between neuropathy and obesity independent of diabetes,[14,15] but this relationship has not been explored longitudinally.

The purpose of this dissertation was to characterize peripheral neuropathy in mid-life women. The goal of this study was to estimate the prevalence of peripheral neuropathy and to determine if trajectories of physical functioning and obesity differed by peripheral neuropathy status in the longitudinal, bi-ethnic Study of Women's Health Across the Nation (SWAN)—Michigan site.

STUDY OBJECTIVES

The specific objectives of this dissertation included the following:

Paper 1

1. To estimate the prevalence of peripheral neuropathy using three assessment methods.
2. To determine if risk factors for peripheral neuropathy and the prevalence of peripheral neuropathy differ by race/ethnicity.
3. To determine the cross-sectional agreement between the three assessment methods for peripheral neuropathy.

Paper 2

1. To determine the cross-sectional association between peripheral neuropathy and performance-based physical functioning.

2. To determine if trajectories of performance-based physical functioning as women age differ by peripheral neuropathy status.

Paper 3

1. To determine the cross-sectional association between peripheral neuropathy and body size.
2. To determine if trajectories of body size as women age differ by peripheral neuropathy status.

PUBLIC HEALTH IMPLICATIONS

Most previous epidemiological evaluations of peripheral neuropathy have been conducted in primarily diabetic-only or elderly populations.[7-12,16] Further, assessments of physical functioning or obesity and peripheral neuropathy are limited to cross-sectional evaluations. The utility of the present study is not only its population-based approach to the evaluation of peripheral neuropathy which includes both diabetic and non-diabetic individuals, but also its unique longitudinal study design which allows for the evaluation of how trajectories of physical functioning and obesity differ by peripheral neuropathy status. In addition, the prevalence of neuropathy-related conditions like diabetes and obesity is known to vary by race/ethnicity.[17,18] The bi-racial Michigan SWAN cohort study is well-positioned to provide an assessment of peripheral neuropathy in mid-life women and contribute to the sparse but growing body of literature on the risk factors and sequelae of peripheral neuropathy in the general population. This investigation may identify women at risk for future disability. If

peripheral neuropathy is highly prevalent, detectable in the preclinical stage, and the implementation of effective interventions could prevent disease sequelae, neuropathy screening in the general population may be warranted. Furthermore, screening for obesity may prevent neuropathy if obesity is causally related to neuropathy.

BACKGROUND

Peripheral Nerve Biology

The nervous system is comprised of the central nervous system, which includes the brain and spinal cord, and the peripheral nervous system, which includes the cranial and spinal nerves. Functionally, the peripheral nervous system encompasses somatic (voluntary muscle control) and autonomic (involuntary control of organs) systems.[19] Large- and medium-sized peripheral nerves contain a series of connective tissue sheaths enclosing the nerve fibers.[19] However, small peripheral nerves lack this outer fibrous sheath and instead have a sheath of more delicate Schwann cells, which produce the myelin sheath that surrounds the nerves.[19]

Schwann cells are separated by short gaps called nodes of Ranvier where the myelin is missing. These gaps allow a nerve conduction impulse to jump from node to node and increase the rate of conduction transmission. This increased velocity is particularly important for peripheral nerves in the extremities with long distances to travel between the central nervous system and the periphery.

Because of the specificity of nerve cell function, neurons are less able to regenerate than other cell types; in fact, cell division ceases by birth and in the subsequent life years the neuronal cell body is unable to divide.[19] However, peripheral nerves are more resilient than nerves of the central nervous system and it is often possible for dendrites and axons to regenerate as long as the cell body is not damaged.[19] Nerve cell biology has important implications for disease and damage, as nerve cells are less likely to achieve full repair compared to other biological cells.[19]

Peripheral Neuropathy Pathogenesis

Numerous disease processes may injure the peripheral nerves. Peripheral neuropathy is defined as any primary disorder of the peripheral nerves and can involve single or multiple nerves.[19] Mononeuropathies (injury to a single nerve) typically result from localized trauma, compression, or infection, while polyneuropathies (injury to a system of nerves) can result from a wider variety of etiologies, including immune responses, toxins, pharmacotherapy, metabolic and nutritional abnormalities, and aging.[19] Despite numerous known causes, a large proportion of individuals are diagnosed with idiopathic neuropathy. The hallmark characteristic of peripheral neuropathy is loss of sensation with or without pain, particularly in the extremities.

Diabetes and peripheral neuropathy

Diabetic polyneuropathy (peripheral neuropathy) is a common consequence of both Type 1 and Type 2 diabetes mellitus and chronic hyperglycemia which can involve a

number of different disease-causing vascular or metabolic pathways.[20] There are three primary ways in which diabetes is thought to damage peripheral nerves.

First, nerve tissue does not require insulin for glucose transport and instead uses the alternative metabolic polyol pathway for glucose metabolism.[20] Glucose is converted to sorbitol, and in turn sorbitol is very slowly converted to fructose.[20] The buildup of glucose from chronic hyperglycemia combined with the extremely slow conversion rate of sorbitol to fructose results in an accumulation of sorbitol in the peripheral nerves.[20] Increased sorbitol results in interference with ion pumps by producing osmotic stress by drawing in fluid.[20] This decreases nitric oxide and leads to an increase in reactive oxygen molecules and increased oxidative stress.[20] Together, these elements damage the Schwann cells and lead to a disruption of nerve conduction.[20]

Second, protein kinase C can become inappropriately activated as a result of hyperglycemia, which may also contribute to neurologic complications.[20] Protein kinase C is an intracellular signaling molecule that regulates many vascular functions; its levels are elevated in diabetes.[20] This activation of protein kinase C in the blood vessels of nerves can produce vascular damage and decrease nerve conduction.[20]

Third, advanced glycosylation end products (AGEs) are the result of attachments of glucose metabolites onto proteins.[20] Although they are normal components of the basement membranes in smaller blood vessels, uncontrolled blood glucose levels favor

the over-production of AGEs.[20] Increased AGEs cause basement membrane thickening, contributing to diminished oxygen supply.[20] Because neuronal dysfunction is closely associated with vascular abnormalities, nerve damage results from AGEs.[20] Additional microvascular damage includes trapping of proteins (including LDL), inactivation of nitric oxide, and loss of vasodilation.[20]

A build-up of sorbitol and the polyol pathway, activation of protein kinase C, and excess accumulation of AGEs all contribute to nerve damage through the degeneration of myelin, causing nerves to lose their ability to transmit signals. Peripheral neuropathy results when the nerves have sustained enough damage to result in decreased or absent nerve transmission. This presents as a number of possible symptoms including numbness, pain, or tingling.

Cardiometabolic risk and peripheral neuropathy

Peripheral neuropathy pathogenesis outside of the diabetic etiology is gaining attention.[21] Although diabetic peripheral neuropathy is the most common type of neuropathy, not all diabetic patients with neuropathy have diabetic neuropathy.[20,21] It is estimated that even among diabetic patients, up to 50% may have an additional cause of generalized neuropathy.[21] The development of peripheral neuropathy in diabetic patients with tight glycemic control also suggests risk factors outside of diabetes-related risk factors like chronic hyperglycemia.[14]

Cardiovascular disease and diabetes share many cardiometabolic risk factors, including hypertension, dyslipidemia, and increased weight,[14] and recent peripheral neuropathy literature has focused on exploring these potential risk factors. It is hypothesized that cardiovascular risk factors, which influence lower-limb blood flow, also influence neuropathy risk.[6,14]

For example, among a diabetic cohort with mean 7.3 years of follow-up, patients who developed neuropathy had higher baseline levels of total cholesterol, LDL, and triglycerides, and were more likely to have hypertension, cardiovascular disease, and a history of smoking.[14] After adjustment for duration of diabetes and glycosylated hemoglobin, body mass index, total and low-density cholesterol, and triglycerides were significantly associated with incident neuropathy, with smoking and hypertension remaining as significant covariates as well.[14] After simultaneously adjusting for all other risk factors, triglycerides, body mass index, smoking, hypertension, glycosylated hemoglobin, and duration of diabetes were all significantly associated with incident neuropathy.[14]

Characteristic of obesity is the presence of excess adipose tissue, which secretes hormones and other bioactive molecules that act on different organ systems in the body.[22] Adipose tissue is a metabolically active organ that also causes chronic hyperleptinemia. Animal models have shown that leptin has effects on hypertension, nitric oxide, and oxidative stress. The direct effect of leptin in humans suggests

mechanisms of increased oxidative stress and LDL, in addition to the generation of prothrombotic and proinflammatory cytokines,[22] which provides support for the shared cardiovascular risk factors.

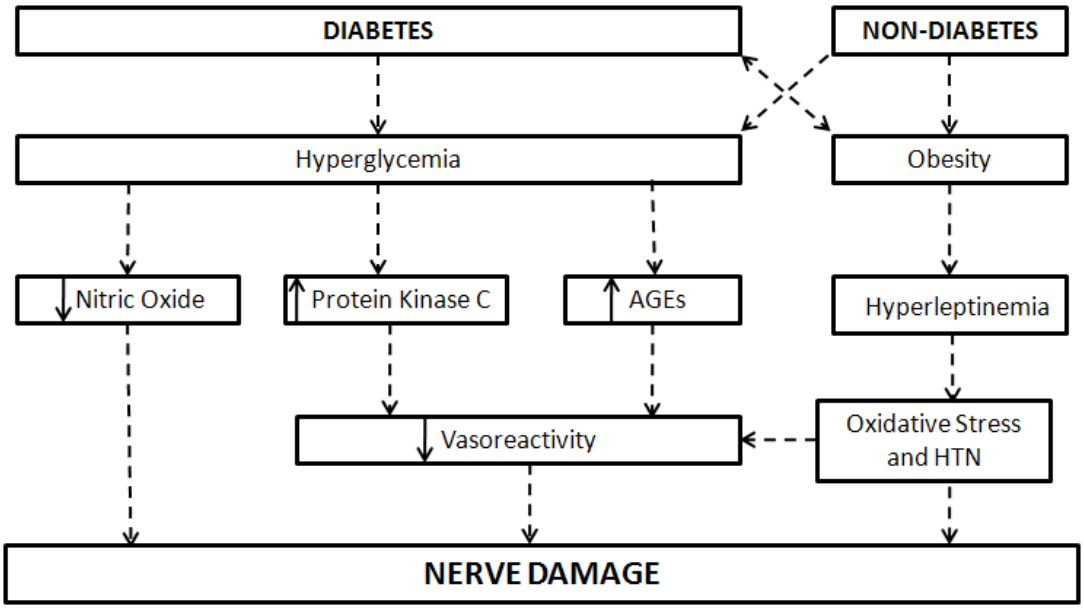
The co-occurrence of abnormal cardiometabolic factors and obesity deserves attention. A recent investigation using the 1999-2004 National Health and Nutrition Examination Survey (NHANES) found a high prevalence of cardiometabolic abnormalities among individuals of normal weight and a high prevalence of metabolically healthy but obese individuals.[23] This new research suggests that while body mass index is an important indicator of health, it may be the co-occurrence of obesity and cardiometabolic factors that actually confer risk of future disease.

Abnormal cardiometabolic factors, similar to those described by the ATP III panel as "metabolic syndrome,"[24] may be important in the pathogenesis of peripheral neuropathy due to shared microvascular dysfunction mechanisms.[25] This grouping of abnormal cardiometabolic factors includes hypertension, hyperlipidemia, hyperglycemia, and increased adiposity. The EuroDiab study found that hypertension, lipids, and body mass index were each independently associated with the risk of developing peripheral neuropathy among a group of diabetic subjects.[26] Smith, Rose, and Singleton[27] found that among subjects with symptomatic peripheral neuropathy, each component of the metabolic syndrome (ATP III criteria) was more prevalent among neuropathy subjects as a group than hyperglycemia. Comparing neuropathy patients

with normal glucose tolerance to controls with normal glucose tolerance, individuals with neuropathy had significantly higher rates of dyslipidemia and hypertension.[27] In addition, women with neuropathy were significantly more obese than women without neuropathy.[27] The authors concluded that features of the metabolic syndrome other than impaired glucose tolerance represented independent risk factors for peripheral neuropathy.[27] In our investigation of lower extremity disease in the National Health and Nutrition Examination Survey, we found that cardiometabolic risk factors increased the odds of peripheral neuropathy among normal weight individuals, but that obesity increased the odds of peripheral neuropathy over and above cardiometabolic risk factors.[15] However, not all studies suggest that abnormal cardiometabolic factors confer an increased risk of neuropathy. In the Finnish Botnia Study, the metabolic syndrome was strongly associated with cardiovascular disease but demonstrated little effect on the development of neuropathy.[28] None of these studies have addressed whether the differential distribution of cardiometabolic characteristics and prevalence of obesity in race/ethnic groups may account for race differences in prevalence estimates of peripheral neuropathy.

Figure 1.1 summarizes the potential mechanisms of peripheral neuropathy pathogenesis that have been discussed above. Obesity and hyperglycemia are highlighted as potential pathways that influence the development of neuropathy.

Figure 1.1. Summary of Potential Mechanisms of Peripheral Neuropathy Pathogenesis



Epidemiology of Peripheral Neuropathy

The prevalence of peripheral neuropathy is difficult to determine because of the variation in assessment methodologies, definitions, and populations, as well as the difficulty of timely diagnosis.[4] It is most recognized and studied as a complication of diabetes mellitus; as many as 50% of individuals with diabetes will develop peripheral neuropathy in their lifetime.[25]

The prevalence of neuropathy in the general population is much lower, based on the few investigations of this population available in the literature. Using monofilament testing of peripheral sensation of the foot to characterize peripheral neuropathy, the overall prevalence of neuropathy among non-institutionalized adults aged 40 years and

older in the United States was 14.8%.[4] The prevalence of neuropathy was 10.5% among those with normal fasting glucose levels (<100 mg/dl), with a similar prevalence (11.9%) observed for impaired fasting glucose (100 to <126 mg/dl), a higher prevalence (16.6%) among those with undiagnosed diabetes, and the highest prevalence (19.4%) among those with diagnosed diabetes.[6] Individuals with diabetes were approximately two times more likely to have peripheral neuropathy compared to individuals without diabetes, and most neuropathy was reported as asymptomatic.[6] Among individuals without diabetes, non-Hispanic Whites are more likely to have peripheral neuropathy.[5] For women with and without diabetes, the prevalence of neuropathy increases linearly with age, from 3.0% among 40-44 year old women to 32.9% among women aged 85 and older.[5]

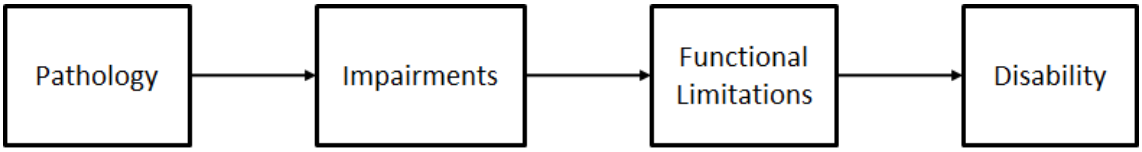
The 10% prevalence of neuropathy observed among individuals with normal fasting glucose levels suggests that there are disease-causing pathways outside of overt diabetes. Transient hyperglycemia and microvascular damage from subclinical cardiovascular abnormalities associated with obesity may contribute to neuropathy in the general population. However, no studies of the general population to date have evaluated obesity as a risk factor for peripheral neuropathy nor have any attempted to investigate pathways outside of overt diabetes.

Consequences of Peripheral Neuropathy

Common symptoms of peripheral neuropathy include numbness, pain, sensory loss, and

tingling in the extremities, particularly the legs and feet. In addition, the risk of foot complications like dryness, callus, infection, ulceration, and even amputation is increased with advanced disease. Overt physical signs of advanced disease can be treated clinically. However, the effect of neuropathy on physical performance, physical functioning, and quality of life is often under-appreciated in the clinical setting.[29] Functional limitations, as measured by physical performance, are extremely important because they are risk factors for disability, as conceptualized by The Disablement Process (Figure 1.2).[30-32]

Figure 1.2. The Disablement Process.



Nerve damage, particularly to the sensory fibers, reduces the amount of perception feedback from receptors and causes impairments like reduced strength and position sense.[16] In the lower extremities, impairments can cause instability while walking or standing and predispose to falls. Individuals with neuropathy have decreased speed and stride length as well as increased time spent in double support (shuffling) compared to individuals without neuropathy.[33] Impaired balance and unsteadiness and the resulting functional limitations, particularly in walking speed, can lead to loss of independence because activities like walking are critical for the maintenance of independence in a community.[16,29] It is through these physical functioning limitations that peripheral

neuropathy is conceptualized as a risk factor for disability, which is the inability to fulfill activities of daily living in an individual's environment or context.[16,32]

Performance-based measures of physical functioning are objective tests used in health research to measure functional limitations.[34] Higher performance on tests of lower extremity function is indicative of better functional status, which is associated with a lower risk of subsequent disability.[35] It appears that peripheral neuropathy may modify performance on physical functioning tests. In a cross-sectional study of disabled women aged 65 years or older, 58% had mild, moderate, or severe nerve dysfunction as assessed by the vibration perception threshold and 18.5% of the women self-reported diabetes.[16] Even after adjusting for diabetes and other risk factors for functional limitations like age, body mass index, osteoarthritis, history of stroke, and visual acuity, peripheral nerve dysfunction was significantly associated with functional limitations.[16] Women with even mild nerve dysfunction were two times more likely to fail a performance-based balance test like the tandem foot stand and have significantly slower walking speeds compared to women with normal peripheral nerve function.[16] Physical functioning is of great public health importance because inadequate walking speeds compromise an individual's ability to safely negotiate their physical environment; in fact, one-third of mid-life women in the Michigan SWAN study walk at speeds inadequate for pedestrian clearance at crosswalks.[36]

The deleterious effects of peripheral neuropathy extend beyond physical manifestations to quality of life as well. Patients in diabetic clinics with foot complications report decreased physical, emotional, and social functions which reduce quality of life. In particular, depression is associated with severity of neuropathy, pain, and loss of sensation in the feet.[29] Moreover, painful peripheral neuropathy is associated with poorer mental quality of life among women.[37]

Measurement of Peripheral Neuropathy

Peripheral neuropathy can be measured in a variety of ways. Nerve biopsy and electrophysiological assessments like nerve conduction studies are the definitive standards of diagnosis because they can differentiate between different pathogeneses of nerve damage. These methods are used to validate other instruments; however, because of their invasive nature and expense, these methods are not used in large, epidemiologic screening efforts.

One method of assessment is the Michigan Neuropathy Screening Instrument (MNSI).[38] It was developed in 1994 and includes a symptom component and a clinical examination component. The MNSI symptom questionnaire obtains information about the presence of common neuropathy symptoms and signs including numbness, burning pain, sensitivity, prickling feelings, hot/cold differentiation, open sores, dryness, and amputation. The MNSI clinical examination includes a visual foot inspection for physical

abnormalities (deformity, dry or callus skin, infection, fissure, or ulceration), assessment of vibration sensation, and grading of ankle reflexes.[38]

Another peripheral neuropathy screening instrument is Semmes-Weinstein monofilament testing, which uses a pre-stressed single-fiber nylon thread filament briefly (<1 second) placed on different areas of the foot.[39] The filament generates a reproducible buckling, and a site is determined to be sensate or insensate based on an individual's response to the filament stimulus. Filaments are assigned different values, with higher values indicating greater stiffness and thus more force required to generate a buckle. The 10-gram monofilament is the most widely used to assess peripheral neuropathy in clinical practice.[40]

The few population-based efforts to characterize the prevalence of peripheral neuropathy have used monofilament testing; however, different cutpoints have been employed to determine insensate feet and thus the presence of peripheral neuropathy. A wide variety of protocols regarding number and location of testing sites have been employed in the current literature.[41] Cutpoints include fewer than 4 out of 5 correct responses in either foot,[42] or at least one insensate site on either foot out of six total sites on both feet.[4] The choice of cutpoints is closely related to the sensitivity and specificity, and increasing the number of incorrect answers required for a diagnosis subsequently decreases the sensitivity and increases the specificity.[41] When validated to the nerve conduction study in a sample of mostly type 1 and type 2 diabetic subjects,

10-g monofilament testing was fairly sensitive (57-93%) and highly specific (75-100%) compared to the gold standard nerve conduction study.[41] In addition, monofilament testing has been reported as moderately reproducible in diabetic subjects.[43]

Similarly, the MNSI has also been validated to nerve conduction studies. In a large cohort of type 1 diabetic subjects with a mean age of 47 years and a mean duration of diabetes of 26 years, ≥4 signs or symptoms reported on the symptom component of the MNSI had a sensitivity of 40% and a specificity of 92%.[44] The clinical examination component of the MNSI (composite score ≥2.5) had a sensitivity of 61% and a specificity of 79%.[44]

An ideal screening test is inexpensive, easy and quick to perform, reliable, and easy to interpret.[45] Monofilament testing is an ideal screening tool because of its ease of use and non-invasive procedure, and the routine use of monofilament testing to screen for peripheral neuropathy in diabetic patients has been recommended by the American Diabetes Association.[43] However, the validity and reproducibility of monofilament testing and the MNSI have not been evaluated in populations containing both diabetic and non-diabetic individuals. It is unclear if these neuropathy assessment methods have the same performance for non-diabetic individuals, or for diabetic patients whose duration of diabetes varies from that of the validated populations.

