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Moderators of Peripheral Neuropathy on Overall and Cardiovascular Mortality in People Without Diabetes

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Walden University

College of Health Sciences and Public Policy

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Walden University
2023

Abstract

Moderators of Peripheral Neuropathy on Overall and Cardiovascular Mortality in People Without Diabetes

by

Adeoye Muideen Adenekan

MPH, University of Liverpool, United Kingdom, 2016

M-B-B-S., University of Lagos, Nigeria, 1997

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

August 2023

Abstract

Peripheral neuropathy (PN), a group of common heterogeneous disorders with varied etiologies, is associated with substantial morbidity and mortality. PN presents both as a diagnostic and therapeutic challenge to physicians and other healthcare providers. Socioeconomic moderators of PN in adults without diabetes in the United States have not been well studied. The consequences of PN can be devastating and include foot ulcers, amputations, a general decline in the quality of life, and death. The overall prevalence of PN in the United States is 13.5% in adults with diabetes and 11.6% in adults without diabetes. Clearly, these statistics indicate a public health burden. This current longitudinal study employed the socioecological model as the theoretical framework to examine whether poverty income ratio, veteran/military status, and health insurance status moderated the effect of PN on overall and cardiovascular mortality among adults without diabetes. The National Health and Nutrition Examination Survey (NHANES) 1999-2015 secondary dataset with linked-mortality data through December 31, 2015, resulting in a longitudinal dataset was analyzed using complex sample Cox regression analysis. Only poverty income ratio moderated the effect of PN on overall mortality; veteran/military status did not moderate the effect of PN on overall mortality, nor did health insurance status moderate the effect of PN on cardiovascular mortality. The results of this study have implications for positive social change. Policies that reduce poverty income ratio, such as those that reduce income inequality and help provide gainful employment, can improve the health outcomes of these adults not suffering from diabetes, but who have been diagnosed with PN in either foot.

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Dedication

I dedicate this dissertation to my late father, Barrister Akanni Adenekan. You gave me life and ensured that my siblings and I had a good education. You always wanted the best for my siblings and me. I miss and will always miss and be proud of you. I also dedicate this dissertation to my late siblings. My elder brother, Adewuyi and my elder sister, Jumoke. Thank you both for being part of my life. I miss and will always miss and be proud of you both. May you continue to rest in peace. Amen.

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I would like to take this opportunity to pay special tributes to those individuals who supported me unconditionally throughout my journey toward earning my Doctorate in Public Health. I thank the Almighty God for the good health and sound mind throughout this journey. I am proud of my perseverance, tenacity, and desire to achieve more. All of these would not have been possible, though, without the wonderful network of family and friends who have guided and supported me.

To my mother, Adunyinka Adenekan, who gave me a life of love and continues to encourage me to finish this journey, I thank God for your longevity to witness this memorable journey till the end. To my eldest brother, Adegboyega, my eldest sister, Mojisola, and my younger brother, Adetunji, who all encouraged and supported me from the beginning of this journey, thank you for all your love and words of encouragement. A special appreciation to my wife, Yetunde and my son, Adewunmi. You both inconvenienced yourselves on many occasions to ensure this moment became a reality. Your presence has provided me with such a sense of calm and peace at times when I thought all was lost, and never let me lose sight of my goals. I LOVE YOU BOTH!

To my academic professionals, who have not only been an inspiration, but an excellent source of confidence and motivation. Professor Sri Banerjee, my dissertation chair and committee member, whose guidance, professional advice, and words of encouragement, have taken me this far. Professor Peter Braun Anderson, my second committee member, who painstakingly read my manuscripts and offered invaluable suggestions and advice.

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Part 1: Overview

Introduction to the Study

Peripheral neuropathy (PN) is among the most common neurological diseases globally, with an estimated incidence of 77/100,000 inhabitants per year and a prevalence of 1% - 12% in all age groups (Lehmann et al., 2020). The estimated 30% prevalence of PN among older people is quite high (Callaghan et al., 2018). Considering that PN is associated with significant morbidity, and sometimes mortality (Hicks et al., 2020), from a public health perspective, clearly this is a public health burden. Hicks et al. (2020) highlighted in their study that the overall prevalence of PN in adults with diabetes in the United States was 13.5%, whereas the prevalence in adults without diabetes in the United States was 11.6%. Furthermore, according to Hicks et al. (2020), PN was significantly associated with all-cause or overall mortality (hazard ratio [HR]= 1.49); CI, [-1.15, 1.94], $p < .001$) and cardiovascular mortality (HR=1.66, CI, [-1.07, 2.57], $p < .001$) in participants with diabetes. As Hicks et al. (2020) further highlighted, in adults without diabetes, PN was significantly associated with all-cause or overall mortality (HR=1.31, CI, [1.15, 1.50], $p < .001$), but no significant association was found between PN and cardiovascular mortality after adjustment (HR= 1.27, CI, [0.98, 1.66]). Judging from these statistics, the prevalence of PN among adults without diabetes in the United States is quite high, when compared to the global prevalence of PN of 1% -12% in all age groups (Lehmann et al., 2020). This clearly makes PN a significant public health problem in the United States. Some of the most common identifiable causes of PN include diabetes mellitus, nerve compression or injury, alcohol use, and toxin exposure (Castelli

et al., 2020). Other common identifiable causes include hereditary causes and nutritional deficiencies (Castelli et al., 2020).

Although many studies have examined the risk factors for PN in the United States, most of these studies examined risk factors for PN in adults with diabetes. The socioeconomic risk factors for PN in adults without diabetes, especially as they moderate the effect of PN on overall and cardiovascular mortality, have not been well studied in the United States. To corroborate this, Dusendang et al. (2019) highlighted that because many studies on PN have been limited to populations with diabetes, there is limited evidence on potential contributing risk factors, including salient psychosocial risk factors such as discrimination and social status. Furthermore, according to Kirthi et al. (2020), there is a growing body of evidence of excess PN in people with pre-diabetes. As Kirthi opined in their systematic review, many studies conducted reported a higher prevalence of PN in pre-diabetic patients, mostly of a small nerve fiber origin, than would be expected in the background population. This situation is a justification for conducting this research study, which examined whether socioeconomic risk factors, such as poverty income ratio, veteran/military status, and health insurance status, moderated the effect of PN on overall and cardiovascular mortality in adults without diabetes in the United States. Knowledge of these socioeconomic risk factors could enhance the development of risk-stratification tools, which might facilitate earlier interventions that may prevent the development of some of the serious complications associated with PN and bring about a positive social change by improving the health outcomes for these patients.

Definition

Peripheral neuropathy (PN) generally refers to a broad range of disorders that affect the peripheral nervous system in a variety of different patterns (Barrell & Smith, 2019). The most commonly encountered pattern of this disorder is the *distal sensory polyneuropathy* (DSP), a term generally used to refer to a group of disorders that present with length-dependent peripheral nerve injury that results in distal predominant sensory loss, pain, and when severe, weakness, which results in gait instability, fall risk, and sometimes foot ulceration and amputation (Barrell & Smith, 2019). Less commonly encountered patterns of PN are mononeuritis multiplex, a condition in which multiple nerves are damaged, resulting in a patchy pattern of injury (Barrell & Smith, 2019), neuronopathy, which results in non-length-dependent pan-modal sensory loss or weakness (Barrell & Smith, 2019), and polyradiculopathies, which causes proximal and distal weakness and numbness (Barrell & Smith, 2019).

Since PN is heterogeneous in its presentation and has a varied etiology, a systematic approach is critical for its evaluation and management. PN can be encountered by clinicians and healthcare providers in a multitude of clinical settings (Nold & Nozaki, 2020). This can range from a patient who presents at the emergency department with Guillain-Barre syndrome, to a patient with a suspected tarsal tunnel syndrome needing referral to orthopedic surgery, a patient suffering from diabetes, now presenting with new onset paresthesia in the lower limbs, or a patient in the oncology unit who recently developed adverse medication reactions to chemotherapy (Nold & Nozaki, 2020). In view of the number of systemic conditions with which PN is associated, it is important

for clinicians and relevant healthcare providers to understand the basic definition and diagnostic principles of this condition (Nold & Nozaki, 2020).

Epidemiology

According to the Foundation for Peripheral Neuropathy (FFPN, 2021), an estimated 30 million Americans presently suffer from PN. The prevalence of PN in the general population is estimated to range from 1% to 7% (Castelli et al., 2020), with higher prevalence rates found among people older than 50 years (Castelli et al., 2020). According to Alkandari et al. (2019), PN is a common neurological disorder affecting people from both developed and developing countries, while diabetes is the most common cause of PN in Western societies. Diabetes is still the leading cause of PN globally, with diabetic PN accounting for an estimated 60% of all cases of PN in the United States (FFPN, 2021). Other important identified causes of PN in the United States include chemotherapy induced PN (CIPN), HIV, and idiopathic PN which has no identifiable known cause and therefore is considered a primary disease (FFPN, 2021). Globally, PN has been associated with a wide variety of causes. According to Castelli et al. (2020), some of the causes of PN include connective tissue diseases such as amyloidosis, alcohol use, infectious diseases such as leprosy, Lyme disease, and nutritional deficiencies such as vitamins B6, B12, E, and thiamine deficiencies. According to the Centers for Disease Control and Prevention (CDC, 2021), Lyme disease is an inflammatory disease caused by the spirochete bacterium, Borrelia burgdorferi. This organism is transmitted by the bite of an infected deer tick (CDC, 2021). Lyme disease affects an estimated 300,000 people annually in the United States (CDC, 2021), but it is

most common in the Northeast section of the United States (CDC, 2021). The neurologic symptoms of Lyme disease occur when the causative agent invades or affects the peripheral or central nervous system. Peripheral nerve involvement leads to the development of numbness, tingling, pain, or weakness in the upper or lower limbs (CDC, 2021). Other identified causes of PN include endocrine disorders such as acromegaly, hypothyroidism, hyperthyroidism, autoimmune diseases such as Celiac disease and vasculitis, and exposure to toxins, such as acute arsenic poisoning, heavy metal poisoning, carbon monoxide, and acrylamide poisoning (Castelli et al., 2020). PN has been found to be more prevalent in older adults (Hicks et al., 2021).

In the study conducted by Hicks et al. (2021), the authors highlighted an increased risk of development of PN in the male sex; similarly, the Black race and greater height of participants were associated with an increased risk of the development of PN (Hicks et al., 2021). Similarly, Hicks et al. (2021) found that body mass index (BMI) and peripheral arterial disease were important associated risk factors for PN. As Hicks et al. (2021) posited the burden of PN, defined by abnormal monofilament testing in their study, was substantial, even among adults without diabetes. This is a justification for conducting this research study which examined some of the socioeconomic mediators of the effect of PN on overall and cardiovascular mortality among adults without diabetes in the United States. Moreover, PN has an insidious onset (Nold & Nozaki, 2020), and early recognition and treatment is important to prevent the associated morbidity and mortality and to improve the overall quality of life of the patients. It was therefore important to

determine whether these socioeconomic factors moderated the effect of PN on overall and cardiovascular mortality among adults without diabetes.

Classification

PN can be broadly classified by its distribution patterns. According to (Nold & Nozaki, 2020), three main distribution patterns are distal symmetric polyneuropathy (DSPN), mononeuropathy, and mononeuropathy multiplex. Of these patterns, DSPN is the most common (Nold & Nozaki, 2020); furthermore, diabetes is the most common cause of DSPN (Nold & Nozaki, 2020). In the United States, the estimated prevalence of DSPN in 2015 was 15% in people older than 40 years and approximately 30% among patients with diabetes (Callaghan et al, 2020). Individuals suffering from DSPN usually present with numbness, pain, tingling, and/or weakness, which start in the toes and spreads proximally in a stocking-glove distribution (Callaghan et al, 2020). Other common causes of DSPN include vitamin B12 deficiency, alcohol use, hereditary diseases, chemotherapy, chronic kidney disease, paraproteinemia, and thyroid disease (Nold & Nozaki, 2020). In addition, DSPN can be associated with vasculitis sarcoidosis, carcinoma, lymphoma, leprosy, HIV, Lyme disease, or amyloidosis (Nold & Nozaki, 2020).

Mononeuropathy refers to the damage or dysfunction of a single peripheral nerve (Nold & Nozaki, 2020). Most mononeuropathies cause both motor and sensory impairment, usually affecting the hands, arms, or feet (Nold & Nozaki, 2020), and people suffering from mononeuropathy usually experience numbness, tingling, pain, and weakness in the distribution of one nerve (Nold & Nozaki, 2020). The possible causes of

mononeuropathy include trauma, focal compression, and entrapment (Nold & Nozaki, 2020). Examples of mononeuropathy include median neuropathy at the wrist (carpal tunnel syndrome), ulnar neuropathy at the elbow (cubital tunnel syndrome), and peroneal neuropathy at the fibular head (Nold & Nozaki, 2020).

Mononeuropathy multiplex, also known as mononeuritis multiplex, is a type of PN that occurs when there is damage to two or more different nerve areas (Nold & Nozaki, 2020). This form of PN is actually a group of symptoms rather than its own disease (Nold & Nozaki, 2020). In this pattern of PN, the patient exhibits symptoms such as pain, which is often acute or subacute in onset and numbness in the distribution of multiple noncontiguous nerves (Nold & Nozaki, 2020). This type of neuropathy can be associated with vasculitis, sarcoidosis, lymphoma, carcinoma, leprosy, HIV, diabetes, Lyme disease, or amyloidosis (Nold & Nozaki, 2020).

Mechanism or Pathogenesis

PN has increasingly been linked to oxidative stress (Mallet et al., 2020). As Betteridge (2020) highlighted in Mallet et al. (2020), oxidative stress develops whenever there is disequilibrium between damaging free radicals and protective antioxidants and tipping in favor of oxidation. While the most common identified types of free radicals belong to the reactive oxygen species (ROS) and have been identified as products of mitochondrial metabolism (Mallet et al., 2020), these molecules cause chain reactions of molecular instability (Mallet et al., 2020). According to Mallet et al. (2020), an example of this type of chain reaction leading to molecular instability is lipid peroxidation, a situation where the chain reaction occurs and causes damage within the lipid bilayer

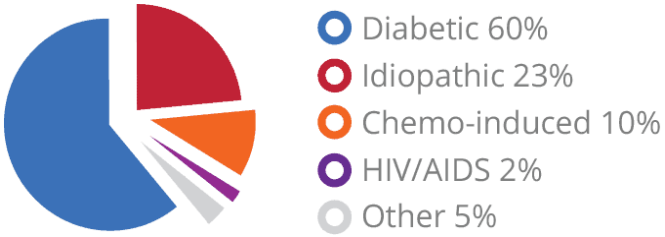
membranes of cells (Mallet et al., 2020). The destruction of the lipid bilayer membranes from oxidative stress leads to intracellular deoxyribonucleic acid (DNA) damage, cellular dysfunction, and apoptosis (Mallet et al., 2020). The end result of this chain reaction leads to a dysfunction of the peripheral nerves, with the development of PN.

Background

There is a substantial burden of PN with the associated cardiovascular and overall mortality among adults without diabetes in the United States. Unfortunately, most of the studies that have examined the burden and risk factors for PN in the United States, have examined people with diabetes. Although diabetic PN (DPN) remains the most common cause of PN in the United States as estimated 30 million Americans presently suffer from PN in the United States (FFPN, 2021), with a significant proportion of this number of people not suffering from diabetes.

Figure 1

Prevalence of Different Types of Peripheral Neuropathy in the United States



Note. The prevalence of the different types of peripheral neuropathy. Diabetes remains the most common cause of peripheral neuropathy, although other important causes include chemotherapy and HIV/AIDS. Adapted from Foundation for Peripheral Neuropathy, 2021 (https://www.foundationforpn.org/types-risk-factors/). In the public domain.

CIPN in particular, is a common and significant clinical entity (Colvin, 2019). It arises from treatment with many commonly used anticancer agents, which are potentially neurotoxic, with increasing impact on oncological treatments (Colvin, 2019). Acute CIPN is believed to occur during chemotherapy (Colvin, 2019), and unfortunately, this situation sometimes requires either a reduction in the dosage of the anticancer agent or cessation (Colvin, 2019), which can impact on the survival of patients. According to Colvin (2019), CIPN develops as a glove and stocking neuropathy, but in severe cases, it can spread proximally to affect most of the limbs. While the mechanisms underlying the development of CIPN are complex (Colvin, 2019), altered ion channel activity and changes in intracellular systems are some of the mechanisms involved (Colvin, 2019). Alterations in sodium channel type and activity, as well as decreased potassium channel expression in primary sensory neurons, have all been associated with the development of CIPN (Colvin, 2019). Similarly, mitochondrial dysfunction has also been identified as one of the pathways that mediate the development of CIPN (Colvin, 2019). Chemotherapeutic agents are thought to disrupt the oxidative phosphorylation that produces adenosine triphosphate (ATP) in neuronal cells (Colvin, 2019). This eventually leads to the development of CIPN in these cells.

Unfortunately, PN is a common neurological disorder that has been found to be independently associated with mortality among the adult population in the United States, even in the absence of diabetes (Hicks et al., 2021). According to Callaghan et al. (2018), patients suffering from PN experience pain, decreased quality of life, falls, ulcerations, which can eventually lead to amputations. Regrettably, outside of pharmaceutical agents

that are used to treat neuropathic pain associated with the disease, few therapies exist to help patients with PN (Callaghan et al., 2018). Moreover, even in patients suffering from Type 2 diabetes, strict glycemic control has shown only a modest effect on the prevention of the development of PN (Callaghan et al., 2018). In addition, the underlying cause of PN is not known in a significant population of patients with PN (Callaghan et al., 2018). Although diabetes has been identified as the strongest and most well-established metabolic driver of PN (FFPN, 2021), determining the socioeconomic contributors is critical to understand the population at risk and to facilitate new strategies to prevent and or treat this common neurological disorder. These challenges highlight the serious public health problem of PN and the need for researchers to examine the pertinent socioeconomic moderators of the effect of PN on overall and cardiovascular mortality. Hence, there was a justification for my research study.

Even though it has been highlighted in many studies that diabetes is the most common cause of PN worldwide, there is a growing body of literature suggesting that prediabetes, obesity, and metabolic syndrome (MetS) are increasingly linked to the development of PN (Stino & Smith, 2017). Prediabetes is regarded as the earliest stage of glucose dysregulation (Stino & Smith, 2017), while MetS is the combination of dyslipidemia, defined as elevated serum triglycerides and reduced high-density lipoprotein cholesterol, central obesity, insulin resistance, and hypertension (Stino & Smith, 2017). As Stino and Smith (2017) opined, several studies have highlighted that patients with MetS and prediabetes have an increased risk of developing a type of PN known as cryptogenic sensory polyneuropathy (CSPN). This form of PN is common,

slowly progressive, and begins in late adulthood with the development of limited motor impairment. This evidence suggests that PN has a varied etiology, especially in the nondiabetic population, and bolsters the argument for researchers to conduct more studies, especially on the socioeconomic risk factors for PN. Hence, there was a justification for my research study, where I examined the socioeconomic moderators of the effect of PN on overall and cardiovascular mortality.

To further highlight the public health significance of PN, Oaklander et al. (2022) highlighted in their study that the recent and ongoing COVID-19 pandemic has been linked to the development of PN. The authors highlighted that small-fiber neuropathy was the most prevalent in the group of patients studied with long COVID, a term referred to as post-acute sequelae of SARS CoV-2 infection (Oaklander et al., 2022). Oaklander et al. highlighted that autopsy findings of some of the patients who died from COVID-19 infection, revealed the presence of inflammatory cells such as macrophages. The absence of viral antigens from autopsy findings probably suggests that inflammatory processes, rather than direct infection, were more important in the development of PN in these patients. It is unclear whether inflammatory responses, which have been linked to other metabolic diseases or socioeconomic risk factors (Stino & Smith, 2017) played a role in the etiopathogenesis of PN in these group of patients. Therefore, more research is needed in this area, particularly on the socioeconomic risk factors that increase the risk of the development of PN. Hence, there was justification for my research study, where I examined the socioeconomic moderators of the effect of PN on overall and cardiovascular mortality.

Some socioeconomic risk factors have also been implicated in the development of PN Trivedi et al. (2017) highlighted the varied etiologies of PN, including some of the socioeconomic risk factors. The authors found in particular that the prevalence of PN was higher in the urban slum areas, when compared to the rural areas. This pattern, the authors highlighted, could probably have been due to nutritional and adverse environmental factors in the urban slum areas such as poor nutritional status and exposure to environmental toxins. However, the authors suggested that further studies were needed in this area. This was justification for my research study, as there is some evidence in the literature that socioeconomic factors might play a role in the development of PN However, there are no studies in the literature that have examined how poverty income ratio, veteran/military status moderate the effect of PN on overall mortality and how health insurance status moderates the effect of PN on cardiovascular mortality respectively.

Theoretical Framework/Model

The theory or conceptual framework that grounds this study is the socioecological model, first introduced by Urie Bronfenbrenner in the 1970s (Kilanowski (2017). The justification for choosing this framework for this study is that socioecological model focusses on the nature of people's interactions or transactions with their physical and sociocultural environments, and whether such multiple interactions or transactions can impact health and lead to the development of diseases (Kilanowski, 2017). The original constructs of the socioecological model at the time of its introduction were (a) the microsystem: interactions of individuals with their immediate surroundings; (b)

mesosystem: interactions at work, school, church, and neighborhood; (c) ecosystem: community contexts and social networks; (d) macrosystem: societal, religious, and cultural values and influences; and (e) chronosystem: both internal and external elements of time and historical content (Kilanowski, 2017). However, these constructs or layers of the socioecological model have now been revised and include individual, network, community, and structural (Cowan et al., 2021).

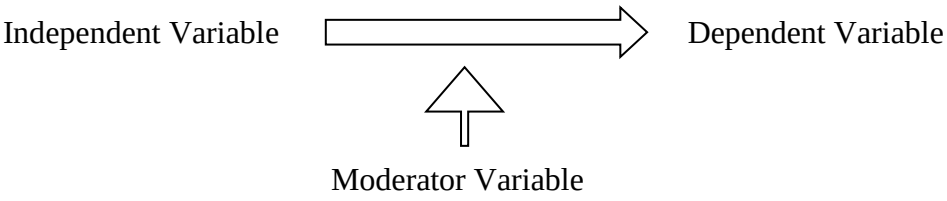
The socioecological model was applied to guide the discussion in this study. Veteran/military status, an independent variable, was explained by the community construct. A veteran or military personnel might be deployed to different locations or communities during her or his career. The kind of environment, exposure to herbicides, the food she or he eats in the environment, as well as interactions with other people in that particular environment can all influence a veteran/ military personnel's health outcome. Health insurance may be influenced by factors acting at the structural level. As Cowan et al. (2021) highlighted, structural factors are mediated through laws and policies, as well as society and economics. For example, if a government institutes a universal health insurance coverage system, it is likely that the most vulnerable in the population will be protected or have at least some insurance coverages, which will likely improve their health outcomes. Similarly, poverty income ratio can also be influenced by factors acting at the structural level. These factors are mediated through laws and policies, as well as society and economics. A viable economy brought about by the right set of economic policies or laws will likely result in more gainful employment opportunities for the people, thereby reducing or improving their poverty income ratio.

The main independent variable in my study, PN can be explained by the structural construct. Evidence from available studies suggests that PN develops as a result of multiple risk factors ranging from chronic noncommunicable diseases to exposure to environmental chemicals, herbicides or toxins, and infectious diseases. The structural construct emphasizes economic policies or laws, which can enable individuals gain access to adequate medical treatment and protect them from exposure to noxious or toxic environmental agents, and institute preventative measures from and prompt treatment of infectious diseases. All these measures can influence the development of PN.

Furthermore, it is important to clarify or highlight that the independent variables in each of the three manuscripts included in this dissertation - poverty income ratio and veteran/military status were tested to determine whether they moderated the effect of PN on overall mortality, and health insurance status was tested to determine whether it moderated the effect of PN on cardiovascular mortality respectively.

Figure 2

Moderator Variable



Note. A moderator variable influences the level, direction, or presence of a relationship between an independent and dependent variable. Adapted from *Mediator vs Moderator Variables: Differences & Examples*, by P. Bhandari, 2021, Scribbr. (https://www.scribbr.com/methodology/mediator-vs-moderator). Copyright 2021 by Scribbr.