METHODS AND PROCEDURES

The SWAN study is an ongoing multi-ethnic, population-based longitudinal study of middle-aged women from seven sites around the United States. This dissertation utilized site-specific data from the Michigan study site because Michigan is the only site with peripheral neuropathy assessments and the only site with ongoing performance-based physical functioning measurements.

The Michigan SWAN study population was recruited using a two-stage design from two suburban communities (Ypsilanti and Inkster) near Detroit. In the first stage of sampling in 1995, 24,283 households located in pre-selected census tracts identified eligible women aged 40 to 55 years. Telephone (25%) or in-person (75%) contact resulted in a cross-sectional interview of 2621 eligible women. This first stage sampling served as the sampling frame for the longitudinal cohort. For the second stage sampling of the cohort for the Michigan site, eligible women were aged 42-52 years, had an intact uterus, did not use hormone therapy, had a menstrual period in the previous three months, and self-identified as either Caucasian or African American. A longitudinal cohort of 543 women (72% of those eligible; 218 Caucasian and 325 African American) was enrolled at the Michigan SWAN site.

Of this original 1996 study cohort, 418 (77%) had complete study visits in 2008 (study year 12) and were eligible to participate in the peripheral neuropathy assessment. Of the total completed visits, 371 (89%) participants underwent a foot examination and

completed a symptom questionnaire for peripheral neuropathy. Twenty-five (6%) completed only the symptom questionnaire administered via telephone or mail, and 22 (5%) refused participation in the peripheral neuropathy sub-study. For this dissertation, the analytic sample included 396 participants who completed the physical foot examination or symptom questionnaire for peripheral neuropathy in 2008. There were no statistically significant differences observed by age, race/ethnicity, baseline diabetes status, baseline body size, or baseline physical functioning between women who participated in the peripheral neuropathy sub-study and women who did not (Table 1.1).

Table 1.1. Baseline differences between women who participated in the 2008 Peripheral Neuropathy Sub-Study and women who did not participate in the Sub-Study.

	Any Neuropathy Assessment (n=396)	No Neuropathy assessment (n=147)	p-value
Age, years (SD)	46.5 (2.8)	46.2 (2.8)	0.32
Race, %			
African American	59.6	60.5	0.84
Caucasian	40.4	39.5	
Weight, kg (SD)	86.4 (21.9)	84.1 (21.7)	0.30
Height, cm (SD)	163.4 (6.1)	163.5 (6.4)	0.81
BMI	32.4 (8.1)	31.2 (8.0)	0.13
Waist, cm (SD)	94.4 (17.3)	93.3 (17.0)	0.49
Hip, cm (SD)	114.3 (16.2)	112.7 (16.2)	0.33
Waist-to-Hip ratio	0.82 (0.07)	0.82 (0.07)	0.87
Systolic blood pressure, mmHg (SD)	119.1 (19.2)	121.4 (20.1)	0.22
Diastolic blood pressure, mmHg (SD)	71.2 (10.9)	72.6 (11.5)	0.18
Glucose, mg/dL (SD)	103.4 (38.4)	103.7 (39.5)	0.93
Stair Climb, sec (SD)	19.6 (5.3)	20.7 (7.5)	0.11

Measurement of Main Study Variables

Peripheral Neuropathy

Peripheral neuropathy was assessed in 2008 (study year 12) using three instruments: (1) the MNSI symptom questionnaire, (2) the MNSI clinical examination, and (3) monofilament testing.

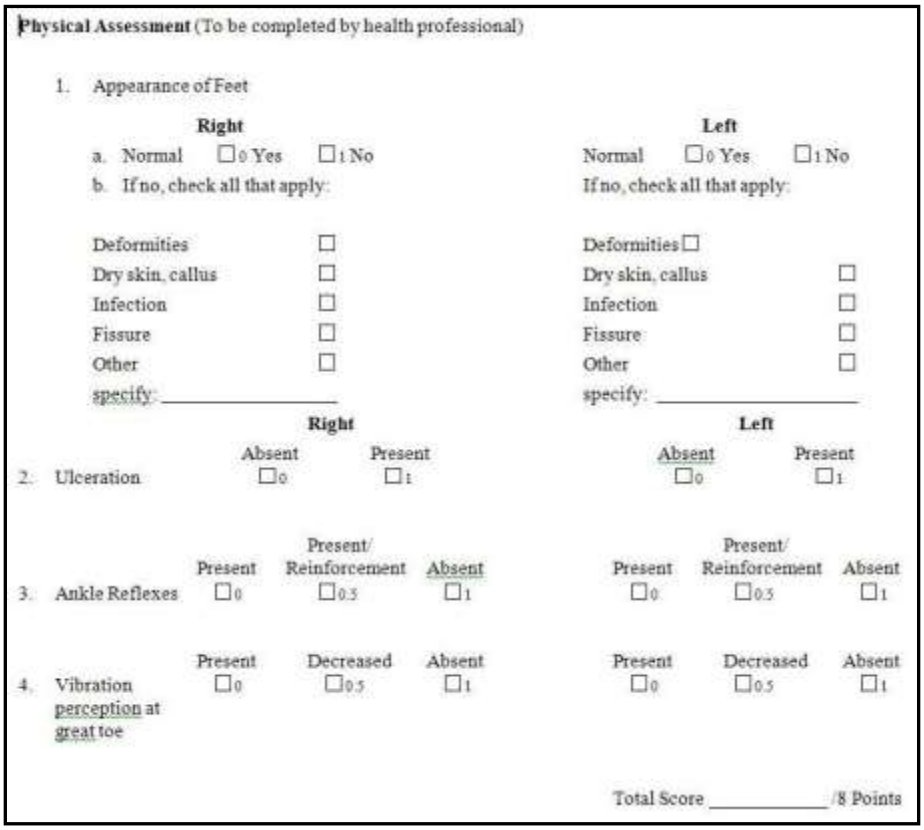
The MNSI symptom questionnaire obtained information on the presence (yes/no) of fifteen common symptoms and signs reported by individuals with neuropathy including numbness, burning pain, sensitivity, prickling feelings, hot/cold differentiation, open sores, dryness, and amputation (Table 1.2). The number of positive symptoms were calculated (see Appendix A) with two items (7 and 13) reverse-scored. Higher scores were indicative of more neuropathy symptoms and thus an increased likelihood of neuropathy. For the purposes of these analyses, participants with ≥4 symptoms were defined as having neuropathy.

Table 1.2. Michigan Neuropathy Screening Instrument Symptom Questionnaire

1. Are your legs and/or feet numb?
2. Do you ever have any burning pain in your legs and/or feet?
3. Are your feet too sensitive to touch?
4. Do you get muscle cramps in your legs and/or feet? (EXCLUDED)
5. Do you ever have any prickling feelings in your legs or feet?
6. Does it hurt when the bed covers touch your skin?
7. When you get into the tub or shower, are you able to tell the hot water from the cold water?
8. Have you ever had an open sore on your foot?
9. Has your doctor ever told you that you have diabetic neuropathy?
10. Do you feel weak all over most of the time? (EXCLUDED)
11. Are your symptoms worse at night?
12. Do your legs hurt when you walk?
13. Are you able to sense your feet when you walk?
14. Is the skin on your feet so dry that it cracks open?
15. Have you ever had an amputation?

The MNSI clinical examination included a visual foot inspection by trained examiners, assessment of vibration sensation, and grading of ankle reflexes. The visual inspection emphasized deformity, severe dry or callused skin, infection, fissure, and ulceration. Vibration sensation was evaluated using a 128 Hz tuning fork placed over the dorsum of the participant's great toe while held by the examiner with the distal interphalangeal joint of the first finger. Vibration sensation was considered "present" if the examiner felt the vibration for less than 10 seconds longer than the participant, "decreased" if the examiner felt the vibration for more than 10 seconds longer than the participant, and "absent" if the participant did not sense the vibration. Ankle reflexes were obtained by percussing the Achilles tendon. Reflexes were graded as "present" if the reflex was obtained. If the reflex was absent, the participant was instructed to perform the Jendrassic maneuver (fingers locked together and pulling; this serves as a distraction and helps to elicit a natural reflex) to ensure the reflex was truly absent; if the reflex was obtained with this maneuver, the reflex was graded as "present with reinforcement." If reflex was not obtained using either method, the reflex was graded as "absent." A composite score was obtained by combining the elements of the clinical exam, as seen in Figure 1.3. For each of the right and left feet for a total of 8 possible points, one point was given for abnormalities (deformity, severe dry or callus skin, infection, or fissure), ulceration, absent ankle reflexes, and absent vibration perception. Half a point was given for present with reinforcement ankle reflexes and decreased vibration perception. Using the MNSI clinical examination, a composite score of ≥2.5 defined neuropathy.

Figure 1.3. Michigan Neuropathy Screening Instrument Clinical Examination



Physical Assessment (To be completed by health professional)

1. Appearance of Feet

	Right	Left
a. Normal	☐0 Yes ☐1 No	Normal ☐0 Yes ☐1 No
b. If no, check all that apply:		If no, check all that apply:
Deformities	☐	Deformities ☐
Dry skin, callus	☐	Dry skin, callus ☐
Infection	☐	Infection ☐
Fissure	☐	Fissure ☐
Other	☐	Other ☐
specify: _____		specify: _____

	Right			Left		
2. Ulceration	Absent ☐0		Present ☐1	Absent ☐0		Present ☐1
3. Ankle Reflexes	Present ☐0	Present/ Reinforcement ☐0.5	Absent ☐1	Present ☐0	Present/ Reinforcement ☐0.5	Absent ☐1
4. Vibration perception at great toe	Present ☐0	Decreased ☐0.5	Absent ☐1	Present ☐0	Decreased ☐0.5	Absent ☐1

Total Score _____ /8 Points

Thirdly, the monofilament testing used a 10-gram prestressed filament that was briefly (<1 second) placed on the dorsal side of the big toe, midway between the nail fold and the distal interphalangeal joint. The participant was asked to respond if she felt the filament. This process was repeated ten times. Peripheral neuropathy was defined as 80% or fewer correct responses to the 10-g monofilament sensation in either foot. The Michigan SWAN site data collection forms used for monofilament testing and the MNSI clinic examination are included in Appendix B of this dissertation.

Finally, peripheral neuropathy was defined using a combination of monofilament testing and the MNSI symptom questionnaire. Peripheral neuropathy from this combined method was operationalized as the presence of ≥ 4 symptoms or signs, or 80% or fewer correct responses to the 10-g monofilament sensation in either foot.

Physical Functioning

Performance-based physical functioning was measured by trained examiners, based on the participant's performance on a variety of tests. The timed stair climb measured the time in seconds that elapsed while the participant climbed three stairs in three continuous repetitions (3x3). Participants could use the hand railings if needed. The 40-foot walk measured the time in seconds that elapsed while the participant walked at a brisk, purposeful pace for 40 feet. If the participant typically used an assistive device, she could use it during the timed walk assessment. The sit to stand assessment measured the time in seconds that elapsed while the participant rose from a normal-height bench with arms crossed over the chest and was standing with both arms down at the sides. The unipedal foot stand measured the time in seconds that the participant was able to balance using only the right foot, up to a maximum of 30 seconds. The tandem foot stand measured the time in seconds that the participants was able to balance with the right foot in front of the left foot in a tandem position, up to a maximum of 30 seconds.

Anthropometric Measures

Annual (1996-2008) anthropometric measures were collected from each study participant. Height was measured in centimeters by stadiometer and weight was measured in kilograms by balance beam scale. Body mass index (BMI) was calculated as weight [kg]/height[m^2]. Waist circumference and hip circumference were measured in centimeters by a non-stretching tape measure. Anthropometric obesity was defined as BMI ≥30 kg/m^2 or waist circumference ≥ 88 cm.

Other Covariates

Age was counted in years based on birth date relative to visit date. Race/ethnicity was determined by self-identification during initial population sampling in 1996 and is either Caucasian or African American. The Michigan SWAN site is 60% African American and 40% Caucasian, by design.

Annual blood pressure measures were also obtained. Blood pressure (mmHg) was measured in the sitting position twice using a mercury sphygmomanometer following an initial minimum 5 minute resting period and a 2 minute resting period between each measure. The two systolic measurements and the two diastolic measurements were averaged. Current use of hypertension treatment was determined by an affirmative response to the following two questions: “Since your last visit, have you taken any [medication for blood pressure/diuretics for water retention]?” and “Have you been taking [medication for blood pressure/diuretics for water retention] at least 2 times per week for the last month?” Participants were classified as hypertensive if their average

systolic blood pressure was ≥140mmHg, average diastolic blood pressure was ≥90mmHg, or if they reported current use of antihypertensive treatment.

Fasting blood samples were collected from participants annually. In 2008, samples were assayed for glycosylated hemoglobin (HbA1c) percentage using the immunoassay kit Unimate 3 from Roche Diagnostics and blood glucose (mg/dL) using the hexokinase assay on a Cobas Mira Chemistry Analyzer from Roche Diagnostics at the Michigan Diabetes Research and Training Center in Ann Arbor, MI. Hemoglobin genetic variant C trait and S trait have documented interference on HbA1c measurement with the Unimate kit.[46] The inter-assay coefficient of variation (CV) was 4.0% and 3.0% at HbA1c values of 5.7% and 10.8%, respectively; the intra-assay CV was 0.97% and 0.57% at HbA1c values of 5.7% and 10.8%, respectively. For blood glucose, the inter-assay CV was 3.6% at 92 mg/dL and 2.8% at 310 mg/dL; the intra-assay CV was 2.0% at both 84 mg/dL and 283 mg/dL. Diabetes mellitus status (yes/no) was determined by a fasting glucose ≥126 mg/dL or affirmative responses to questions regarding ever diagnosis with diabetes, treatment for diabetes, or current use of diabetes medication as identified from an affirmative response to the following questions: “Since your last visit, have you taken [insulin/pills for sugar in your blood]?” and “Have you been taking [insulin/pills for sugar in your blood] at least 2 times per week for the last month?”.

Data Collection and Management

Data were collected, stored, and managed in compliance with guidelines of the Institutional Review Board at the University of Michigan. All data used for this research proposal were de-identified so as to protect the confidentiality of the human research participants. Data management and analyses were performed in SAS v9.3.

Funding Support

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Analysis Plan

In general, descriptive statistics including means for continuous variables and frequencies for categorical variables were used to examine all variables of interest in this investigation. Student's t-tests or chi square tests were used to generate p-values and compare variables of interest between race/ethnic groups and between women with and without neuropathy. Continuous variables were examined for normality and log transformed where appropriate to meet model assumptions of normality and constant variance. The assessment of physical functioning and obesity trajectories utilized multiple data points for each woman. Thus, a repeated measures approach was used to account for within-woman correlations. Regression models were built beginning

with primary independent and dependent variables, adding potential confounders by *a priori* evidence or a model-building approach to create multivariable regression models.

Chapter 2 is a cross-sectional evaluation of peripheral neuropathy in 2008 (study year 12) in the Michigan SWAN cohort. Three peripheral neuropathy prevalence estimates were made from the MNSI symptom questionnaire, MNSI clinical examination, and monofilament testing. For each assessment method, the sociodemographic and clinical differences between women with peripheral neuropathy and women without peripheral neuropathy were determined by p-values generated from student's t-tests for continuous variables and chi-square tests for categorical variables. In addition, to examine the racial/ethnic heterogeneity of the Michigan SWAN site, the sociodemographic and clinical differences between African American women and Caucasian women were determined. A venn diagram was used to show the agreement between the three neuropathy assessment methods.

Chapter 3 is a cross-sectional and longitudinal analysis of the association between peripheral neuropathy and physical functioning. Chi-square tests for categorical variables and student's t-tests for continuous variables were used to compare baseline (1996) characteristics between women who had peripheral neuropathy in 2008 and women who did not have peripheral neuropathy in 2008. Multivariable linear and logistic regression was used to determine the association between physical functioning in 2008 and peripheral neuropathy in 2008. Linear mixed models were used to

determine if the association between age and physical functioning over time differed between women who had neuropathy in 2008 and women who did not have neuropathy in 2008.

Chapter 4 is a cross-sectional and longitudinal analysis of the association between peripheral neuropathy and anthropometric measures. Student's t-tests were used to compare baseline body size measurements between women who had peripheral neuropathy in 2008 and women who did not have peripheral neuropathy in 2008. Multivariable regression was used to determine the association between baseline body size and peripheral neuropathy status in 2008. Linear mixed models were used to determine if the association between age and body size over time differed between women who had neuropathy in 2008 and women who did not have neuropathy in 2008.

SUMMARY

In summary, this dissertation characterizes peripheral neuropathy in a cohort of mid-life women. We assess the prevalence of peripheral neuropathy and evaluate the association between peripheral neuropathy, obesity, and physical functioning. Finally, we present implications for public health practice and future research directions.

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CHAPTER 2

Characterization of peripheral neuropathy in a population-based sample of mid-life African American and Caucasian women

ABSTRACT

Characterizing peripheral neuropathy in persons with and without diabetes is of increasing interest. Prevalence estimates of neuropathy vary considerably, but the degree to which this is a function of the study population, type of testing, or diagnostic criteria employed is unknown. The purpose of this investigation was to determine the prevalence of peripheral neuropathy in a population-based cohort of African American and Caucasian mid-life women using three independent peripheral neuropathy assessment methods, to assess the concordance of the three methods, and to describe how individual characteristics differed by method.

Data from the Study of Women's Health Across the Nation – Michigan site were used. In 2008, 396 women completed the Michigan Neuropathy Screening Instrument (MNSI) clinical examination, MNSI symptom questionnaire, and/or monofilament testing. Chi-

square and student's t-tests were used to compare population characteristics between women with and without neuropathy.

The prevalence of peripheral neuropathy by monofilament testing was 14.3% (95% Confidence Interval (CI): 10.7-17.9%; n=53), by symptom questionnaire was 19.4% (95% CI: 15.5-23.3%; n=77), and by clinical exam was 20.0% (95% CI: 15.9-24.0%; n=74). Of the 166 women with neuropathy by any method, only 2 women were identified concurrently by all three methods. Women with monofilament-defined and symptom-defined neuropathy had larger body sizes than women without neuropathy. Women with neuropathy by the clinical exam were more likely to be African American and have higher blood pressure than women without neuropathy. Regardless of assessment method, women with co-occurring neuropathy and diabetes had larger body sizes, higher HbA1c values, and were more likely to be hypertensive.

The prevalence of peripheral neuropathy was substantial but varied according to method of assessment. Our finding that larger body size was significantly associated with neuropathy deserves greater public health attention as a topic of future research and as a potentially modifiable risk factor for peripheral neuropathy.

INTRODUCTION

Although peripheral neuropathy has been extensively studied as a common complication of type 1 and type 2 diabetes mellitus, examination of this complex

condition to ascertain its impact within the general population is increasingly of interest.[1] Most neuropathy research has been undertaken in diabetic, elderly, or clinical populations with poor health.[2-5] In diabetic populations, prevalence estimates of neuropathy range from 7.2% to 54%.[6-13] Among individuals with normal fasting glucose levels, the prevalence of peripheral neuropathy ranges from 2.9% to 13.3%,[6,10-13] and a recent analysis from the National Health and Nutrition Examination Survey III (NHANES) identified the prevalence of peripheral neuropathy as 11.5% in a sample selected to be representative of the non-institutionalized adult population in the United States (US).[14] Whether these prevalence differences can be attributed to differential distribution of risk factors or to differential use of methodologies is unknown.

Many diabetic individuals already have peripheral neuropathy at the time of their diabetes diagnosis, and it has been speculated that episodic hyperglycemia may contribute to the etiology of neuropathy prior to actual diagnosis for diabetes.[15-19] This is supported by studies that have shown the propensity for increasing neuropathy risk across categories of fasting glucose levels, as prevalence increases progressively across normal fasting glucose, impaired fasting glucose, and diabetic groups.[12,13] Considerably less is known about the association between neuropathy risk and other individual characteristics. Given the potential debilitating consequences of peripheral neuropathy and the substantial prevalence, further evaluation of peripheral neuropathy in general populations to identify risk factors is warranted. The purpose of this investigation was to characterize peripheral neuropathy prevalence in a population-based cohort of African

American and Caucasian mid-life women in the United States using three independent peripheral neuropathy assessments, to assess the concordance of neuropathy classification using the three methods, and to describe how individual characteristics differed across classification methods.

METHODS

The Study of Women's Health Across the Nation (SWAN) is an ongoing population-based longitudinal study of women entering menopause from seven sites in the United States that has been described previously.[20] This investigation is from the Michigan SWAN study population which consists of 543 women (325 African American and 218 Caucasian) from two communities near Detroit, MI. Of the original sample selected at the 1996 baseline based on pre-menopause status, 418 (77%) were still active in study year 12 (2008) and eligible to participate in the peripheral neuropathy sub-study. Of these, 371 (89%) participants completed a foot examination for peripheral neuropathy and a neuropathy symptom questionnaire; 25 (6%) completed a neuropathy questionnaire administered via telephone or mail without completing the foot examination, and 22 (5%) refused participation in the sub-study. There were no statistically significant differences by age, race/ethnicity, or baseline diabetes status observed between women who completed the full sub-study and women who did not. The parent and sub-study were approved by the University of Michigan Health Institutional Review Board.

Peripheral neuropathy was assessed using three independent approaches: (1) the Michigan Neuropathy Screening Instrument (MNSI) symptom questionnaire,[21,22] (2) the MNSI clinical examination,[21,22] and (3) monofilament testing.[23] The MNSI symptom questionnaire is used to acquire information about the presence (yes/no) of common neuropathy symptoms and characteristics including numbness, burning pain, sensitivity, prickling feelings, hot/cold differentiation, open sores, dryness, and amputation. The number of positive symptoms was calculated (see Appendix A), with higher scores indicative of more neuropathy symptoms and thus an increased likelihood of neuropathy. For the purposes of analyses, participants reporting ≥4 symptoms or signs out of a total of 15 were classified as having neuropathy.[24]

The MNSI clinical examination included a visual foot inspection by trained examiners, assessment of vibration sensation, and grading of ankle reflexes.[21,22] The visual inspection emphasized deformity, dry or callused skin, infection, fissure, and ulceration. Vibration sensation was evaluated using a 128 Hz tuning fork placed over the dorsum of the participant's great toe at the distal interphalangeal joint while being held by the examiner's thumb and index finger. Vibration sensation was considered "present" if the examiner felt the vibration for less than 10 seconds longer than the participant, "decreased" if the examiner felt the vibration for more than 10 seconds longer than the participant, and "absent" if the participant could not sense the vibration. Ankle reflexes were obtained by percussing the Achilles tendon. Reflexes were graded as "present" if the reflex was obtained. If the reflex was absent, the participant was instructed to

perform the Jendrassic maneuver (fingers locked together and pulling; this prevents conscious flexing and helps to elicit a natural reflex) to ensure the reflex was truly absent. If the reflex was obtained with this maneuver, the reflex was graded as "present with reinforcement." If reflex was not obtained using either method, the reflex was graded as "absent." A composite score was obtained by combining the elements of the clinical exam. For each of the right and left feet, there were 8 possible points; one point was given for abnormalities (deformity, moderate or severe dry and callused skin, infection, or fissure), ulceration, absent ankle reflexes, and absent vibration perception. Half a point was given for each determination of ankle reflexes present with reinforcement and decreased vibration perception. A composite score of ≥2.5 on the MNSI clinical examination defined neuropathy. This cutpoint is reported to have a sensitivity of 80% and a specificity of 95% in a clinical population with diabetes.[21,22]

Monofilament testing used the placement of a 10-gram pre-stressed filament on the dorsal side of the great toe, midway between the nail fold and the distal interphalangeal joint briefly (<1 second) for 10 repetitions. The participant was asked to respond if she felt the filament following each repetition. Peripheral neuropathy was defined as 80% or fewer correct responses to the brief sensation in either foot.[13]

Four participants were unable to complete the physical foot assessments on either the right or the left foot due to amputation or the presence of surgical bandages. In these

cases, the score from the assessed foot was extrapolated to the non-assessed/absent foot to classify neuropathy status.

Age (years) was identified from the interval of date of birth to 2008. Race/ethnicity was self-identified at the 1996 baseline as African American or Caucasian. Anthropometric measurements were collected in 2008. Weight (kg) was measured by balance beam scale and height (cm) was measured by a stadiometer; body mass index (BMI) was calculated as weight (kg)/height (m^2). Waist circumference (cm) at exhalation and hip circumference (cm) were measured using a non-stretching tape measure.

Participants' responses on the annual study questionnaire were used to categorize current smoking status (yes/no) and current alcohol consumption (yes/no) in 2008. Participants were identified as current smokers if they provided an affirmative answer to the question "Since your last study visit, have you smoked cigarettes regularly?" Participants were identified as current alcohol consumers if they provided an affirmative answer to the question "Since your last study visit, did you drink any beer, wine, liquor, or mixed drinks?" and they reported more than one drink of beer, wine, or liquor per month (>180 grams/year).

Blood pressure (mmHg) was measured twice using a mercury sphygmomanometer following an initial minimum 5 minute resting period and a 2 minute resting period between each measure. The two systolic measurements and the two diastolic

measurements were averaged. Current hypertension treatment was determined by an affirmative response to the following two questions “Since your last visit, have you taken any [medication for blood pressure/diuretics for water retention]?” and “Have you been taking [medication for blood pressure/diuretics for water retention] at least 2 times per week for the last month?” Participants were classified as hypertensive if their average systolic blood pressure was ≥140mmHg, average diastolic blood pressure was ≥90mmHg, or if they reported current use of antihypertensive treatment.

Fasting blood samples were collected from participants annually. For this sub-study, samples were assayed for glycosylated hemoglobin (HbA1c) percentage using the immunoassay kit Unimate 3 from Roche Diagnostics and blood glucose (mg/dL) using the hexokinase assay on a Cobas Mira Chemistry Analyzer from Roche Diagnostics at the Michigan Diabetes Research and Training Center in Ann Arbor, MI. The inter-assay coefficient of variation (CV) was 4.0% and 3.0% at HbA1c values of 5.7% and 10.8%, respectively; the intra-assay CV was 0.97% and 0.57% at HbA1c values of 5.7% and 10.8%, respectively. For blood glucose, the inter-assay CV was 3.6% at 92 mg/dL and 2.8% at 310 mg/dL; the intra-assay CV was 2.0% at both 84 mg/dL and 283 mg/dL. Diabetes mellitus status (yes/no) was determined by a fasting glucose ≥126 mg/dL or affirmative responses to questions regarding ever diagnosis with diabetes, treatment for diabetes, or current use of diabetes medication as identified from an affirmative response to the following questions: “Since your last visit, have you taken [insulin/pills

for sugar in your blood]?" and "Have you been taking [insulin/pills for sugar in your blood] at least 2 times per week for the last month?".

We estimated the prevalence of peripheral neuropathy based on the MNSI symptom questionnaire, the MNSI clinical examination, and the 10-g monofilament evaluation. Chi-square tests for categorical variables and student's t-tests for continuous variables were used to compare population characteristics between African American and Caucasian women and between the peripheral neuropathy groups defined using the 3 instruments. Additionally, we used chi-square tests and t-tests to compare women with and without diabetes in a sub-population of 166 women who were classified as having peripheral neuropathy by any of the three assessment methods. Multivariable logistic regression was used to determine the association between peripheral neuropathy and other variables, including age, race/ethnicity, anthropometric measures, blood pressure, and diabetes. SAS (version 9.3) was used for all data management and analyses. Statistical tests were 2-sided with the level of significance defined as p-value <0.05.

RESULTS

The average age of participants was 57.6 (SD 2.8) years and 30% were characterized as having diabetes (Table 2.1). The average HbA1c level was 6.3%, with 26% of the population characterized as having diabetes using the American Diabetes Assocation-specified HbA1c cut point of 6.5%.[25] Among those reporting current diabetes

treatments, the average HbA1c was 7.5% as compared to 5.9% among those reporting no diabetes treatment.

Approximately 60% of the study population was African American and 40% was Caucasian, by study design. African American women were slightly taller and slightly younger than Caucasian women. Treated and untreated African American women had higher blood pressures than Caucasian women, as well as higher HbA1c percentage (Table 2.1).

The prevalence of peripheral neuropathy was substantial but differed according to the method of assessment. The prevalence of neuropathy by monofilament evaluation was 14.3% (95% CI: 10.7 – 17.9%; n=53), by MNSI Symptom Questionnaire was 19.4% (95% CI: 15.5 – 23.3%; n=77), and by MNSI clinical examination was 20.0% (95% CI: 15.9 – 24.0%; n=74).

Although the prevalence across assessment methods was similar, neuropathy was identified concurrently by all three methods in only 2 of 166 women (0.5%). Neuropathy was identified by both the MNSI clinical examination and the monofilament testing in 8 women, by both the MNSI clinical examination and the symptom questionnaire in 12 women, and by both the symptom questionnaire and the monofilament testing in 20 women (Figure 2.1). A total of 208 women (55.6%) were classified as not having neuropathy by all three assessment methods.

Individual characteristics of women with neuropathy varied according to how neuropathy was measured (Table 2.2). Women with peripheral neuropathy assessed by monofilament testing and the symptom questionnaire had larger body sizes as measured by weight, BMI, and waist circumference. In addition, women with peripheral neuropathy identified by monofilament testing were slightly taller than women without sensory neuropathy. Women with neuropathy by the MNSI symptom questionnaire had significantly higher HbA1c percentage and diabetes prevalence. Women with symptom-defined neuropathy also had higher systolic blood pressure and more hypertension compared to women without neuropathy, and this pattern persisted among women who reported current antihypertensive treatment. Using the MNSI clinical examination composite score ≥2.5, women with neuropathy were more likely to be African American than were women without neuropathy and had higher diastolic blood pressure than women without neuropathy, but did not differ by body size.

In a multivariate model adjusting for age, race/ethnicity, weight, height, blood pressure, and diabetes status, weight was significantly associated with neuropathy as measured by the monofilament test and symptom questionnaire (Table 2.3). Women who weighed 104.3 kg (75^{th} percentile) were 1.8 times more likely to have monofilament-defined sensory neuropathy (OR=1.81; 95% CI:1.17, 2.81) and 2.3 times more likely to have symptom-defined neuropathy (OR=2.34; 95% CI:1.56, 3.53) compared to women who weighed 73.2 kg (25^{th} percentile).

A sub-population analysis was conducted in the group of 166 women who were classified as having peripheral neuropathy by at least one of the assessment methods. In this group, the presence of neuropathy and diabetes was associated with a larger body size, indicated by significantly higher weight, BMI, and waist and hip circumference. Additionally, women with co-occurring neuropathy and diabetes had significantly higher HbA1c values and almost 80% were hypertensive (Table 2.4).

DISCUSSION

We assessed neuropathy in a biracial cohort of community-dwelling women in the US using three different neuropathy assessment instruments: the MNSI symptom questionnaire, MNSI clinical examination, and monofilament testing. In this mid-life cohort, the prevalence of neuropathy ranged from 14.3% to 20.0%, depending on the method. The variation in prevalence was based on the evaluation method used, but these methods did not identify the same women as having neuropathy. Historically, the monofilament method is used to identify diabetic feet at high risk for ulceration and amputation[26] and the MNSI clinical examination is used to identify diabetic neuropathy in a clinical population.[21,22] However, recent research has applied monofilament testing to the general population as well.[10,13]

The prevalence of peripheral neuropathy determined by monofilament testing in our population was consistent with other reports using similar monofilament testing

methods in community-dwelling populations. Reports from NHANES in the US indicate that lower extremity diseases have a prevalence of ten to fifteen percent in the general adult population[10,11,14] and a cross-sectional evaluation in Singapore revealed that the prevalence of neuropathy in the overall population was 7.5%.[13] However, estimates of monofilament-defined neuropathy from diabetic populations are much higher. Gregg et al.[10] found that 28.5% of individuals with diabetes had neuropathy compared to 13.3% of those without diabetes. Additional assessment methods include symptom questionnaires, clinical scoring systems, and electrophysiological evaluations, each with different sensitivities and specificities.[21,22,27] Not surprisingly, differences in neuropathy screening and diagnostic methodologies may contribute to the variability observed in the population prevalence estimates of neuropathy.

In our study, neuropathy was identified concurrently by all three methods in only 2 women (0.5%). The low correlation of the MNSI symptom questionnaire with other clinical assessments has been previously reported.[22] We anticipated that all or most of peripheral neuropathy identified with monofilament testing would also be identified by the MNSI clinical examination. This absence of correspondence between these two approaches may have occurred because the MNSI was designed as a screening instrument for diabetic neuropathy or because monofilament testing was designed as a marker of ulcer risk in diabetic patients. In a diabetic-only population, the MNSI instrument has a specificity of 95%.[21,22] The MNSI clinical examination emphasizes a visual foot inspection to evaluate deformities, dry skin, callus, infection, and ulceration.

These physical abnormalities may be etiologically more important for diabetic neuropathy than for neuropathy in non-diabetic individuals. By extension, this may be a reflection of the contribution of both macro- and micro-vascular disease. By administering the MNSI exam to our entire population that included individuals without diabetes, we may have over-estimated the prevalence of non-diabetic neuropathy using this method.

For monofilament-defined sensory neuropathy, we found that body size measures, including weight, height, BMI, and waist circumference, were all significantly associated with peripheral neuropathy. Although the relationship between height and neuropathy is not entirely understood, neuropathy is thought to be a length-dependent disorder, with the distal extremities affected first.[11] Therefore, individuals of taller stature may be at increased risk of neuropathy considering they have longer peripheral nerves than individuals of shorter stature.[11] One small study has documented subclinical nerve impairment in obese individuals independent of diabetes.[16] To date, there is no evidence that obesity alone causes neuropathy; rather, the relationship between obesity and glucose intolerance suggests a pathway between obesity and neuropathy in non-diabetic individuals through impaired glucose metabolism. Although obesity is hypothesized to be causally related to peripheral neuropathy, women with neuropathy could also be less likely to exercise due to loss of foot sensation or pain, which in turn could lead to obesity. We were unable to differentiate between these scenarios based on the currently available neuropathy measures in our population. Nonetheless, the

association between obesity, impaired glucose metabolism and peripheral neuropathy is debated[17,28] and clearly deserves further investigation.

This investigation has some limitations, including the cross-sectional design which precludes inferences of causality and provides the possibility of reverse causation when evaluating the association between weight, for example, and peripheral neuropathy. Peripheral neuropathy has many causes, and although neuropathy is a common complication of diabetes, it is likely that even among persons with diabetes there is a background rate of other neuropathy etiologies. We did not differentiate among neuropathy pathogeneses with invasive testing to determine whether or not neuropathy as measured by our study was in fact diabetic neuropathy.

Nevertheless, the use of simple screening methods in an epidemiological investigation is desirable. Recent investigations in population-based samples have used similar, noninvasive procedures to determine the presence of a neuropathy[11,13] despite the fact that the complexity of peripheral neuropathy means that a single noninvasive test may not capture these differences in affected nerve fibers.[29]

CONCLUSIONS

In this population-based sample of adult women, the estimated prevalence of peripheral neuropathy was instrument-dependent but ranged from 14% to 20%. Using monofilament testing to define neuropathy, 14% of women had neuropathy, and 19% of

women reported at least 4 neuropathy symptoms. Measures of obesity, including weight, waist circumference, and BMI, were significantly associated with neuropathy, a finding which deserves greater public health attention as both a topic of future research and a potential modifiable risk factor. Given the high prevalence of peripheral neuropathy reported by this and other population-based studies, neuropathy should be considered a common condition in the general population and not merely a consequence of overt diabetes. The shifting age and obesity distributions of the United States and the substantial morbidity associated with neuropathy may warrant the implementation of neuropathy testing among mid-life adults of the general population.

Figure 2.1. Counts of coinciding peripheral neuropathy assessments using three independent measures, Peripheral Neuropathy Substudy, Michigan SWAN, 2008.

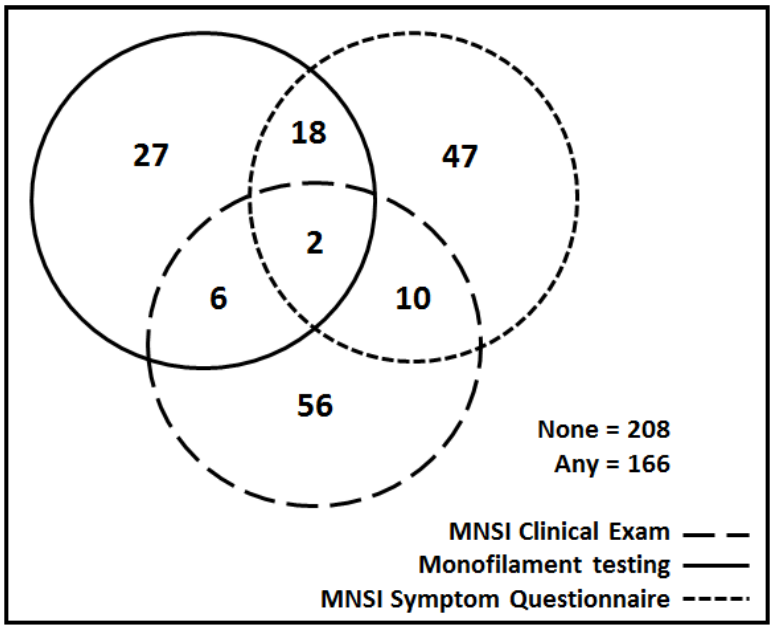

Table 2.1. Characteristics* of study population, Peripheral Neuropathy Substudy, Michigan SWAN, 2008.

Overall, % (n)	**Total population** 100.0 (n=416)	**Caucasian** 39.2 (n=163)	**African American** 60.8 (n=253)	**p-value`**
Age, years	57.6 (2.8)	58.0 (2.7)	57.3 (2.8)	**0.02**
Weight, kg	89.9 (22.0)	88.1 (20.9)	91.0 (22.5)	0.20
Height, cm	162.7 (6.1)	161.8 (6.0)	163.2 (6.2)	**0.04**
Waist circumference, cm	101.3 (17.2)	100.5 (17.7)	101.8 (16.9)	0.48
Hip circumference, cm	117.4 (17.0)	117.0 (16.6)	117.6 (17.3)	0.73
BMI, kg/m2	34.0 (8.3)	33.6 (7.9)	34.2 (8.5)	0.48
Current smoker, %	20.9	14.4	25.3	**0.01**
Alcohol consumption	31.7	36.8	28.9	0.09
Blood pressure, %				
Systolic, mmHg	123 (18.2)	117 (14.0)	127 (19.4)	**<0.0001**
Diastolic, mmHg	69 (9.8)	66 (9.3)	70 (9.7)	**<0.0001**
Hypertension, %	57.5	45.4	65.4	**0.0001**
Blood pressure among those treated for hypertension (n=203)				
Systolic, mmHg	126 (17.6)	120 (12.4)	128 (18.8)	**0.001**
Diastolic, mmHg	69 (10.2)	65 (9.5)	70 (10.1)	**0.002**
Blood pressure among those not treated for hypertenion (n=194)				
Systolic, mmHg	120 (18.3)	114 (14.5)	125 (20.0)	**<0.0001**
Diastolic, mmHg	69 (9.4)	67 (9.2)	70 (9.2)	**0.01**
Fasting plasma glucose (mg/dL)	110 (38.5)	110 (33.8)	110 (41.4)	0.99
HbA1c, %	6.3 (1.3)	5.9 (1.0)	6.5 (1.4)	**<0.0001**
Treated for diabetes (n = 85)				
Fasting glucose, mg/dL	142 (57.1)	152 (51.1)	136 (60.1)	0.22
HbA1c, %	7.5 (1.9)	7.2 (1.5)	7.7 (2.1)	0.26
Not treated for diabetes (n = 310)				
Fasting glucose, mg/dL	102 (25.6)	100 (14.4)	103 (30.9)	**0.17**
HbA1c, %	5.9 (0.8)	5.6 (0.4)	6.1 (1.0)	**<0.0001**
Diabetes mellitus, %	29.8	29.3	30.2	0.84

*Data presented as mean (standard deviation) for continuous variables or as % for categorical variables.