In this study, I examined whether the independent variables (poverty income ratio and military/veteran status) moderated the effect of the main independent variable (PN) on the dependent variable (overall mortality) and whether the independent variable (health insurance status) moderated the effect of the main independent variable (PN) on the dependent variable (cardiovascular mortality) respectively.

Although researchers have investigated the issue of PN and all-cause and cardiovascular mortality among adults in the United States, there is no literature on whether socioeconomic risk factors such as poverty income ratio, veteran/military status, and health insurance status, moderate the effect of PN on overall and cardiovascular mortality among the adult population without diabetes in the United States.

Overview of the Manuscripts

Poverty Income Ratio

According to the U.S. Census Bureau (USCB, 2023), poverty is measured based on how an individual's or family's income compares to a set federal threshold. If the total family or individual income is less than the federal poverty threshold, then that family or individual is considered to be in poverty (USCB, 2023). Similarly, if the total family or individual income is greater than the federal poverty threshold, then that family or individual is not considered to be in poverty (USCB, 2023). The ratio of this defined poverty to income is regarded as the poverty income ratio. According to Mathis et al. (2020), PN has long been linked or associated with the development of pellagra, a disease of poverty and social inequality (Mathis et al., 2020). Pellagra, which is characterized by the "four D's" (Mathis et al., 2020, p. 896)—dermatitis, diarrhea, dementia, and death, has been linked to high maize and low protein diets (Mathis et al., 2020). This kind of diet was rampant in some European countries during the eighteenth century, especially Southern Europe, where maize became a common staple food, and in Northern Italy where the poor diet of the low socioeconomic class in the Italian population was almost exclusively based on maize flour (Mathis et al., 2020). It is important to highlight that pellagra was also rampant in the early 1900s, especially among the poor communities and populations of the Southern United States (Mathis et al., 2020) which increased their risk of developing PN. According to the Alcohol Research Group (ARG, 2022), people with greater chronic poverty and lower educational levels experience a higher risk of alcohol problems, with an increased incidence of alcohol induced PN.

Furthermore, smoking, a risk factor for PN (Celik et al., 2017), is strongly associated with poverty (Action on Smoking and Health [ASH], 2021). The link between smoking and poverty or low socioeconomic status is well established; in research conducted in the United Kingdom using national government data on households, one in five (21%) of smoking households were found to be living below the poverty line (ASH, 2021). Smoking in turn increases the risk of oxidative stress on peripheral neurons, which eventually leads to neuronal dysfunction and the development of PN (Celik et al., 2017). Hence, there was justification for my research study, in which I examined whether poverty income ratio moderated the effect of PN on overall mortality.

Veteran/Military Status

Several factors associated with a person's veteran or military status contribute to an increased risk of the development of PN. According to the National Institutes of Health (NIH, 2019), deployment among military personnel is associated with smoking initiation, unhealthy drinking, and drug use, which have all been linked to the development of PN among individuals. Service members or military personnel who test positive for illicit drug use can face dishonorable discharge and even criminal prosecution. However, substance use becomes a critical problem once active-duty personnel leave the military, as some of the protective influences of being in the service is lost. Reported cases of illicit drug use, which is strongly associated with the development of PN (Castelli et al., 2020), increase when active-duty personnel leave military service (NIH, 2019). It is documented that marijuana accounts for most of the

cases of illicit drug use among veterans with 3.5% reporting use (NIH, 2019), and 1.7% reporting use of illicit drugs other than marijuana in a 1-month period (NIH, 2019).

Furthermore, according to de la Monte and Goel (2022), previous exposures to herbicides such as Agent Orange, a dioxin-containing toxin, which was used as an herbicide during the Vietnam War, has been linked to the development of PN and neurodegeneration among military personnel and veterans (de la Monte & Goel, 2022). According to Inoue et al. (2021), the current U.S. Census reports estimate that there are roughly 18 million veterans and 2.1 million active-duty and reserve service members. It is clear that veteran/military status is strongly associated with the development of PN, through exposure to different herbicide chemicals (Mathis et al., 2021). Hence, there was justification for my research study, in which I examined whether veteran/military status moderated the effect of PN on overall mortality.

Health Insurance Status

About 28 million Americans are presently uninsured (Woolhandler & Himmelstein, 2017), and available evidence supports the fact that compared to people who do not have any form of insurance coverage, those with private insurance coverage have about 21% lower cardiovascular mortality risk (Song et al., 2020). Furthermore, the United States has lower life expectancy than most other wealthy or industrialized countries, and it is the only country in this group with substantial numbers of uninsured residents (Woolhandler & Himmelstein, 2017). Although many factors may influence or confound cross-national comparisons of life expectancies, according to Woolhandler and Himmelstein (2017), a recent study suggests that worse access to good-quality health care

and health insurance, contributes to United States higher mortality from medically preventable causes or amenable mortality such as cardiovascular mortality.

Furthermore, Khatana et al. (2019) highlighted in their study on the association of Medicaid expansion with cardiovascular mortality, that counties in the United States that embraced the expansion of Medicaid eligibility had fewer deaths from cardiovascular causes, when compared to counties that did not expand Medicaid eligibility to their residents. Hence, there was justification for my research study which examined whether health insurance status moderated the effect of PN on cardiovascular mortality.

The overall problem addressed in this research study is that there are no studies in the United States that have examined how socioeconomic risk factors such as poverty income ratio, veteran/military status, and health insurance status moderate the effect of PN on overall and cardiovascular mortality among adults without diabetes.

Hence, there was justification for conducting the three studies, which examined whether poverty income ratio moderated the effect of PN on overall mortality, whether veteran/military status moderated the effect of PN on overall mortality, and whether health insurance status moderated the effect of PN on cardiovascular mortality. These three manuscripts were designed as integrated parallel projects to determine whether the independent variables (poverty income ratio, veteran/military status, and health insurance status) moderated the effect of the main independent variable (PN) on the outcome or dependent variables (overall mortality and cardiovascular mortality).

Manuscript 1

- **Specific problem:** The specific problem is the substantial burden of PN and the associated overall mortality among adults without diabetes in the United States. PN results in decreased lower-extremity sensation that can lead to serious complications in affected adults (Hicks et al., 2021). Unfortunately, PN is common and has been found to be independently associated with mortality in the U.S. population, even in the absence of diabetes (Hicks et al., 2021). The prevalence of PN in some studies is as high as 10.4% for middle-aged (40-69 years) and 26.8% for older (> 70 years) adults in the U.S. population. This suggests that decreased sensation in the foot or PN, may be an underrecognized risk factor for death among the adult population in the United States (Hicks et al., 2021). Apart from the high incidence rate of 34.3 (per 1000 person-years) of all-cause mortality in adults with PN but no diabetes (Hicks et al., 2021), PN can also severely impact the quality of life of patients. The risk factors for PN in adults without diabetes, especially the socioeconomic risk factors such as poverty income ratio, as it moderates the effect of PN on overall mortality remains largely uncharacterized. In particular, there are no published studies that have examined how poverty income ratio moderates the effect of PN on overall mortality. This made it imperative to conduct this study on whether poverty income ratio moderated the effect of PN on overall mortality in adults without diabetes in the United States, while controlling for age, gender, and ethnicity.

- **Research question:** Does poverty income ratio moderate the effect of PN on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity?
- **Null hypothesis:** Poverty income ratio does not moderate the effect of PN on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity.
- **Alternative hypothesis:** Poverty income ratio does moderate the effect of PN on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity.
- **Nature of study and design:** This is a quantitative research study, with a longitudinal design (see Frankfort-Nachmias & Leon-Guerrero, 2018).
- **Source of data:** The secondary data for this study was from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2015 dataset. The justification for choosing the 1999 to 2015 dataset was that the main independent variable in this study PN—an important public health problem associated with mortality and significant morbidity among adults in the United States (Hicks et al., 2021), was only studied and was only available in the 1999 to 2004 NHANES dataset. It was not available in the other NHANES dataset years. The only way I could examine this variable was to include the 1999 to 2004 NHANES dataset. Similarly, the dependent or outcome variable in my study, overall mortality, was only documented in the December 2015

NHANES mortality follow-up dataset, so the only way I could examine this variable and link it with my main independent variable (i.e., PN), was to include the 2015 NHANES dataset.

Manuscript 2

- **Specific problem:** The specific problem is the substantial burden of PN and the associated overall mortality among adults without diabetes in the United States. PN results in decreased lower-extremity sensation that can lead to serious complications in affected adults (Hicks et al., 2021). Unfortunately, PN is common and has been found to be independently associated with mortality in the U.S. population, even in the absence of diabetes (Hicks et al., 2021). The prevalence of PN in some studies is as high as 10.4% for middle-aged (40-69 years) and 26.8% for older (> 70 years) adults in the U.S. population. This suggests that decreased sensation in the foot or PN, may be an underrecognized risk factor for death among the adult population in the United States (Hicks et al., 2021). Apart from the high incidence rate of 34.3 (per 1000 person-years) of all-cause mortality in adults with PN but no diabetes (Hicks et al., 2021), PN can also severely impact the quality of life of patients. The risk factors for PN in adults without diabetes, especially the socioeconomic risk factors such veteran/military status, as it moderates the effect of PN on overall mortality remains largely uncharacterized. In particular, there are no published studies that have examined whether veteran/military status moderates the effect of PN on overall mortality. This

made it imperative to conduct this study which examined whether veteran/military status moderated the effect of PN on overall mortality in adults without diabetes in the United States, while controlling for age, gender, and ethnicity.

- **Research question:** Does veteran/military status moderate the effect of PN on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity?
- **Null hypothesis:** Veteran/military status does not moderate the effect of PN on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity.
- **Alternative hypothesis:** Veteran/military status moderates the effect of PN on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity.
- **Nature of study and design:** This is a quantitative research study, with a longitudinal design (Frankfort-Nachmias & Leon-Guerrero, 2018).
- **Source of data:** The secondary data for this study was from the NHANES 1999 to 2015 dataset. The justification for choosing the 1999 to 2015 dataset was that the main independent variable in this study, PN—an important public health problem that is associated with mortality and significant morbidity among adults in the United States (Hicks et al., 2021), was the only studied

and was only available in the 1999 to 2004 NHANES dataset. It was not available in the other NHANES dataset years. The only way I could examine this variable was to include the 1999 to 2004 NHANES dataset. Similarly, the dependent or outcome variable in my study – overall mortality, was only documented in the December 2015 NHANES mortality follow-up dataset. The only way I could examine this variable and link it with my main independent variable – PN, was to include the 2015 NHANES dataset.

Manuscript 3

- **Specific problem:** The specific problem is the substantial burden of PN and the associated cardiovascular mortality among adults without diabetes in the United States. PN results in decreased lower-extremity sensation that can lead to serious complications in affected adults (Hicks et al., 2021). Unfortunately, PN is common and has been found to be independently associated with mortality in the U.S. population, even in the absence of diabetes (Hicks et al., 2021). The prevalence of PN in some studies is as high as 10.4% for middle-aged (40-69 years) and 26.8% for older (> 70 years) adults in the U.S. population. This suggest that decreased sensation in the foot, or PN, may be an underrecognized risk factor for death among the adult population in the United States (Hicks et al., 2021). There is a strong association between PN and cardiovascular mortality in adults without diabetes (Hicks et al., 2021), however, the socioeconomic risk factors as they moderate the effect of PN on cardiovascular mortality remain largely uncharacterized. In particular, there

are no published studies that have examined whether health insurance status moderates the effect of PN on cardiovascular mortality. This made it imperative to conduct this study which examined whether health insurance status moderated the effect of PN on cardiovascular mortality in adults without diabetes in the United States, while controlling for age, gender, and ethnicity.

- **Research question:** Does health insurance status moderate the effect of PN on cardiovascular mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity?
- **Null hypothesis:** Health insurance status does not moderate the effect of PN on cardiovascular mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity.
- **Alternative hypothesis:** Health insurance status moderates the effect of PN on cardiovascular mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity
- **Nature of study and design:** This is a quantitative research study, with a longitudinal design (Frankfort-Nachmias & Leon-Guerrero, 2018).
- **Source of data:** The secondary data for this study was from the NHANES 1999 to 2015 dataset. The justification for choosing the 1999 to 2015 dataset

was that the main independent variable in this study, PN—an important public health problem that is associated with mortality and significant morbidity among adults in the United States (Hicks et al., 2021), was only studied and is only available in the 1999 to 2004 NHANES dataset. It was not available in the other NHANES dataset years. The only way I could examine this variable was to include the 1999 to 2004 NHANES dataset. Similarly, the dependent or outcome variable in my study – cardiovascular mortality, was only documented in the December 2015 NHANES mortality follow-up dataset. The only way I could examine this variable and link it with my main independent variable – PN, was to include the 2015 NHANES dataset.

Significance

This study is significant in that it provided useful insights into how poverty income ratio and veteran/military status moderated the effect of PN on overall mortality and health insurance moderated the effect of PN on cardiovascular mortality respectively. Since PN is an important public health problem that causes significant morbidity and mortality among adults in the United States (Hicks et al., 2021), it was critical to determine whether these socioeconomic factors (poverty income ratio, veteran/military status, and health insurance) moderated the effect of PN on overall and cardiovascular mortality in adults without diabetes. The magnitude of how each of these three independent variables respectively moderated the effect of the main independent variable, PN, on overall and cardiovascular mortality, might enable relevant stakeholders in the United States, such as the government, healthcare providers, health insurance companies,

veterans/military associations, nongovernment agencies, and patients, to institute preventative measures and policies to mitigate any adverse associations caused by these socioeconomic factors on the effect of PN on overall and cardiovascular mortality. For example, economic policies aimed at reducing inequality and improving income in the society, targeted and aggressive screening of veterans/military personnel for PN by healthcare professionals, and universal insurance coverage for the most vulnerable in the society, are just some of the measures that could be taken to mitigate the adverse moderating effects of PN on overall and cardiovascular mortality among adults without diabetes in the United States. Instituting these measures could bring about positive social change by improving the health outcomes of adults without diabetes who suffer from PN.

Summary

Globally, PN is an important public health problem and is associated with significant overall and cardiovascular mortality, especially in adults without diabetes in the United States (Hicks et al., 2021). While PN has been well studied among adults with diabetes in the United States, the risk factors for PN in adults without diabetes, especially the socioeconomic risk factors as they moderate the effect of PN on overall and cardiovascular mortality remain largely uncharacterized. Therefore, it was important to examine whether poverty income ratio and veteran/military status moderated the effect of PN on overall mortality, and whether health insurance status moderated the effect of PN on cardiovascular mortality respectively.

Part 2: Manuscripts

Manuscript 1

Poverty Income Ratio as a Moderator of Peripheral Neuropathy on Overall Mortality in Non-Diabetic Adults

by

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Outlet for Manuscript

The intended journal for the publication of this manuscript is the *American Journal of Public Health* (https://www.apha.org/AJPH). The formatting expectations of this journal are that the contents of this manuscript should conform to a scholarly writing and the guidelines recommended by the seventh edition of *Publication Manual of the American Psychological Association* (APA). The *American Journal of Public Health* publishes a variety of articles on public health issues, health, and medical, nursing, and allied health. The contents of this manuscript are mainly of the public health discipline and also partly health and medical issues. Hence, the *American Journal of Public Health* aligns with the contents of this manuscript.

Abstract

Peripheral neuropathy (PN) is a disorder of the peripheral nervous system associated with significant morbidity and mortality. PN is common among U.S. adults, even in the absence of diabetes, where it presents with sensory symptoms such as tingling, numbness, burning, pain, and sensory ataxia. Motor symptoms include muscle cramps, stiffness, weakness, and wasting. The overall prevalence of PN in the United States is 13.5% in adults with diabetes and 11.6% in adults without diabetes, clearly indicating that PN is a significant public health problem among U.S. adults. Poverty and low income have been associated with poor health outcomes. There are no published studies examining whether poverty income ratio moderates the effect of PN on overall mortality among U.S. adults without diabetes. Using the socioecological model as the theoretical framework, the purpose of this longitudinal study was to examine whether poverty income ratio moderated the effect of PN on overall mortality. Secondary data from the NHANES 1999-2015 dataset were analyzed using complex sample Cox regression analysis with the threshold for statistical significance taken at $p < .05$. Poverty income ratio significantly moderated the effect of PN in either foot ($p < .001$). Participants without diabetes but who were less poor (with a reduced poverty income ratio of 0–1.99), had a reduced hazard risk for overall mortality when diagnosed with PN in either foot. This study is significant in its implications for positive social change. The results can enable relevant stakeholders to institute policies to reduce income inequality, promote gainful employment, and institute appropriate targeted screening for PN among U.S. adults without diabetes who are poor and are of low-income status.

Introduction

There is a significant burden of PN with an associated overall mortality among adults without diabetes in the United States (Hicks et al., 2021). PN is very prevalent, particularly in the older population (Callaghan et al., 2018) and presents with significant morbidity that reduces the quality of life (QoL) of affected patients or individuals (Girach et al., 2019). Approximately two-thirds of patients suffering from PN experience neuropathic pain which can be so disabling as to have a detrimental effect on their mental health and eventually culminating in a reduced QoL (Girach et al., 2019). Moreover, PN is such a prevalent disease, especially among adults and it presents both diagnostic and therapeutic challenge to physicians and other healthcare providers (Callaghan et al., 2018). It is estimated that the prevalence of PN in some studies is as high as 10.4% for middle-aged (40-69 years) and 26.8% for older (> 70 years) adults in the U.S. population (Hicks et al., 2021). Clearly, these statistics indicate that PN is a significant public health problem among adults in the United States. However, many of the studies that have examined the risk factors for PN in the United States have mainly examined patients or adults with diabetes. In particular, there are no published studies on how poverty income ratio moderates the effect of PN on overall mortality. This situation has created a social problem, as it has been shown by Hicks et al. (2021) that the all-cause or overall mortality associated with PN, even in adults without diabetes, is high at 34.3 (per 1000 person-years), hence the justification for conducting this research in which I examined whether poverty income ratio moderated the effect of PN on overall mortality.

Poverty and low income have been associated with poor health outcomes (Oshio, 2019). Lower income will likely reduce an individual's opportunity to purchase essentials for good health, such as sufficient quantities of high-quality food, medications, and other healthcare products (Oshio, 2019). Furthermore, individuals with lower incomes tend to exhibit higher odds of behavioral risk factors such as smoking, physical inactivity, and obesity, which increases their poor health outcomes (Oshio, 2019). It is also argued that individuals with lower incomes tend to have lower educational achievements and less social capital and live in less affluent neighborhoods, where crime and other life stressors may be prevalent (Oshio, 2019). All these factors are likely to culminate in poor health outcomes. In addition, poor health can also contribute to low income or poverty by limiting an individual's ability to engage in productive employment and reducing economic opportunities. As Oshio (2019) opined, this two-way causal relationship between income and health highlights the importance of health-related measures to address the issue of income poverty in the wider society. Hence, there is a justification for this research study in which I examined whether poverty income ratio moderated the effect of peripheral neuropathy on overall mortality among adults without diabetes in the United States.

Significance/Importance

Peripheral neuropathy (PN) is a chronic debilitating disorder that often develops insidiously, making early diagnosis and management difficult for physicians and other healthcare providers (Brown et al., 2017). Globally, PN has been associated with significant mortality and morbidity (Brown et al., 2017); in the United States, PN also

causes significant morbidity and mortality among adults even without diabetes (Hicks et al. (2021). Patients suffering from PN experience poor QoL which can be detrimental to their mental health, in addition to the neuropathic symptoms of pain, muscle cramps, numbness, falls, weakness, and stiffness, that they experience (Girach et al., 2019). This study is significant in that it highlighted that poverty income ratio moderated the effect of PN on overall mortality. Poverty and poor income have been linked to poor health outcomes (Oshio, 2019); however, what was not known before now was whether poverty income ratio moderated the effect of PN on overall mortality. Since PN develops insidiously and is often difficult to diagnose, knowing whether poverty income ratio moderates the effect of PN on overall mortality will enable relevant stakeholders to institute targeted screening for individuals with low income and in the poverty bracket.

The targeted screening of these individuals will likely result in early and timely diagnosis of PN, and allow for more positive health outcomes, which can bring about the desired positive social change for these individuals. Furthermore, this study is significant for the discipline of public health, as it would fill a huge gap in the knowledge on the topic of whether poverty income ratio moderates the effect of PN on overall mortality. Presently, there are no published studies in literature that have examined this topic.

Theoretical Framework

The theory of the socioecological model was first introduced by Urie Bronfenbrenner in the 1970s (Kilanowski, 2017). Bronfenbrenner proposed that the nature of individuals' interaction with their physical and sociocultural environments can impact health and lead to the development of diseases (Kilanowski, 2017). The revised

constructs of the socioecological model are individual, network, community, and structural (Cowan et al., 2021). It implies that factors or influences operating at every level or construct of this theoretical framework can impact on an individual's health and eventually lead to the development of diseases such as PN or even play a role in determining whether poverty income ratio moderates the effect of PN on overall mortality. As Cowan et al. (2021) highlighted, the influence of the structural construct or structural level factors are exerted through laws and policies, as well as society and economics. It is already well established that economic growth, which is determined in part by economic policies, has a profound effect on poverty and peoples' income (Islam et al., 2017).

The socioecological model was applied to organize the discussion in this study. The poverty income ratio can also be influenced by factors acting at the structural level. These factors are mediated through laws and policies, as well as society and economics. A viable economy brought about by the right set of economic policies or laws, will likely result in more gainful employment opportunities for the people, thereby increasing their purchasing power, and reducing or improving their poverty income ratio, with the result of better health outcomes. The main independent variable in my study, peripheral neuropathy, was explained by the structural construct. Evidence from available studies suggests that peripheral neuropathy develops as a result of multiple risk factors ranging from chronic non-communicable diseases to exposure to environmental chemicals, herbicides or toxins, and infectious diseases. The structural construct emphasizes economic policies or laws, which can enable individuals to gain access to adequate

medical treatment and also protect them from exposure to noxious or toxic environmental agents; in addition, the right set of public health policies or laws can protect individuals from exposure to infectious diseases and ensure prompt treatment of such infectious diseases during an outbreak. All these measures can influence the development of peripheral neuropathy.

This research study makes an original contribution to the discipline of public health as there are presently no published studies in the literature that have examined whether poverty income ratio moderates the effect of PN on overall mortality. Furthermore, poverty and income have been associated with health outcomes in many societies around the world. Hence, this research study further makes an original contribution to the discipline as it highlighted that these important social determinants of health moderated the effect of PN on overall mortality.

The purpose of this quantitative secondary data analysis study was to examine whether poverty income ratio moderated any effect of PN on overall mortality among an adult population not suffering from diabetes in the United States, while controlling for age, gender, and ethnicity.

Relevant Scholarship/Literature Review

Part of my search strategy for this literature review included employing the following search terms, words and/or phrases: *peripheral neuropathy; risk factors for peripheral neuropathy; social determinants of peripheral neuropathy; peripheral neuropathy in non-diabetics; peripheral neuropathy in the United States; peripheral neuropathy and overall mortality; effect of poverty and income on health outcomes; effect*

of poverty on peripheral neuropathy; effect of income on peripheral neuropathy peripheral neuropathy in developed countries; peripheral neuropathy in developing countries. The search was limited to articles or text written in English from the following search engines or sources: Google and Google Scholar, Walden University library, ProQuest, SAGE Premier, PubMed, MEDLINE, CINHAL Plus, and Science Direct Database.

In the literature review, I included background information on peripheral neuropathy in general and its epidemiology, especially the non-diabetic causes. In addition, I examined the problem of peripheral neuropathy within a global context, looking at patterns of distribution and epidemiology in developed and developing countries. Furthermore, I examined the socioeconomic risk factors for peripheral neuropathy among adults without diabetes, and I tried to demonstrate a logical connection between what is known and what was studied—the gap in research. I synthesized the relevant evidence and research on the topic of peripheral neuropathy by various researchers. I also looked at the clinical consequences of peripheral neuropathy, which usually contributed to the morbidity and mortality of individuals not suffering from diabetes. In addition, I examined how poverty and income could impact health outcomes, and the association between these social determinants of health and the possible development of peripheral neuropathy.