`Calculated by a two-sample student's t-test for means for continuous variables or by a chi-square test for categorical variables to compare Caucasian vs. African American women. Statistical significance considered p-value < 0.05.

Table 2.2.A. Population characteristics by peripheral neuropathy status using three independent neuropathy instruments, Peripheral Neuropathy Substudy, Michigan SWAN, 2008.

	Monofilament testing[†]		
	Neuropathy	No Neuropathy	p-value`
Proportion, % (n)	*14.3 (53)*	*85.7 (318)*	
Race/ethnicity, %			
Caucasian	37.7	39.3	0.83
African American	62.3	60.7	
Weight, kg	99.8 (24.1)	88.0 (21.1)	**0.0003**
Height, cm	164.6 (6.4)	162.4 (6.1)	**0.02**
Waist circumference, cm	108.5 (17.2)	99.9 (16.9)	**0.001**
Hip circumference, cm	124.7 (19.3)	116.0 (16.3)	**0.001**
BMI, kg/m2	36.9 (9.0)	33.4 (8.1)	**0.01**
Current smoker, %	15.1	22.3	0.23
Alcohol consumption, %	28.3	34.6	0.4
Blood pressure			
Systolic, mmHg	123 (18.0)	123 (18.3)	0.93
Diastolic, mmHg	68 (9.9)	69 (9.8)	0.74
Hypertension, %	62.3	55	0.33
<u>Among those treated for hypertension</u>			
Systolic, mmHg	125 (19.4)	126 (17.3)	0.68
Diastolic, mmHg	69 (10.8)	69 (10.1)	0.82
<u>Among those not treated for hypertension</u>			
Systolic, mmHg	121 (15.8)	120 (18.7)	0.77
Diastolic, mmHg	68 (8.6)	69 (9.4)	0.78
Diabetes mellitus, %	36.5	27.3	0.17
Fasting plasma glucose, mg/dl	118 (51.7)	109 (36.0)	0.27
HbA1c, %	6.5 (1.5)	6.2 (1.3)	0.26
Treated	7.8 (2.1)	7.4 (1.9)	0.49
Untreated	5.9 (0.6)	5.9 (0.9)	0.9

†Neuropathy defined as 80% or fewer correct responses to 10-g monofilament sensation in either foot.

`Calculated by a two-sample student's t-test or chi-square test. Statistical significance considered p-value < 0.05.

Table 2.2.B. Population characteristics by peripheral neuropathy status using three independent neuropathy instruments, Peripheral Neuropathy Substudy, Michigan SWAN, 2008.

	MNSI Clinical Examination*		
	Neuropathy	No Neuropathy	p-value`
Proportion, % (n)	*20.0 (74)*	*80.0 (297)*	
Race/ethnicity, %			
Caucasian	25.7	42.4	**0.01**
African American	74.3	57.6	
Weight, kg	88.6 (23.8)	89.9 (21.5)	0.64
Height, cm	163.0 (6.5)	162.6 (6.1)	0.64
Waist circumference, cm	98.9 (18.2)	101.7 (16.9)	0.02
Hip circumference, cm	115.2 (18.1)	117.7 (16.7)	0.25
BMI, kg/m2	33.5 (9.5)	34.0 (8.0)	0.68
Current smoker, %	20.3	21.6	0.81
Alcohol consumption, %	29.7	34.7	0.42
Blood pressure			
Systolic, mmHg	125 (16.3)	123 (18.7)	0.34
Diastolic, mmHg	72 (10.5)	68 (9.4)	**0.003**
Hypertension, %	58.1	55.6	0.69
Among those treated for hypertension			
Systolic, mmHg	126 (17.4)	126 (17.7)	0.82
Diastolic, mmHg	73 (11.7)	68 (9.5)	**0.01**
Among those not treated for hypertension			
Systolic, mmHg	123 (14.8)	119 (19.0)	0.32
Diastolic, mmHg	70 (8.7)	68 (9.4)	0.23
Diabetes mellitus, %	25	29.6	0.44
Fasting plasma glucose, mg/dl	109 (41.6)	111 (38.0)	0.78
HbA1c, %	6.2 (1.2)	6.3 (1.4)	0.8
Treated	7.6 (1.8)	7.5 (1.9)	0.91
Untreated	5.9 (0.7)	5.9 (0.9)	0.95

*Neuropathy defined as MNSI clinical examination composite score ≥2.5.

`Calculated by a two-sample student's t-test or by a chi-square test. Statistical significance considered p-value < 0.05.

Table 2.2.C. Population characteristics by peripheral neuropathy status using three independent neuropathy instruments, Peripheral Neuropathy Substudy, Michigan SWAN, 2008.

	MNSI Symptom Questionnaire[#]		
	Neuropathy	No Neuropathy	p-value`
Proportion, % (n)	*19.4 (77)*	*80.6 (319)*	
Race/ethnicity, %			
Caucasian	44.2	39.5	0.45
African American	55.8	60.5	
Weight, kg	101.1 (25.9)	87.09 (20.0)	**<0.0001**
Height, cm	162.2 (5.5)	162.8 (6.3)	0.48
Waist circumference, cm	110.1 (18.8)	99.1 (16.1)	**<0.0001**
Hip circumference, cm	125.9 (19.3)	115.3 (15.8)	**<0.0001**
BMI, kg/m2	38.4 (9.7)	32.9 (7.5)	**<0.0001**
Current smoker, %	23.4	20.4	0.56
Alcohol consumption, %	24.7	35.7	0.07
Blood pressure			
Systolic, mmHg	127 (19.4)	122 (17.7)	**0.02**
Diastolic, mmHg	69 (10.6)	69 (9.5)	0.99
Hypertension, %	65.3	55.6	0.13
<u>Among those treated for hypertension</u>			
Systolic, mmHg	132 (20.1)	124 (16.4)	**0.02**
Diastolic, mmHg	69 (11.4)	69 (9.8)	0.86
<u>Among those not treated for hypertension</u>			
Systolic, mmHg	121 (16.8)	119.5 (18.6)	0.62
Diastolic, mmHg	69 (9.6)	69 (9.3)	0.86
Diabetes mellitus, %	46.6	25.3	**0.0003**
Fasting plasma glucose, mg/dl	121 (49.9)	108 (34.9)	**0.04**
HbA1c, %	6.6 (1.7)	6.2 (1.2)	**0.03**
Treated	7.7 (2.0)	7.4 (1.8)	0.57
Untreated	6.0 (1.0)	5.9 (0.8)	0.41

#Neuropathy defined as MNSI symptom questionnaire composite score ≥4.

`Calculated by a two-sample student's t-test or chi-square test. Statistical significance considered p-value < 0.05.

Table 2.3. Multivariable associations (Odds Ratio (OR) [95% Confidence Interval (CI)]) of individual characteristics with peripheral neuropathy status using three independent neuropathy instruments, Peripheral Neuropathy Substudy, Michigan SWAN, 2008.

	Monofilament testing†		MNSI Clinical Examination*		MNSI Symptom Questionnaire#	
	OR (95% CI)	p-value`	OR (95% CI)	p-value`	OR (95% CI)	p-value`
Race/ethnicity (AA vs. Caucasian)	1.05 (0.54, 2.02)	0.90	2.21 (1.20, 4.08)	**0.01**	0.70 (0.39, 1.26)	0.41
Weight, kg (75^{th} vs. 25^{th} percentile)	1.81 (1.17, 2.81)	**0.01**	0.93 (0.62, 1.39)	0.72	2.34 (1.56, 3.53)	**<0.0001**
Height, cm (75^{th} vs. 25^{th} percentile)	1.51 (1.03, 2.21)	**0.04**	1.07 (0.77, 1.49)	0.68	0.81 (0.56, 1.16)	0.25
Blood pressure						
Systolic, mmHg (75^{th} vs. 25^{th} percentile)	0.97 (0.62, 1.51)	0.9	0.75 (0.50, 1.11)	0.15	1.50 (1.02, 2.19)	**0.04**
Diastolic, mmHg (75^{th} vs. 25^{th} percentile)	0.93 (0.57, 1.53)	0.79	1.97 (1.25, 3.09)	**0.004**	0.80 (0.51, 1.24)	0.31
Diabetes mellitus (Yes vs. No)	1.36 (0.69, 2.67)	0.37	0.95 (0.50, 1.81)	0.87	1.72 (0.96, 3.08)	0.07

†Neuropathy defined as 80% or fewer correct responses to 10-g monofilament sensation in either foot.

*Neuropathy defined as MNSI clinical examination composite score ≥2.5.

#Neuropathy defined as MNSI symptom questionnaire composite score ≥4.

`Statistical significance considered p-value < 0.05.

Table 2.4. Characteristics of women with peripheral neuropathy (PN) by any assessment method (n=166), with and without diabetes, Peripheral Neuropathy Substudy, Michigan SWAN, 2008.

	With PN by any assessment method		p-value[+]
	No Diabetes	Diabetes	
Age, years	57.8 (2.7)	57.6 (2.6)	0.64
Race/ethnicity, %			
Caucasian	34.0	38.9	0.54
African American	66.0	61.1	
Weight, kg	88.9 (22.8)	102.1 (22.9)	**0.001**
Height, cm	163.2 (6.4)	162.3 (6.0)	0.42
Waist circumference, cm	100.0 (18.0)	112.5 (16.1)	**<0.0001**
Hip circumference, cm	117.1 (17.6)	124.8 (18.1)	**0.01**
BMI, kg/m2	33.4 (8.5)	38.8 (8.7)	**0.0003**
Current smoker, %	19.8	24.1	0.53
Alcohol consumption, %	55.9	20.4	**0.04**
Blood pressure			
Systolic, mmHg	123.1 (17.0)	129.0 (21.6)	0.08
Diastolic, mmHg	70.2 (10.0)	68.5 (11.2)	0.32
Hypertension, %	50.0	79.6	**0.0003**
HbA1c, %	5.9 (0.6)	7.4 (1.8)	**<0.0001**

Neuropathy defined as 80% or fewer correct responses to 10-g monofilament sensation in either foot, MNSI clinical examination composite score ≥2.5, or MNSI symptom questionnaire composite score ≥4.

+Calculated by a two-sample student's t-test for means for continuous variables or by a chi-square test for categorical variables. Statistical significance considered p-value < 0.05.

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CHAPTER 3

Performance-based physical functioning and peripheral neuropathy in a population-based cohort of mid-life women

ABSTRACT

Limitations in physical functioning are risk factors for future disability. Many studies measure physical functioning limitations in persons over the age of 65 without appreciating the likelihood of their initiation and progression during the mid-life years. Peripheral neuropathy is underappreciated as a potential cause of functional limitations. The purpose of this investigation was to determine the association between peripheral neuropathy and physical functioning in a population-based cohort of African American and Caucasian mid-life women in the United States.

Data (n=396) from 1996-2008 from the Study of Women's Health Across the Nation – Michigan site were used. Annual physical functioning was measured by performance (in seconds) on a timed stair climb, 40-foot walk, sit to stand, unipedal balance stand, and tandem balance stand. Peripheral neuropathy was measured in 2008 and defined as an abnormal monofilament test or ≥ 4 symptoms or signs. Linear mixed models were used

to determine trajectories of physical functioning over time in relation to subsequently-identified peripheral neuropathy status.

Overall, 27.8% of women had peripheral neuropathy. Time to complete the stair climb differed significantly by neuropathy status at mean baseline age (p-value=0.045), and for every one-year increase in age, women who would have neuropathy in 2008 had a 1.82% (95% Confidence Interval (CI): 1.42-2.21%) increase in time compared to a 0.95% (95% CI: 0.71-1.20) increase for women who would not have neuropathy in 2008. At mean baseline age, time to complete the sit to stand task differed significantly by neuropathy status (p-value=0.01) but there were no significant differences in the rate of change over time. For the timed walk, there were no significant differences between neuropathy groups at mean baseline age (p-value=0.09) and there were no significant differences in the rate of change over time. In 2008, women with neuropathy had poorer performance on the unipedal balance stand (p-value=0.003) compared to women without neuropathy.

Even at baseline, 12 years before the assessment of peripheral neuropathy, physical functioning differed between women who would and would not be subsequently-identified with peripheral neuropathy in 2008, and these differences were maintained or exacerbated over time for a variety of performance-based tasks. Peripheral neuropathy may play an important role in physical functioning limitations and in the development of future disability.

INTRODUCTION

Understanding the determinants of health, disease, and disability are essential to the overarching goal of Healthy People 2020, to create "a society in which all people live long, healthy lives."[1] Persisting knowledge gaps about the determinants of poor physical functioning limits our ability to achieve this goal. Many studies estimate the prevalence of disability or limitations in physical functioning in persons over the age of 65 without appreciating the likelihood that these limitations may be initiated and progress during the mid-life years. In 2009, the National Health Interview Survey identified that almost 20% of mid-life adults aged 45-64 had some functional limitation or disability.[2] Women are also more likely to report functional limitations than men.[2,3] Expanding assessments of physical limitations to include the mid-life years among women is warranted because middle-aged women with limitations in physical functioning are at high risk for future disability and decreased quality of life.

One seldom explored cause of physical functioning limitations is peripheral neuropathy, a disorder of the peripheral nerves. Common symptoms of peripheral neuropathy include numbness, pain, sensory loss, and tingling in the lower extremities. Overt signs of advanced disease, such as dryness, callous, infection, and ulceration, can be treated clinically; however, it is the effect of neuropathy on physical performance and

functioning, often prior to overt clinical manifestations in the foot, that is under-appreciated in the clinical setting.[4]

Peripheral neuropathy has been well-described as a complication of diabetes mellitus, but the risk factors and sequelae of peripheral neuropathy have not been fully explored. Neuropathy is only beginning to attract attention as a health condition that occurs in persons without diabetes.[5,6] Many individuals with diabetes have peripheral neuropathy at the time of their diabetes diagnosis,[7] and it has been speculated that episodic hyperglycemia or obesity may contribute to the etiology of peripheral neuropathy prior to the actual diagnosis for diabetes.[8-10] The co-occurrence of peripheral neuropathy with diabetes, obesity, and limitations in physical functioning may help explain the high prevalence of disability reported among women in the United States. The purpose of this investigation was to determine the association between peripheral neuropathy and performance-based physical functioning in a population-based cohort of African American and Caucasian mid-life women in the United States. We hypothesized that women with peripheral neuropathy would have poorer physical functioning trajectories compared to women without peripheral neuropathy.

METHODS

Study Population

The Study of Women's Health Across the Nation (SWAN) is an ongoing population-based longitudinal study of women from seven sites in the United States. The study has been

described in detail previously.[11] This investigation focuses on the Michigan SWAN study cohort which consists of 543 women (325 African American and 218 Caucasian) from two communities near Detroit who at baseline in 1996 were 42-52 years of age, had an intact uterus and at least one ovary, reported no current use of hormones, and had at least one menstrual period in the prior three months. Of the original sample, 418 (77%) were still active in study year 12 (2008) and eligible to participate in the peripheral neuropathy sub-study. Of these, 371 (89%) underwent a foot examination and completed a symptom questionnaire for peripheral neuropathy. Twenty-five (6%) completed only the symptom questionnaire administered via telephone or mail, and 22 (5%) refused participation in the sub-study. Women who participated in the neuropathy sub-study and completed any peripheral neuropathy assessment in follow-up year 12 did not differ by race/ethnicity or baseline age, weight, height, waist and hip circumference, blood pressure, and fasting glucose from women who did not participate. The parent and sub-study were approved by the University of Michigan Health Institutional Review Board and all participants provided written informed consent.

Study Variables

Peripheral neuropathy was assessed using two independent approaches: (1) the Michigan Neuropathy Screening Instrument (MNSI) symptom questionnaire[12] and (2) monofilament testing.[13] The MNSI symptom questionnaire is a 15-item questionnaire used to acquire information about the presence (yes/no) of common neuropathy

symptoms and signs, including numbness, pain, sensitivity, cramping, prickling feelings, hot/cold differentiation, open sores, dryness, weakness, and amputation. The number of positive symptoms and signs was calculated, with higher scores indicative of more neuropathy symptoms and signs and thus an increased likelihood of PN. Participants reporting ≥ 4 symptoms or signs out of a total of 15 were classified as having neuropathy.[14]

Monofilament testing used the placement of a 10-gram pre-stressed filament on the dorsal side of the great toe, midway between the nail fold and the distal interphalangeal joint briefly (<1 second) for 10 repetitions. The participant was asked to respond if she felt the filament following each repetition. Peripheral neuropathy was defined as 80% or fewer correct responses to the brief sensation in either foot.[15]

In addition, a third definition of peripheral neuropathy combined the MNSI symptom questionnaire and the monofilament testing. The two neuropathy methods were combined because in a preliminary analysis they appeared to identify women with similar characteristics. Neuropathy is considered a syndrome because different sizes of nerve fibers may be affected, so using more than one test for peripheral neuropathy increases the sensitivity of our assessment and allows us to capture different types and sizes of nerve involvement.[16] If the participant either reported ≥ 4 symptoms or signs on the questionnaire or had 80% or fewer correct responses in either foot from the monofilament testing, the participant was classified as having neuropathy.

Performance-based physical functioning was measured by trained examiners, based on the participant's performance on a variety of tests. The stair climb measured the time in seconds that elapsed while the participant climbed three stairs in three repetitions (3x3). Participants could use the hand railings if needed. The 40-foot walk measured the time in seconds that elapsed while the participant walked at a brisk, purposeful pace for 40 feet. If the participant typically used an assistive device, she could use it during the timed walk. The sit to stand assessment measured the time in seconds that elapsed while the participant rose from a normal-height bench with arms crossed over the chest and was standing with both arms down at the sides. Balance was measured by the unipedal and tandem foot stands. The unipedal foot stand measured the time in seconds that the participant was able to balance using only the right foot, up to a maximum of 30 seconds. The tandem foot stand measured the time in seconds that the participants was able to balance with the right foot in front of the left foot in a tandem position, up to a maximum of 30 seconds. For regression analyses, physical functioning stands were dichotomized as <30 seconds (i.e., failing the stand) vs. 30 seconds. The timing of peripheral neuropathy and physical functioning data collection in the longitudinal study is summarized in Table 3.1.

Age (years) was calculated from the interval of birth to follow-up visit date. Race/ethnicity was self-identified at the 1996 baseline as African American or Caucasian. Annual (baseline through study year 12) anthropometric and blood pressure

measurements were collected using a standardized protocol. Weight (kg) was measured by balance beam scale and height (cm) was measured by a stadiometer; body mass index (BMI) was calculated as weight (kg)/height (m^2). Blood pressure (mmHg) was measured twice using a mercury sphygmomanometer following an initial minimum 5 minute resting period and a 2 minute resting period between each measure. The two systolic measurements and the two diastolic measurements were averaged. Current hypertension treatment was determined by an affirmative response to the following two questions: "Since your last visit, have you taken any [medication for blood pressure/diuretics for water retention]?" and "Have you been taking [medication for blood pressure/diuretics for water retention] at least 2 times per week for the last month?" Participants were classified as hypertensive if their average systolic blood pressure was ≥140mmHg, average diastolic blood pressure was ≥90mmHg, or if they reported current use of hypertension treatment.