Background Information, Global Trends and Epidemiology

Understanding the background information and the epidemiology of PN especially in non-diabetic individuals, is an important aspect of this study. This study

focused mainly on whether poverty income ratio moderated the effect of PN on overall mortality in non-diabetic adults in the United States. Hence, having a good understanding of the non-diabetic causes among these individuals would be a good starting point. PN is an important public health condition with a prevalence of almost 15% in the adult population of age over 40 years in the United States (Valentine, 2019). Globally, PN is among the most common neurological diseases, with an estimated incidence of 77/100,000 inhabitants per year and a prevalence of 1%–12% in all age groups (Lehmann et al., 2020). By definition, peripheral neuropathies encompass all conditions that cause damage to the peripheral nervous system (PNS), which may include mechanical, toxic, and metabolic causes (Szewczyk et al., 2021). Furthermore, the clinical symptoms exhibited by sufferers of this chronic debilitating disease depend on its severity, distribution, affected structure of the nerve cell, as well as the type of affected neurons (Szewczyk et al., 2021). Because of this, multiple classifications, or types of PN can be encountered in clinical practice, with an overlap between the various types. According to Szewczyk et al. (2021), the prevalence of PN is slightly higher in women than men, and the occurrence of PN may be influenced by the type of work performed (Szewczyk et al., 2021).

Globally, the prevalence of PN also varies considerably from one geographical location to another. As Hanewinckel et al. (2016, as cited in Szewczyk et al., 2021) highlighted, African and Middle Eastern countries generally have a low prevalence of PN of 0.8 to 2.5 per 1000 among adults, when compared to a prevalence of 7.3 to 32.5 per 1000 among adults in Europe. It is argued that some of the differences in prevalence rates

of PN observed in these different geographical locations could be partly explained by differences in assessment protocol for PN.

In the general population, it is estimated that the average prevalence of PN ranges from 1% to 3% (Szewczyk et al., 2021), whereas the prevalence of PN is slightly higher at 7% among the elderly (Szewczyk et al., 2021). The prevalence of PN also varies in the developed or industrialized countries. In comparing the prevalence of PN in some of the developed countries, Szewczyk et al. (2021) highlighted that the prevalence of PN in the Netherlands is 5.5% in comparison to a prevalence of 3.9% among the U.S. population.

Szewczyk et al. (2021) opined that the prevalence of PN is influenced by socioeconomic status, the population structure, and other risk factors. However, the authors did not examine or highlight whether an important socioeconomic status such as poverty income ratio moderated the effect of PN on overall mortality. Hence, this is the justification for this study in which I examined whether poverty income ratio moderated the effect of PN on overall mortality.

Peripheral Neuropathy in People Without Diabetes

While diabetes mellitus remains the most common cause of PN worldwide, the development of PN may have many other different causes which can lead to generalized, and sometimes to isolated PN (Roth et al., 2021). According to Roth et al., normal aging has been associated with the development of some form of PN in the population. As earlier pointed out by Szewczyk et al. (2021), the prevalence of PN is slightly higher at 7% among the elderly. Although oxidative stress has been postulated as a possible mechanism or pathogenesis for PN (Mallet et al., 2020), it is argued that the genesis of

PN is multifactorial and not fully explained (Roth et al., 2021). However, hyperglycemia, dyslipidemia, inflammation and immune responses, and macro-and microvascular diseases, along with a host of other pathological conditions, have been proposed as possible mechanisms for the development of PN by Roth et al. I discussed in detail infection-related and autoimmune causes of PN, while at the same time, highlighted the top 3 non-diabetic causes of PN.

Infection-related PN is an important cause of non-diabetic PN (Roth et al., 2021). A wide range of various infectious diseases caused by viruses and bacteria lead to different levels of peripheral nerve dysfunction. These infectious diseases include Varicella-zoster virus infection, which belongs to the human herpesvirus group that is responsible for the primary varicella infection (Roth et al., 2021). After the acute infection has subsided, the virus continues to live in the peripheral ganglia, where it can be reactivated spontaneously or after following other triggers, to cause herpes zoster; herpes zoster is usually accompanied by PN with symptoms such as pain, numbness, and paresthesia (Roth et al., 2021).

Chagas disease, caused by the hemoflagellate parasite, Trypanosoma cruzi (Roth et al., 2021) is another important cause of PN. The disease is endemic in Central and South America, and it is caused through bites from Triatominae bugs (Roth et al., 2021). The chronic phase of this disease is typified by the destruction of ganglion cells both in the central and peripheral nervous system, resulting in the development of PN, among other disorders (Roth et al., 2021).

While Guillain Barre syndrome (GBS) is sometimes regarded as an autoimmune disease, the exact mechanism is unknown. As Roth et al. (2021) highlighted, 50% to 70% of cases of GBS usually follow a respiratory infection, gastrointestinal infection, or any other immune stimulus that induces autoimmune attacks against the peripheral nerves. The development of PN in these patients is accompanied by symptoms such as symmetric weakness, paresthesia, numbness, and pain (Roth et al., 2021).

Autoimmune or inflammation related PN is an important cause of PN (Roth et al., 2021). Autoimmune PN encompasses systemic autoimmune diseases, autoimmune disorders which specifically cause damage to peripheral nerves, or malignancies (Roth et al., 2021). In cases of autoimmune PN, damage to the peripheral nerves occur through autoantibodies which may be directed against membrane receptors of peripheral nerves directed against cell surface glycoproteins, or in the case of cancers or paraneoplastic, such autoantibodies are directed against intracellular onconeural antigens (Roth et al., 2021). In addition, the higher the level of antibodies formed, the more severe the level of PN. However, paraneoplastic or cancer antibodies tend to correlate more with a unique cancer form than to a specific neuropathy, and their levels do not correlate with the degree or severity of the PN (Roth et al., 2021).

While non-diabetic PN has a varied etiology, idiopathic PN, CIPN, and HIV-related PN are among the top 3 causes of non-diabetic PN. According to FFPN (2022), idiopathic PN occurs for no reason; it usually affects people over 60 years old and can sometimes slowly progress or doesn’t progress at all after the initial onset. CIPN in particular, is a common and significant clinical entity (Colvin, 2019). It arises from

treatment with many commonly used anticancer agents, which are potentially neurotoxic, with increasing impact on oncological treatments. Acute CIPN is believed to occur during chemotherapy, and unfortunately, this situation sometimes requires either a reduction in the dosage of the anticancer agent or cessation (Colvin, 2019), which can impact on the survival of patients. HIV-related PN is an important clinical entity which has been documented among HIV infected patients undergoing long-term treatment with antiviral drugs (Lu et al., 2021). Three mechanisms have been identified in the development of HIV-related PN. According to Lu et al., injury caused by the HIV envelope protein (Gp 120) on the peripheral nerves, central and peripheral sensitization, as well as the side effects of antiretroviral therapy all lead to the development of neuroinflammation and PN.

Alcohol use or abuse has been linked to the development of PN. According to Julian et al. (2019), the prevalence of Alcohol-related PN amongst chronic users or abusers is quite high, estimated at 46.3% (95% CI [35.7, 57.3]), when confirmed by nerve conduction studies. The pattern of PN developed in alcohol-abusers is a predominantly progressive damage of the sensory axons in a length-dependent manner (Julian et al., 2019); in addition, the development of alcohol-related PN is dependent on the total lifetime amount of ethanol consumed, male gender, genetics and the type of alcohol consumed (Julian et al., 2019). It is presently unclear what pathogenetic pathways lead to the development of PN in chronic alcohol users; hence, it is unknown whether the direct toxic effects of ethanol or another currently unidentified agent is directly linked to damage of the peripheral nerves. However, according to Julian et al., based on the

available limited data, the associated deficiency of the B-vitamins, inclusive of thiamine, observed in chronic alcohol users could be responsible for the development of PN.

Toxic PN is another important form of non-diabetic or acquired PN. This type of PN is caused by various xenobiotics such as drugs, chemicals, pesticides, and carcinogens that damage components of the peripheral nervous system (Valentine, 2020). The various causes of toxic PN can be classified as environmental, occupational, recreational, or iatrogenic (Valentine, 2020). In wealthy or developed countries, drug toxicity associated with chemotherapy has been identified as the most common cause of toxic PN (Valentine, 2020); however, in developing countries, occupational and environmental exposures to xenobiotics such as arsenic, lead, mercury, and organophosphates found in various pesticides, insecticides, and herbicides, are the leading causes toxic PN (Valentine, 2020). A possible reason why occupational exposures to these xenobiotics account for the development of PN in many developing countries is that there is less strict monitoring associated with many manufacturing processes, which generate many of these neurotoxicants. Generally speaking, these xenobiotics cause damage to the neuronal perikaryons, axons, the Schwan cell, or the synapse (Valentine, 2020). The damage to the peripheral nerves by these neurotoxicants is dose dependent, symmetrical, and reversible, provided there is adequate time following exposure to such agents (Valentine, 2020); in addition, individuals exposed to these agents present with numbness, paresthesia, or weakness in a characteristic stocking glove distribution (Valentine, 2020).

Fluoroquinolone is an antibiotic that is widely used worldwide and is associated with the development of PN (Morales et al., 2019). In a nested case-control study that included 5357 incident PN cases and 17, 285 matched controls, Morales et al. highlighted that exposure or use of oral fluoroquinolone was associated with an increased relative incidence of PN, when compared with non-exposure to fluoroquinolone (adjusted incident rate ratio, 1.47; 95% CI [1.13, 1.92]). The risk of developing PN following the use of fluoroquinolone antibiotic was found to have increased by an additional 3% following each day of the antibiotic use, and the risk persisted for up to six months following exposure to the antibiotic (Morales et al., 2019). In comparison, Morales et al. did not find any significant increased risk in the development of PN with exposure to or use of oral amoxicillin-clavulanate, another widely used antibiotic. These findings suggest that health care providers, particularly physicians, should consider these potential side effects when prescribing fluoroquinolone antibiotics.

Monoclonal gammopathy-associated PN is another important non-diabetic cause of PN. Monoclonal gammopathies encompass a spectrum of disorders that involves the secretion of a monoclonal immunoglobulin known as a monoclonal (M) protein (Chaudhry et al., 2017). The different categories of monoclonal gammopathy-associated PN include monoclonal gammopathy of undetermined significance (MGUS), which can either be IgM, non-IgM, IgG, or IgA (Chaudhry et al., 2017). As Chaudhry et al. highlighted, other categories of monoclonal gammopathy-associated PN are multiple myeloma (which includes smoldering multiple myeloma), Waldenstrom macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, M

protein, and skin changes) syndrome, systemic immunoglobulin light chain amyloidosis, and coincidental PN in patients with a monoclonal protein. While the pathological pathways associated with monoclonal gammopathy-associated PN is not clearly understood, Chaudhry et al. (2017) argued that Waldenstrom macroglobulinemia and IgM MGUS-associated PN might be associated with demyelination and widening of the myelin lamellae respectively. Furthermore, demyelination has also been associated with PN in some patients with IgG MGUS (Chaudhry et al., 2017), while in a significant proportion of patients with IgM monoclonal gammopathy-associated PN, Chaudhry et al. (2017) found that the pathological pathways involved the binding of the M protein to myelin associated glycoprotein (MAG) in the peripheral nerves.

Hereditary PN is also an important cause of non-diabetic peripheral neuropathy. As Eggermann et al. (2018) highlighted, hereditary PN constitutes a significant group of genetic diseases, and the overall prevalence of hereditary PN is estimated at 1 in 2500 (Eggermann et al., 2018). The use of next-generation sequencing (NGS) has improved the detection of many hitherto unknown involved genes and genetic defects that cause PN (Eggermann et al., 2018). According to Eggermann et al. (2018), the forms of hereditary PN that have been identified include Charcot-Marie-Tooth disease (CMT, also referred to as hereditary motor sensory neuropathy, HMSN), the hereditary sensory and autonomic neuropathies (HSAN, also referred to as hereditary sensory neuropathy, HSN), the hereditary motor neuropathies (HMN), and small fiber neuropathies (SFN). Generally speaking, mutations have been identified in more than 100 genes which cause hereditary PN (Eggermann et al., 2018).

Some socioeconomic factors have been implicated as possible causes of PN. However, because many studies on PN have been restricted to populations with diabetes, this has resulted in limited evidence of the potential contribution of some socioeconomic and psychosocial risk factors to the development of PN in non-diabetic populations. Dusendang et al. (2019) highlighted that perceived discrimination in midlife was associated with the development of PN later in life. According to Dusendang et al. in their study, women who reported perceived discrimination had 29% higher odds of PN when compared with women who did not report perceived discrimination (95% CI [1.01, 1.66]). In addition, the authors highlighted that 30% of total effect of discrimination on PN was mediated indirectly by the participant's body mass index (BMI). Dusendang et al. argued that discrimination was a form of chronic stressor, and the pathogenesis of PN in individuals who had experienced discrimination was probably related to the release of proinflammatory substances in the body, with associated dysregulation of the cardiovascular and metabolic functions, leading to the damage of the peripheral nerves.

Low socioeconomic status, irrespective of the participants' diabetic status, was also found to be associated with prevalent PN in the study by Dusendang et al. (2019). Most of these women from low socioeconomic status also reported an associated financial strain. As Dusendang et al. highlighted, the combination of low socioeconomic status and the associated financial strain could result in increased secretion of stress hormones which ultimately could lead to an increase in allostatic load – the cumulative effects that chronic stress has on mental and physical health. As Dusendang et al. opined, one of the pathophysiologic consequences of this increase in allostatic load is the

development of PN. In addition, as Dusendang et al. argued, people of low socioeconomic status generally have poorer nutritional status, engage is less physical activity or exercise, tend to have more exposure to environmental pollutants or toxins, and usually have less access to quality health care, when compared to people of higher socioeconomic status. These situations increase the risk of development of PN in people of low socioeconomic status. Furthermore, even people of low socioeconomic status who seek care for PN symptoms may be less likely to receive appropriate and proper diagnostic workup based on their socioeconomic status. This situation may lead to poorer management of their PN and further exacerbate their medical condition.

Poor housing, homelessness, and disadvantaged neighborhood conditions have all been linked to poorer health outcomes, such as the development of PN, infectious diseases, and other chronic medical conditions (Boch et al., 2020). The exact pathways by which poor or sub-standard housing is associated with the development of PN is not clearly understood. However, as Valentine (2020) highlighted, the risk of environmental exposures to various xenobiotics, particularly lead, is higher is people living in poor or sus-standard housing units. Chronic exposure to lead has been associated with the development of PN (Valentine, 2020). According to the United States Department of Housing and Urban Development (2017, as cited in Boch et al., 2020), almost 8.3 million very low-income rental households in the United States had worst case needs and the occupants were regarded as living in severely inadequate conditions. Furthermore, Raymond et al. (2011, as cited in Boch et al., 2020), noted that 5.8 million residencies in the United States were considered inadequate based on significant deficiencies in

plumbing, heating, electricity, and upkeep (including exposures to xenobiotics such as lead). Living in these poor and sub-standard housing units, with the associated increased exposure to various xenobiotics, can lead to the development of various chronic diseases such as PN.

Synthesis of Research Findings

Roth et al. (2021) found that normal aging was associated with the development of PN; however, the authors pointed out in their systematic review of the literature that the etiology of PN was multifactorial and not fully explained by one mechanism. While Roth et al. proposed a multicausal mechanism for the etiopathogenesis of PN, they however highlighted some major specific causes for PN which include diabetes, diseases involving tissues deposits, infections, autoimmunity, cancers or malignancies, and metabolic diseases. Roth et al. did not examine whether important social determinants of health, such as poverty income ratio moderated the effect of PN on overall mortality, although PN has been linked to overall mortality in adults.

While Szewczyk et al. (2021) highlighted in their retrospective cross-sectional study that the prevalence of PN is slightly higher at 7% among the elderly, the authors also opined that women have a slightly higher prevalence of PN when compared to men. In addition, Szewczyk et al. suggested that one's socioeconomic status, occupation, and the population structure were all associated with the development of PN. Of particular note was the statistically significant finding ($p < 0.05$) of the association of the place of residence and gender, and the development of PN. Szewczyk et al. highlighted that more affected women live in the urban areas, whereas more men diagnosed with PN inhabit the

rural areas. The authors suggested that the statistically significant differences could be partly explained by the work performed, as well as the external or internal factors or mechanisms that influence the manifestation of PN. However, the authors did not specifically examine whether poverty income ratio, an important social determinant of health, could moderate the effect of PN on overall mortality.

Julian et al. (2019) in their systematic review of the literature, highlighted a high prevalence of PN of 43% (95% CI [35.7,57.3]) particularly amongst chronic alcohol consumers or abusers. While the authors posited that the pathogenetic pathways to the development of PN in chronic alcohol consumers is not clearly understood, Julian et al. highlighted that the development of PN in such individuals is dependent on the total lifetime amount of alcohol consumed, male gender, and probably some associated genetic factors. However, although many studies have found an association between low or disadvantaged socioeconomic status and alcohol use disorders, the authors did not examine whether poverty income ratio moderated the effect of PN on overall mortality.

In a systematic review of literature, Valentine (2020) highlighted various xenobiotics or peripheral nervous system toxicants that can lead to the development of PN, if an individual is exposed to such xenobiotics. Such toxic agents could be classified as environmental, occupational recreational, or iatrogenic. Prominent among these agents are drug toxicity, especially chemotherapeutic agents, arsenic, lead, mercury, and organophosphates, which are constituents of many commonly used herbicides and pesticides. All these agents can lead to the development of PN. However, Valentine did

not examine whether poverty income ratio moderated the effect of PN on overall mortality.

Chaudry et al. (2017) in their systematic review, highlighted that PN can occur in patients suffering from various plasma cell disorders, ranging from the premalignant MGUS stage to the readily apparent malignant stages of multiple myeloma and Waldenstrom macroglobulinemia. The authors did not examine whether poverty income ratio, an important social determinant of health, could contribute to the development of PN in patients suffering from these various plasma cell disorders, nor did they examine whether poverty income ratio moderates the effect of PN on overall mortality. While Eggermann et al. (2018) in their systematic review of the literature highlighted that hereditary peripheral neuropathies constitute a large group of genetic disorders and are important causes of non-diabetic neuropathy, the authors did not examine whether poverty income ratio moderated the effect of PN on overall mortality.

Dusendang et al. (2019) in their national longitudinal study of Women's Health, highlighted that woman who had experienced perceived discrimination in midlife had 29% higher odds of developing PN, when compared to women who did not report perceived discrimination. Furthermore, Dusendang et al. highlighted that each increasing level of perceived discrimination in midlife was associated with 43% higher odds of developing PN. However, the authors did not examine whether poverty income ratio moderated the effect of PN on overall mortality. Boch et al. (2020) in their national survey found that poor housing, homelessness, and disadvantaged neighborhood conditions are associated with poor health outcomes such as the development of PN.

While the exact pathways by which poor or substandard housing is associated with the development of PN is not fully understood, it is postulated that the risk of environmental exposures to various xenobiotics, particularly lead, is increased in people living in poor or sub-standard housing units. However, while poor or sub-standard housing may be linked to poverty, the authors did not specifically examine whether poverty income ratio moderated the effect of PN on overall mortality.

Logical Connection Between What is Known and What Needs to be Studied.

From this literature review, the various important non-diabetic causes of PN were clearly highlighted. In addition, the important risk factors for PN were also highlighted. However, an important gap in literature still existed, on whether poverty income ratio moderated the effect of PN on overall mortality. Poverty has been linked to poor health outcomes, such as the development of PN. Similarly, PN has been linked to overall mortality. What is however not known is whether poverty income ratio moderated the effect of PN on overall mortality.

Research Questions and Design

Research Question: Does poverty income ratio moderate the effect of peripheral neuropathy on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity?

Null Hypothesis: Poverty income ratio does not moderate the effect of peripheral neuropathy on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity.

Alternative Hypothesis: Poverty income ratio does moderate the effect of peripheral neuropathy on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity.

Rationale for Research Question

The rationale for choosing this research question was that there is a substantial burden of PN and the associated overall mortality among adults without diabetes in the United States (Hicks et al., 2021). However, there was a huge gap in the literature as to whether poverty income ratio moderated the effect of PN on overall mortality among adults without diabetes in the United States.

Research Design

The specific quantitative research design for this study was a longitudinal design (Frankfort-Nachmias & Leon-Guerrero, 2018), with the outcome variable, overall mortality, examined in the follow-up mortality dataset of 2015, following the initial diagnosis of PN in the 1999-2000 NHANES dataset. This quantitative analysis helped determine whether poverty income ratio (independent variable) moderated the effect of PN (main independent variable) on overall mortality (dependent variable), while controlling or adjusting for age, gender, and ethnicity (covariates).

Approach Used to Address the Research Problem

The epistemological approach I employed in addressing this research problem was that of positivism (Park et al., 2019). The approach of positivism relies on the hypothetico-deductive method to ascertain or verify priori hypotheses that are often stated quantitatively (Park et al., 2019). The hypothetico-deductive method is a circular

process that starts with theory from the literature (Park et al., 2019). This enables the researcher to build or construct testable hypotheses, design an experiment through operationalizing variables, and finally conduct an empirical study based on experimentation (Park et al., 2019). The findings from such a study are employed to help inform theory, bring about a desired positive social change, and contribute to the literature, thereby completing the circular process (Park et al., 2019): theory – hypothesis – operationalizing variables – experimentation – theory (Park et al., 2019). The positivist paradigm or approach is based on the notion that knowledge can and must be developed objectively, without the values or ideas of the researcher or participants influencing its development (Park et al., 2019).

Methods

Participants

The target population for this study were adults who did not suffer from diabetes in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2015 dataset.

Sample and Power

This study employed a secondary dataset from the NHANES 1999 to 2015 dataset. The sampling strategy used was simple random sampling (Frankfort-Nachmias & Leon-Guerrero, 2018). Participants who satisfied the inclusion criteria (all adults without diabetes and who had the complete set of the variables of interest in this study) were randomly recruited into the study. This sampling strategy gave each of the participants an

equal chance of being selected into the study (Frankfort-Nachmias & Leon-Guerrero, 2018).

To determine the appropriate sample size for this study, G* Power 3.1.9.7 (Faul et al., 2009) was employed. As Bhandari (2022) highlighted, the criteria for choosing effect size prior to estimating sample size, depends on what has been documented on previous research studies on the topic of interest. However, since there were no published studies on whether poverty income ratio moderated the effect of PN on overall mortality, the effect size f^2 was set at medium value (0.15) in G* Power (Faul et al., 2009). F test was selected along with the statistical test of: Cox Regression, Fixed model, R^2 deviation from zero in G* Power (Faul et al., 2009). Since there were six predictor variables in this study (peripheral neuropathy, poverty income ratio, diabetes, age, gender, and ethnicity), and with the *p* value set at 0.05 and power set at 80% in G* Power (Faul et al., 2009, the sample size calculated was 98 participants. This was the minimum sample size required for this study.

Variables/Sources of Data

The main independent variable in this study was PN, the independent variable or moderating variable was poverty income ratio, the dependent variable was overall mortality, while the covariates were age, gender, and ethnicity. The participants were stratified according to their diabetes status. According to the alternative hypothesis in this study, it was expected that the independent variable (poverty income level) would moderate the association between PN and overall mortality, while adding the covariates could increase the accuracy of the results from the research study. The sources of the data

used to operationalize the variables were the NHANES 1999 to 2000 and the 2015 follow-up mortality datasets.

The main independent variable was PN, a Categorical Nominal variable, and coded as: None = 1, Insensate site group = 2. The other independent variable was poverty income ratio, a Categorical Nominal variable, and coded as 0 to 1.99 =1, 2 through highest = 2. In addition, Diabetes, a Categorical Nominal variable, coded as Yes = 1 and No = 2. The covariates were age (years), a Categorical Nominal variable, and coded as: 0 to 84 = 1, $\geq$ 85 = 2; Gender, a Categorical Nominal variable, and coded as: Male = 1, Female = 2, and Ethnicity, a Categorical Nominal variable, and coded as: Non-Hispanic White = 1, Non-Hispanic Black = 2, Mexican American = 3, Other Race – Including Multi-Racial = 4, Other Hispanic = 5. The dependent variable was overall mortality, a Categorical Nominal variable, and coded as 0 = Assumed alive, 1 = Assumed deceased.

Instrumentation or Measures

Secondary data from the NHANES 1999 to 2015 dataset were used in this study. This data was collected by the Centers for Disease Control and Prevention, and hence, the data was assumed to be valid and reliable. The dataset was freely available; hence, no special instruments or data-collection tools were employed. The data for the research study was assembled in SPSS before performing the statistical analyses.