Fasting blood samples were collected from participants annually. For this sub-study, samples were assayed for blood glucose (mg/dL) at the Michigan Diabetes Research and Training Center in Ann Arbor, MI. The inter-assay coefficient of variation (CV) in study year 12 was 3.6% at 92 mg/dL and 2.8% at 310 mg/dL; the intra-assay CV was 2.0% at 84 mg/dL and 283 mg/dL. Annual diabetes mellitus status (yes/no) was determined by a fasting glucose ≥126 mg/dL or affirmative responses to questions about diagnosed diabetes or current use of medication: "Since your last study visit, has a doctor, nurse practitioner or other health care provider told you that you had [diabetes]?," or "Since

your last visit, have you taken [insulin/pills for sugar in your blood]?" and "Have you been taking [insulin/pills for sugar in your blood] at least 2 times per week for the last month?".

Statistical Analysis

First, means (± STD) and frequencies were calculated to quantify baseline study population characteristics. Chi-square tests for categorical variables and student's t-tests for continuous variables were used to compare baseline population characteristics between women who would have prevalent peripheral neuropathy in study year 12 and women who would not have prevalent peripheral neuropathy in study year 12, defined using monofilament testing, the MNSI symptom questionnaire, and by either method. Second, multivariable logistic regression was used to determine the association between baseline study population characteristics and prevalent peripheral neuropathy in study year 12.

Third, we evaluated the cross-sectional association between peripheral neuropathy and physical functioning. Multivariable linear regression was used to determine the association between continuous physical functioning performance measures in study year 12 and prevalent peripheral neuropathy in study year 12, adjusted for other covariates measured in study year 12. The timed stair climb, timed walk, and timed sit to stand were log-transformed to meet model assumptions of homoscedasticity, and then back-transformed to their original scale for presentation as percent change with

corresponding 95% confidence intervals. Multivariable logistic regression was used to determine the association between dichotomous physical functioning performance measures in study year 12 and prevalent peripheral neuropathy in study year 12, adjusted for other covariates measured in study year 12. The tandem stand and the unipedal stand were modeled as the log-odds of failing (i.e., standing for <30 seconds) the stand and associations were presented as odds ratios with corresponding 95% confidence intervals. Interaction terms between diabetes and neuropathy and BMI and neuropathy were considered but were not significant at the α=0.05 level and therefore were not retained in the final models.

Fourth, we evaluated the change in performance-based physical functioning over time. Physical functioning measures (seconds ± STD) were reported for the study population at baseline, study year 4, study year 8, and study year 12. Student's t-tests were used to compare functioning measures between the women who would have prevalent peripheral neuropathy in study year 12 and women who would not have prevalent peripheral neuropathy in study year 12.

Finally, linear mixed models (PROC MIXED) with random intercepts and slopes for age were used to determine if trajectories of physical functioning differed between women who would have prevalent peripheral neuropathy in year 12 and women who would not, adjusting for baseline BMI and race/ethnicity. We adjusted for baseline BMI rather than time-varying BMI because BMI could be conceptualized as a mediator between

neuropathy and poor physical functioning. Continuous outcome measurements (timed walk, timed stair climb, and timed sit-to-stand) were log-transformed to meet model assumptions of homoscedasticity, and then-back transformed to the geometric mean of their original scale (seconds) for presentation. Predicted trajectories of the performance-based physical functioning measures with corresponding 95% confidence bands were graphed by peripheral neuropathy group using PROC SGPLOT. SAS (v9.3) was used for all data management and analysis. Statistical tests were 2-sided with the level of significance defined as p-value <0.05.

RESULTS

The average baseline age of participants was 46.1 years (STD 2.7), 8.5% were characterized as having diabetes at baseline, and 60% were African American. The prevalence of neuropathy by monofilament evaluation was 14.3% (95% CI: 10.7 – 17.9%; n=53), by MNSI symptom questionnaire was 19.4% (95% CI: 15.5 – 23.3%; n=77), and by the combined definition was 27.8% (95% CI: 23.4 – 32.3%; n=110).

Women with prevalent neuropathy in study year 12 defined by monofilament testing, symptom questionnaire, and the combined method had bigger body sizes at baseline than women without prevalent neuropathy in study year 12, as measured by BMI (Table 3.2). In addition, these women were also significantly more likely to have diabetes. In the multivariable model (Table 3.3), baseline BMI remained a significant predictor of prevalent neuropathy at year 12.

In the cross-sectional multivariable analysis of study year 12 (Table 3.4 and Table 3.5), peripheral neuropathy was significantly associated with poorer performance on the stair climb and 40-foot walk tasks. African American race/ethnicity was significantly associated with longer stair climb and sit to stand times and failing the unipedal stand. BMI was significantly associated with poorer performance on the stair climb, walk, sit to stand, and unipedal stand. Diabetes status was significantly associated with poorer performance for only the stair climb assessment; thus, after adjusting for peripheral neuropathy, diabetes was not associated with other physical functioning limitations.

On average, all women had increasingly poor physical functioning over time, as evidenced by the increasing time required to complete the stair climb, walk, and sit-to-stand (Table 3.6). Women with prevalent neuropathy at year 12 were significantly different from women without neuropathy on all physical functioning assessments in year 12 and at every prior study year. Women with neuropathy required significantly more time to complete the stair climb, the 40-foot walk, and the sit-to-stand trial compared to women without neuropathy. In addition, women with neuropathy were unable to maintain the unipedal and tandem balance stands for as long as women without neuropathy.

The longitudinal analysis characterized the trajectory of physical functioning over time by prevalent peripheral neuropathy status in year 12, adjusted for baseline BMI and

race/ethnicity. There were significant differences in time to complete the stair climb at 46 years of age (mean baseline age) by neuropathy status (p-value=0.045). For every one-year increase in age, women who would have prevalent neuropathy in year 12 had a 1.82% (95% CI: 1.42, 2.21) average increase in time to complete the stair climb compared to a 0.95% (95% CI: 0.71, 1.20) average increase for women who would not have neuropathy. Time to complete the sit to stand at 46 years of age also differed significantly by neuropathy status (p-value=0.01). For every one-year increase in age, women who would have prevalent neuropathy in year 12 had a 3.12% (95% CI: 2.11, 4.15) average increase in time to complete the sit to stand compared to 3.07% (95% CI: 2.44, 3.70) average increase for women who would not have neuropathy. Time to complete the 40-foot walk at 46 years of age did not differ by neuropathy status (p-value=0.09). For every one-year increase in age, women who would have prevalent neuropathy in year 12 had a 2.63% (95% CI: 2.14, 3.11) average increase in time to complete the 40-foot walk compared to a 2.24% (95% CI: 1.94, 2.54) average increase for women who would not have neuropathy. Figure 3.1 presents the trajectories of the physical functioning assessments over time by peripheral neuropathy status with corresponding 95% confidence bands, adjusted for baseline BMI and race/ethnicity.

DISCUSSION

To our knowledge, this is the first investigation of peripheral neuropathy and longitudinal physical functioning performance in community-dwelling mid-life women. Overall, 27.8% of Michigan SWAN participants had neuropathy characterized by either

≥4 neuropathy symptoms or an abnormal monofilament test in study year 12. Even at baseline, 12 years before the neuropathy assessment, physical functioning differed between women who would and would not have positive neuropathy assessments 12 years later. Importantly, these differences persisted over time on a variety of physical functioning assessments. Even after adjusting for BMI and race/ethnicity, peripheral neuropathy remained associated with diminished physical functioning at year 12 and when considering trajectories of physical functioning over time. Notably, the effect of peripheral neuropathy appeared to be independent of diabetes.

Our results are consistent with other studies. In a cross-sectional study of disabled women over 65 years of age, over half had some level of nerve dysfunction but less than 20% self-reported diabetes.[17] Even after adjusting for diabetes and other risk factors for functional limitations, peripheral nerve dysfunction was significantly associated with functional limitations.[17] Women with minimal nerve dysfunction were two times more likely to fail performance-based balance tests and have significantly slower walking speeds compared to women with normal peripheral nerve function.[17] Likewise, another study of older Caucasian and African American adults demonstrated that peripheral neuropathy was significantly associated with poorer lower extremity physical performance, independent of diabetes.[18] Similarly, in our population of women in their forties and fifties, we found that peripheral neuropathy was significantly associated with the stair climb and walk assessments, even after adjusting for diabetes status. However, we found no association between peripheral neuropathy and balance assessments.

Mobility is fundamental to the healthy aging process. Physical functioning is of great public health relevance because mobility impairments, like inadequate walking speeds, compromise an individual's ability to safely negotiate his or her physical environment. National standards require the minimum pedestrian clearance velocity at a crosswalk to be 3.5 feet/second.[20] In other words, an individual must walk at a pace of 3.5 feet per second from curb to curb during the "walk" indication signal to safely use a crosswalk. In a previous investigation, it was reported that approximately one-third of Michigan SWAN participants walked at speeds slower than the federal standard for crossing a controlled intersection.[21] In our investigation, we found that the ability to walk at the minimum pedestrian clearance velocity differed by peripheral neuropathy status. In 2008, women with peripheral neuropathy completed the 40-foot walk, on average, in 14.6 seconds for a calculated velocity of 2.7 feet/second, while women without neuropathy ambulated at a velocity of 3.6 feet/second. Although we did not assess the individual participant's environment, performance-based physical functioning measures in a controlled setting are highly predictive of future disability and loss of independence.[22,23]

To our knowledge, no similar reference points exist with which to evaluate our other physical functioning assessments like stair climbing. Individuals with neuropathy may employ compensatory mechanisms while walking such as decreased speed and stride length as well as increased time spent in double support (shuffling) compared to

individuals without neuropathy.[24] However, stair ascent and descent may be particularly hazardous since they are controlled from a single support limb without such compensatory mechanisms. As such, it may be the "purest" physical functioning assessment in our study. Our only measure of physical functioning at study baseline was stair climbing. We found significant baseline differences in stair climb times between women who would have prevalent neuropathy at year 12 compared to women who would not, and these differences persisted over time.

The association between peripheral neuropathy and poor physical functioning is not surprising considering the debilitating pathway of peripheral neuropathy. Nerve damage reduces the amount of perception feedback from receptors and causes impairments like reduced balance and position sense.[17] In the lower extremities, impairments can cause instability while walking or standing and lead to falls as well as functional limitations.[17] Limitations in physical functioning can lead to loss of independence because activities like walking are critical for the maintenance of independence in a community.[4,17] It is through these physical functioning limitations that peripheral neuropathy becomes a risk factor for future functional disability, defined as the inability to fulfill activities of daily living in an individual's environment or context.[17,25]

In our study, BMI appeared to be the most consistent predictor of physical functioning and may mediate the relationship between peripheral neuropathy and physical functioning. Even at baseline, women who would and would not have peripheral

neuropathy in study year 12 had significant differences in body size. Women who would have prevalent neuropathy in year 12 appeared to have a larger body size to start and to stay larger during the course of our study. Obesity is hypothesized as a potential causal mechanism for peripheral neuropathy, independent of diabetes.[9,10] Its co-occurrence with abnormal cardiometabolic factors like hypertension, hyperlipidemia, hyperglycemia, and increased central adiposity may confer risk of peripheral neuropathy;[26] in fact, one study demonstrated that hypertension, lipids, and BMI were independently associated with the risk of developing peripheral neuropathy among diabetic subjects.[27] It is also possible that obesity is a consequence of peripheral neuropathy. Individuals who experience numbness or pain in the lower extremities may be less likely to be physically active, and inactivity, particularly in the mid-life years, may be a risk factor for obesity. The role of BMI clearly deserves greater attention in future research. Future longitudinal studies may wish to explore the relationship between obesity and peripheral neuropathy.

The present study has some limitations. Notably, we measured peripheral neuropathy in study year 12. This single measure of neuropathy precludes inferences of causality with respect to physical functioning as it is unclear when neuropathy developed. Furthermore, residual confounding may exist in the relationship between peripheral neuropathy and physical functioning. BMI has been proposed as a causal mechanism as well as a consequence of neuropathy. We adjusted only for baseline BMI in our longitudinal models so as not to dilute artificially the effect of neuropathy on

functioning, but poorer physical functioning at baseline may be due to obesity and not neuropathy. As such, unmeasured confounding by BMI is possible.

Studies of physical functioning do not typically evaluate neuropathy. Our results suggest that peripheral neuropathy is a prevalent but underappreciated condition in the general population and is associated with decreased physical functioning. Clinicians may wish to implement neuropathy testing for individuals in the general population who exhibit diminished functional capacity. Neuropathy assessment should be considered for inclusion in future studies of functional status and disability, and longitudinal studies of incident peripheral neuropathy should identify potentially modifiable risk factors for disease prevention.

Table 3.1. Timing of peripheral neuropathy and performance-based physical functioning measures, Peripheral Neuropathy Substudy, Michigan SWAN.

	Data Collection Year and Visit (V) Number												
Measure	Baseline	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
	V 0	V 1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12
Peripheral Neuropathy													X
Physical Functioning													
3x3 Stair Climb	X	X	X	X	X	X	X	X	X	X	X	X	X
40' walk					X	X	X	X	X	X	X	X	X
Sit to Stand					X	X	X	X	X	X	X	X	X
Balance (Tandem & Unipedal)													X

Table 3.2. Baseline (1996) characteristics of women who had and did not have peripheral neuropathy in 2008, Peripheral Neuropathy Substudy, Michigan SWAN.

	Monofilament testing			Symptom Questionnaire			Either		
	PN (n=53)	No PN (n=318)	p-value	PN (n=77)	No PN (n=319)	p-value	PN (n=110)	No PN (n=286)	p-value
Age, years (SD)	46.7 (2.8)	46.4 (2.8)	0.53	46.6 (2.9)	46.5 (2.8)	0.68	46.3 (2.6)	46.1 (2.8)	0.39
Race, %									
African American	62.3	60.7	0.83	55.8	60.5	0.45	59.1	59.8	0.90
Caucasian	37.7	39.3		44.2	39.5		40.9	40.2	
Body mass index, kg/m2 (SD)	35.4 (7.3)	31.8 (8.0)	**0.003**	35.9 (9.3)	31.5 (7.5)	**0.0003**	34.9 (8.5)	31.4 (7.7)	**0.0002**
Blood pressure									
Systolic, mmHg (SD)	124 (21.0)	118 (18.3)	0.06	120 (19.1)	119 (19.3)	0.49	120 (19.2)	119 (19.3)	0.51
Diastolic, mmHg (SD)	71 (12.7)	71 (10.6)	0.74	71 (11.3)	71 (10.8)	0.95	71 (12.1)	71 (10.4)	0.70
Hypertension, %	34.0	25.8	0.21	32.5	25.1	0.19	30.9	24.8	0.22
Glucose, mg/dL (SD)	113 (46.3)	102 (35.6)	**0.03**	116 (54.2)	100 (32.7)	**0.02**	110 (46.5)	101 (34.4)	0.06
Diabetes, %	17.0	6.9	**0.01**	19.5	5.6	**<0.0001**	13.6	6.3	**0.02**

Table 3.3. Multivariable associations (odds ratios (95% CI)) between baseline characteristics and having peripheral neuropathy in year 12, Peripheral Neuropathy Substudy, Michigan SWAN.

	OR (95% CI)	p-value
Race/ethnicity (African American vs. Caucasian)	0.96 (0.60, 1.54)	0.87
BMI, kg/m^2	1.05 (1.02, 1.08)	0.001
Hypertension (Yes vs. No)	1.07 (0.63, 1.81)	0.81
Diabetes (Yes vs. No)	1.66 (0.78, 3.57)	0.19

Notes: Models also adjusted for age; BMI centered at mean 32.1.

Table 3.4. Intercept (seconds) and percent difference from intercept for year 12 characteristics by year 12 performance-based physical functioning, Peripheral Neuropathy Substudy, Michigan SWAN.

	Stair Climb		40-foot Walk		Sit to Stand	
Intercept (seconds (95% CI))	16.86 (14.76, 19.25)		10.34 (9.38, 11.41)		1.56 (1.28, 1.91)	
	% difference (95% CI)	p-value	% difference (95% CI)	p-value	% difference (95% CI)	p-value
PN (Yes vs. No)	14.07 (6.78, 21.87)	0.0001	10.79 (5.55, 16.28)	<0.0001	7.79 (-2.40, 19.03)	0.14
Age, years	0.64 (-0.43, 1.72)	0.24	-0.09 (-0.87, 0.70)	0.82	-0.94 (-2.53, 0.67)	0.25
Race (African American vs. Caucasian)	7.88 (1.58, 14.58)	0.01	4.04 (-0.53, 8.81)	0.08	10.94 (1.25, 21.57)	0.03
BMI, kg/m2	1.21 (0.81, 1.60)	<0.0001	1.13 (0.85, 1.42)	<0.0001	0.84 (0.25, 1.43)	0.005
Hypertension (Yes vs. No)	2.23 (-4.05, 8.92)	0.49	1.37 (-3.32, 6.29)	0.57	-0.47 (-9.62, 9.60)	0.92
Diabetes (Yes vs. No)	7.37 (0.23, 15.03)	0.04	3.54 (-1.61, 8.95)	0.18	5.04 (-5.32, 16.54)	0.35

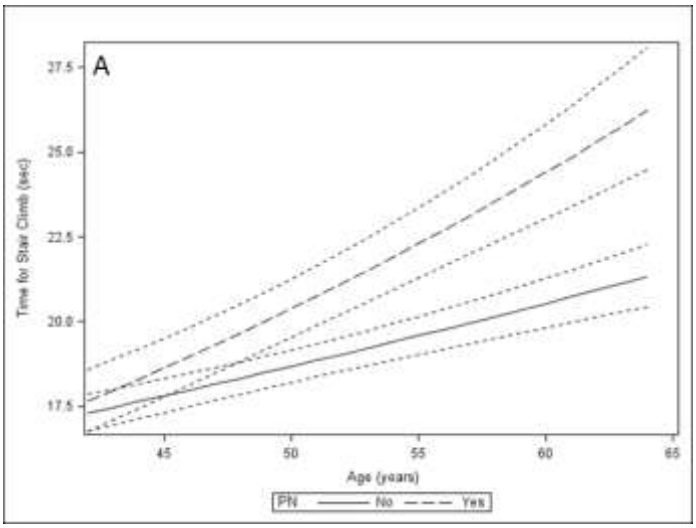
Table 3.5. Multivariable associations (OR (95% CI)) between year 12 characteristics and year 12 performance-based physical functioning stands, Peripheral Neuropathy Substudy, Michigan SWAN.

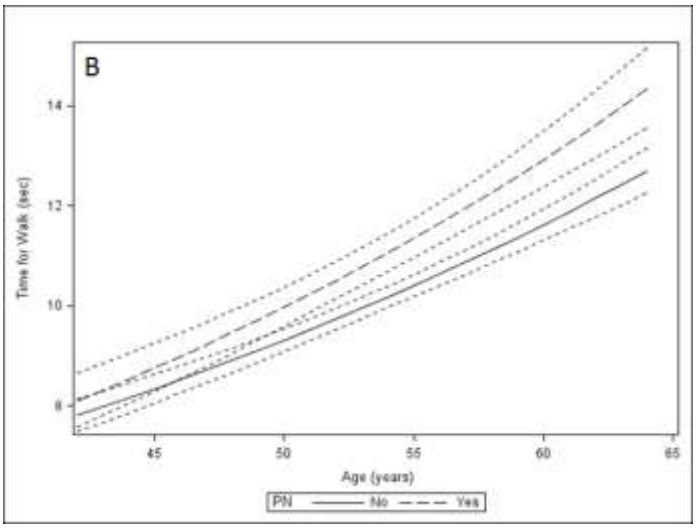
	Tandem Stand (30 vs. <30 seconds)		Unipedal Stand (30 vs. <30 seconds)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PN (Yes vs. No)	1.38 (0.85, 2.25)	0.19	1.78 (0.94, 3.35)	0.08
Age, years	1.05 (0.97, 1.14)	0.22	1.05 (0.95, 1.15)	0.36
Race (African American vs. Caucasian)	1.47 (0.93, 2.33)	0.10	2.13 (1.26, 3.59)	0.005
BMI, kg/m2	1.01 (0.98, 1.04)	0.59	1.12 (1.08, 1.17)	<0.0001
Hypertension (Yes vs. No)	1.28 (0.79, 2.07)	0.31	1.32 (0.77, 2.26)	0.31
Diabetes (Yes vs. No)	1.61 (0.97, 2.67)	0.07	1.32 (0.68, 2.55)	0.41

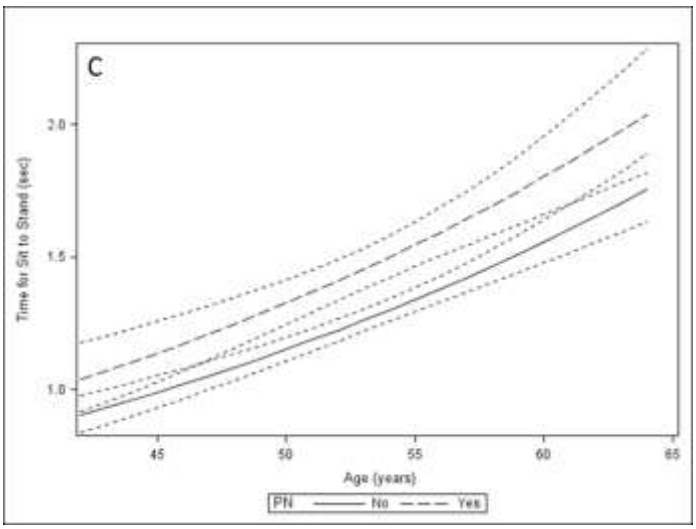
Table 3.6. Performance-based physical functioning measures (seconds ± STD) by selected visit and peripheral neuropathy status, Peripheral Neuropathy Substudy, Michigan SWAN.

Measure	Visit	**Total**	PN	No PN	p-value
Stair Climb	**Baseline**	19.6 ± 5.3	22.0 ± 7.9	19.2 ± 4.8	0.02
	Year 4	19.6 ± 7.8	22.2 ± 9.3	19.1 ± 7.7	0.02
	Year 8	20.6 ± 5.9	23.1 ± 8.2	20.2 ± 5.5	0.04
	Year 12	22.0 ± 9.1	27.8 ± 13.7	21.1 ± 7.9	0.002
40-foot Walk	**Year 4**	9.2 ± 2.5	10.1 ± 4.2	9.1 ± 2.0	0.15
	Year 8	12.0 ± 4.6	14.3 ± 10.3	11.6 ± 2.7	0.08
	Year 12	11.6 ± 3.5	14.6 ± 6.8	11.1 ± 2.4	0.13
Sit to Stand	**Year 4**	1.3 ± 0.6	1.4 ± 0.6	1.3 ± 0.6	0.72
	Year 8	1.4 ± 0.6	1.6 ± 0.7	1.3 ± 0.6	0.01
	Year 12	1.8 ± 1.1	2.0 ± 1.5	1.7 ± 1.0	0.13
Tandem Stand	**Year 12**	21.8 ± 10.9	19.1 ± 11.7	22.3 ± 10.7	0.06
Unipedal Stand	**Year 12**	15.6 ± 11.5	10.7 ± 9.5	16.4 ± 11.6	0.003

Figure 3.1. Predicted trajectories of timed stair climb (A), timed 40-foot walk (B), and timed sit to stand (C) by peripheral neuropathy status in 2008, adjusted for race/ethnicity and baseline BMI, Peripheral Neuropathy Substudy, Michigan SWAN.







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CHAPTER 4

Obesity and peripheral neuropathy in mid-life women

ABSTRACT

Currently, two-thirds of adults in the United States are overweight or obese. Obesity is a well-documented risk factor for diabetes mellitus, but the independent role of obesity in the development of peripheral neuropathy, a complication of diabetes, is unclear. The purpose of this investigation was to assess the association between obesity and peripheral neuropathy in a population-based cohort of African-American and Caucasian mid-life women in the United States.

Data (n=396) from the Study of Women's Health Across the Nation – Michigan site were used. Annual (1996-2008) anthropometric measures of weight (kg), height (cm), waist circumference (cm), and body mass index (BMI, weight [kg]/height [m^2]) were collected. Peripheral neuropathy was measured in 2008 and defined as an abnormal monofilament test or at least 4 symptoms or signs. Linear mixed models were used to determine trajectories of anthropometric measures in relation to subsequently-identified peripheral neuropathy status.

Mean baseline BMI in 1996 was 32.4 kg/m^2 and 27.8% of women had peripheral neuropathy in 2008. Between baseline and 2008, BMI, weight, and waist circumference increased, and women who had peripheral neuropathy in 2008 were significantly larger at every measurement than women who did not have neuropathy in 2008. When women without ever-diabetes were excluded, results were slightly attenuated but remained statistically significant. At mean baseline age, there were significant differences between women who would and would not have peripheral neuropathy in 2008 in BMI (p-value=0.002), weight (p-value=0.0004), and waist circumference (p-value=0.001), but no difference in percent change over time by neuropathy status.

Even at baseline, 12 years before the assessment of peripheral neuropathy, anthropometric measures differed between women who would and would not be subsequently-identified with peripheral neuropathy in 2008, and these differences were maintained over time. Independent of diabetes, obesity may be an important risk factor or correlate of peripheral neuropathy and deserves greater research attention in future studies of neuropathy etiology.

INTRODUCTION

Currently, two-thirds of adults in the United States are overweight or obese.[1] The high prevalence of obesity is a major public health problem because obesity is associated with a variety of chronic diseases, decreased quality of life, and premature death.[2] In

particular, obesity is a well-documented risk factor for diabetes mellitus.[3,4] Peripheral neuropathy is a common complication of diabetes mellitus, but the role of obesity in the development of peripheral neuropathy, independent of diabetes, is not well understood.[5-7]

Peripheral neuropathy pathogenesis outside of the diabetic etiology has gained recent attention as an important focus of scientific study.[8] Although diabetic peripheral neuropathy is the most common type of neuropathy, not all diabetic patients with peripheral neuropathy have diabetic neuropathy. It is estimated that even among diabetic patients, up to 50% may have an additional cause of generalized neuropathy.[8] Furthermore, many diabetic patients have neuropathy at the time of their diagnosis,[9] suggesting that idiopathic neuropathy may be a marker for prediabetes and thus may precede, rather than follow, overt type 2 diabetes.[10-12] In addition, the development of peripheral neuropathy in diabetic patients with tight glycemic control also suggests a role for risk factors outside of diabetes-related risk factors like chronic hyperglycemia.[13]

Obesity may be an important catalyst in a cascade of factors leading to insulin resistance and peripheral nerve damage. Obesity may increase the risk of peripheral neuropathy through diabetes and hyperglycemia by damaging the microvasculature. However, obesity may also affect the peripheral nerves independent of chronic hyperglycemia. Obesity is associated with impaired glucose tolerance in the pre-diabetic individual.[14,15] Transient hyperglycemia without overt diabetes may damage small nerve fibers and

may be the earliest detectable sign of peripheral neuropathy in glucose deregulation.[10,16] Alternatively, neuronal dysfunction is closely related to vascular dysfunction.[10] Microvascular damage from subclinical cardiovascular abnormalities may contribute to neuropathy in the general population.[10] These factors include increased LDL cholesterol, which causes vascular damage by trapping proteins, hypertension through decreased vasoreactivity, or obesity, which damages nerves through leptin and oxidative stress.[10] Alternatively, obesity may be an important consequence of peripheral neuropathy if individuals with sensory deficits or pain in the lower extremities experience declining levels of physical functioning and increasing adiposity.

Assessing the potential role for obesity in the development of peripheral neuropathy is important because obesity can be prevented or managed through education, diet, and physical activity. The purpose of this study was to assess the association between obesity and peripheral neuropathy. We evaluated trajectories of anthropometric measures by peripheral neuropathy status in a population-based cohort of African American and Caucasian mid-life women in the United States. We hypothesized that women who had peripheral neuropathy would be more obese and have a greater change in their obesity status over time than women without peripheral neuropathy.

METHODS

Study Population

The Study of Women's Health Across the Nation (SWAN) is an ongoing population-based longitudinal study of women from seven sites in the United States. The study has been described in detail previously.[17] This investigation focuses on the Michigan SWAN study cohort which consists of 543 women (325 African American and 218 Caucasian) from two communities near Detroit who at baseline were aged 42-52 years, had an intact uterus and at least one ovary, reported no current use of hormones, and had at least one menstrual period in the prior three months. Of the original sample selected at the 1996 baseline, 418 (77%) were still active in study year 12 (2008) and eligible to participate in the peripheral neuropathy sub-study. Of these, 371 (89%) underwent a foot examination and completed a symptom questionnaire for peripheral neuropathy. Twenty-five (6%) completed only the symptom questionnaire administered via telephone or mail, and 22 (5%) refused participation in the sub-study. Women who participated in the neuropathy sub-study and had any peripheral neuropathy assessment in follow-up year 12 did not differ by race/ethnicity or baseline age, weight, height, waist and hip circumference, blood pressure, and fasting glucose between from women who did not participate. The parent and sub-study were approved by the University of Michigan Health Institutional Review Board and all participants provided written informed consent.

Study Variables

Peripheral neuropathy was assessed using the Michigan Neuropathy Screening Instrument (MNSI) symptom questionnaire[18] and monofilament testing.[19] The MNSI

symptom questionnaire is a 15-item questionnaire used to acquire information about the presence (yes/no) of common neuropathy symptoms and signs, including numbness, pain, sensitivity, cramping, prickling feelings, hot/cold differentiation, open sores, dryness, weakness, and amputation. The number of positive symptoms and signs was calculated, with higher scores indicative of more neuropathy symptoms and signs and thus an increased likelihood of PN. Monofilament testing used the placement of a 10-gram pre-stressed filament on the dorsal side of the big toe, midway between the nail fold and the distal interphalangeal joint briefly (<1 second) for 10 repetitions. The participant was asked to respond if she felt the filament following each repetition. Peripheral neuropathy was defined as 80% or fewer correct responses to the brief sensation in either foot,[20] or at least four symptoms or signs reported on the MNSI questionnaire.[21] The two different instruments used to assess the presence of peripheral neuropathy may capture different types and/or sizes of damaged nerves.[22] Peripheral neuropathy was measured in year 12 (2008) of the study.

Age (years) was calculated from the interval of birth to follow-up visit date. Race/ethnicity was self-identified at the 1996 baseline as African American or Caucasian. Annual (baseline through year 12) anthropometric measures were also collected from each participant. Height was measured without shoes in centimeters by stadiometer. Weight was measured in light clothing in kilograms by balance beam scale. Body mass index (BMI) was calculated as weight [kg]/height[m^2]. Waist circumference and hip circumference were measured in centimeters by a non-stretching tape measure. BMI,

weight, and waist circumference were identified *a priori* as the primary obesity measures of interest for our investigation. BMI ≥ 30 kg/m^2 and waist circumference ≥ 88 cm were used as risk cut points to identify anthropometric obesity.

Hypertension was also assessed at each study visit. Blood pressure (mmHg) was measured twice using a mercury sphygmomanometer following an initial minimum 5 minute resting period and a 2 minute resting period between each measure. The two systolic measurements and the two diastolic measurements were averaged. Current hypertension treatment was determined by an affirmative response to the following two questions: "Since your last visit, have you taken any [medication for blood pressure/diuretics for water retention]?" and "Have you been taking [medication for blood pressure/diuretics for water retention] at least 2 times per week for the last month?" Participants were classified as hypertensive if their average systolic blood pressure was ≥140mmHg, average diastolic blood pressure was ≥90mmHg, or if they reported current use of hypertension treatment.

Fasting blood samples were collected from participants annually. For this sub-study, samples were assayed for blood glucose (mg/dL) at the Michigan Diabetes Research and Training Center in Ann Arbor, MI. The inter-assay coefficient of variation (CV) in study year 12 was 3.6% at 92 mg/dL and 2.8% at 310 mg/dL; the intra-assay CV was 2.0% at 84 mg/dL and 283 mg/dL. Diabetes mellitus status (yes/no) was determined by a fasting glucose ≥126 mg/dL or affirmative responses to questions about diagnosed diabetes or

current use of medication: “Since your last study visit, has a doctor, nurse practitioner or other health care provider told you that you had [diabetes]?,” or “Since your last visit, have you taken [insulin/pills for sugar in your blood]?” and “Have you been taking [insulin/pills for sugar in your blood] at least 2 times per week for the last month?”.

Statistical Analysis

First, means (± STD) and frequencies were calculated to quantify baseline study population characteristics. Chi-square tests for categorical variables and student’s t-tests for continuous variables were used to compare baseline population characteristics between women who would have prevalent peripheral neuropathy in study year 12 and women who would not have prevalent peripheral neuropathy in study year 12.

Next, multivariable logistic regression was used to determine the association between baseline anthropometric measures and peripheral neuropathy in year 12, adjusted for other baseline covariates. Model 1 evaluated the association between baseline BMI and peripheral neuropathy in year 12, adjusted for baseline age, race/ethnicity, baseline hypertension, and baseline diabetes status. Model 2 evaluated the association between baseline weight and peripheral neuropathy in year 12, adjusted for baseline age, race/ethnicity, baseline height, baseline hypertension, and baseline diabetes status. Model 3 evaluated the association between baseline waist circumference and peripheral neuropathy in year 12, adjusted for baseline age, race/ethnicity, baseline height, baseline hypertension, and baseline diabetes status.

Third, we evaluated how obesity changed over time from baseline to year 12. BMI (kg/m^2 ± STD), weight (kg ± STD), and waist circumference (cm ± STD) were calculated for baseline and study year 12. Student's t-tests were used to compare baseline and year 12 anthropometric measures between women with neuropathy in year 12 and women without neuropathy in year 12. In order to examine obesity independent of diabetes, we then repeated this analysis by excluding 129 women who were ever-diagnosed with diabetes between baseline and study year 12.

Fourth, we compared the prevalence of neuropathy and other characteristics in year 12 between women who were obese in year 12 and women who were not obese in year 12 according to BMI and waist circumference risk cut points. Chi-square tests for categorical variables and student's t-tests for continuous variables were used to generate p-values.

Finally, linear mixed models (PROC MIXED) with random intercepts and slopes for age were used to measure trajectories of anthropometry over time by subsequent peripheral neuropathy status. BMI, weight, and waist circumference were log-transformed to meet model assumptions of homoscedasticity, and then back-transformed to the geometric mean of their original scale for graphical and numerical presentation. SAS (version 9.3) was used for all data management and analysis. Statistical tests were 2-sided with the level of significance defined as p-value <0.05.

RESULTS

Average age at baseline was 46.2 years. The study population was 40% Caucasian and 60% African American, by design. Mean baseline BMI was 32.4 kg/m^2, mean baseline weight was 86.4 kg, and mean baseline waist circumference was 94.4 cm. At baseline, approximately 8% of participants were diabetic and 27% were hypertensive.

At the 1996 baseline, women who would have peripheral neuropathy in study year 12 already had larger body sizes than women who would not have peripheral neuropathy in study year 12. Women with peripheral neuropathy had significantly higher baseline weight, height, BMI, waist and hip circumferences, and waist to hip ratio than women without neuropathy. In addition, women who would have neuropathy were more likely to have diabetes at baseline compared to women who would not have neuropathy (Table 4.1).

In the multivariable models adjusted for age, race/ethnicity, hypertension, and diabetes, baseline BMI (p-value=0.001) was a significant predictor of having peripheral neuropathy 12 years later. Baseline weight (p-value=0.001) and waist circumference (p-value=0.0001), independent of height, were also significant predictors of peripheral neuropathy in study year 12 in multivariable models (Table 4.2).

In the total study population, BMI, weight, and waist circumference increased during the course of the study (Table 4.3). Between baseline and study year 12, average BMI increased from 32.4 kg/m^2 to 34.0 kg/m^2, average weight increased from 86.4 kg to 89.9 kg, and average waist circumference increased from 94.5 cm to 101.3 cm. Baseline and year 12 body size measurements differed significantly between women with peripheral neuropathy in study year 12 and women without peripheral neuropathy in study year 12.

In the sub-group of women never-diagnosed with diabetes, BMI, weight, and waist circumference also increased during the course of the study (Table 4.3). Between baseline and study year 12, average BMI in these women increased from 30.4 kg/m^2 to 32.3 kg/m^2, average weight increased from 81.6 kg to 85.8 kg, and average waist circumference increased from 89.8 cm to 97.1 cm. Even among women never-diagnosed with diabetes, body size measurements differed significantly between peripheral neuropathy groups.

In study year 12, 63.0% of the study population had a BMI ≥ 30 kg/m^2. Women who were obese according to BMI measurements were more likely to have peripheral neuropathy, a waist circumference ≥ 88 cm, hypertension, a higher fasting glucose value, and to have diabetes. In study year 12, 75.6% of the study population had a waist circumference ≥ 88 cm. Women who were obese according to waist circumference measurements were more likely to have a BMI ≥ 30 kg/m^2, hypertension, a higher

fasting glucose value, and to have diabetes. They were more likely to have peripheral neuropathy but the difference was not statistically significant (Table 4.4).

In the mixed model analysis at the mean baseline age of 46.1 years, we observed significant differences by peripheral neuropathy status in BMI (p-value=0.002), waist circumference (p-value=0.001), and weight (p-value=0.0004). However, although obesity changed over time, there were no differences in annual percent increase in obesity by peripheral neuropathy status. On average, BMI increased by 0.34% (95% CI: 0.14, 0.54) per year for women who would subsequently be found to have neuropathy in year 12 and by 0.35% (95% CI: 0.23, 0.48) for women who would not have neuropathy in year 12. On average, waist circumference increased by 0.61% (95% CI: 0.46, 0.76) per year for women who would subsequently be found to have neuropathy in year 12 and by 0.60% (95% CI: 0.50, 0.69) for women who would not have neuropathy in year 12. On average, weight increased by 0.29% (95% CI: 0.09, 0.49) per year for women who would subsequently be found to have neuropathy in year 12 and by 0.32% (95% CI: 0.20, 0.45) for women who would not have neuropathy in year 12 (Table 4.5). The trajectories of body sizes over time by peripheral neuropathy status in year 12 are depicted in Figure 4.1.

DISCUSSION

To our knowledge, this is the first investigation to evaluate the prevalence of peripheral neuropathy and trajectories of body size in a population-based cohort of community-

dwelling women. We found that there were significant differences in BMI, waist circumference, and weight between women with peripheral neuropathy and women without peripheral neuropathy 12 years before the assessment of peripheral neuropathy, and that these differences persisted over time. Notably, these body size differences were present even among women without diabetes, suggesting a possible independent role of obesity or obesity-related factors beyond overt diabetes. Differences in obesity between women with and without subsequently identified neuropathy were maintained over time. Trajectories of BMI, waist circumference, and weight were approximately parallel (Figure 4.1), suggesting that women who would have peripheral neuropathy in study year 12 did not get obese at a faster rate than women without peripheral neuropathy in study year 12.

Our findings that anthropometric measurements are associated with peripheral neuropathy are consistent with other studies of diabetic-only populations. BMI has been demonstrated as a significant predictor of incident neuropathy in diabetic research subjects, independent of duration of diabetes and glucose control.[13] The EuroDiab study found that hypertension, lipids, and BMI were each independently associated with the risk of developing peripheral neuropathy among diabetic subjects.[13,23] Similarly, among subjects with symptomatic peripheral neuropathy, each component of the metabolic syndrome (waist circumference ≥ 88 cm [women], triglycerides ≥ 150 mg/dL, HDL < 50 mg/dL [women], blood pressure ≥130 mm Hg/≥85 mm Hg) was more prevalent among neuropathy subjects than hyperglycemia.[12] Comparing neuropathy patients with

normal glucose tolerance to controls with normal glucose tolerance, individuals with neuropathy had significantly higher rates of dyslipidemia and hypertension and women with neuropathy were significantly more obese than women without neuropathy.[12] Features of the metabolic syndrome other than impaired glucose tolerance represent independent risk factors for peripheral neuropathy.