Design and Analysis

The research design for this study was longitudinal design (Frankfort-Nachmias & Leon-Guerrero, 2018). The main independent variable for this research study was PN, the other independent variable was poverty income ratio, the dependent or outcome variable

was overall mortality, while the covariates are age, gender, and ethnicity. The participants were stratified according to their diabetes status. PN is a categorical nominal variable; Poverty income ratio is a categorical nominal variable; Overall mortality is a categorical nominal variable; Age is a categorical nominal variable, and Gender is a categorical nominal variable. Diabetes is a categorical nominal variable.

Descriptive statistics for PN, poverty income ratio, overall mortality, diabetes, age, gender, and ethnicity were displayed in frequency tables. Inferential statistics for PN, poverty income ratio, overall mortality, age, gender, and ethnicity was performed using complex sample cox regression analysis.

The justification for the selection of a longitudinal study design (Frankfort-Nachmias & Leon-Guerrero, 2018) for this study, was that this study examined secondary dataset for a population of interest - all adults who did not suffer from diabetes in the NHANES 1999 to 2004, and then linked them up with the 2015 follow-up mortality dataset. The event of interest was whether the patient died or was alive, at the time of this study.

Results

This quantitative longitudinal study was designed to investigate whether poverty income ratio moderated the effect of PN on overall mortality among an adult population in the United States, who did not suffer from diabetes, while controlling for age, gender, and ethnicity. The data used in this study to operationalize the variables was the NHANES 1999 to 2015 dataset. This chapter elaborates on how the study was conducted, data manipulation techniques, data treatment procedures such as data cleaning and data

weighting. The 1999 to 2015 NHANES dataset employed for this study had adequate sample size (more than the minimum sample size estimated for this study) for all the variables of interest. Hence, there was no need for the treatment of missing data.

Execution

This study was approved by the Walden University's Institutional Review Board (IRB) on 03/08/2023, with the approval number 03-08-23-0753053. In this study, I employed the use of the NHANES dataset from 1999 to 2000, and the follow-up mortality dataset of 2015. The variables of interest from the 1999 to 2000 dataset were merged with the variables of interest in the 2015 follow-up mortality dataset in SPSS version 27, using the participant's respondent sequence number (SEQN). After the merger, the data was cleaned. Because this was a complex sample of data from a nationally representative dataset from the NHANES 1999 to 2015 dataset, it was essential to perform weighting before the statistical analysis. In a nationally representative dataset such as the NHANES 1999 to 2015, there is usually an underrepresentation and overrepresentation of certain groups. Weighting of the data was necessary to ensure that the data used for the statistical analysis was representative of the population from which it was collected.

To perform weighting of the dataset, a complex sample analysis (CSA) plan was created in SPSS version 27. The variables SDMVSTRA (strata), SDMVPSU (clusters), and MEC6YR (sample weight) were employed in performing weighting during the creation of the CSA. Inferential statistics of complex sample cox regression and descriptive statistics of frequency tables were performed using SPSS version 27.

In the NHANES 1999-2000 dataset, PN was defined as one or more insensate sites of three sites tested per foot based on the Semmes-Weinstein 10g monofilament. The results of this study include the descriptive statistics – frequency tables, of the variables in the study. This is followed by the diagnostic tests of the proportional hazards assumptions, diagnostic tests of model effects, and the inferential statistics results of complex sample cox regression analyses.

Descriptive Statistics

Table 1

Frequencies and Percentages of Participants With Peripheral Neuropathy in the Right Foot

Right foot	*n*	%
Insensate site	66	0.1
None	183	0.2
Not enough information to collect	2315	1.9
Missing	118218	97.8
Total	120782	100.0

Note. This table demonstrates that 66 participants with all the variables of interest in the study, had peripheral neuropathy, compared to 183 participants without peripheral neuropathy in the right foot (Learpn) in the NHANES dataset.

Table 2

Frequencies and Percentages of Participants With Peripheral Neuropathy in the Left Foot

Left foot	*n*	%
Insensate site	73	0.1
None	227	0.2
Not enough information to collect	2334	1.9
Missing	118148	97.8
Total	120782	100.0

Note. This table demonstrates that 73 participants with all the variables of interest in the study, had peripheral neuropathy, compared to 227 participants without peripheral neuropathy in the left foot (Lealpn) in the NHANES dataset.

Table 3

Frequencies and Percentages of Participants' Poverty Income Ratios (PIR)

Category of PIR	*n*	%
1 = 0 through 1.99	4773	4.0
2 = 2 through highest	3709	3.1
Missing	112300	93.0
Total	120782	100.0

Note. This table highlights that more participants had a poverty income ratio of less than 2 (4773), when compared to participants with poverty income ratio of 2 or higher (3709), from the entire NHANES dataset.

Table 4

Frequencies and Percentages of Participants' Overall Mortality Status (mortstat)

Overall mortality status	*n*	%
0 = Assumed alive	48936	40.5
1= Assumed dead	10404	8.6
Missing	61442	50.9
Total	120782	100.0

Note. This table highlights fewer participants (8.6%) experienced the terminal event of mortality, when compared to participants that were alive (40.5%) at the end of the follow-up period.

Table 5

Frequencies and Percentages of Participants Without Diabetes

Diabetes	*n*	%
1 = Yes	489	0.4
2 = No	8936	7.4
Missing	111357	92.2
Total	120782	100.0

Note. This table highlights that more participants did not suffer from diabetes (7.4%), compared to participants with diabetes (0.4%).

Table 6

Frequencies and Percentages of Participants' Ages

Category	*n*	%
1 = 18 to 49 years	3028	2.5
2 = 50 years and over	2420	2.0
Missing	115334	95.5
Total	120782	100.0

Note. This table highlights that more of the participants fell within the 18 to 49 years age group (2.5%) of the entire NHANES dataset, compared to participants within the age group 50 years and over (2.0%).

Table 7

Frequencies and Percentages of Participants' Gender

Category	*n*	%
1 = Male	4883	4.0
2 = Female	5082	4.2
Missing	110817	91.8
Total	120782	100.0

Note. This table highlights that more of the participants were females (4.2%) of the entire NHANES dataset, compared to males (4.0%) of the entire NHANES dataset.

Table 8

Frequencies and Percentages of Participants' Ethnicity

Ethnicity	*n*	%
1= Non-Hispanic White	3423	2.8
2= Non-Hispanic Black	2273	1.9
3= Mexican American	3393	2.8
4= Other Race–Including Multiracial	287	0.2
5= Other Hispanic	589	0.5
Missing	110817	91.7
Total	120782	100.0

Note. This table highlights the percentages of the different participants. Non-Hispanic Whites constituted the majority of the participants (2.8%), while other race – Including Multi-Racial, constituted the least of the participants (0.2%).

Diagnostic Tests/ Tests of Assumptions

Table 9 highlights the Tests of Model Effects. Peripheral neuropathy in the right foot (LEARPN) with $p > .05$, Gender, with $p > .05$, and Ethnicity, with $p > .05$, did not significantly contribute to the complex sample cox regression model. However, Poverty income ratio, Diabetes status, and Age, all significantly contributed to the model, with $p < .001$respectively. Hence, one can conclude that Poverty income ratio, Diabetes status, and Age, all had a statistically significant effect on the survival of the participants or their overall mortality.

Table 9

Tests of Model Effects

Variable	*df*1	*df*2	Wald *F*	Sig.
LEARPN	1.000	13.000	1.067	.321
PIR	1.000	13.000	23.130	.000
Diabetes	1.000	13.000	32.412	.000
AGE	1.000	13.000	29.172	.000
RIAGENDR	1.000	13.000	.067	.800
RIDRETH2	1.000	13.000	2.871	.114

Note. Table 9 highlights that only Poverty income ratio ($p < .001$), Diabetes status ($p < .001$), and Age ($p < .001$) significantly contributed to the cox model or the participants' survival/overall mortality.

Table 10 highlights the overall tests of proportional hazards. According to Dessai and Patil (2019), the proportional hazards assumption states that the relationship between the hazard for the terminating event and time is not dependent (or conditional) on the levels of the covariates. This assumption is violated if the p is < .05 or significant (Dessai & Patil, 2019).

Table 10

Overall Tests of Proportional Hazards

*df*1	*df*2	Wald *F*	Sig.
6.000	8.000	.813	.588

Note. Table 10 highlights that the proportional hazards assumption was not violated, as p>.05.

Table 11 highlights Parameter Estimates for Alternative Model. The negative B coefficient (-.479; Hazard ratio [HR], 0.62), for PN in the right foot indicates that PN in the right foot was associated with a reduced hazard rate of overall mortality, although this association was not significant ($p > .05$, from Table 9). Poverty income ratio significantly moderated the effect of PN on overall mortality ($p < .001$, from Table 9). Since Poverty income ratio has a negative B coefficient (-4.388; HR, 0.01) and Diabetes also has a negative B coefficient (-1.010; HR, 0.36), it implies that participants who did not suffer from diabetes, with reduced poverty income ratio (0 through 1.99) had a reduced hazard rate of overall mortality when diagnosed with PN in the right foot.

Table 11

Parameter Estimates for Alternative Model

Parameter	B	Std. Error	95% Confidence Interval	
			Lower	Upper
LEARPN	-.479	.881	-2.383	1.424
PIR	-4.388	3.519	-11.990	3.215
DIABETES	-1.010	1.561	-4.383	2.363
AGE	-.789	1.479	-3.984	2.406
RIAGENDR	1.168	1.282	-1.601	3.937
RIDRETH2	.370	.785	-1.326	2.067

Note. Table 11 highlights the different coefficients (B) for the terminal event in this study (overall mortality).

Table 12 highlights the Tests of Model Effects. Gender, with $p > .05$, and Ethnicity, with $p > .05$, did not significantly contribute to the complex sample cox regression model. However, PN in the left foot (LEALPN) with $p < .05$, Poverty income ratio ($p < .001$), Diabetes status ($p < .001$), and Age ($p < .001$), all significantly contributed to the model. Hence, one can conclude that PN in the left foot, Poverty income ratio, Diabetes status, and Age, all had a statistically significant effect on the survival of the participants or their overall mortality.

Table 12

Tests of Model Effects

Variable	*df*1	*df*2	Wald *F*	Sig.
LEALPN	1.000	13.000	7.574	.016
PIR	1.000	13.000	28.650	.000
Diabetes	1.000	13.000	30.886	.000
AGE	1.000	13.000	31.180	.000
RIAGENDR	1.000	13.000	.223	.644
RIDRETH2	1.000	13.000	3.324	.091

Note. Table 12 highlights that PN in the left foot – LEALPN ($p < .05$), Poverty income ratio ($p < .001$), Diabetes status ($p < .001$), and Age ($p < .001$) significantly contributed to the cox model or the participants' survival/overall mortality.

Table 13

Overall Tests of Proportional Hazards

*df*1	*df*2	Wald *F*	Sig.
6.000	8.000	1.765	.224

Note. Table 13 highlights that the proportional hazards assumption was not violated, as $p > .05$.

Table 14 highlights Parameter Estimates for Alternative Model. The negative B coefficient (-1.581) for PN in the left foot indicates that PN in the left foot was associated with a reduced hazard rate of overall mortality and this association was significant ($p <$

.05, from Table 12). Poverty income ratio significantly moderated the effect of PN on overall mortality ($p < .001$, from Table 12). Since Poverty income ratio has a negative B coefficient (-4.237; HR, 0.01) and Diabetes also has a negative B coefficient (-1.007; HR, 0.37), it implies that participants who did not suffer from diabetes, with reduced poverty income ratio (0 through 1.99) had a reduced hazard rate of overall mortality when diagnosed with PN in the left foot.

Table 14

Parameter Estimates for Alternative Model

			95% Confidence Interval	
Parameter	B	Std. Error	Lower	Upper
LEALPN	-1.581	.699	-3.091	-.071
PIR	-4.237	3.412	-11.610	3.135
DIABETES	-1.007	1.366	-3.958	1.945
AGE	.014	1.434	-3.058	3.112
RIAGENDR	1.358	1.246	-1.334	4.050
RIDRETH2	.336	.734	-1.249	1.921

Note. Table 14 highlights the different coefficients (B) for the terminal event in this study (overall mortality).

PN in the right foot was associated with a reduced hazard risk of overall mortality, although this association was not significant (HR, 0.62; 95% CI [-2.383, 1.424]; $p > .05$). Poverty income ratio significantly moderated the effect of PN in the right foot on overall mortality ($p < .001$). Since poverty income ratio has a negative B

coefficient (-4.388; HR, 0.01) and Diabetes also has a negative coefficient (B= -1.010; HR, 0.36), it implies that participants who did not suffer from diabetes but had a reduced poverty income ratio (0 - 1.99) had a reduced hazard rate or risk for overall mortality, when diagnosed with PN in the right foot. Age has a negative B coefficient (-.789; HR, 0.45), and since age was coded 0 to 84 years = 1 and $\geq$ 85 years = 2, hence, when adjusted for age, older participants had a reduced hazard rate or risk for overall mortality, when diagnosed with PN in the right foot, but this was not significant ($p > .05$). When adjusted for ethnicity, other Hispanic (coded 5) had a higher hazard risk for overall mortality when diagnosed with PN in the right foot, when compared to Non-Hispanic White (coded 1), since ethnicity has a positive B coefficient (.370; HR, 1.45), but this was not significant ($p > .05$). Similarly, gender was coded Male = 1 and Female = 2; since gender has a positive B coefficient (1.168; HR, 3.22), it implies that females, when compared to males, had a higher hazard risk for overall mortality when diagnosed with peripheral neuropathy in the right foot, but this was not significant ($p > .05$).

PN in the left foot was associated with a reduced hazard risk of overall mortality and this association was significant (HR, 0.21; 95% CI [-3.091, -.071]) $p < .05$). Poverty income ratio significantly moderated the effect of PN in the left foot on overall mortality ($p < .001$). Since poverty income ratio has a negative B coefficient (-4.237; HR, 0.01) and Diabetes also has a negative B coefficient (-1.007; HR, 0.37), it implies that participants who did not suffer from diabetes but had a reduced poverty income ratio (0 - 1.99) had a reduced hazard rate or risk for overall mortality, when diagnosed with PN in the left foot. Age has a positive B coefficient (014; HR, 1.01), and since age was coded 0 to 84 years =

1 and ≥ 85 years = 2, hence, when adjusted for age, older participants had an increased hazard rate or risk for overall mortality, when diagnosed with PN in the left foot, but this was not significant ($p > .05$). When adjusted for ethnicity, other Hispanic (coded 5) had a higher hazard risk for overall mortality when diagnosed with PN in the left foot, when compared to Non-Hispanic White (coded 1), since ethnicity has a positive B coefficient (.336; HR, 1.45), but this was not significant ($p > .05$). Similarly, gender was coded Male = 1 and Female = 2; since gender has a positive B coefficient (1.358; HR, 3.89), it implies that females, when compared to males, females had a higher hazard risk for overall mortality when diagnosed with peripheral neuropathy in the left foot, but this was not significant ($p > .05$).

Discussion

Interpretation

There are no previous studies in the literature that have examined whether poverty income ratio moderated the effect of PN on overall mortality among adults who did not suffer from diabetes. In this study, poverty income ratio moderated the effect of PN in the right foot on overall mortality, and this moderation was significant ($p < .001$). Similarly, poverty income ratio significantly moderated the effect of PN in the left foot on overall mortality ($p < .001$). In the complex sample cox regression analyses of each foot, it was found that poverty income ratio had negative coefficients; similarly, the coefficients for diabetes were also negative. This implied that participants or adults who did not suffer from diabetes but had a reduced poverty income ratio (0 - 1.99), had a reduced hazard rate or risk for overall mortality when diagnosed with PN in either the right or left foot.

According to Oshio (2019), poverty and low income have been associated with poor health outcomes. The results of this study confirmed this trend. Participants who did not suffer from diabetes, but with a reduced poverty income ratio (0 - 1.99), had a reduced hazard for overall mortality when diagnosed with PN in either the right or left foot, when compared to participants with a higher poverty income ratio ($\geq$ 2). In the study by Hicks et al. (2021), the authors found that PN was independently associated with overall mortality in the United States population, even in the absence of diabetes. This study found that PN in both the right and left feet was associated with a reduced hazard risk of overall mortality. This difference in the findings between the study by Hicks et al. and the present study could be due to the fact that Hicks et al. examined PN in its entirety (both feet), while the present study only examined PN in either the right or left foot.

The findings of this study can be interpreted or analyzed in the context of the theoretical framework of the socioecological model (Cowan et al., 2021). The constructs of the Socio-Ecological Model include individual, network, community, and structural (Cowan et al., 2021). The poverty income ratio can be influenced by factors acting at the structural levels. These factors are mediated through laws and policies as well as society and economics (Cowan et al., 2021). A viable economy, brought about by the right set of policies or laws, will improve gainful employment, and likely reduce inequality in society. This situation will improve people's purchasing power and their access to good and affordable health care. Their poverty income ratio will be reduced or improved, with better health outcomes such as a reduced hazard risk for overall mortality from a diagnosis of PN, as demonstrated by the results of this study.

Limitations

This study has some limitations. One of the limitations is that there are other important causes of PN in the United States, such as AIDS/HIV and chemotherapy which were not controlled for in this study because of the sample size and availability of data constraints. In addition, trans or non-binary gender respondents were not controlled for in this study because there was not a large enough sample size for this category of respondents.

Implications

This study has implications for the discipline of public health, the practice of public health as a profession, and finally, for social change. The results of this study demonstrated poverty income ratio moderated the effect of PN in either the right or left foot on overall mortality. Participants who did not suffer from diabetes, but with reduced poverty income ratio had a reduced hazard risk for overall mortality, when diagnosed with PN in either foot. These results build on existing evidence that low income and poverty are associated with poor health outcomes. For the discipline of public health and public health practitioners, it serves as a reminder that there should be a renewed interest in policies and laws that address and seek to reduce income inequality within society. Furthermore, Walden University defines positive social change as a deliberate process of the creation and application of ideas, strategies, and actions to promote the worth, dignity, and development of individuals and societies (Walden University, 2023). Hence, policy makers and government should strive to work towards having a viable economy brought about by the right set of economic policies or laws, as these will likely result in

more gainful employment opportunities for the people, thereby reducing or improving their poverty income ratio. The implications for social change are that adults without diabetes who have been diagnosed with PN in either foot, could enjoy better health outcomes such as reduced overall mortality, if they have reduced poverty income ratio as a result of viable economic policies that seek to reduce income inequality and promote gainful employment.

Recommendations for Further Research

The findings of this study, within its limitations, highlight that adults who do not suffer from diabetes but with reduced poverty income ratio, when diagnosed with PN in either foot, had a reduced hazard risk of overall mortality. Further research should aim to examine PN in its entirety (both feet), since this study only examined PN in either the right or left foot.

Conclusion

PN is associated with a substantial burden among adults not suffering from diabetes in the United States. Poverty and low income, as demonstrated by the results of this study, increases the hazard risk of overall mortality among these adults not suffering from diabetes, especially when diagnosed with PN in either or both feet. Thus, in order to improve the health outcomes of these adults suffering from PN, there should be concerted effort on the part of relevant stakeholders, to advocate for and ensure policies that reduce income inequality and promote gainful employment, which will improve the health outcomes for these individuals.

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Manuscript 2

Veteran/Military Status as a Moderator of Peripheral Neuropathy on Overall Mortality in Non-Diabetic Adults

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Abstract

Peripheral neuropathy (PN) is a disorder of the peripheral nerves that is highly prevalent particularly in older populations. PN causes pain, falls, ulcerations, amputations, and it is associated with significant mortality. PN is common among adults in the United States (U.S.), even in the absence of diabetes. PN has a prevalence of 1% to 12% in all age groups, while the overall prevalence of PN in the U.S. is 13.5% in adults with diabetes, and 11.6% in adults without diabetes. Clearly, these statistics indicate that PN is a serious public health problem among U.S. adults. Reported cases of substance abuse by veterans/military personnel and exposure to toxic chemicals increase the development of PN. There are no published studies examining whether veteran/military status moderated the effect of PN on overall mortality among U.S. adults. Using the socioecological model, the purpose of this longitudinal study was to examine whether veteran/military status moderated the effect of PN on overall mortality. Secondary data from the NHANES 1999-2015 dataset were analyzed using complex sample Cox regression analysis with the threshold for statistical significance taken at $p < 0.05$. Veteran/military status did not moderate the effect of PN on either foot (RT. Foot, $p > .05$; LT. Foot, $p > .05$) on overall mortality, although participants who did not suffer from diabetes but had a veteran/military status had an increased hazard risk for overall mortality when diagnosed with PN in either foot. The results have implications for positive social change. Targeted screening for PN among veterans/military personnel can lead to early detection and management of PN among these individuals, which can lead to better health outcomes and reduced overall mortality.

Introduction

There is a significant burden of peripheral neuropathy (PN), with an associated overall mortality among adults without diabetes in the United States (Hicks et al., 2021). PN is very common, particularly in the older population (Callaghan et al., 2018) and presents with significant morbidity that reduces the quality of life (QoL) of affected patients or individuals (Girach et al., 2019). Approximately two-thirds of patients suffering from PN experience neuropathic pain which can be so disabling as to have a detrimental effect on individuals' mental health and eventually culminating in a reduced QoL (Girach et al., 2019). Moreover, PN is a prevalent disease, especially among adults, and it presents both diagnostic and therapeutic challenges to physicians and other healthcare providers (Callaghan et al., 2018). It is estimated that the prevalence of PN in some studies is as high as 10.4% for middle-aged (40-69 years) and 26.8% for older (> 70 years) adults in the U.S. population (Hicks et al., 2021). Clearly, these statistics indicate that PN is a significant public health problem among adults in the United States. However, many of the studies that have examined the risk factors for PN in the United States, have mainly examined patients or adults with diabetes. In particular, there are no published studies that have examined whether veteran/military status moderated the effect of PN on overall mortality. This situation has created a gap or social problem, as it has been shown by Hicks et al. (2021) that the all-cause or overall mortality associated with PN, even in adults without diabetes, is high at 34.3 per 1000 person-years. The justification for conducting this research in which I examined whether veteran/military status moderated the effect of PN on overall mortality, apart from the gap in the

literature, was that veterans and military personnel have an increased risk or rate of developing combat-sustained peripheral nerve injuries (CSPNIs) as highlighted by Dunn et al. (2020); furthermore, another justification was that substance abuse disorders, including alcohol use and other drugs, which has been linked to the development of PN, was a frequent problem among veterans and military personnel (Inoue et al., 2021).

Veterans and military personnel are at an increased risk of developing CSPNIs, which can eventually lead to the development of PN (Dunn et al., 2020). United States military personnel and veterans alike, who are currently engaged in contemporary warfare are particularly at risk of high-energy blast injuries that can lead to peripheral nerves damage and the subsequent development of PN (Dunn et al., 2020). The situation with veterans and military personnel in the battlefield is sometimes compounded when there is a delay in appropriate evaluation of such individuals for peripheral nerve injury (PNI), as some of them present with multiple injuries (Dunn et al., 2020). Inoue et al. (2021) further highlighted that substance abuse disorders, including alcohol use and other drugs, is frequent problem among veterans and military personnel. These drugs and alcohol fall within the category of neurotoxic agents referred to as xenobiotics (Valentine, 2020), which can cause lasting damage to the peripheral nerves, leading to the development of PN (Valentine, 2020) among Veterans and military personnel. For these reasons, the risk of the development of PN is quite high among Veterans and military personnel. What is not known however, is whether Veteran/military status moderates the effect of PN on overall mortality. Hence, there was justification for this research study in

which I examined whether Veteran/military status moderated the effect of PN on overall mortality among adults without diabetes in the U.S.

Significance/Importance

PN is a chronic debilitating disorder that often develops insidiously, making early diagnosis and management difficult for physicians and other healthcare providers (Brown et al., 2017). Globally, PN has been associated with significant mortality and morbidity (Brown et al., 2017); in the U.S., PN also causes significant morbidity and mortality among adults even without diabetes (Hicks et al. (2021). Patients suffering from PN experience poor QoL which can be detrimental to their mental health, in addition to the neuropathic symptoms of pain, muscle cramps, numbness, falls, weakness, and stiffness, that they experience (Girach et al., 2019). This study is significant in that it provided useful insights on whether Veteran/military status moderated the effect of PN on overall mortality. Veteran/military status has been linked to poor health outcomes (Inoue et al., 2021); however, what was not known is whether Veteran/military status moderated the effect of PN on overall mortality. Since PN develops insidiously and is often difficult to diagnose, knowing whether Veteran/military status moderates the effect of PN on overall mortality will enable relevant stakeholders to institute targeted screening of Veterans and military personnel.

The targeted screening of these individuals could result in early and timely diagnosis of PN, and allow for more positive health outcomes, which could bring about the desired positive social change for these individuals. Furthermore, this study is significant for the discipline of public health, as it would fill an important gap in the

knowledge on the topic of whether Veteran/military status moderated the effect of PN on overall mortality. Presently, there are no published studies in literature that have examined this topic.

Theoretical Framework

The theory of the socioecological model was first introduced by Urie Bronfenbrenner in the 1970s (Kilanowski, 2017). Bronfenbrenner proposed that the nature of individuals' interaction with their physical and sociocultural environments can impact health and lead to the development of diseases (Kilanowski, 2017). The revised constructs of the socioecological model are individual, network, community, and structural (Cowan et al., 2021). Factors or influences operating at every level or construct of this theoretical framework can impact on an individual's health and eventually lead to the development of diseases such as PN. As Cowan et al. (2021) highlighted, the influence of the structural construct or structural level factors are exerted through laws and policies, as well as society and economics. The community construct is useful in explaining whether what an individual is exposed to in her, or his environment may lead to the development of disease or not. As it pertains to my study, veteran/military status, an independent variable, might be explained by both the community and structural constructs.

The socioecological model was applied to organize the discussion in this study. Veteran/military status could be influenced by factors acting at the structural and community levels. The government usually decides through its policies to engage or get involved in contemporary warfare. Military personnel and veterans that are usually

involved in these military operations have an increased risk of developing CSPNIs (Dunn et al., 2020). Similarly, veterans or military personnel might be deployed to different locations or communities during their career. The kind of community or environment and exposure to various xenobiotics such as herbicides or pesticides can influence a veteran/ military personnel's health outcome, probably including the development of PN. The main independent variable in my study, PN, was explained by the structural construct. Evidence from available studies suggests that PN develops as a result of multiple risk factors ranging from chronic non-communicable diseases to exposure to environmental chemicals, herbicides or toxins, and infectious diseases. The structural construct emphasizes economic policies or laws, which can enable individuals to gain access to adequate medical treatment and also protect them from exposure to noxious or toxic environmental agents; in addition, the right set of public health policies or laws can protect individuals from exposure to infectious diseases and ensure prompt treatment of such infectious diseases during an outbreak. All of these measures can influence the development of PN.

This research study can make an original contribution to the discipline of public health as there are presently no published studies in the literature that have examined whether Veteran/military status moderated the effect of PN on overall mortality. Furthermore, Veteran/military status has been associated with health outcomes in many societies around the world. Hence, this research study made an original contribution to the discipline as it provided useful insights on whether veteran/military status moderated the effect of PN on overall mortality.

The purpose of this quantitative secondary data analysis study was to examine whether veteran/military status moderated any effect of PN on overall mortality among an adult population not suffering from diabetes in the United States, while controlling for age, gender, and ethnicity.

Relevant Scholarship/Literature Review

Part of my search strategy for this literature review included employing the following search terms, words and/ or phrases*: peripheral neuropathy; risk factors for peripheral neuropathy; social determinants of peripheral neuropathy; peripheral neuropathy in non-diabetics; peripheral neuropathy in the United States; peripheral neuropathy and overall mortality; effect of veteran/military status on health outcomes; effect of veteran/military status on peripheral neuropathy; effect of military status on peripheral neuropathy; effect of veteran status on peripheral neuropathy; peripheral neuropathy in developed countries; peripheral neuropathy in developing countries*. The search was limited to articles or text written in English from the following search engines or sources: Google and Google Scholar, Walden University library, ProQuest, SAGE Premier, PubMed, MEDLINE, CINHAL Plus, and Science Direct Database. In the literature review, I included background information on peripheral neuropathy in general and its epidemiology, especially the non-diabetic causes. In addition, I examined the problem of peripheral neuropathy within a global context, looking at patterns of distribution and epidemiology in developed and developing countries. Furthermore, I examined the socioeconomic risk factors for peripheral neuropathy among adults without diabetes and an attempt was made to demonstrate a logical connection between what is

known and what was studied – the gap in research. I synthesized the relevant evidence and research on the topic of peripheral neuropathy by various researchers. I also looked at the clinical consequences of peripheral neuropathy, which usually contributed to the morbidity and mortality of individuals not suffering from diabetes. In addition, I examined how veteran/military status could impact health outcomes, and the association between veteran/military status and the possible development of peripheral neuropathy.

Background Information, Global Trends and Epidemiology

Understanding the background information and the epidemiology of peripheral neuropathy (PN), especially in non-diabetic individuals, was an important aspect of this study. This study was focused on whether Veteran/military status moderated the effect of PN on overall mortality in non-diabetic adults in the United States. Hence, I determined that having a good understanding of the non-diabetic causes of PN among adults in the United States would be a good starting point. PN is an important public health condition with a prevalence of almost 15% in the adult population of age over 40 years in the United States (Valentine, 2019). Globally, PN is among the most common neurological diseases, with an estimated incidence of 77/100,000 inhabitants per year and a prevalence of 1 – 12% in all age groups (Lehmann et al., 2020). By definition, peripheral neuropathies encompass all conditions that cause damage to the peripheral nervous system (PNS), which may include mechanical, toxic, and metabolic causes (Szewczyk et al., 2021). Furthermore, the clinical symptoms exhibited by sufferers of this chronic debilitating disease depend on its severity, distribution, affected structure of the nerve cell, as well as the type of affected neurons (Szewczyk et al., 2021). Because of this,

multiple classifications, or types of PN can be encountered in clinical practice, with an overlap between the various types. According to Szewczyk et al. (2021), the prevalence of PN is slightly higher in women than men, and the occurrence of PN may be influenced by the type of work performed (Szewczyk et al., 2021).

Globally, the prevalence of PN also varies considerably from one geographical location to another. As Hanewinckel et al. (2016, as cited in Szewczyk et al., 2021), African and Middle Eastern countries generally have a low prevalence of PN of 0.8 to 2.5 per 1000 adults, when compared to a prevalence of 7.3 to 32.5 per 1000 adults in Europe. Szewczyk et al. (2021) highlighted that some of the differences in prevalence rates of PN observed in these different geographical locations could be partly explained by differences in assessment protocol for PN. In the general population in Europe, the average prevalence of PN ranges from 1% to 3% (Szewczyk et al., 2021), whereas the prevalence of PN is slightly higher at 7% among the elderly (Szewczyk et al., 2021). In comparing the prevalence of PN in some of the developed countries, Szewczyk et al. highlighted that the prevalence of PN in the Netherlands is 5.5% in comparison to a prevalence of 3.9% among the U.S. population.

Szewczyk et al. (2021) opined that the prevalence of PN is influenced by socioeconomic status, the population structure, and other risk factors. However, the authors did not examine or highlight whether veteran/military status moderated the effect of PN on overall mortality. Hence, this is the justification for this study in which I examined whether veteran/military status moderated the effect of PN on overall mortality.

Non-diabetic Causes of Peripheral Neuropathy

While diabetes mellitus remains the most common cause of PN worldwide, the development of PN may have many other different causes which can lead to generalized, and sometimes to isolated PN (Roth et al., 2021). According to Roth et al. (2021), normal aging has been associated with the development of some form of PN in the population. As earlier pointed out by Szewczyk et al. (2021), the prevalence of PN is slightly higher at 7% among the elderly. Even though oxidative stress has been postulated as a possible mechanism or pathogenesis for PN (Mallet et al., 2020), Roth et al. (2021) highlighted that the genesis of PN is multifactorial and not fully explained. However, hyperglycemia, dyslipidemia, inflammation and immune responses, and macro-and microvascular diseases, along with a host of other pathological conditions, have been proposed as possible mechanisms for the development of PN (Roth et al., 2021).

Amyloidosis is an important non-diabetic cause of PN. It comprises of a group of diseases usually characterized by the accumulation or deposition of amyloid fibrils in various tissues throughout the human body (Roth et al., 2021). Amyloid fibrils are extremely strong, highly ordered and organized insoluble fibers or aggregates, formed by different peptides and proteins. The deposition of these amyloid deposits in the epineurium, perineurium, and endoneurium of the peripheral nerves results in dysfunction of such nerves, with subsequent development of PN (Roth et al., 2021). PN can result from either primary amyloidosis or secondary amyloidosis (Roth et al., 2021). Primary amyloidosis results from the accumulation of light-chain amyloid fibrils, while secondary amyloidosis results from the deposition of acute-phase reactant protein or serum amyloid

A protein, which is produced during chronic inflammatory or infectious diseases (Roth et al., 2021).

Sarcoidosis is a chronic disease of unknown etiology characterized by lymph node enlargement in many parts of the body and widespread appearance of granulomas derived from the reticuloendothelial system (Roth et al., 2021). These granulomas may accumulate within the peripheral nerves, resulting in the development of PN (Roth et al., 2021). PN in sarcoidosis consists of granulomatous and non-granulomatous small fiber neuropathy (SFN), as highlighted by Roth et al. (2021), with SFN reported in over 40% of the systemic cases of sarcoidosis (Roth et al., 2021).

Autoimmune or inflammation-related peripheral neuropathy is an important cause of PN (Roth et al., 2021). Autoimmune PN encompasses systemic autoimmune diseases, autoimmune disorders which specifically cause damage to peripheral nerves, or malignancies (Roth et al., 2021). In cases of autoimmune PN, damage to the peripheral nerves occur through autoantibodies which may be directed against membrane receptors of peripheral nerves (Roth et al., 2021), directed against cell surface glycoproteins (Roth et al., 2021), or in the case of cancers or paraneoplastic, such autoantibodies are directed against intracellular onconeural antigens (Roth et al., 2021). In addition, the higher the level of antibodies formed, the more severe the level of PN (Roth et al., 2021). However, paraneoplastic or cancer antibodies tend to correlate more with a unique cancer form than to a specific neuropathy, and their levels do not correlate with the degree or severity of the PN (Roth et al., 2021).

Infection-related peripheral neuropathy is an important cause of non-diabetic peripheral neuropathy (Roth et al., 2021). A wide range of various infectious diseases caused by viruses and bacteria lead to different levels of peripheral nerve dysfunction. These infectious diseases include Varicella-zoster virus infection (Roth et al., 2021), which belongs to the human herpesvirus group that is responsible for the primary infection, varicella (Roth et al., 2021). After the acute infection has subsided, the virus continues to live in the peripheral ganglia, where it can be reactivated spontaneously or after following other triggers, to cause herpes zoster (Roth et al., 2021); herpes zoster is usually accompanied by PN with symptoms such as pain, numbness, and paresthesia (Roth et al., 2021).

Chagas disease, caused by the hemoflagellate parasite, Trypanosoma cruzi (Roth et al., 2021) is another important cause of PN. The disease is endemic in Central and South America, and it is caused through bites from Triatominae bugs (Roth et al., 2021). The chronic phase of this disease is typified by the destruction of ganglion cells both in the central and peripheral nervous system, resulting in the development of PN, among other disorders (Roth et al., 2021).

While Guillain Barre syndrome (GBS) is sometimes regarded as an autoimmune disease, the exact mechanism is unknown. As Roth et al. (2021) highlighted, 50 to 70% of cases of GBS usually follow a respiratory infection, gastrointestinal infection, or any other immune stimulus that induces autoimmune attacks against the peripheral nerves. The development of PN in these patients is accompanied by symptoms such as symmetric weakness, paresthesia, numbness, and pain (Roth et al., 2021).

According to Julian et al. (2019), the prevalence of Alcohol-related PN amongst chronic users or abusers is quite high, estimated at 46.3% (95% CI [35.7, 57.3]), when confirmed by nerve conduction studies. The pattern of PN developed in alcohol-abusers is a predominantly progressive damage of the sensory axons in a length-dependent manner (Julian et al., 2019); in addition, the development of alcohol-related PN is dependent on the total lifetime amount of ethanol consumed (Julian et al., 2019), male gender (Julian et al., 2019), genetics and the type of alcohol consumed (Julian et al., 2019). It is presently unclear what pathogenetic pathways lead to the development of PN in chronic alcohol users; hence, it is unknown whether the direct toxic effects of ethanol or another currently unidentified agent is directly linked to damage of the peripheral nerves. However, according to Julian et al. (2019), based on the available limited data, the associated deficiency of the B-vitamins, inclusive of thiamine, observed in chronic alcohol users could be responsible for the development of PN.

Toxic PN is another important form of non-diabetic or acquired PN. This type of PN is caused by various xenobiotics such as drugs, chemicals, pesticides, and carcinogens that damage components of the peripheral nervous system (Valentine, 2020). The various causes of toxic peripheral neuropathies can be classified as environmental, occupational, recreational, or iatrogenic (Valentine, 2020). In wealthy or developed countries, drug toxicity associated with chemotherapy has been identified as the most common cause of toxic PN (Valentine, 2020); however, in developing countries, occupational and environmental exposures to xenobiotics such as arsenic, lead, mercury, and organophosphates found in various pesticides, insecticides, and herbicides, are the

leading causes toxic PN (Valentine, 2020). A possible reason why occupational exposures to these xenobiotics account for the development of PN in many developing countries is that there is less strict monitoring associated with many manufacturing processes, which generate many of these neurotoxicants. Generally speaking, these xenobiotics cause damage to the neuronal perikaryons, axons, the Schwan cell, or the synapse (Valentine, 2020). The damage to the peripheral nerves by these neurotoxicants is dose dependent, symmetrical, and reversible, provided there is adequate time following exposure to such agents (Valentine, 2020); in addition, individuals exposed to these agents present with numbness, paresthesia, or weakness in a characteristic stocking glove distribution (Valentine, 2020).

Pharmaceutical agents, especially certain antibiotics, have been associated with the development of PN. Fluoroquinolone is an antibiotic that is widely used worldwide and is associated with the development of PN (Morales et al., 2019). In a nested case-control study that included 5357 incident PN cases and 17, 285 matched controls, Morales et al. (2019) highlighted that exposure or use of oral fluoroquinolone was associated with an increased relative incidence of PN, when compared with non-exposure to fluoroquinolone (adjusted incident rate ratio, 1.47; 95% CI [1.13, 1.92]). The risk of developing PN following the use of fluoroquinolone antibiotic was found to have increased by an additional 3% following each day of the antibiotic use, and the risk persisted for up to six months following exposure to the antibiotic (Morales et al., 2019). In comparison, Morales et al. (2019) did not find any significant increased risk in the development of PN with exposure to or use of oral amoxicillin-clavulanate, another

widely used antibiotic. These findings suggest that health care providers, particularly physicians, should consider these potential side effects when prescribing fluoroquinolone antibiotics.

Monoclonal gammopathy-associated PN is another important non-diabetic cause of PN. Monoclonal gammopathies encompass a spectrum of disorders that involves the secretion of a monoclonal immunoglobulin known as a monoclonal (M) protein (Chaudhry et al., 2017). The different categories of monoclonal gammopathy-associated PN include monoclonal gammopathy of undetermined significance (MGUS), which can either be IgM, non-IgM, IgG, or IgA (Chaudhry et al., 2017). As Chaudhry et al. (2017) highlighted, other categories of monoclonal gammopathy-associated PN are multiple myeloma (which includes smoldering multiple myeloma), Waldenstrom macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome, systemic immunoglobulin light chain amyloidosis, and coincidental PN in patients with a monoclonal protein. While the pathological pathways associated with monoclonal gammopathy-associated PN is not clearly understood, Chaudhry et al. (2017) argued that Waldenstrom macroglobulinemia and IgM MGUS-associated PN might be associated with demyelination and widening of the myelin lamellae respectively. Furthermore, demyelination has also been associated with PN in some patients with IgG MGUS (Chaudhry et al., 2017), while in a significant proportion of patients with IgM monoclonal gammopathy-associated PN, Chaudhry et al. (2017) found that the pathological pathways involved the binding of the M protein to myelin associated glycoprotein (MAG) in the peripheral nerves.

Hereditary PN is also an important cause of non-diabetic peripheral neuropathy. As Eggermann et al. (2018) highlighted, hereditary peripheral neuropathies constitute a significant group of genetic diseases, and the overall prevalence of hereditary PN is estimated at 1 in 2500 (Eggermann et al., 2018). The use of next-generation sequencing (NGS) has improved the detection of many hitherto unknown involved genes and genetic defects that cause PN (Eggermann et al., 2018). Hereditary PN is another important, but rare cause of PN. According to Eggermann et al. (2018), the forms of hereditary PN that have been identified include Charcot-Marie-Tooth disease (CMT). This is a rare form of hereditary PN, with a prevalence of 1 in 200,000 (Eggermann et al., 2018). It may be that PN is strongly associated with CMT.

Some socioeconomic factors have been implicated as possible causes of PN. However, because many studies on PN have been restricted to populations with diabetes, this has resulted in limited evidence of the potential contribution of some socioeconomic and psychosocial risk factors to the development of PN in non-diabetic populations. Dusendang et al. (2019) highlighted that perceived discrimination in midlife was associated with the development of PN later in life. According to Dusendang et al. in their study, women who reported perceived discrimination had 29% higher odds of PN when compared with women who did not report perceived discrimination (95% CI [1.01, 1.66]). In addition, the authors highlighted that 30% of total effect of discrimination on PN was mediated indirectly by the participant's body mass index (BMI). Dusendang et al. argued that discrimination was a form of chronic stressor, and the pathogenesis of PN in individuals who had experienced discrimination was probably related to the release of

proinflammatory substances in the body, with associated dysregulation of the cardiovascular and metabolic functions, leading to the damage of the peripheral nerves.

Low socioeconomic status, irrespective of the participants' diabetic status, was also found to be associated with prevalent PN in the study by Dusendang et al. (2019). Most of these women from low socioeconomic status also reported an associated financial strain. As Dusendang et al. highlighted, the combination of low socioeconomic status and the associated financial strain could result in increased secretion of stress hormones which ultimately could lead to an increase in allostatic load – the cumulative effects that chronic stress has on mental and physical health. As Dusendang et al. opined, one of the pathophysiologic consequences of this increase in allostatic load is the development of PN. In addition, as Dusendang et al. argued, people of low socioeconomic status generally have poorer nutritional status, engage is less physical activity or exercise, tend to have more exposure to environmental pollutants or toxins, and usually have less access to quality health care, when compared to people of higher socioeconomic status. These situations increase the risk of development of PN in people of low socioeconomic status. Furthermore, even people of low socioeconomic status who seek care for PN symptoms may be less likely to receive appropriate and proper diagnostic workup based on their socioeconomic status. This situation may lead to poorer management of their PN and further exacerbate their medical condition.

Poor housing, homelessness, and disadvantaged neighborhood conditions have all been linked to poorer health outcomes, such as the development of PN, infectious diseases, and other chronic medical conditions (Boch et al., 2020). The exact pathways

by which poor or sub-standard housing is associated with the development of PN is not clearly understood. However, as Valentine (2020) highlighted, the risk of environmental exposures to various xenobiotics, particularly lead, is higher is people living in poor or sus-standard housing units. Chronic exposure to lead has been associated with the development of PN (Valentine, 2020). According to the United States Department of Housing and Urban Development (2017) as highlighted in Boch et al. (2020), almost 8.3 million very low-income rental households in the United States had worst case needs and the occupants were regarded as living in severely inadequate conditions. Furthermore, Raymond et al. (2011, as cited in Boch et al., 2020), noted that 5.8 million residencies in the United States were considered inadequate based on significant deficiencies in plumbing, heating, electricity, and upkeep (including exposures to xenobiotics such as lead). Living in these poor and sub-standard housing units, with the associated increased exposure to various xenobiotics, can lead to the development of various chronic diseases such as PN.

Synthesis of Research Findings

Roth et al. (2021) found that normal aging was associated with the development of PN; however, the authors pointed out in their systematic review of the literature that the etiology of PN was multifactorial and not fully explained by one mechanism. While Roth et al. proposed a multicausal mechanism for the etiopathogenesis of PN, they however highlighted some major specific causes for PN which include diabetes, diseases involving tissues deposits, infections, autoimmunity, cancers or malignancies, and metabolic diseases. Roth et al. did not examine whether veteran/military status moderated

the effect of PN on overall mortality, although PN has been linked to overall mortality in adults.

While Szewczyk et al. (2021) highlighted in their retrospective cross-sectional study that the prevalence of PN of 7% is slightly higher among the elderly, the authors also opined that women have a slightly higher prevalence of PN when compared to men. In addition, Szewczyk et al. suggested that one's socioeconomic status, occupation, and the population structure were all associated with the development of PN. Of particular note was the statistically significant finding ($p < 0.05$) of the association of the place of residence and gender, and the development of PN. Szewczyk et al. highlighted that more affected women live in the urban areas, whereas more men diagnosed with PN inhabit the rural areas. The authors suggested that the statistically significant differences could be partly explained by the work performed, as well as the external or internal factors or mechanisms that influence the manifestation of PN. However, the authors did not specifically examine whether veteran/military status moderated the effect of PN on overall mortality.

Julian et al. (2019) in their systematic review of the literature, highlighted a high prevalence of PN of 43% (95% CI [35.7, 57.3%]) particularly amongst chronic alcohol consumers or abusers. While the authors posited that the pathogenetic pathways to the development of PN in chronic alcohol consumers is not clearly understood, Julian et al. highlighted that the development of PN in such individuals is dependent on the total lifetime amount of alcohol consumed, male gender, and probably some associated genetic factors. However, even though some studies have found an association between

veteran/military status and substance and alcohol abuse, the authors did not examine whether veteran/military status moderated the effect of PN on overall mortality.

In a systematic review of literature, Valentine (2020) highlighted various xenobiotics or peripheral nervous system toxicants that can lead to the development of PN, if an individual is exposed to such xenobiotics. Such toxic agents could be classified as environmental, occupational recreational, or iatrogenic. Prominent among these agents are drug toxicity, especially chemotherapeutic agents, arsenic, lead, mercury, and organophosphates, which are constituents of many commonly used herbicides and pesticides. All these agents can lead to the development of PN. However, Valentine did not examine whether veteran/military status moderated the effect of PN on overall mortality.

Chaudry et al. (2017) in their systematic review, highlighted that PN can occur in patients suffering from various plasma cell disorders, ranging from the premalignant MGUS stage to the readily apparent malignant stages of multiple myeloma and Waldenstrom macroglobulinemia. The authors did not examine whether being veteran/military personnel could contribute to the development of PN in patients suffering from these various plasma cell disorders, nor did they examine whether veteran/military status moderated the effect of PN on overall mortality. While Eggermann et al. (2018) in their systematic review of the literature highlighted that hereditary peripheral neuropathies constituted a large group of genetic disorders and are important causes of non-diabetic neuropathy, the authors did not examine whether veteran/military status moderated the effect of PN on overall mortality.

Dusendang et al. (2019) in their national longitudinal study of Women's Health, highlighted that woman who had experienced perceived discrimination in midlife had 29% higher odds of developing PN, when compared to women who did not report perceived discrimination. Furthermore, Dusendang et al. highlighted that each increasing level of perceived discrimination in midlife was associated with 43% higher odds of developing PN. However, the authors did not examine whether veteran/military status moderated the effect of PN on overall mortality. Boch et al. (2020) in their national survey found that poor housing, homelessness, and disadvantaged neighborhood conditions are associated with poor health outcomes such as the development of PN. While the exact pathways by which poor or substandard housing is associated with the development of PN is not fully understood, it is postulated that the risk of environmental exposures to various xenobiotics, particularly lead, is increased in people living in poor or sub-standard housing units. However, while veteran/military personnel have been associated with exposure to various xenobiotics in the course of their duties or deployment, the authors did not specifically examine whether veteran/military status moderated the effect of PN on overall mortality.

Logical Connection Between What is Known and What Needs to be Studied.

From this literature review, the various important non-diabetic causes of PN were clearly highlighted. In addition, the important risk factors for PN were also highlighted. However, an important gap in literature still existed on whether veteran/military status moderates the effect of PN on overall mortality. Veteran/military status has been linked to exposure to various xenobiotics and substance abuse, which can all lead to poor health

outcomes, such as the development of PN. Similarly, PN has been linked to overall mortality. What is however not known, is whether veteran/military status moderates the effect of PN on overall mortality.

Research Questions and Design

Research Question: Does veteran/military status moderate the effect of peripheral neuropathy on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity?

Null Hypothesis: Veteran/military status does not moderate the effect of peripheral neuropathy on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity

Alternative Hypothesis: Veteran/military status moderates the effect of peripheral neuropathy on overall mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity.