Few investigations of peripheral neuropathy have been conducted in non-diabetic populations; however, two analyses of peripheral neuropathy in the National Health and Nutrition Examination Survey found a significant association between anthropometric measures of body size and peripheral neuropathy measured with monofilament testing. One study reported that weight was significantly associated with neuropathy in persons without diabetes, independent of height, age, and glycated hemoglobin A1c.[24] Another cross-sectional study reported that obesity (BMI ≥ 30 kg/m^2) and the clustering of abnormal cardiovascular risk factors were positively associated with peripheral neuropathy in U.S. adults.[25]

The mechanisms by which obesity confers a greater risk of peripheral neuropathy await further elucidation. Adipose tissue produces metabolic products like adipocytokines and causes chronic hyperleptinemia. The metabolic products of adipose tissue may act as inflammatory mediators in systemic inflammation and vascular resistance in diabetes and cardiovascular disease.[14,26] Direct effects of leptin suggest mechanisms of increased oxidative stress and LDL, in addition to the generation of prothrombotic and

proinflammatory cytokines,[27] which provide support for the shared cardiovascular risk factors. Research assessing the role of specific metabolic products of adipose tissue may explain the epidemiologic observation that obesity is associated with peripheral neuropathy; thus, anthropometric measures alone may be an incomplete proxy to represent the obesity metabolic environment,[14] particularly considering the proportion of metabolically unhealthy but non-obese individuals in the United States.[28]

Nevertheless, BMI, waist circumference, and weight are important indicators of an individual's metabolic environment. We found that women who were obese according to BMI and waist circumference risk cut points were also more likely to have hypertension and have been ever-diagnosed with diabetes. BMI and waist circumference in particular correlate well to body composition values, and the use of waist circumference over waist-to-hip ratio is gaining support as a simpler alternative to identify adiposity.[14,29,30] BMI and waist circumference are also highly correlated with abnormal metabolic values, over and above measures of percent body fat mass.[31] In addition, anthropometric measures like BMI, waist circumference, and weight are simple to measure and readily available to the clinician.

One possible explanation for our findings is that obesity is causally associated with peripheral neuropathy. High levels of hyperglycemia in the diabetic patient are suggestive of diabetes as the causative mechanism for peripheral neuropathy.[32] However, at lower levels of glycemia, other etiologies may be more likely. One

hypothesis is that obesity and the impaired fasting glucose associated with obesity damages peripheral nerves. In our study, only 32 women at study year 12 had impaired fasting glucose (>110 and <126 mg/dL) but no diabetes. Low statistical power due to the small sample size of women in this category prevented us from assessing the relationship of impaired fasting glucose and peripheral neuropathy. In addition, peripheral neuropathy has many known causes, including autoimmune disorders, infections, vitamin deficiencies, hypothyroidism, and injury. We were unable to distinguish between the different hypothesized mechanisms by which obesity may cause neuropathy, or distinguish between other causes of peripheral neuropathy.

The measurement of peripheral neuropathy in our study is a prevalent measure taken 12 years after enrollment of the cohort. We were unable to establish the timing of disease onset, which is known to vary considerably.[9] We hypothesized that obesity would both cause neuropathy and increase as a result of neuropathy. However, we found no difference in the trajectories (i.e., slopes) of body size measures by peripheral neuropathy status. Either peripheral neuropathy developed late during the course of the study and did not have a chance to change the trajectory of obesity, or obesity causes neuropathy but does not change as a result of neuropathy. Given the low likelihood that many of the study participants had neuropathy at baseline and the parallel anthropometric trajectories of women with and without neuropathy that were observed in our study, the reverse causation scenario- that peripheral neuropathy

causes obesity- is unlikely. However, future studies should tease apart the timing and causal relationship between obesity and peripheral neuropathy over time.

In the present study, women who were obese were more likely to have hypertension and diabetes than women who were not obese; however, we did not have longitudinal measures of triglycerides and cholesterol so we could not evaluate the clustering of cardiovascular risk factors termed “metabolic syndrome” in our study population. Nevertheless, our findings showing the relationship between anthropometric obesity and peripheral neuropathy support evidence for the relationship between metabolic syndrome and peripheral neuropathy. Future studies may wish to evaluate which correlates of obesity are most strongly associated with neuropathy so that targeted interventions can be developed.

Identifying easy-to-measure and modifiable risk factors for chronic diseases is an important epidemiologic endeavor, particularly as our population ages. In a small study of subjects with impaired glucose tolerance and neuropathy, diet and exercise education to improve impaired glucose tolerance also lowered BMI and neuropathic pain.[33] BMI, waist circumference, and weight are easy to measure and readily available to the patient and clinician alike. These anthropometric measures may prove to be important targets for interventions to prevent neuropathy or improve pain. Anthropometric measurements are also simple to track over time. Clinicians who attend obese patients may wish to employ neuropathy testing.

In conclusion, women with peripheral neuropathy had higher BMIs, waist circumferences, and weights than women without peripheral neuropathy. Baseline body size measures were significantly associated with prevalent peripheral neuropathy twelve year later, and these differences in body size between women who would go on to have peripheral neuropathy and women who would not go on to have peripheral neuropathy persisted over time. However, trajectories of body size were not different in women who would and would not have neuropathy, suggesting that neuropathy did not cause obesity. Obesity may be an important risk factor or indicator of peripheral neuropathy and deserves greater research attention, particularly in the general population.

Table 4.1. Baseline (1996) characteristics of women who did and did not have peripheral neuropathy (PN) in 2008, PN Substudy, Michigan SWAN.

	Total (n=396)	PN (n=110)	No PN (n=286)	p-value
Age, years (SD)	46.2 (2.7)	46.3 (2.6)	46.1 (2.8)	0.39
Race/Ethnicity, %				
African American	59.6	59.1	59.8	0.90
Caucasian	40.4	40.9	40.2	
Weight, kg (SD)	86.4 (21.9)	94.2 (23.8)	83.4 (20.4)	**<0.0001**
Height, cm (SD)	163.4 (6.1)	164.4 (6.1)	163.0 (6.1)	**0.04**
Body mass index, kg/m2 (SD)	32.4 (8.1)	34.9 (8.5)	31.4 (7.7)	**0.0002**
Waist, cm (SD)	94.4 (17.3)	100.9 (19.3)	92.0 (15.8)	**<0.0001**
Hip, cm (SD)	114.3 (16.2)	119.5 (18.5)	112.3 (14.8)	**0.0003**
Waist-to-hip ratio	0.82 (0.07)	0.84 (0.08)	0.82 (0.07)	**0.005**
Hypertension, %	26.5	30.9	24.8	0.22
Diabetes, %	8.3	13.6	6.3	**0.02**

Table 4.2. Association (Odds Ratio (95% CI)) between baseline measures and peripheral neuropathy in year 12, Peripheral Neuropathy Substudy, Michigan SWAN.

	Model 1		Model 2		Model 3	
Baseline Measures	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years	1.04 (0.96, 1.14)	0.32	1.06 (0.97, 1.15)	0.18	1.05 (0.97, 1.15)	0.25
Race/ethnicity (AA vs. Caucasian)	0.96 (0.60, 1.54)	0.87	0.92 (0.57, 1.48)	0.72	0.95 (0.59, 1.54)	0.84
BMI, kg/m^2 (per 5 units)	1.27 (1.23, 1.31)	0.001	---		---	
Weight, kg (per 5 units)	---		1.10 (1.09, 1.12)	0.001	---	
Height, cm	---		1.03 (0.99, 1.08)	0.10	1.04 (1.00, 1.08)	0.03
Waist circumference, cm (per 5 units)	---		---		1.15 (1.13, 1.17)	0.0001
Hypertension (Yes vs. No)	1.07 (0.63, 1.81)	0.81	1.12 (0.66, 1.91)	0.68	1.05 (0.62, 1.80)	0.85
Diabetes (Yes vs. No)	1.66 (0.78, 3.57)	0.19	1.82 (0.84, 3.95)	0.13	1.70 (0.78, 3.70)	0.18

Notes: Age, BMI, weight, height, and waist circumference centered at mean baseline values.

Table 4.3. Anthropometric measures (± STD) by selected visit and peripheral neuropathy (PN) status, PN Substudy, Michigan SWAN.

Total Study Population					
Measure	Study Visit	Total (n=396)	PN (n=110)	No PN (n=286)	p-value
BMI	**Baseline**	32.4 ± 8.1	34.9 ± 8.5	31.4 ± 7.7	0.0002
	Year 12	34.0 ± 8.3	36.8 ± 9.1	32.9 ± 7.7	0.0001
Weight	**Baseline**	86.4 ± 21.9	94.2 ± 23.8	83.4 ± 20.4	<0.0001
	Year 12	89.9 ± 22.0	98.1 ± 24.3	86.6 ± 20.1	<0.0001
Waist Circumference	**Baseline**	94.5 ± 17.3	100.9 ± 19.3	92.0 ± 15.8	<0.0001
	Year 12	101.3 ± 17.2	108.1 ± 17.9	98.6 ± 16.2	<0.0001
Women Without Diabetes					
Measure	Study Visit	Total (n=267)	PN (n=63)	No PN (n=204)	p-value
BMI	**Baseline**	30.4 ± 7.4	32.3 ± 8.1	29.9 ± 7.1	0.03
	Year 12	32.3 ± 7.8	34.8 ± 8.6	31.5 ± 7.4	0.003
Weight	**Baseline**	81.6± 20.5	88.5 ± 23.9	79.5 ± 19.0	0.01
	Year 12	85.8 ± 20.9	94.2 ± 23.7	83.1 ± 19.3	0.001
Waist Circumference	**Baseline**	89.8 ± 15.9	94.1 ± 17.7	88.5 ± 15.1	0.01
	Year 12	97.1 ± 16.6	103.9 ± 17.7	94.9 ± 15.7	0.0002

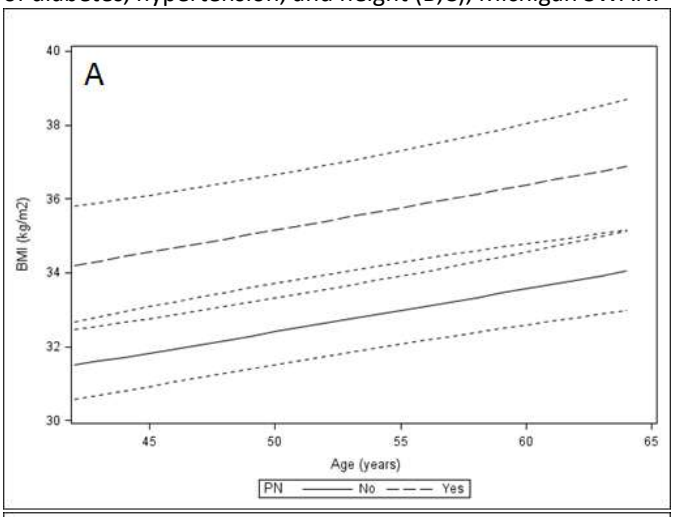
Table 4.4. Characteristics of women in study year 12 by obesity status, Peripheral Neuropathy Substudy, Michigan SWAN, 2008.

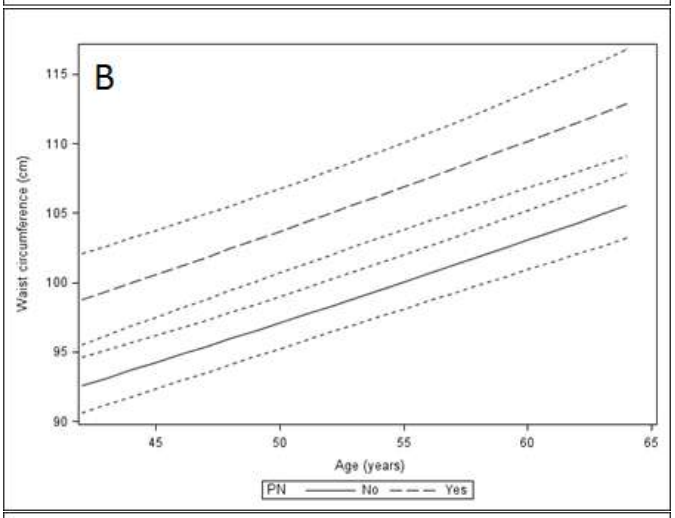
	BMI ≥30 kg/m^2	BMI < 30 kg/m^2	p-value	Waist ≥ 88 cm	Waist < 88 cm	p-value
% (n)	63.0 (235)	37.0 (135)		75.6 (282)	24.4 (91)	
Peripheral neuropathy, %	33.2	20.3	0.01	30.9	20.9	0.07
Age, years (STD)	57.5 (2.8)	57.8 (2.8)	0.25	57.6 (2.8)	57.7 (2.7)	0.77
Race/Ethnicity, %						
African American	61.3	60.9	0.94	61.7	59.3	0.69
Caucasian	38.7	39.1		38.3	40.7	
Waist ≥ 88cm, %	97.4	38.4	<0.0001	---	---	
BMI ≥ 30 kg/m^2, %	---	---		81.1	6.6	<0.0001
Hypertension, %	64.7	42.0	<0.0001	63.1	34.1	<0.0001
Glucose, mg/dL (STD)	116.9 (44.0)	99.1 (22.3)	<0.0001	114.3 (41.7)	97.8 (22.2)	<0.0001
Ever Diabetes, %	42.1	18.8	<0.0001	40.1	12.1	<0.0001

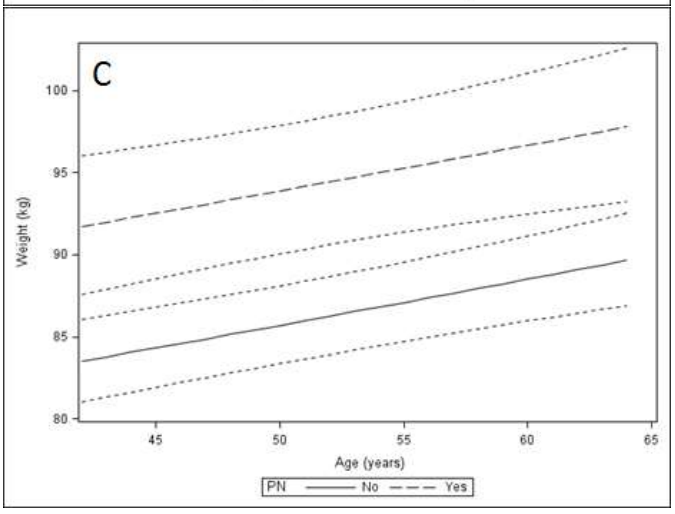
Table 4.5. Predicted value at mean baseline age and annual percent increase of anthropometric measures by peripheral neuropathy status, Peripheral Neuropathy Sub-Study, Michigan SWAN.

Anthropometric Measure	Peripheral Neuropathy		No Peripheral Neuropathy	
	Predicted value at mean baseline age	Annual % increase (95% CI)	Predicted value at mean baseline age	Annual % increase (95% CI)
BMI (kg/m^2)	34.7	0.34 (0.14, 0.54)	31.9	0.35 (0.23, 0.48)
Waist Circumference (cm)	101.2	0.61 (0.46, 0.76)	94.8	0.60 (0.50, 0.69)
Weight (kg)	92.8	0.29 (0.09, 0.49)	84.6	0.32 (0.20, 0.45)

Figure 4.1. Predicted trajectories of BMI (A), waist circumference (B), and weight (C) by peripheral neuropathy status in 2008, adjusted for ever-diagnosis of diabetes and hypertension (A), or ever-diagnosis of diabetes, hypertension, and height (B,C), Michigan SWAN.







CHAPTER 4 REFERENCES

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CHAPTER 5

Discussion

OVERVIEW

Peripheral neuropathy is a complex condition defined by progressive loss of nerve fibers and characterized by a loss of sensation with or without pain, particularly in the lower extremities. This dissertation focused on identifying the prevalence, risk factors, and sequelae of peripheral neuropathy. Prior investigations of peripheral neuropathy have been limited by their study populations, which primarily include diabetic or clinic populations or the elderly.[1-4] Furthermore, in community-dwelling populations, risk factors and sequelae of peripheral neuropathy have been limited to cross-sectional evaluations.[5-7] In our study, we assessed the prevalence of peripheral neuropathy in a community-dwelling population of mid-life women in southeast Michigan, and we evaluated how trajectories of obesity and physical functioning were associated with prevalent peripheral neuropathy as women aged.

In Chapter 2, we evaluated the prevalence of peripheral neuropathy using 3 independent methods. The prevalence of peripheral neuropathy was substantial and ranged from 14% to 20%, but differed according to method of assessment. Although the three methods had poor agreement with one another, each method identified significant differences between women with neuropathy and women without neuropathy, which suggested that the different assessment methodologies may have identified different types or classes of nerves damaged by peripheral neuropathy. However, regardless of assessment method, the co-occurrence of neuropathy and diabetes was associated with a larger body size, poorer glucose control, and hypertension.

In Chapter 3, we evaluated the association between physical functioning and peripheral neuropathy over time. Declines in performance-based physical functioning over time were associated with peripheral neuropathy. We found that women who would have prevalent peripheral neuropathy at the end of the study had lower functioning on the timed stair climb, timed 40-foot walk, and timed sit-to-stand tasks at the beginning of the study, eight to twelve years prior to the assessment of peripheral neuropathy. For each of the three longitudinal performance-based physical functioning tasks, the differences between women with neuropathy and women without neuropathy were maintained or exacerbated over time.

In Chapter 4, we evaluated the association between body size and peripheral neuropathy over time. Body mass index, waist circumference, and weight were significantly higher in women with neuropathy compared to women without neuropathy. Body size differences between neuropathy groups were observed twelve years before the assessment of peripheral neuropathy, and the differences between groups were maintained over time. Notably, although average body size increased with age for both women with and without prevalent peripheral neuropathy, women with peripheral neuropathy did not get obese at a faster rate than women without neuropathy, suggesting that neuropathy did not cause weight gain. Adjusting for or excluding women with diabetes only slightly attenuated the association between obesity and peripheral neuropathy, suggesting an independent association.

Peripheral neuropathy is a prevalent condition of the general population and is associated with decreased physical functioning and increased obesity. The shifting age and obesity distribution of the United States calls for an increased understanding of healthy aging. This dissertation has shown that peripheral neuropathy is an important component of the aging process, is a condition relevant to mid-life women, and has important implications for quality of life and disability.

STRENGTHS AND LIMITATIONS

Major strengths of this dissertation included our bi-racial community-dwelling study population and 12 years of data on peripheral neuropathy covariates. Much of the

available literature on peripheral neuropathy is limited to an elderly or diabetic-only clinical population.[1-4] Our cohort of African American and Caucasian women included both diabetic and non-diabetic women who were not selected based on diabetes status for cohort enrollment. To our knowledge, no other studies have used 12 years of longitudinal physical functioning and body size measures to characterize peripheral neuropathy. This methodological approach and our population-based mid-life study population are unique to the peripheral neuropathy literature.

The assessment of peripheral neuropathy in this dissertation was cross-sectional and was measured 12 years after the enrollment of the Michigan SWAN cohort. Because women may have had peripheral neuropathy at the time of their enrollment in the study in 1996 and there was no baseline neuropathy measure, we were unable to identify the timing of disease onset, which is known to vary considerably.[8] However, the 543 women enrolled in the longitudinal study in 1996 were generally "healthy." It is unlikely that a large proportion of the cohort had neuropathy at the time of their enrollment and instead developed it sometime during the course of the study. Nevertheless, our measure of prevalent peripheral neuropathy is still useful. We modeled past trajectories of physical functioning and obesity, and evaluated the difference in those trajectories by subsequently-identified peripheral neuropathy. Clinicians may find this approach useful in targeting peripheral neuropathy testing to women who are experiencing greater-than-average declines in physical functioning or increases in body size as they age.

Confirmed diagnosis of peripheral neuropathy generally requires electrophysiological assessment, and even then there are debates about the minimally-required criteria for a diagnosis of neuropathy using invasive methods.[9] Such invasive and painful procedures were neither appropriate for nor acceptable by our epidemiologic cohort of women. We used the Michingan Neuropathy Screening Instrument (MNSI) clinical examination, MNSI symptom questionnaire, and 10-gram Semmes Weinstein monofilament testing to measure peripheral neuropathy. We experienced difficulties administering the MNSI clinical exam in our population-based sample of women because the exam required the examiner to observe and interpret "foot deformities," which is a relative term. The presentation of foot deformities in the general population is likely much different than the presentation of foot deformities in a diabetic population. In our study population, we believe that the prevalence of foot deformities may have been overestimated. Therefore, data from the MNSI clinical examination were used only for the analysis in Chapter 2. In Chapters 3 and 4, we operationalized the definition of neuropathy to ≥ 4 symptoms or signs reported on the MNSI symptom questionnaire or abnormal monofilament testing to identify individuals with neuropathy and we dropped the MNSI clinical exam. Monofilament testing is favored over the conventional clinical exam in terms of reproducibility and identifying an at-risk patient,[10] and this testing has been used with success in other epidemiologic investigations.[11,12] Peripheral nerves are anatomically distributed, have different functional classes, and include motor, sensory, and autonomic fibers; as such, peripheral neuropathy is considered a syndrome because

different classes and sizes of nerve fibers can be damaged, which results in varying disease and symptom presentations.[9] It is extremely difficult to diagnose neuropathy with a single method.[13] Therefore, peripheral nerve dysfunction should be evaluated using multiple measurements, including symptoms and signs, irrespective of the mechanism thought to have caused the nerve damage.[9] Our use of the combined symptom questionnaire and monofilament testing to identify women with peripheral neuropathy allowed us to capture a wider spectrum of the disease than we would have with a single assessment method. Even so, women may have been non-differentially misclassified with respect to their peripheral neuropathy status.