Rationale for Research Question

The rationale for choosing this requestion question was that there is a substantial burden of peripheral neuropathy and the associated overall mortality among adults without diabetes in the United States (Hicks et al., 2021). However, there was a gap in the literature as to whether veteran/military status moderated the effect of peripheral neuropathy on overall mortality among adults without diabetes in the United States.

Research Design

The specific quantitative research design for this study is a longitudinal design (Frankfort-Nachmias & Leon-Guerrero, 2018), with the outcome variable – overall

mortality, examined in the follow-up mortality dataset of 2015. This quantitative analysis helped determine whether veteran/military status (independent variable) moderated the effect of peripheral neuropathy (main independent variable) on overall mortality (dependent variable), while controlling or adjusting for age, gender, and ethnicity (covariates).

Approach Used to Address the Research Problem

The epistemological approach I employed in addressing this research problem is that of positivism (Park et al., 2019). The approach of positivism relies on the hypothetico-deductive method to ascertain or verify priori hypotheses that are often stated quantitatively (Park et al., 2019). The hypothetico-deductive method is a circular process that starts with theory from the literature (Park et al., 2019). This enables the researcher to build or construct testable hypotheses, design an experiment through operationalizing variables, and finally conduct an empirical study based on experimentation (Park et al., 2019). The findings from such a study are employed to help inform theory, bring about a desired positive social change, and contribute to the literature, thereby completing the circular process (Park et al., 2019): theory – hypothesis – operationalizing variables – experimentation – theory (Park et al., 2019). The positivist paradigm or approach is based on the notion that knowledge can and must be developed objectively, without the values or ideas of the researcher or participants influencing its development (Park et al., 2019).

Methods

Participants

The target population for this study was all adults who did not suffer from diabetes in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2015 dataset.

Sample and Power

This study employed a secondary dataset from the NHANES 1999 to 2015 dataset. The sampling strategy used was simple random sampling (Frankfort-Nachmias & Leon-Guerrero, 2018). Participants who satisfied the inclusion criteria (all adults without diabetes and who had the complete set of the variables of interest in this study) were randomly recruited into the study. This sampling strategy gave each of the participants an equal chance of being selected into the study (Frankfort-Nachmias & Leon-Guerrero, 2018).

To determine the appropriate sample size for this study, G* Power 3.1.9.7 (Faul et al., 2009) was employed. As Bhandari (2022) highlighted, the criteria for choosing effect size prior to estimating sample size, depends on what has been documented on previous research studies on the topic of interest. However, since there were no published studies on whether veteran/military status moderated the effect of PN on overall mortality, the effect size f^2 was set at medium value (0.15) in G* Power (Faul et al., 2009). F test was selected along with the statistical test of: Cox Regression, Fixed model, R^2 deviation from zero in G* Power (Faul et al., 2009). Since there were six predictor variables in this study (peripheral neuropathy, veteran/military status, diabetes, age, gender, and

ethnicity), and with the *p* value set at 0.05 and power set at 80% in G* Power (Faul et al., 2009, the sample size calculated was 98 participants. This was the minimum sample size required for this study.

Variables/Sources of Data

The main independent variable in this study was Peripheral neuropathy, the independent variable or moderating variable was veteran/military status, the dependent variable was overall mortality, while the covariates are age, gender, and ethnicity. The participants were stratified according to their diabetes status. According to the alternative hypothesis in this study, it was expected that the independent variable (veteran/military status) could moderate the association between peripheral neuropathy and overall mortality, while adding the covariates could increase the accuracy of the results from the research study. The sources of the data used to operationalize the variables were the NHANES 1999 to 2000 and the 2015 follow-up mortality datasets.

The main independent variable was peripheral neuropathy, a Categorical Nominal variable, and coded as: None = 1, Insensate site group = 2. The other independent variable was veteran/military status, a Categorical Nominal variable, and coded as: Yes = 1, No = 2. In addition, Diabetes, a Categorical Nominal variable, coded as Yes = 1 and No = 2. The covariates were age (years), a Categorical Nominal variable, and coded as: 0 to 84 = 1, $\geq$ 85 = 2; Gender, a Categorical Nominal variable, and coded as: Male = 1, Female = 2, and Ethnicity, a Categorical Nominal variable, and coded as: Non-Hispanic White = 1, Non-Hispanic Black = 2, Mexican American = 3, Other Race – Including

Multi-Racial = 4, Other Hispanic = 5. The dependent variable is overall mortality, a Categorical Nominal variable, and coded as 0 = Assumed alive, 1 = Assumed deceased.

Instrumentation or Measures

Secondary data from the NHANES 1999 to 2015 dataset were used in this study. This data was collected by the Centers for Disease Control and Prevention, and hence, the data was assumed to be valid and reliable. The dataset was freely available; hence, no special instruments or data-collection tools were employed. The data for the research study was assembled in SPSS before performing the statistical analyses.

Design and Analysis

The research design for this study is a longitudinal design (Frankfort-Nachmias & Leon-Guerrero, 2018). The main independent variable for this research study is peripheral neuropathy, the other independent variable is veteran/military status, the dependent or outcome variable is overall mortality, while the covariates are age, gender, and ethnicity. The participants were stratified based on their diabetes status. Peripheral neuropathy is a categorical nominal variable; military/veteran status is a categorical nominal variable; Overall mortality is a categorical nominal variable; Diabetes is a categorical nominal variable; Age is a categorical nominal variable, Ethnicity is a categorical nominal variable, and Gender is a categorical nominal variable.

Descriptive statistics for peripheral neuropathy, veteran/military status, overall mortality, diabetes, age, gender, and ethnicity were frequency tables. Inferential statistics for peripheral neuropathy, military/veteran status, overall mortality, age, gender, and ethnicity was performed using complex sample cox regression analyses, since

veteran/military status could moderate the effect of peripheral neuropathy on overall mortality.

The justification for the selection of a longitudinal study design (Frankfort-Nachmias & Leon-Guerrero, 2018) for this study, was that this study examined secondary dataset for a population of interest - all adults who did not suffer from diabetes in the NHANES 1999 to 2004, and then linked them up with the 2015 follow-up mortality dataset. The event of interest was whether the patient died or was alive, at the time of this study.

Results

This quantitative longitudinal study was designed to investigate whether veteran/military status moderated the effect of peripheral neuropathy on overall mortality among an adult population in the United States, who did not suffer from diabetes, while controlling for age, gender, and ethnicity. The data used in this study to operationalize the variables was NHANES 1999 to 2015 dataset. This chapter elaborates on how the study was conducted, data manipulation techniques, data treatment procedures such as data cleaning and data weighting. The 1999 to 2015 NHANES dataset employed for this study had an adequate sample size of 120782 participants, more than the estimated minimum sample size of 98 participants for the study for all the variables of interest. Missing data was treated by the technique of multiple imputation.

Execution

This study was approved by the Walden University's Institutional Review Board (IRB) on 03/08/2023, with the approval number 03-08-23-0753053. In this study, I

employed the use of the NHANES dataset from 1999 to 2000, and the follow-up mortality dataset of 2015. The variables of interest from the 1999 to 2000 dataset were merged with the variables of interest in the 2015 follow-up mortality dataset in SPSS version 27, using the participant's respondent sequence number (SEQN). After the merger, the data was cleaned. Because this was a complex sample of data from a nationally representative dataset from the NHANES 1999 to 2015 dataset, it was essential to perform weighting before the statistical analysis. In a nationally representative dataset such as the NHANES 1999 to 2015, there is usually an underrepresentation and overrepresentation of certain groups. Weighting of the data was necessary to ensure that the data used for the statistical analysis was representative of the population from which it was collected.

To perform weighting of the dataset, a complex sample analysis (CSA) plan was created in SPSS version 27. The variables SDMVSTRA (strata), SDMVPSU (clusters), and MEC6YR (sample weight) were employed in performing weighting during the creation of the CSA. Inferential statistics of complex sample cox regression and descriptive statistics of frequency tables were performed using SPSS version 27.

Results

In the HNANES 1999-2000 dataset, peripheral neuropathy was defined as one or more insensate sites of three sites tested per foot based on the Semmes-Weinstein 10g monofilament. The results of this study include the descriptive statistics – frequency tables, of the variables in the study. This is followed by the diagnostic tests of the

proportional hazards assumptions, diagnostic tests of model effects, and the inferential statistics results of complex sample cox regression analyses.

Descriptive Statistics

Table 1

Frequencies and Percentages of Participants With Peripheral Neuropathy in the Right Foot

Right foot	*n*	%
Insensate site	66	0.1
None	183	0.2
Not enough information to collect	2315	1.9
Missing	118218	97.8
Total	120782	100.0

Note. This table demonstrates that 66 participants with all the variables of interest in the study, had peripheral neuropathy, compared to 183 participants without peripheral neuropathy in the right foot (Learpn).

Table 2

Frequencies and Percentages of Participants With Peripheral Neuropathy in the Left Foot

Left foot	*n*	%
Insensate site	73	0.1
None	227	0.2
Not enough information to collect	2334	1.9
Missing	118148	97.8
Total	120782	100.0

Note. This table demonstrates that 73 participants with all the variables of interest in the study, had peripheral neuropathy, compared to 227 participants without peripheral neuropathy in the left foot (Lealpn).

Table 3

Frequencies and Percentages of Participants With Veteran/Military Status

Veteran/military status	*n*	%
1 = Yes	717	0.6
2 = No	5004	4.1
Missing	115061	95.3
Total	120782	100.0

Note. This table highlights that fewer participant identified as Veterans or Military personnel (717), when compared to those who had no Veteran/Military status (5004).

Table 4

Frequencies and Percentages of Participants' Overall Mortality Status (mortstat)

Overall mortality status	*n*	%
0 = Assumed alive	48936	40.5
1= Assumed dead	10404	8.6
Missing	61442	50.9
Total	120782	100.0

Note. This table highlights fewer participants (8.6%) experienced the terminal event of mortality, when compared to participants that were alive (40.5%) at the end of the follow-up period.

Table 5

Frequencies and Percentages of Participants Without Diabetes

Diabetes	*n*	%
1 = Yes	489	0.4
2 = No	8936	7.4
Missing	111357	92.2
Total	120782	100.0

Note. This table highlights that more participants did not suffer from diabetes (7.4%), compared to participants with diabetes (0.4%).

Table 6

Frequencies and Percentages of Participants' Ages

Category	*n*	%
1 = 18 to 49 years	3028	2.5
2 = 50 years and over	2420	2.0
Missing	115334	95.5
Total	120782	100.0

Note. This table highlights that more of the participants fell within the 18 to 49 years age group (2.5%), compared to participants within the age group 50 years and over (2.0%).

Table 7

Frequencies and Percentages of Participants' Gender

Category	*n*	%
1 = Male	4883	4.0
2 = Female	5082	4.2
Missing	110817	91.8
Total	120782	100.0

Note. This table highlights that more participants were females (4.2%), compared to males (4.0%).

Table 8

Frequencies and Percentages of Participants' Ethnicity

Ethnicity	*n*	%
1= Non-Hispanic White	3423	2.8
2= Non-Hispanic Black	2273	1.9
3= Mexican American	3393	2.8
4= Other Race – Including Multi-Racial	287	0.2
5= Other Hispanic	589	0.5
Missing	110817	91.7
Total	120782	100.0

Note. This table highlights the percentages of the different participants. Non-Hispanic Whites constituted the majority of the participants (2.8%), while other race – Including Multi-Racial, constituted the least of the participants (0.2%).

Diagnostic Tests/ Tests of Assumptions

Table 9 highlights the Tests of Model Effects. Peripheral neuropathy in the right foot (LEARPN) with $p > .05$, Military/veteran status with $p > .05$, Gender, with $p > .05$, and Ethnicity, with $p > .05$, did not significantly contribute to the complex sample cox regression model. However, Diabetes status, and Age, both significantly contributed to the model, with $p < .001$, respectively. Hence, one can conclude that Diabetes status and Age both had a statistically significant effect on the survival of the participants or their overall mortality.

Table 9

Tests of Model Effects

Variable	*df*1	*df*2	Wald *F*	Sig.
LEARPN	1.000	13.000	1.678	.218
Military/Veteran	1.000	13.000	1.966	.184
Diabetes	1.000	13.000	36.558	0.000
AGE	1.000	13.000	30.581	0.000
RIAGENDR	1.000	13.000	.598	.453
RIDRETH2	1.000	13.000	.795	.389

Note. Table 9 highlights that only Diabetic status ($p < .001$) and Age ($p < .001$) significantly contributed to the Cox model or the participants' survival/overall mortality.

Table 10 highlights the overall tests of proportional hazards. According to Dessai and Patil (2019), the proportional hazards assumption states that the relationship between the hazard for the terminating event and time is not dependent (or conditional) on the levels of the covariates. This assumption is violated if the p is < .05 or significant (Dessai & Patil, 2019).

Table 10

Overall Tests of Proportional Hazards

*df*1	*df*2	Wald *F*	Sig.
6.000	8.000	1.514	.265

Note. Table 10 highlights that the proportional hazards assumption was not violated, as $p > .05$.

Table 11 highlights parameter estimates for alternative model. The negative B coefficient (-.750; Hazard ratio [HR], 0.47) for PN in the right foot indicates that PN in the right foot was associated with a reduced hazard rate of overall mortality, although this association was not significant ($p > .05$, from Table 9). Veteran/military status did not moderate the effect of PN on overall mortality ($p > .05$, from Table 9). Since Veteran/military status has a positive B coefficient (.774; HR, 2.17) and Diabetes has a negative B coefficient (-.741; HR, 0.48), it implies that participants who did not suffer from diabetes but had Veteran/military status had an increased hazard rate of overall mortality when diagnosed with PN in the right foot, but this association was not significant ($p > .05$).

Table 11

Parameter Estimates for Alternative Model

			95% Confidence Interval	
Parameter	B	Std. Error	Lower	Upper
LEARPN	-.750	.741	-2.351	.851
DMQMILIT	.774	.285	.158	1.391
DIABETES	-.741	.993	-2.886	1.404
AGE	-1.691	1.027	-3.910	.529
RIAGENDR	-.899	.883	-2.807	1.009
RIDRETH2	.509	.351	-.251	1.268

Note. Table 11 highlights the different coefficients (B) or hazard rates for the terminal event in this study (overall mortality).

Table 12 highlights the Tests of Model Effects. PN in the left foot (LEALPN) with $p >$. 05, Veteran military status, $p > .05$, Gender, with $p > .05$ and Ethnicity, with $p > .05$, did not significantly contribute to the complex sample cox regression model. However, Diabetes status, $p < .001$ and Age, $p < .001$, both significantly contributed to the model. Hence, one can conclude that PN in the left foot, Veteran military Status, Gender, and Ethnicity, did not have a statistically significant effect on the survival of the participants or their overall mortality.

Table 12

Tests of Model Effects

Variable	*df*	*df*2	Wald *F*	Sig.
LEALPN	1.000	13.000	.817	.382
Veteran/military	1.000	13.000	2.104	.171
Diabetes	1.000	13.000	37.027	.000
AGE	1.000	13.000	38.349	.000
RIAGENDR	1.000	13.000	.863	.370
RIDRETH2	1.000	13.000	.491	.496

Note. Table 12 highlights that Peripheral neuropathy in the left foot ($p > .05$), Veteran/military status ($p >$. 05), Gender ($p >$ .05), and Ethnicity ($p > .05$) did not significantly contribute to the cox model or the participants' survival/overall mortality.

Table 13

Overall Tests of Proportional Hazards

df1	*d2*	Wald *F*	Sig.
6.000	8.000	2.292	.135

Note. Table 13 highlights that the proportional hazards assumption was not violated, as $p > .05$.

Table 14 highlights Parameter Estimates for Alternative Model. The negative B coefficient (-1.686; HR, 0.19) for PN in the left foot indicates that PN in the left foot was associated with a reduced hazard risk of overall mortality and this association was not significant ($p > .05$, from Table 12). Veteran/military status did not moderate the effect of peripheral neuropathy on overall mortality, ($p > .05$, from Table 12). Since veteran/military status has a positive B coefficient (.774; HR, 2.17) and Diabetes has a negative B coefficient (-.977; HR, 0.38), it implies that participants who did not suffer from diabetes, but had veteran/military status, had an increased hazard rate of overall mortality when diagnosed with PN in the left foot, although this association was not significant ($p > .05$).

Table 14

Parameter Estimates for Alternative Model

Parameter	B	Std. Error	95% Confidence Interval	
			Lower	Upper
LEALPN	-1.686	.745	-3.295	1.077
VETERAN/MILITARY	.774	.304	.117	1.430
DIABETES	-.977	.976	-3.085	1.132
AGE	-1.459	1.077	-3.785	.868
RIAGENDR	-.711	.944	-2.750	1.328
RIDRETH2	.444	.329	-.267	1.155

Note. Table 14 highlights the different coefficients (B) for the terminal event in this study (overall mortality).

PN in the right foot was associated with a reduced hazard risk of overall mortality, although this association was not significant (HR, 0.47; 95% CI [-2.351, 0.851], $p > .05$). Veteran/military status did not moderate the effect of PN in the right foot on overall mortality ($p > .05$). Since Veteran/military status has a positive B coefficient (.774; HR, 2.17) and Diabetes has a negative B coefficient (-.741; HR, 0.48), it implies that participants who did not suffer from diabetes but had Vetera/military status, had an increased hazard rate or risk for overall mortality, when diagnosed with PN in the right foot, but this association was not significant ($p > .05$). Age has a negative B coefficient (-1.691; HR, 0.18), and since age was coded 0 to 84 years = 1 and $\geq$ 85 years = 2, hence, when adjusted for age, older participants had a reduced hazard rate or risk for overall

mortality, when diagnosed with PN in the right foot, but this was not significant ($p > .05$). When adjusted for ethnicity, other Hispanic (coded 5) had a higher hazard risk for overall mortality when diagnosed with PN in the right foot, when compared to Non-Hispanic White (coded 1), since ethnicity has a positive B coefficient (.509; HR, 1.66), but this was not significant ($p > .05$). Similarly, gender was coded Male = 1 and Female = 2; since gender has a negative B coefficient (-.899; HR, 0.41), it implies that males, when compared to females, had a higher hazard risk for overall mortality when diagnosed with PN in the right foot, but this was not significant ($p > .05$).

PN in the left foot was associated with a reduced hazard risk of overall mortality and this association was not significant (HR, 0.19; 95% CI [-3.295, 1.077], $p > .05$). Veteran/military status did not moderate the effect of PN in the left foot on overall mortality ($p > .05$). Since Veteran/military status has a positive B coefficient (.774; HR, 2.17) and Diabetes has a negative B coefficient (-.977; HR, 0.38), it implies that participants who did not suffer from diabetes but had a Veteran/Military status had an increased hazard rate or risk for overall mortality, when diagnosed with PN in the left foot, but this association was not significant ($p > .05$). Age has a negative B coefficient (-1.459; HR=0.23), and since age was coded 0 to 84 years = 1 and $\geq$ 85 years = 2, hence, when adjusted for age, older participants had a reduced hazard rate or risk for overall mortality, when diagnosed with PN in the left foot, but this was not significant ($p > .05$). When adjusted for ethnicity, other Hispanic (coded 5) had a higher hazard risk for overall mortality when diagnosed with PN in the left foot, when compared to Non-Hispanic White (coded 1), since ethnicity has a positive B coefficient (.444; HR, 1.56), but this

was not significant ($p > .05$). Similarly, gender was coded Male = 1 and Female = 2; since gender has a negative B coefficient (-.711; HR, 0.49), it implies that males, when compared to females, males had a higher hazard risk for overall mortality when diagnosed with PN in the left foot, but this was not significant ($p > .05$).

Discussion

Interpretation

There are no previous studies in literature that have examined whether veteran/military status moderated the effect of PN on overall mortality. In this study, veteran/military status did not moderate the effect of PN in the right foot on overall mortality ($p > .05$). Similarly, veteran/military status did not moderate the effect of PN in the left foot on overall mortality ($p > .05$). In the complex sample cox regression analyses of both feet, it was found that veteran/military status had positive coefficients; however, the coefficients for diabetes were negative. This implied that participants or adults who did not suffer from diabetes but had veteran/military status, had an increased hazard rate or risk for overall mortality when diagnosed with PN in either the right or left foot, but this association was not significant ($p > .05$)

According to Dunn et al. (2019), veterans and military personnel are at an increased risk of developing CSPNIs, which can eventually lead to the development of PN. Furthermore, Inoue et al. (2021) highlighted that substance abuse disorders, including alcohol use and other drugs that fall within the category of neurotoxic agents known as xenobiotics (Valentine, 2020), were also responsible for the development of PN among veterans and military personnel. The results of this study confirm this trend.

Participants who did not suffer from diabetes, but had veteran/military status, had an increased hazard rate or risk for overall mortality when diagnosed with PN in either the right or left foot, when compared to participants without veteran/military status. In the study by Hicks et al. (2021), the authors found that PN was independently associated with overall mortality in the United States population, even in the absence of diabetes. In this study, there was an insignificant association ($p >$. 05) between PN in either the right or left foot and the risk of overall mortality. This difference in the findings between the study by Hicks et al. (2021) and the present study could be due to the fact that Hicks et al. (2021) examined PN in its entirety (both feet), while the present study only examined PN in either the right or left foot.

The findings of this study can be interpreted or analyzed in the context of the theoretical framework of the socioecological model (Cowan et al., 2021). The constructs of the socioecological model include individual, network, community, and structural (Cowan et al., 2021). Veteran/military status can be influenced by factors acting at both the individual and community levels. Inoue et al. (2021) opined that veterans and military personnel usually indulge in the use of alcohol and other drugs that fall within the category of neurotoxic agents known as xenobiotics (Valentine, 2020); these agents are responsible for the development of PN among veterans and military personnel. At the community level, military personnel or veterans might be deployed to environments where they are exposed to various chemicals such as herbicides or pesticides, in addition to developing CSPNIs (Dunn et al., 2020). These situations increase their risk of developing PN.

Limitations

This study has some limitations. One of the limitations is that there are other important causes of PN in the United States, such as AIDS/HIV and chemotherapy which were not controlled for in this study because of the sample size and availability of data constraints. In addition, trans or non-binary gender respondents were not controlled for in this study because there was not a large enough sample size for this category of respondents.

Implications

This study has implications for the discipline of public health, the practice of public health as a profession, and finally, for social change. The results of this study demonstrated that veteran/military status did not moderate the effect of PN in either the right or left foot on overall mortality in adults without diabetes. However, participants or adults who did not suffer from diabetes but had veteran/military status, had an increased hazard rate or risk for overall mortality when diagnosed with PN in either the right or left foot, but this association was not significant ($p > .05$)

These results build on existing evidence that having veteran/military status increases the risk of the development of PN, a disease that has been associated with significant morbidity and mortality (Hicks et al., 2021). Furthermore, Walden University defines positive social change as a deliberate process of the creation and application of ideas, strategies, and actions to promote the worth, dignity, and development of individuals and societies (Walden University, 2023). For government officials, relevant stakeholders, as well as public health practitioners, it should serve as a reminder that

there should be a renewed interest in policies that promote the health and welfare of veterans and military personnel. These results should be considered when advocating for funding for improved and targeted screening for PN among veterans and military personnel either at the local, state, or federal levels. The implications for social change are that adult veterans and military personnel without diabetes who have been diagnosed with PN in either foot, could enjoy better health outcomes if early screening for PN and aggressive management is instituted, to prevent unnecessary morbidity and overall mortality.

Recommendations for Further Research

The findings of this study, within its limitations, highlight that adult veteran/military personnel who did not suffer from diabetes but were diagnosed with PN in either foot, were at an increased risk for overall mortality, even though such association was not significant. Further research is recommended to examine PN in its entirety (both feet), since this study only examined PN in either the right or left foot.

Conclusion

PN is associated with a substantial burden among adult veterans and military personnel not suffering from diabetes in the United States. Having a veteran/military status without suffering from diabetes, as demonstrated by the results of this study, increased the hazard risk of overall mortality among these adults, especially when diagnosed with PN in either foot, although this association was not significant. Thus, in order to improve the health outcomes of these adult veterans/military personnel suffering from PN, there should be concerted effort on the part of relevant stakeholders, to

advocate for adequate funding at all levels of government (local, state, and federal) to ensure widespread targeted screening and aggressive management of PN among non-diabetic veteran/military personnel, in order to improve their health outcomes.

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Manuscript 3

Health Insurance Status as a Moderator of Peripheral Neuropathy on Cardiovascular Mortality in Non-Diabetic Adults

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Abstract

Peripheral neuropathy (PN) is a disorder of the peripheral nerves that connect the body to the central nervous system. It is highly prevalent among the older population, with an estimated prevalence of 30%, and usually presents with pain, numbness, weakness, ulceration, falls, amputations, and cardiovascular mortality. The overall prevalence of PN in the United States is 13.5% in adults with diabetes, and 11.6% in adults without diabetes, clearly indicating that PN is a significant public health problem among U.S. adults. Lack of access to health insurance has been associated with cardiovascular mortality and poor health outcomes in the United States. There are no published studies examining whether health insurance status moderates the effect of PN on cardiovascular mortality among U.S. adults without diabetes. Using the socioecological model as the theoretical framework, the purpose of this longitudinal study was to examine whether health insurance status moderated the effect of PN on cardiovascular mortality. Secondary data from the NHANES 1999-2015 dataset were analyzed using complex sample Cox regression analysis with the threshold for statistical significance taken at $p < 0.05$. Health insurance status did not moderate the effect of PN on either foot (RT. Foot, $p >$. 05; Lt. Foot, $p >$. 05) on cardiovascular mortality, although participants who had health insurance but did not suffer from diabetes had a reduced hazard risk for cardiovascular mortality when diagnosed with PN in either foot. The results have implications for positive social change. Provision of universal health insurance coverage, coupled with targeted screening for PN among adults not suffering from diabetes and who lack health insurance, can improve health outcomes for these adults.

Introduction

There is a significant burden of peripheral neuropathy (PN) with an associated cardiovascular mortality among adults without diabetes in the United States (U.S.), as highlighted by Hicks et al. (2021). PN is quite prevalent, particularly in the older population (Callaghan et al., 2018) and presents with significant morbidity that reduces the quality of life (QoL) of affected patients or individuals (Girach et al., 2019). Approximately two-thirds of patients suffering from PN experience neuropathic pain which is detrimental on their mental health and eventually culminate in a reduced QoL (Girach et al., 2019). Moreover, PN is a prevalent disease, especially among adults and it presents both diagnostic and therapeutic challenge to physicians and other healthcare providers (Callaghan et al., 2018). The prevalence of PN in some studies is as high as 10.4% for middle-aged (40-69 years) and 26.8% for older (> 70 years) U.S. adults (Hicks et al., 2021). Clearly, these statistics indicate that PN is a significant public health problem among adults in the United States. However, many of the studies that have examined the risk factors for PN in the United States., have mainly examined patients or adults with diabetes. In particular, there are no published studies on how health insurance status moderates the effect of PN on cardiovascular mortality. This situation has created a social problem, as it has been shown by Hicks et al. (2021) that cardiovascular mortality is associated with PN, even in adults without diabetes, hence, this was the justification for conducting this research in which I examined whether health insurance status moderated the effect of PN on cardiovascular mortality.

Health insurance status has been associated with health outcomes, particularly cardiovascular disease (CVD), and mortality (Akhabue et al., 2018). Similarly, PN has been associated with cardiovascular mortality (Hicks et al., 2021). Akhabue et al. (2018) highlighted that cardiovascular disease is the leading primary hospital discharge diagnosis, while cardiovascular mortality is the most common mortality in the United States. According to Akhabue et al., since the first open enrollment period began in October 2013, the Affordable Care Act (ACA) enabled millions of previously uninsured American to acquire health insurance coverage, although not all the States in the United States opted to expand Medicaid. However, States in the United States that expanded Medicaid during the ACA implementation reported a significantly greater reduction in the number of uninsured hospitalizations for serious cardiovascular events, when compared with the States that did not embrace the expansion of Medicaid (Akhabue et al., 2018). There is enough evidence in literature that suggests that having health insurance improves health outcomes and having health insurance reduces cardiovascular mortality. As Woolhandler and Himmelstein (2017) posited, the United States has a lower life expectancy when compared to other wealthy industrialized countries and is the only country with substantial numbers of uninsured residents. However, what is not known is whether health insurance status moderates the effect of PN on cardiovascular mortality. Since PN has been associated with cardiovascular mortality (Hicks et al., 2021), it is important to know whether health insurance status moderates the effect of PN on cardiovascular mortality. Hence, this was the justification for this research study in

which I examined whether health insurance status moderated the effect of PN on cardiovascular mortality among adults without diabetes in the U.S.

Significance/Importance

PN is a chronic debilitating disorder that often develops insidiously, making early diagnosis and management difficult for physicians and other healthcare providers (Brown et al., 2017). Globally, PN has been associated with significant mortality and morbidity (Brown et al., 2017); in the United States., PN has been associated with cardiovascular mortality and significant morbidity even among adults without diabetes (Hicks et al. (2021). Patients suffering from PN experience poor QoL which can be detrimental to their mental health, in addition to the neuropathic symptoms of pain, muscle cramps, numbness, falls, weakness, and stiffness, that they experience (Girach et al., 2019). This study is significant in that it provided useful insights on whether health insurance status moderated the effect of PN on cardiovascular mortality. Lack of health insurance has been linked to poor health outcomes (Akhabue et al., 2018); however, what was not known was whether health insurance status moderated the effect of PN on cardiovascular mortality. Since PN develops insidiously and is often difficult to diagnose, knowing whether health insurance status moderates the effect of PN on cardiovascular mortality will enable relevant stakeholders to institute targeted screening for individuals without health insurance.

The targeted screening of these individuals would likely result in early and timely diagnosis of PN, and allow for more positive health outcomes, which could bring about the desired positive social change for these individuals. Furthermore, this study is

significant for the discipline of public health, as it would fill a huge gap in the knowledge on the topic of whether health insurance status moderated the effect of PN on cardiovascular mortality. Presently, there are no published studies in literature that have examined this topic.

Theoretical Framework

The theory of the socioecological model was first introduced by Urie Bronfenbrenner in the 1970s (Kilanowski, 2017). Bronfenbrenner proposed that the nature of individuals' interaction with their physical and sociocultural environments can impact health and lead to the development of diseases (Kilanowski, 2017). The revised constructs of the socioecological model are individual, network, community, and structural (Cowan et al., 2021). It implies that factors or influences operating at every level or construct of this theoretical framework can impact on an individual's health and eventually lead to the development of diseases such as PN or even play a role in determining whether health insurance status moderates the effect of PN on cardiovascular mortality. As Cowan et al. (2021) highlighted, the influence of the structural construct or structural level factors are exerted through laws, policies, society, and economics. It is already well established that government policies that expanded Medicaid during the Affordable Care Act (ACA) in the U.S. led to a significant reduction in the number of uninsured hospitalizations for major cardiovascular events and cardiovascular mortality (Akhabue et al., 2018).

The socioecological model was applied to organize the discussion in this study. Health insurance status can be influenced by factors acting at the structural level. These

factors are mediated through government laws and policies, as well as society and economics. Government policies, for example, that emphasizes or ensures universal health insurance coverage for the population, would likely result in better health outcomes for such populations, thereby bringing about the desired positive social change in such populations. The main independent variable in this study, PN, can be explained by the structural construct. Evidence from available studies suggests that PN develops as a result of multiple risk factors ranging from chronic non-communicable diseases to exposure to environmental chemicals, herbicides or toxins, and infectious diseases. In the structural construct, emphasis is placed on economic policies or laws, which can enable individuals gain access to adequate medical treatment and also protect them from exposure to noxious or toxic environmental agents; in addition, the right set of public health policies or laws can protect individuals from exposure to infectious diseases and ensure prompt treatment of such infectious diseases during an outbreak. All these measures can influence the development of PN.

Furthermore, health insurance status has been associated with health outcomes in many societies around the world (Akhabue et al., 2018). Hence, this research study further makes an original contribution to the discipline of public health as it highlighted whether health insurance status moderated the effect of PN on cardiovascular mortality.

The purpose of this quantitative secondary data analysis study was to examine whether health insurance status moderated any effect of PN on cardiovascular mortality among an adult population not suffering from diabetes in the United States, while controlling for age, gender,

and ethnicity.

Relevant Scholarship/Literature Review

Part of my search strategy for this literature review included employing the following search terms, words and/ or phrases: *peripheral neuropathy; risk factors for peripheral neuropathy; social determinants of peripheral neuropathy; peripheral neuropathy in non-diabetics; peripheral neuropathy in the United States; peripheral neuropathy and overall mortality; effect of health insurance status on health outcomes; effect of health insurance status on peripheral neuropathy; peripheral neuropathy in developed countries; peripheral neuropathy in developing countries.* The search was limited to articles or text written in English from the following search engines or sources: Google and Google Scholar, Walden University library, ProQuest, SAGE Premier, PubMed, MEDLINE, CINHAL Plus, and Science Direct Database. In the literature review, I included background information on peripheral neuropathy in general and its epidemiology, especially the non-diabetic causes. In addition, I examined the problem of peripheral neuropathy within a global context and examined patterns of distribution and epidemiology in developed and developing countries. Furthermore, I examined the socioeconomic risk factors for peripheral neuropathy among adults without diabetes and I tried to demonstrate a logical connection between what is known and what needed to be studied – the gap in research. I synthesized the relevant evidence and research on the topic of peripheral neuropathy by various researchers. I also examined the clinical consequences of peripheral neuropathy, which usually contributed to the morbidity and mortality of individuals not suffering from diabetes. In addition, I examined if lack of

health insurance could impact health outcomes, and the association between this social determinant of health and the possible development of peripheral neuropathy.

Background Information, Global Trends and Epidemiology

Understanding the background information and the epidemiology of PN, especially in non-diabetic individuals, is an important aspect of this study. This study focused mainly on whether health insurance status moderated the effect of PN on cardiovascular mortality in non-diabetic adults in the United States. Hence, having a good understanding of the non-diabetic causes among adults in the U.S. was a good starting point. PN is an important public health condition with a prevalence of almost 15% in the adult population of age over 40 years in the United States (Valentine, 2019). Globally, PN is among the most common neurological diseases, with an estimated incidence of 77/100,000 inhabitants per year and a prevalence of 1% – 12% in all age groups (Lehmann et al., 2020). By definition, peripheral neuropathies encompass all conditions that cause damage to the peripheral nervous system (PNS), which may include mechanical, toxic, and metabolic causes (Szewczyk et al., 2021). Furthermore, the clinical symptoms exhibited by sufferers of this chronic debilitating disease depend on its severity, distribution, affected structure of the nerve cell, as well as the type of affected neurons (Szewczyk et al., 2021). Because of this, multiple classifications, or types of PN can be encountered in clinical practice, with an overlap between the various types. According to Szewczyk et al. (2021), the prevalence of PN is slightly higher in women than men, and the occurrence of PN may be influenced by the type of work performed (Szewczyk et al., 2021).

Globally, the prevalence of PN also varies considerably from one geographical location to another. As Hanewinckel et al. (2016, as cited in Szewczyk et al., 2021) highlighted, African and Middle Eastern countries generally have a low prevalence of PN of 0.8 to 2.5 per 1000 among adults, when compared to a prevalence of 7.3 to 32.5 per 1000 among adults in Europe. Szewczyk et al. (2021) highlighted that some of the differences in prevalence rates of PN observed in these different geographical locations could be partly explained by differences in assessment protocol for PN. In the general population in Europe, the average prevalence of PN ranges from 1% to 3% (Szewczyk et al., 2021), whereas the prevalence of PN is slightly higher at 7% among the elderly (Szewczyk et al., 2021). In comparing the prevalence of PN in some of the developed countries, Szewczyk et al. (2021) highlighted that the prevalence of PN in the Netherlands is 5.5% in comparison to a prevalence of 3.9% among the U.S. population.

Szewczyk et al. (2021) opined that the prevalence of PN is influenced by socioeconomic status, the population structure, and other risk factors. However, the authors did not examine or highlight whether an important social determinant of health such as health insurance status moderated the effect of PN on cardiovascular mortality. Hence, this was the justification for this study in which I examined whether health insurance status moderated the effect of PN on cardiovascular mortality.

Non-diabetic Causes of Peripheral Neuropathy

While diabetes mellitus remains the most common cause of PN worldwide, the development of PN may have many other different causes which can lead to generalized, and sometimes to isolated PN (Roth et al., 2021). According to Roth et al. (2021), normal

aging has been associated with the development of some form of PN in the population. As earlier pointed out by Szewczyk et al. (2021), the prevalence of PN is slightly higher at 7% among the elderly. Even though oxidative stress has been postulated as a possible mechanism or pathogenesis for PN (Mallet et al., 2020), Roth et al. (2021) highlighted that the genesis of PN is multifactorial and not fully explained. However, hyperglycemia, dyslipidemia, inflammation and immune responses, and macro-and microvascular diseases, along with a host of other pathological conditions, have been proposed as possible mechanisms for the development of PN (Roth et al., 2021).

Amyloidosis is an important non-diabetic cause of PN. It comprises of a group of diseases usually characterized by the accumulation or deposition of amyloid fibrils in various tissues throughout the human body (Roth et al., 2021). Amyloid fibrils are extremely strong, highly ordered and organized insoluble fibers or aggregates, formed by different peptides and proteins. The deposition of these amyloid deposits in the epineurium, perineurium, and endoneurium of the peripheral nerves results in dysfunction of such nerves, with subsequent development of PN (Roth et al., 2021). PN can result from either primary amyloidosis or secondary amyloidosis (Roth et al., 2021). Primary amyloidosis results from the accumulation of light-chain amyloid fibrils, while secondary amyloidosis results from the deposition of acute-phase reactant protein or serum amyloid A protein, which is produced during chronic inflammatory or infectious diseases (Roth et al., 2021).

Sarcoidosis is a chronic disease of unknown etiology characterized by lymph node enlargement in many parts of the body and widespread appearance of granulomas

derived from the reticuloendothelial system (Roth et al., 2021). These granulomas may accumulate within the peripheral nerves, resulting in the development of PN (Roth et al., 2021). PN in sarcoidosis consists of granulomatous and non-granulomatous small fiber neuropathy (SFN), as highlighted by Roth et al. (2021), with SFN reported in over 40% of the systemic cases of sarcoidosis (Roth et al., 2021).

Autoimmune or inflammation related PN is an important cause of PN (Roth et al., 2021). Autoimmune PN encompasses systemic autoimmune diseases, autoimmune disorders which specifically cause damage to peripheral nerves, or malignancies (Roth et al., 2021). In cases of autoimmune PN, damage to the peripheral nerves occur through autoantibodies which may be directed against membrane receptors of peripheral nerves (Roth et al., 2021), directed against cell surface glycoproteins (Roth et al., 2021), or in the case of cancers or paraneoplastic, such autoantibodies are directed against intracellular onconeural antigens (Roth et al., 2021). In addition, the higher the level of antibodies formed, the more severe the level of PN (Roth et al., 2021). However, paraneoplastic or cancer antibodies tend to correlate more with a unique cancer form than to a specific neuropathy, and their levels do not correlate with the degree or severity of the PN (Roth et al., 2021).

Infection-related PN is an important cause of non-diabetic PN (Roth et al., 2021). A wide range of various infectious diseases caused by viruses and bacteria lead to different levels of peripheral nerve dysfunction. These infectious diseases include Varicella-zoster virus infection (Roth et al., 2021), which belongs to the human herpesvirus group that is responsible for the primary infection, varicella (Roth et al.,

2021). After the acute infection has subsided, the virus continues to live in the peripheral ganglia, where it can be reactivated spontaneously or after following other triggers, to cause herpes zoster (Roth et al., 2021); herpes zoster is usually accompanied by PN with symptoms such as pain, numbness, and paresthesia (Roth et al., 2021).

Chagas disease, caused by the hemoflagellate parasite, Trypanosoma cruzi (Roth et al., 2021) is another important cause of PN. The disease is endemic in Central and South America, and it is caused through bites from Triatominae bugs (Roth et al., 2021). The chronic phase of this disease is typified by the destruction of ganglion cells both in the central and peripheral nervous system, resulting in the development of PN, among other disorders (Roth et al., 2021).

While Guillain Barre syndrome (GBS) is sometimes regarded as an autoimmune disease, the exact mechanism is unknown. As Roth et al. (2021) highlighted, 50 to 70% of cases of GBS usually follow a respiratory infection, gastrointestinal infection, or any other immune stimulus that induces autoimmune attacks against the peripheral nerves. The development of PN in these patients is accompanied by symptoms such as symmetric weakness, paresthesia, numbness, and pain (Roth et al., 2021).

According to Julian et al. (2019), the prevalence of Alcohol-related PN amongst chronic users or abusers is quite high, estimated at 46.3% (95% CI [35.7, 57.3]), when confirmed by nerve conduction studies. The pattern of PN developed in alcohol-abusers is a predominantly progressive damage of the sensory axons in a length-dependent manner (Julian et al., 2019); in addition, the development of alcohol-related PN is dependent on the total lifetime amount of ethanol consumed (Julian et al., 2019), male

gender, genetics and the type of alcohol consumed (Julian et al., 2019). It is presently unclear what pathogenetic pathways lead to the development of PN in chronic alcohol users; hence, it is unknown whether the direct toxic effects of ethanol or another currently unidentified agent is directly linked to damage of the peripheral nerves. However, according to Julian et al., based on the available limited data, the associated deficiency of the B-vitamins, inclusive of thiamine, observed in chronic alcohol users could be responsible for the development of PN.

Toxic PN is another important form of non-diabetic or acquired PN. This type of PN is caused by various xenobiotics such as drugs, chemicals, pesticides, and carcinogens that damage components of the peripheral nervous system (Valentine, 2020). The various causes of toxic PNs can be classified as environmental, occupational, recreational, or iatrogenic (Valentine, 2020). In wealthy or developed countries, drug toxicity associated with chemotherapy has been identified as the most common cause of toxic PN (Valentine, 2020); however, in developing countries, occupational and environmental exposures to xenobiotics such as arsenic, lead, mercury, and organophosphates found in various pesticides, insecticides, and herbicides, are the leading causes toxic peripheral neuropathy (Valentine, 2020). A possible reason why occupational exposures to these xenobiotics account for the development of PN in many developing countries is that there is less strict monitoring associated with many manufacturing processes, which generate many of these neurotoxicants. Generally speaking, these xenobiotics cause damage to the neuronal perikaryons, axons, the Schwan cell, or the synapse (Valentine, 2020). The damage to the peripheral nerves by these

neurotoxicants is dose dependent, symmetrical, and reversible, provided there is adequate time following exposure to such agents (Valentine, 2020); in addition, individuals exposed to these agents present with numbness, paresthesia, or weakness in a characteristic stocking glove distribution (Valentine, 2020).

Fluoroquinolone is an antibiotic that is widely used worldwide and is associated with the development of PN (Morales et al., 2019). In a nested case-control study that included 5357 incident PN cases and 17, 285 matched controls, Morales et al., highlighted that exposure or use of oral fluoroquinolone was associated with an increased relative incidence of PN, when compared with non-exposure to fluoroquinolone (adjusted incident rate ratio, 1.47; 95% CI [1.13, 1.92]). The risk of developing PN following the use of fluoroquinolone antibiotic was found to have increased by an additional 3% following each day of the antibiotic use, and the risk persisted for up to six months following exposure to the antibiotic (Morales et al., 2019). In comparison, Morales et al. (2019) did not find any significant increased risk in the development of PN with exposure to or use of oral amoxicillin-clavulanate, another widely used antibiotic. These findings suggest that health care providers, particularly physicians, should consider these potential side effects when prescribing fluoroquinolone antibiotics.

Monoclonal gammopathy-associated PN is another important non-diabetic cause of PN. Monoclonal gammopathies encompass a spectrum of disorders that involves the secretion of a monoclonal immunoglobulin known as a monoclonal (M) protein (Chaudhry et al., 2017). The different categories of monoclonal gammopathy-associated PN include monoclonal gammopathy of undetermined significance (MGUS), which can

either be IgM, non-IgM, IgG, or IgA (Chaudhry et al., 2017). As Chaudhry et al. (2017) highlighted, other categories of monoclonal gammopathy-associated PN are multiple myeloma (which includes smoldering multiple myeloma), Waldenstrom macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome, systemic immunoglobulin light chain amyloidosis, and coincidental PN in patients with a monoclonal protein. While the pathological pathways associated with monoclonal gammopathy-associated PN is not clearly understood, Chaudhry et al. (2017) argued that Waldenstrom macroglobulinemia and IgM MGUS-associated PN might be associated with demyelination and widening of the myelin lamellae respectively. Furthermore, demyelination has also been associated with PN in some patients with IgG MGUS (Chaudhry et al., 2017), while in a significant proportion of patients with IgM monoclonal gammopathy-associated PN, Chaudhry et al. (2017) found that the pathological pathways involved the binding of the M protein to myelin associated glycoprotein (MAG) in the peripheral nerves.

Hereditary PN is also an important cause of non-diabetic PN. As Eggermann et al. (2018) highlighted, hereditary PNs constitute a significant group of genetic diseases, and the overall prevalence of hereditary PN is estimated at 1 in 2500 (Eggermann et al., 2018). The use of next-generation sequencing (NGS) has improved the detection of many hitherto unknown involved genes and genetic defects that cause PN (Eggermann et al., 2018). According to Eggermann et al. (2018), the forms of hereditary PN that have been identified include Charcot-Marie-Tooth disease (CMT, also referred to as hereditary motor sensory neuropathy, HMSN), the hereditary sensory and autonomic neuropathies

(HSAN, also referred to as hereditary sensory neuropathy, HSN), the hereditary motor neuropathies (HMN), and small fiber neuropathies (SFN). Generally speaking, mutations have been identified in more than 100 genes which cause hereditary PN (Eggermann et al., 2018).

Some socioeconomic factors have been implicated as possible causes of PN. However, because many studies on PN have been restricted to populations with diabetes, this has resulted in limited evidence of the potential contribution of some socioeconomic and psychosocial risk factors to the development of PN in non-diabetic populations. Dusendang et al. (2019) highlighted that perceived discrimination in midlife was associated with the development of PN later in life. According to Dusendang et al. in their study, women who reported perceived discrimination had 29% higher odds of PN when compared with women who did not report perceived discrimination (95% CI [1.01, 1.66]). In addition, the authors highlighted that 30% of total effect of discrimination on PN was mediated indirectly by the participant's body mass index (BMI). Dusendang et al. argued that discrimination was a form of chronic stressor, and the pathogenesis of PN in individuals who had experienced discrimination was probably related to the release of proinflammatory substances in the body, with associated dysregulation of the cardiovascular and metabolic functions, leading to the damage of the peripheral nerves.

Low socioeconomic status, irrespective of the participants' diabetic status, was also found to be associated with prevalent PN in the study by Dusendang et al. (2019). Most of these women from low socioeconomic status also reported an associated financial strain. As Dusendang et al. highlighted, the combination of low socioeconomic

status and the associated financial strain could result in increased secretion of stress hormones which ultimately could lead to an increase in allostatic load – the cumulative effects that chronic stress has on mental and physical health. As Dusendang et al. opined, one of the pathophysiologic consequences of this increase in allostatic load is the development of PN. In addition, as Dusendang et al. argued, people of low socioeconomic status generally have poorer nutritional status, engage is less physical activity or exercise, tend to have more exposure to environmental pollutants or toxins, and usually have less access to quality health care, when compared to people of higher socioeconomic status. These situations increase the risk of development of PN in people of low socioeconomic status. Furthermore, even people of low socioeconomic status who seek care for PN symptoms may be less likely to receive appropriate and proper diagnostic workup based on their socioeconomic status. This situation may lead to poorer management of their PN and further exacerbate their medical condition.

Poor housing, homelessness, and disadvantaged neighborhood conditions have all been linked to poorer health outcomes, such as the development of PN, infectious diseases, and other chronic medical conditions (Boch et al., 2020). The exact pathways by which poor or sub-standard housing is associated with the development of PN is not clearly understood. However, as Valentine (2020) highlighted, the risk of environmental exposures to various xenobiotics, particularly lead, is higher in people living in poor or sub-standard housing units. Chronic exposure to lead has been associated with the development of PN (Valentine, 2020). According to the United States Department of Housing and Urban Development (2017, as cited in Boch et al., 2020), almost 8.3 million

very low-income rental households in the United States had worst case needs and the occupants were regarded as living in severely inadequate conditions. Furthermore, Raymond et al. (2011, as cited in Boch et al., 2020), noted that 5.8 million residencies in the United States were considered inadequate based on significant deficiencies in plumbing, heating, electricity, and upkeep (including exposures to xenobiotics such as lead). Living in these poor and sub-standard housing units, with the associated increased exposure to various xenobiotics, can lead to the development of various chronic diseases such as PN.