The possibility of reverse causation must be considered, particularly for the assessment of obesity and peripheral neuropathy. Although obesity was hypothesized to be causally related to peripheral neuropathy through different pathways, women with neuropathy could also be less likely to exercise due to a loss of sensation or pain in the feet, which in turn could increase the risk of obesity. We were unable to differentiate between obesity as a causal risk factor for neuropathy or as a consequence of neuropathy based on the currently available neuropathy measures in our study population. In Chapter 4, we found that women with neuropathy had larger body sizes, but there were no differences in the trajectories of body size measures by peripheral neuropathy status over time. It was unlikely that a large proportion of study participants had neuropathy at baseline. This suggests that either peripheral neuropathy developed late during the course of the study and did not have a chance to change the trajectory of obesity, or obesity causes

neuropathy but does not change as a result of neuropathy. Nevertheless, because little is known about the association between obesity and peripheral neuropathy outside of a clinical population, this study adds substantial information to the current body of literature.

Attrition in this longitudinal cohort must also be considered. The follow-up rate of the Michigan SWAN study in 2008 was 77%, which is an excellent retention rate for 12 years of follow-up. Notably, the retention rate includes 18 deaths between baseline and visit 12. However, the validity of longitudinal analyses is contingent upon the assumption that missing observations are "missing at random."[14] This investigation was restricted to individuals who participated in the peripheral neuropathy assessment in year 12 (2008) of follow-up because peripheral neuropathy was the focus of our study. It is possible that some of the 543 women who were included in the 1996 cohort enrollment but were not active participants in study year 12 were not active because of severe peripheral neuropathy, physical limitations, or disability, so the inactive participants would not be missing at random. Although multiple imputation or other missing-data methodologies were not employed, baseline demographic and other health-related factors were compared between the 396 women who had any peripheral neuropathy assessment in study year 12 and the 147 women who did not have a peripheral neuropathy assessment in study year 12 as a supportive methodology. Baseline age, race/ethnicity, baseline body size, baseline blood pressure, and baseline glucose and diabetes status were not significantly different between women with any neuropathy

assessment and women without a neuropathy assessment, indicating that baseline demographic and other health factors did not predict missingness and that assumptions of "missing at random" for longitudinal analyses were likely adequate.

Although our longitudinal study used repeated measures over time, we still may have been limited by our sample size. In the assessment of peripheral neuropathy and physical functioning, we were interested in examining interactions between neuropathy and diabetes and between neuropathy and obesity. We hypothesized that the effect of obesity on physical functioning would be different for women with neuropathy than women without neuropathy. Likewise, we hypothesized that the effect of diabetes on physical functioning would be compounded by the presence of peripheral neuropathy. However, the interaction terms that were included in multivariable models to test these associations did not reach statistical significance at the α=0.05 level. A larger sample size may have yielded different results. In addition, our population was relatively homogenous, particularly with respect to obesity, as most of the participants in the Michigan SWAN study are obese (the mean BMI in 2008 was 34 kg/m^2). A larger sample size with more heterogeneity may have allowed us to observe these important interactions.

PUBLIC HEALTH IMPLICATIONS

Serious complications of peripheral neuropathy include foot ulcers and lower-limb amputations. Peripheral neuropathy and the loss of sensation in the feet from nerve

damage prevent an individual from noticing minor foot trauma or pressure, which can eventually cause ulceration and lower-extremity amputation.[15] Ulceration and amputation are associated with considerable morbidity, mortality, and health care expenditures.[16,17] Worldwide, approximately 1 million individuals lose a leg each year as a consequence of lower-extremity diseases like peripheral neuropathy;[17] in the United States, a major proportion of the $132 billion annual expenditure on diabetes mellitus is related to long-term microvascular complications and lower extremity amputations.[18]

There are important gender and racial disparities in lower-extremity amputations. Although men are more likely to have an amputation, women have a higher mortality rate associated with amputation than men.[18] Furthermore, for diabetic patients, African American females are almost 5 times as likely to have an amputation than non-Hispanic White females.[18] African American women with diabetes have almost twice the rate of amputation of men of any race/ethnicity. However, the rate of neuropathy-associated ulceration and amputation has not been documented for individuals without diabetes. In our Michigan SWAN study population, 2 of 418 active participants in 2008 had experienced diabetes-related amputations. Clearly, peripheral neuropathy as a risk factor for ulceration and amputation is an important focus of research, particularly for African American and Caucasian women.

Early identification of individuals with peripheral neuropathy may identify individuals at high risk for future ulceration and amputation. Even among diabetic patients who are

known to have peripheral neuropathy, the monofilament test can be used to identify a foot that is at risk for ulceration and lower-extremity amputation.[19] It is estimated that up to 50% of foot ulcers and amputations could be prevented with early identification and education on appropriate foot care.[20,21] When a leading expert on the diabetic foot spoke at a U.S. Department of Health conference on reducing the rate of amputations for persons with diabetes, he did not reference state-of-the-art medical or surgical interventions.[22] Instead, his key recommendation was that physicians remove patients' shoes and socks and examine the feet.[22] Similarly, the monofilament test is inexpensive, accurate, and painless.[15] Visual examination of the foot and monofilament testing are ideal epidemiologic screening tools and should be employed more frequently in diabetes clinics. The United States Public Health Service and the American Diabetes Association recommend annual foot screening for diabetic patients.[10,22] However, our findings that peripheral neuropathy was highly prevalent in a population that included both diabetic and non-diabetic individuals suggest that peripheral neuropathy testing may be warranted for persons outside of the diabetes clinic who exhibit diminished functional capacity or signs or symptoms of neuropathy. Early identification of peripheral neuropathy and promotion of foot health could improve quality of life and decrease health care expenditures by lowering the risk of ulceration and amputation.

Compared to amputation, a less extreme but perhaps even more important consequence of peripheral neuropathy is diminished functional capacity. In our study, we found that women with subsequently-identified peripheral neuropathy had declining

physical functioning twelve years before the assessment of peripheral neuropathy. Our results are not surprising considering the debilitating pathway of peripheral neuropathy. Nerve damage, particularly to the sensory fibers, reduces the amount of perception feedback from receptors and causes impairments like reduced position sense.[6] Impaired balance and unsteadiness and the resulting functional limitations, particularly in walking speed, can lead to loss of independence because activities like walking are critical for the maintenance of independence in a community.[6,23] Impaired balance and unsteadiness also contribute to falls and hip fractures, both important indicators of the healthy aging process.[24,25] It is well-documented that peripheral neuropathy increases the risk of falls.[6] Furthermore, among individuals with peripheral neuropathy, female gender and a larger BMI confer an additional risk of falling.[26,27] Considering that one-third of community-dwelling older adults fall every year,[28,29] obese women may be an important high-risk group for whom to target peripheral neuropathy testing and patient education about reducing risk of falls.

Physical functioning is of great public health importance because limitations in physical functioning have important implications for disability. Measures of performance-based physical functioning, like mobility, balance, and strength, can be useful clinical risk indicators in predicting future functional decline and hospitalization. In particular, walking speed is a sensitive predictor of the onset of difficulties in activities of daily living and functional dependence.[30,31] Inadequate walking speeds compromise an individual's ability to safely negotiate his or her physical community environment.

National standards require the minimum pedestrian clearance velocity at a crosswalk to be 3.5 feet/second.[32] In other words, an individual must walk at a pace of 3.5 feet per second from curb to curb during the "walk" indication signal to safely use a crosswalk. In a previous investigation, approximately one-third of Michigan SWAN participants walked at speeds slower than the federal standard for crossing a controlled intersection.[33] In our investigation, we found that the ability to walk at the minimum pedestrian clearance velocity differed by peripheral neuropathy status. On average, women with peripheral neuropathy in 2008 were unable to walk at the speed required to safely use a crosswalk. Although we did not assess the individual's community environment for walkability, performance-based physical functioning measures in a controlled setting are highly predictive of future disability and loss of independence.[34,35] The high prevalence of inadequate walking speeds in our study population suggests that federal standards for ambulation velocity may be too high. Given the high prevalence of peripheral neuropathy in mid-life women and the shifting age demographic of the United States, the minimum walking speed required to use crosswalks may need to be lowered so that older adults can maintain independence in their communities.

FUTURE RESEARCH DIRECTIONS

The prevalence of peripheral neuropathy increases linearly with age.[36] An investigation from the National Health and Nutrition Examination Survey (NHANES) found that the prevalence of monofilament-defined peripheral neuropathy was 3.0% for 40-44 year old women, 12.6% for 65-69 year old women, and 32.9% in women aged 85 years and

older.[36] In our study of 54-64 year old women, the prevalence of peripheral neuropathy ranged from 14.3 to 20.0%, depending on the method of assessment. The large body sizes and relative homogeneity of the Michigan SWAN participants may have contributed to the higher prevalence observed in our study. Further investigation of the differences in risk factors and effect modifiers between the Michigan SWAN population and the NHANES population may be warranted in order to explain the differences between prevalence estimates. In addition, continued examination of peripheral neuropathy in the Michigan SWAN population is warranted to evaluate the possibility of an age-associated increase in prevalence.

We conceptualized peripheral neuropathy as a pathological condition that would lead to functional limitations and disability, as described by The Disablement Process.[37-39] In our study, we found that peripheral neuropathy was associated with poorer performance-based physical functioning. However, it is unclear if poorer physical functioning among individuals with neuropathy will translate in to future disability for our study participants. Future studies should examine the association between peripheral neuropathy and incident disability.

Diabetes is strongly associated with lower-extremity physical limitations.[40] This relationship is only partly explained by peripheral nerve dysfunction and other comorbidities.[41] Several studies have reported that individuals with good glycemic control have higher physical functioning than individuals with poor glycemic control,[42,43]

but the mechanism by which glycemic control sustains high levels of physical functioning has not yet been elucidated. It is possible that glycemic control, even among persons without diabetes or with pre-diabetes, prevents or delays the development of peripheral neuropathy.[43,44] In our study, we did not have longitudinal measures of glycemic control like glycosylated hemoglobin (HbA1c) and so we could not evaluate the association between physical functioning, glycemic control, and peripheral neuropathy in 2008. However, since 2008, HbA1c has been measured in the Michigan SWAN participants and our future research will evaluate the association between peripheral neuropathy and glycemic control at time points subsequent to the study visits that were included as part of this dissertation. Other future studies may wish to consider longitudinal measurements of HbA1c in investigations of physical functioning and peripheral neuropathy, as it would be of interest as to whether or not glycemic control modifies the effect of peripheral neuropathy on physical functioning. Furthermore, we were unable to observe "pre-diabetic" individuals, in whom glucose control may be particularly relevant for the development of peripheral neuropathy. In 2008, there were only 32 non-diabetic women (8%) whose fasting glucose was impaired (<126 and ≥110 mg/dL), so we were unable to separate women without diabetes in to meaningful risk cutpoint categories for glucose values. Future studies of peripheral neuropathy may wish to include a more heterogeneous sample with respect to glucose values.

This dissertation utilized data from a population-based cohort of African American and Caucasian mid-life women from southeast Michigan. We found that the prevalence of

monofilament-defined neuropathy and symptom-defined neuropathy did not differ by race/ethnicity. However, the prevalence of neuropathy defined using the MNSI clinical exam differed between African American and Caucasian women. It is unclear if neuropathy is associated with race/ethnicity or if race/ethnicity is a proxy for an unmeasured factor that is associated with neuropathy. It has been previously reported that race/ethnicity is associated with diabetes,[45] diabetes-related complications and amputations,[18] physical functioning,[46] and body composition.[47] Future studies may wish to include more racial/ethnic heterogeneity in the study population to examine if the prevalence of peripheral neuropathy differs between races, or if race/ethnicity modifies the association between peripheral neuropathy, physical functioning, and obesity.

In addition, our study population was limited to women. Men are more likely to have peripheral neuropathy than women, likely because neuropathy is associated with height through longer peripheral nerves.[36] Furthermore, the devastating effects of peripheral neuropathy like lower-extremity amputation are more prevalent among men.[18] Future studies should examine the association between neuropathy, physical functioning, and obesity in men and determine if our findings for women can be replicated.

One important goal of epidemiologic research is to identify modifiable risk factors for chronic diseases. In our study, we found that larger body size was positively associated with peripheral neuropathy. Women with peripheral neuropathy had higher BMI, waist circumference, and weight than women without peripheral neuropathy, and this

difference existed even 12 years before the assessment of peripheral neuropathy. One promising direction for future research is obesity and the metabolic syndrome. Obesity is associated a myriad of other abnormal cardiometabolic factors and may be an early step leading to the metabolic syndrome.[48,49] The metabolic syndrome is a major public health problem because its components, including visceral obesity, dyslipidemia, hyperglycemia, and hypertension, are increasing in frequency and strongly associated with cardiovascular and diabetes risk.[50] Another population-based study found that waist circumference, but not dyslipidemia, hyperglycemia, or hypertension, was associated with concurrent peripheral neuropathy in the total population of both diabetic and non-diabetic individuals, as well as in the diabetic subsample.[51] In our previous investigation of the National Health and Nutrition Examination Survey, we found that BMI ≥ 30 kg/m^2 increased the likelihood of peripheral neuropathy beyond the increased likelihood associated with abnormal cardiometabolic risk factors.[5] A small study found that a diet and exercise intervention for patients with neuropathy and impaired glucose tolerance lowered BMI and improved neuropathic pain.[52] If increased adiposity is causally associated with peripheral neuropathy, it may be an appropriate and modifiable point of intervention in the general population to reduce the prevalence and symptoms of peripheral neuropathy. Although our findings showing a longitudinal relationship between body size and peripheral neuropathy are novel, future studies should work to identify the mechanism by which obesity could cause peripheral neuropathy.

CONCLUSIONS

Peripheral neuropathy is a prevalent but underappreciated condition in the general population. Overall, this dissertation contributed to a better understanding of peripheral neuropathy and its relationship with physical functioning and obesity in community-dwelling mid-life women. Our results fill a gap in the understanding of the correlates and sequelae of peripheral neuropathy and may help clinicians and public health officials address peripheral neuropathy as a prevalent condition in the general population. This dissertation should foster discussions about implementing testing for peripheral neuropathy among the general population and education for clinicians and high-risk patients alike on the importance of foot care in order to reduce the morbidity and high costs of health care attributed to peripheral neuropathy and neuropathy-associated health outcomes.

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APPENDIX A

The frequency of symptoms and characteristics of peripheral neuropathy, based on the MNSI symptom questionnaire, are shown below. The most commonly reported symptoms were burning pain (23%), prickling feelings (26%), and muscle cramps in legs and/or feet (54%). Thirty percent of women reported no symptoms, while almost 20% of women reported at least four symptoms of neuropathy.

Table A.1. Frequency of participant-reported affirmative responses from the Michigan Neuropathy Screening Instrument symptom questionnaire, Peripheral Neuropathy Substudy, Michigan SWAN, 2008.

	%
MNSI symptom questionnaire	
1. Are your legs and/or feet numb?	11.8
2. Do you ever have any burning pain in your legs and/or feet?	23.1
3. Are your feet too sensitive to touch?	4.0
4. Do you get muscle cramps in your legs and/or feet?	54.5
5. Do you ever have any prickling feelings in your legs or feet?	26.7
6. Does it hurt when the bed covers touch your skin?	2.5
7. When you get into the tub or shower, are you able to tell the hot water from the cold water?	96.5
8. Have you ever had an open sore on your foot?	4.5
9. Has your doctor ever told you that you have diabetic neuropathy?	5.8
10. Do you feel weak all over most of the time?	8.0
11. Are your symptoms worse at night?	13.1
12. Do your legs hurt when you walk?	21.9
13. Are you able to sense your feet when you walk?	96.7
14. Is the skin on your feet so dry that it cracks open?	9.6
15. Have you ever had an amputation?	1.0
Total number of reported symptoms*	
0	29.8
1	24.8
2	13.9
3	12.1
≥ 4	19.4

*Total number of reported symptoms based on composite score of MNSI symptom questionnaire "yes" responses with questions 7 and 13 reverse-scored.

APPENDIX B

Date Data Entered / Initials _____ Date Verified / Initials _____

FOOT ASSESSMENT FORM

Michigan Study of Women's Health Across the Nation Strength and Functioning Study

SECTION Q. GENERAL INFORMATION

Q1. RESPONDENT ID: AFFIX ID LABEL HERE

Q2. SWAN STUDY VISIT # 12 (S&F Year 2)

Q3. FORM VERSION: 02/08/2008

Q4. DATE FORM COMPLETED: ___ ___ / ___ ___ / ___ ___ ___ ___
M M D D Y Y Y Y

Q5. INTERVIEWER'S INITIALS: ___ ___ ___

Q6. RESPONDENT'S DOB: ___ ___ / ___ ___ / 1 9 ___ ___
M M D D Y Y Y Y

VERIFY WITH RESPONDENT

A. Physical Assessment of the Foot:

A1. RIGHT FOOT ASSESSMENT

1 = Normal (go to Question A2)

2 = Abnormal (check all that apply and describe and/or mark location on diagram below)

- ☐ (A) Deformities
  describe _____
- ☐ (B) Dry skin
  describe _____
  - ☐ Mild Dry Skin ☐ Moderate Dry Skin ☐ Severe Dry Skin
- ☐ (C) Callus
  describe _____
- ☐ (D) Infection
  describe _____
- ☐ (E) Fissure
  describe _____
- ☐ (F) Hematoma
  describe _____
- ☐ (G) Ulcers
  describe _____
- ☐ (H) Bunions
  describe _____
- ☐ (I) Other, specify _____

  describe _____

A2. LEFT FOOT ASSESSMENT

1 = Normal (go to Question B1)

2 = Abnormal (check all that apply and describe and/or mark location on diagram below)

☐ (A) Deformities
describe _____

☐ (B) Dry skin
describe _____

❑ Mild Dry Skin ❑ Moderate Dry Skin ❑ Severe Dry Skin

☐ (C) Callus
describe _____

☐ (D) Infection
describe _____

☐ (E) Fissure
describe _____

☐ (F) Hematoma
describe _____

☐ (G) Ulcers
describe _____

☐ (H) Bunions
describe _____

☐ (I) Other, specify _____

describe _____

B. ANKLE REFLEXES

B1. RIGHT ANKLE REFLEXES (Circle the appropriate responses)

1 = Present (go to B2)

2 = Absent

B1a. RIGHT ANKLE REFLEXES WITH REINFORCEMENT

1 = Present

2 = Absent

B2. LEFT ANKLE REFLEXES

1 = Present (go to C1)

2 = Absent

B2a. LEFT ANKLE REFLEXES WITH REINFORCEMENT

1 = Present

2 = Absent

B3. COMMENTS: _____

C. VIBRATION PERCEPTION AT GREAT TOE

C1. RIGHT ANKLE VIBRATION PERCEPTION

1 = Yes, able to feel vibration (go to C1a)

2 = No, unable to feel vibration (go to C2)

C1a. LENGTH OF TIME (SECONDS) ABLE TO FEEL VIBRATION

_____ _____ seconds

C2. LEFT ANKLE VIBRATION PERCEPTION

1 = Yes, able to feel vibration (go to C2a)

2 = No, unable to feel vibration (go to D2)

C2a. LENGTH OF TIME (SECONDS) ABLE TO FEEL VIBRATION

_____ _____ seconds

C3. COMMENTS: _____

D. MONOFILAMENT TESTING AT GREAT TOE

D1. RIGHT FOOT MONOFILAMENT TESTING

D1A. Number of correct responses _____

D1B. Number of attempts _____

D2. LEFT FOOT MONOFILAMENT TESTING

D2A. Number of correct responses _____

D2B. Number of attempts _____

D3. COMMENTS: _____