Synthesis of Research Findings

Roth et al. (2021) found that normal aging was associated with the development of PN; however, the authors pointed out in their systematic review of the literature that the etiology of PN was multifactorial and not fully explained by one mechanism. While Roth et al. proposed a multicausal mechanism for the etiopathogenesis of PN, they however highlighted some major specific causes for PN which include diabetes, diseases involving tissues deposits, infections, autoimmunity, cancers or malignancies, and metabolic diseases. Roth et al. did not examine whether health insurance status moderated the effect of PN on cardiovascular mortality, even though PN has been linked to cardiovascular mortality in adults (Hicks et al., 2021).

While Szewczyk et al. (2021) highlighted in their retrospective cross-sectional study that the prevalence of PN is slightly higher at 7% among the elderly, the authors also opined that women have a slightly higher prevalence of PN when compared to men. In addition, Szewczyk et al. suggested that one’s socioeconomic status, occupation, and

the population structure were all associated with the development of PN. Of particular note was the statistically significant finding ($p < 0.05$) of the association of the place of residence and gender, and the development of PN. Szewczyk et al. highlighted that more affected women live in the urban areas, whereas more men diagnosed with PN inhabit the rural areas. The authors suggested that the statistically significant differences could be partly explained by the work performed, as well as the external or internal factors or mechanisms that influence the manifestation of PN. However, the authors did not specifically examine whether health insurance status moderated the effect of PN on cardiovascular mortality.

Julian et al. (2019) in their systematic review of the literature, highlighted a high prevalence of PN of 43% (95% CI [35.7, 57.3]) particularly amongst chronic alcohol consumers or abusers. While the authors posited that the pathogenetic pathways to the development of PN in chronic alcohol consumers was not clearly understood, Julian et al. (2019) highlighted that the development of PN in such individuals is dependent on the total lifetime amount of alcohol consumed, male gender, and probably some associated genetic factors. However, even though some studies have found an association between cardiovascular mortality and PN, the authors did not examine whether health insurance status moderated the effect of PN on cardiovascular mortality.

In a systematic review of literature, Valentine (2020) highlighted various xenobiotics or peripheral nervous system toxicants that can lead to the development of PN, if an individual is exposed to such xenobiotics. Such toxic agents could be classified as environmental, occupational recreational, or iatrogenic. Prominent among these agents

are drug toxicity, especially chemotherapeutic agents, arsenic, lead, mercury, and organophosphates, which are constituents of many commonly used herbicides and pesticides. All these agents can lead to the development of PN, which has been associated with cardiovascular mortality. However, Valentine (2020) did not examine whether health insurance status moderated the effect of PN on cardiovascular mortality.

Chaudry et al. (2017) in their systematic review, highlighted that PN can occur in patients suffering from various plasma cell disorders, ranging from the premalignant MGUS stage to the readily apparent malignant stages of multiple myeloma and Waldenstrom macroglobulinemia. The authors did not examine whether health insurance status contributed to the development of PN in patients suffering from these various plasma cell disorders, nor did they examine whether health insurance status moderated the effect of PN on cardiovascular mortality. While Eggermann et al. (2018) in their systematic review of the literature highlighted that hereditary peripheral neuropathies constitute a large group of genetic disorders and are important causes of non-diabetic neuropathy, the authors did not examine whether health insurance status moderated the effect of PN on cardiovascular mortality.

Dusendang et al. (2019) in their national longitudinal study of Women's Health, highlighted that woman who had experienced perceived discrimination in midlife had 29% higher odds of developing PN, when compared to women who did not report perceived discrimination. Furthermore, Dusendang et al. highlighted that each increasing level of perceived discrimination in midlife was associated with 43% higher odds of developing PN. However, the authors did not examine whether health insurance status

moderated the effect of PN on cardiovascular mortality. Boch et al. (2020) in their national survey found that poor housing, homelessness, and disadvantaged neighborhood conditions are associated with poor health outcomes such as the development of PN. While the exact pathways by which poor or substandard housing is associated with the development of PN is not fully understood, Boch et al. postulated that the risk of environmental exposures to various xenobiotics, particularly lead, is increased in people living in poor or sub-standard housing units. However, while health insurance status has been associated with health outcomes, the authors did not specifically examine whether health insurance status moderated the effect of PN on cardiovascular mortality.

Logical Connection Between What is Known and What Needs to be Studied.

From this literature review, the various important non-diabetic causes of PN were clearly highlighted. In addition, the important risk factors for PN were also highlighted. However, an important gap in literature still exists on whether health insurance status moderates the effect of PN on cardiovascular mortality. Lack of health insurance has been linked to poor health outcomes, such as the development of PN and other chronic diseases. Similarly, PN has been linked to cardiovascular mortality. What is however not known, is whether health insurance status moderates the effect of PN on cardiovascular mortality.

Research Questions and Design

Research Question: Does health insurance status moderate the effect of peripheral neuropathy on cardiovascular mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity?

Null Hypothesis: Health insurance status does not moderate the effect of peripheral neuropathy on cardiovascular mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity.

Alternative Hypothesis: Health insurance status moderates the effect of peripheral neuropathy on cardiovascular mortality among an adult population without diabetes in the NHANES 1999 to 2015 dataset, while controlling for age, gender, and ethnicity.

Rationale for Research Question

The rationale for choosing this requestion question was that of the substantial burden of PN and the associated cardiovascular mortality among adults without diabetes in the United States (Hicks et al., 2021). However, there was a huge gap in the literature as to whether health insurance status moderates the effect of peripheral neuropathy on cardiovascular mortality among adults without diabetes in the United States.

Research Design

The specific quantitative research design for this study is a longitudinal design (Frankfort-Nachmias & Leon-Guerrero, 2018), with the outcome variable – cardiovascular mortality, examined in the follow-up mortality dataset of 2015. This quantitative analysis helped to determine whether health insurance status (independent variable) moderated the effect of peripheral neuropathy (main independent variable) on cardiovascular mortality (dependent variable), while controlling or adjusting for age, gender, and ethnicity (covariates).

Approach Used to Address the Research Problem

The epistemological approach that I employed in addressing this research problem is that of positivism (Park et al., 2019). The approach of positivism relies on the hypothetico-deductive method to ascertain or verify priori hypotheses that are often stated quantitatively (Park et al., 2019). The hypothetico-deductive method is a circular process that starts with theory from the literature (Park et al., 2019). This enables the researcher to build or construct testable hypotheses, design an experiment through operationalizing variables, and finally conduct an empirical study based on experimentation (Park et al., 2019). The findings from such a study are employed to help inform theory, bring about a desired positive social change, and contribute to the literature, thereby completing the circular process (Park et al., 2019): theory – hypothesis – operationalizing variables – experimentation – theory (Park et al., 2019). The positivist paradigm or approach is based on the notion that knowledge can and must be developed objectively, without the values or ideas of the researcher or participants influencing its development (Park et al., 2019).

Methods

Participants

The target population for this study was all adults who did not suffer from diabetes in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2015 dataset.

Sample and Power

This study employed a secondary dataset from the NHANES 1999 to 2015 dataset. The sampling strategy used was simple random sampling (Frankfort-Nachmias & Leon-Guerrero, 2018). Participants who satisfied the inclusion criteria (all adults without diabetes and who had the complete set of the variables of interest in this study) were randomly recruited into the study. This sampling strategy gave each of the participants an equal chance of being selected into the study (Frankfort-Nachmias & Leon-Guerrero, 2018).

To determine the appropriate sample size for this study, G* Power 3.1.9.7 (Faul et al., 2009) was employed. As Bhandari (2022) highlighted, the criteria for choosing effect size prior to estimating sample size, depends on what has been documented on previous research studies on the topic of interest. However, since there were no published studies on whether health insurance status moderated the effect of PN on cardiovascular mortality, the effect size f^2 was set at medium value (0.15) in G* Power (Faul et al., 2009). F test was selected along with the statistical test of: Cox Regression, Fixed model, R^2 deviation from zero in G* Power (Faul et al., 2009). Since there were six predictor variables in this study (peripheral neuropathy, health insurance status, diabetes, age, gender, and ethnicity), and with the *p* value set at 0.05 and power set at 80% in G* Power (Faul et al., 2009, the sample size calculated was 98 participants. This was the minimum sample size required for this study. The study had an adequate sample size of 120782 participants, more than the estimated minimum sample size of 98 participants for the study. Missing data was treated by the technique of multiple imputation.

Variables/Sources of Data:

The main independent variable in this study was Peripheral neuropathy, the independent variable or moderating variable was health insurance status, the dependent variable was cardiovascular mortality, while the covariates were age, gender, and ethnicity. The participants were stratified based on their diabetes status. According to the alternative hypothesis in this study, it was expected that the independent variable (health insurance status) would moderate the association between peripheral neuropathy and cardiovascular mortality, while adding the covariates could increase the accuracy of the results from the research study. The sources of the data used to operationalize the variables were the NHANES 1999 to 2000 and the 2015 follow-up mortality datasets.

The main independent variable was peripheral neuropathy, a Categorical Nominal variable, and coded as: None = 1, Insensate site group = 2. The other independent variable was health insurance status, a Categorical Nominal variable, and coded as: Yes =1, No = 2. In addition, Diabetes, a Categorical Nominal variable, coded as Yes = 1 and No = 2. The covariates were age (years), a Categorical Nominal variable, and coded as: 0 to 84 = 1, $\geq$ 85 = 2; Gender, a Categorical Nominal variable, and coded as: Male = 1, Female = 2, and Ethnicity, a Categorical Nominal variable, and coded as: Non-Hispanic White = 1, Non-Hispanic Black = 2, Mexican American = 3, Other Race – Including Multi-Racial = 4, Other Hispanic = 5. The dependent variable was cardiovascular mortality, a Categorical Nominal variable, and coded as 1 = Cardiovascular mortality, 0 = non-Cardiovascular mortality.

Instrumentation or Measures:

Secondary data from the NHANES 1999 to 2015 dataset were employed in this study. This data was collected by the Centers for Disease Control and Prevention, and hence, the data was assumed to be valid and reliable. The dataset was freely available; hence, no special instruments or data-collection tools were employed. The data for the research study was assembled in SPSS before performing the statistical analyses.

Design and Analysis:

The research design for this study was a longitudinal design (Frankfort-Nachmias & Leon-Guerrero, 2018). The main independent variable for this research study was peripheral neuropathy, the other independent variable was health insurance status, the dependent or outcome variable was cardiovascular mortality, while the covariates were age, gender, and ethnicity. Participants were stratified based on their diabetes status. Peripheral neuropathy is a categorical nominal variable; Health insurance status is a categorical nominal variable; Cardiovascular mortality is a categorical nominal variable; Age is a categorical nominal variable, Gender is a categorical nominal variable, and Diabetes is a categorical nominal variable.

Descriptive statistics for peripheral neuropathy, health insurance status, cardiovascular mortality, age, gender, ethnicity, and diabetes were frequency tables. Inferential statistics for peripheral neuropathy, health insurance status, cardiovascular mortality, age, gender, ethnicity, and diabetes, was performed using complex sample cox regression analysis, since health insurance could moderate the effect of peripheral neuropathy on cardiovascular mortality.

The justification for the selection of a longitudinal study design (Frankfort-Nachmias & Leon-Guerrero, 2018) for this study, was that this study examined secondary dataset for the population of interest - all adults who did not suffer from diabetes in the NHANES 1999 to 2004, and then linked them up with the 2015 follow-up cardiovascular mortality dataset. The event of interest was whether the patient died or was alive, at the time of this study.

Results

This quantitative longitudinal study was designed to investigate whether health insurance status moderated the effect of peripheral neuropathy on cardiovascular mortality among an adult population in the United States, who did not suffer from diabetes, while controlling for age, gender, and ethnicity. The data used in this study to operationalize the variables was the NHANES 1999 to 2015 dataset. This chapter elaborates on how the study was conducted, data manipulation techniques, data treatment procedures such as treatment of missing data, data cleaning and data weighting. The 1999 to 2015 NHANES dataset employed for this study had adequate sample size (more than the minimum sample size estimated for this study) for all the variables of interest.

Execution

This study was approved by the Walden University's Institutional Review Board (IRB) on 03/08/2023, with the approval number 03-08-23-0753053. In this study, I employed the use of the NHANES dataset from 1999 to 2000, and the follow-up mortality dataset of 2015. The variables of interest from the 1999 to 2000 dataset were merged with the variables of interest in the 2015 follow-up mortality dataset in SPSS

version 27, using the participant's respondent sequence number (SEQN). After the merger, the data was cleaned. Because this was a complex sample of data from a nationally representative dataset from the NHANES 1999 to 2015 dataset, it was essential to perform weighting before the statistical analysis. In a nationally representative dataset such as the NHANES 1999 to 2015, there is usually an underrepresentation and overrepresentation of certain groups. Weighting of the data was necessary to ensure that the data used for the statistical analysis was representative of the population from which it was collected. Treatment of missing data was performed using the technique of multiple imputation.

To perform weighting of the dataset, a complex sample analysis (CSA) plan was created in SPSS version 27. The variables SDMVSTRA (strata), SDMVPSU (clusters), and MEC6YR (sample weight) were employed in performing weighting during the creation of the CSA. Inferential statistics of complex sample cox regression and descriptive statistics of frequency tables were performed using SPSS version 27.

In the HNANES 1999-2000 dataset, peripheral neuropathy was defined as one or more insensate sites of three sites tested per foot based on the Semmes-Weinstein 10g monofilament. The results of this study include the descriptive statistics – frequency tables, of the variables in the study. This is followed by the diagnostic tests of the proportional hazards assumptions, diagnostic tests of model effects, and the inferential statistics results of complex sample cox regression analyses.

Descriptive Statistics

Table 1

Frequencies and Percentages of Participants With Peripheral Neuropathy in the Right Foot

Right foot	*n*	%
Insensate site	66	0.1
None	183	0.2
Not enough information to collect	2315	1.9
Missing	118218	97.8
Total	120782	100.0

Note. This table demonstrates that 66 participants with all the variables of interest in the study, had peripheral neuropathy, compared to 183 participants without peripheral neuropathy in the right foot (Learpn).

Table 2

Frequencies and Percentages of Participants With Peripheral Neuropathy in the Left Foot

Left foot	*n*	%
Insensate site	73	0.1
None	227	0.2
Not enough information to collect	2334	1.9
Missing	118148	97.8
Total	120782	100.0

Note. This table demonstrates that 73 participants with all the variables of interest in the study, had peripheral neuropathy, compared to 227 participants without peripheral neuropathy in the left foot (Lealpn).

Table 3

Frequencies and Percentages of Participants' Health Insurance Status

Health insurance	*n*	%
1 = Yes	7736	6.4
2 = No	2038	1.7
Missing	111008	91.9
Total	120782	100.0

Note. This table highlights that more participants had health insurance coverage (7736) when compared to participants without health insurance coverage (2038).

Table 4

Frequencies and Percentages of Participants' Cardiovascular Mortality Status (Card_mort)

Cardiovascular mortality status	*n*	%
0 = non-Cardiovascular mortality	8513	7.0
1= Cardiovascular mortality	1863	1.5
Missing	110406	91.4
Total	120782	100.0

Note. This table highlights fewer participants (1.5%) experienced the terminal event of cardiovascular mortality, when compared to participants that did not experience cardiovascular mortality at the end of the follow-up period.

Table 5

Frequencies and Percentages of Participants Without Diabetes

Diabetes	*n*	%
1 = Yes	489	0.4
2 = No	8936	7.4
Missing	111357	92.2
Total	120782	100.0

Note. This table highlights that more participants did not suffer from diabetes (7.4%), compared to participants with diabetes (0.4%).

Table 6

Frequencies and Percentages of Participants' Ages

Category	*n*	%
1 = 18 to 49 years	3028	2.5
2 = 50 years and over	2420	2.0
Missing	115334	95.5
Total	120782	100.0

Note. This table highlights that more participants fell within the 18 to 49 years age group (2.5%), compared to participants within the age group 50 years and over (2.0%).

Table 7

Frequencies and Percentages of Participants' Gender

Category	*n*	%
1 = Male	4883	4.0
2 = Female	5082	4.2
Missing	110817	91.7
Total	120782	100.0

Note. This table highlights that more participants were females (4.2%), compared to males (4.0%).

Table 8

Frequencies and Percentages of Participants' Ethnicity

Ethnicity	*n*	%
1= Non-Hispanic White	3423	2.8
2= Non-Hispanic Black	2273	1.9
3= Mexican American	3393	2.8
4= Other Race – Including Multi-Racial	287	0.2
5= Other Hispanic	589	0.5
Missing	110817	91.7
Total	120782	100.0

Note. This table highlights the percentages of the different participants. Non-Hispanic Whites (2.8%) and Mexican American (2.8%) constituted the majority of the participants, while other race – Including Multi-Racial, constituted the least of the participants (0.2%).

Diagnostic Tests/ Tests of Assumptions

Table 9 highlights the Tests of Model Effects. PN in the right foot (LEARPN) with $p > .05$, Health insurance status with $p > .05$, Diabetes status with $p > .05$, Age with $p > .05$, Gender with $p > .05$, and Ethnicity with $p > .05$, did not contribute significantly to the model. Hence, one can conclude that none of the variables had a statistically significant effect on the survival or cardiovascular mortality of the participants.

Table 9

Tests of Model Effects

Variable	*df1*	*df2*	Wald *F*	Sig.
LEARPN	1.000	10.000	24.251	.071
HEALTH INSURANCE	1.000	10.000	1.038	.332
DIABETES	1.000	10.000	2.315	.159
AGE	1.000	10.000	2.630	.136
RIAGENDR	1.000	10.000	2.508	.144
RIDRETH2	1.000	10.000	1.395	.265

Note. Table 9 highlights that none of the variables significantly contributed to the cox model or the participants' survival/cardiovascular mortality.

Table 10 highlights the overall tests of proportional hazards. According to Dessai and Patil (2019), the proportional hazards assumption states that the relationship between the hazard for the terminating event and time is not dependent (or conditional) on the levels of the covariates. This assumption is violated if the p is < 0.05 or significant (Dessai & Patil, 2019).

Table 10

Overall Tests of Proportional Hazards

df1	*df2*	Wald *F*	Sig.
6.000	5.000	1.243	.341

Note. Table 10 highlights that the proportional hazards assumption was not violated, as $p > .05$.

Table 11 highlights Parameter Estimates for Alternative Model. The positive B coefficient (1.745; Hazard Ratio [HR], 5.73) for PN in the right foot indicates that PN in the right foot was associated with an increased hazard risk of cardiovascular mortality, but this association was not significant ($p > .05$, from Table 9). Health insurance status did not moderate the effect of PN on cardiovascular mortality ($p > .05$, from Table 9). Since health insurance status has a negative coefficient (-3.019; HR, 0.05) and was coded Yes=1 and No =2 and Diabetes also has a negative coefficient (-2.225; HR, 0.11), it implies that participants who did not suffer from diabetes but with health insurance, had a reduced hazard risk of cardiovascular mortality when diagnosed with PN in the right foot, however, this association was not significant ($p > .05$).

Table 11

Parameter Estimates for Alternative Model

Parameter	B	Std. Error	95% Confidence Interval	
			Lower	Upper
LEARPN	1.745	.715	.152	3.338
HEALTH INSURANCE	-3.019	4.171	-12.313	6.275
DIABETES	-2.225	2.298	-7.345	2.896
AGE	1.760	2.397	-3.582	7.101
RIAGENDR	5.987	3.750	-2.368	14.341
RIDRETH2	-.768	.347	-1.541	.006

Note. Table 11 highlights the different coefficients (B) for the terminal event in this study (cardiovascular mortality).

Table 12 highlights the Tests of Model Effects. PN in the left foot with $p > .05$, did not significantly contribute to the complex sample cox regression model. The other variables did not significantly contribute to the model as well. Hence, one can conclude that none of the variables had a statistically significant effect on the survival or cardiovascular mortality of the participants.

Table 12

Tests of Model Effects

Variable	*df1*	*df2*	Wald *F*	Sig.
LEALPN	1.000	11.000	18.397	.077
HEALTH INSURANCE	1.000	11.000	3.340	.095
DIABETES	1.000	11.000	1.969	.188
AGE	1.000	11.000	.000	.990
RIAGENDR	1.000	11.000	3.504	.088
RIDRETH2	1.000	11.000	.310	.589

Note. Table 12 highlights that none of the variables significantly contributed to the cox model or the participants' survival/cardiovascular mortality.

Table 13

Overall Tests of Proportional Hazards

df1	*df2*	Wald *F*	Sig.
6.000	6.000	17.629	.001

Note. Table 13 highlights that the proportional hazards assumption was violated, as $p < .05$.

Table 14 highlights Parameter Estimates for Alternative Model. The negative B coefficient (-2.384; HR, 0.09) for PN in the left foot indicates that PN in the left foot was associated with a reduced hazard rate of cardiovascular mortality and this association was not significant ($p > .05$, from Table 12). Health insurance status did not moderate the effect of PN on cardiovascular mortality ($p > .05$, from Table 12). Since Health insurance status has a negative B coefficient (-6.117; HR, 0.002) and was coded Yes=1 and No =2 and Diabetes also has a negative coefficient (-.976; HR, 0.38), it implies that participants who had health insurance, but did not suffer from diabetes, had a reduced hazard rate of cardiovascular mortality when diagnosed with PN in the left foot; however, this association was not significant ($p > .05$).

Table 14

Parameter Estimates for Alternative Model

			95% Confidence Interval	
Parameter	B	Std. Error	Lower	Upper
LEALPN	-2.384	2.738	-8.409	3.642
HEALTH INSURANCE	-6.117	5.572	-18.382	6.147
DIABETES	-.976	1.464	-4.198	2.246
AGE	3.927	3.023	-2.727	10.581
RIAGENDR	7.136	4.196	-2.100	16.372
RIDRETH2	.359	.417	-.559	1.278

Note. Table 14 highlights the different coefficients (B) for the terminal event in this study (cardiovascular mortality).

PN in the right foot was associated with an increased hazard risk of cardiovascular mortality, although this association was not significant (HR,5.73; 95% CI [0.152, 3.338], $p > .05$). Health insurance status did not moderate the effect of PN in the right foot on cardiovascular mortality ($p > .05$). Since health insurance status has a negative B coefficient (-3.019; HR, 0.05) and was coded Yes= 1 and No= 2 and Diabetes also has a negative B coefficient (-2.225; HR, 0.11), it implies that participants who did not suffer from diabetes but had health insurance, had a reduced hazard rate or risk for cardiovascular mortality, when diagnosed with PN in the right foot, but this association was not significant ($p > .05$). Age has a positive B coefficient (1.760; HR, 5.81), and since age was coded 0 to 84 years = 1 and $\geq$ 85 years = 2, hence, when adjusted for age, older participants had an increased hazard rate or risk for cardiovascular mortality, when diagnosed with PN in the right foot; however, this association was not significant ($p > .05$). When adjusted for ethnicity, other Hispanic (coded 5) had a lower hazard risk for cardiovascular mortality when diagnosed with PN in the right foot, when compared to Non-Hispanic White (coded 1), since ethnicity has a negative B coefficient (-.768; HR, 0.46); this association was significant ($p < .05$) Similarly, gender was coded Male = 1 and Female = 2; since gender has a positive B coefficient (5.987; HR, 398.22), it implies that females, when compared to males, females had a higher hazard risk for cardiovascular mortality when diagnosed with PN in the right foot; however, this association was not significant ($p > .05$).

PN in the left foot was associated with a reduced hazard risk of cardiovascular mortality and this association was not significant (HR, 0.09; 95% CI [-8.409, 3.642], $p >$

.05). Health insurance status did not moderate the effect of PN in the left foot on cardiovascular mortality ($p > .05$). Since health insurance status has a negative B coefficient (-6.117; 0.002) and was coded Yes= 1 and No= 2 and Diabetes also has a negative B coefficient (-.976; HR, 0.38), it implies that participants who did not suffer from diabetes but had health insurance, had a reduced hazard rate or risk for cardiovascular mortality, when diagnosed with PN in the left foot; however, this association was not significant ($p > .05$). Age has a positive B coefficient (3.927; HR, 50.75), and since age was coded 0 to 84 years = 1 and $\geq$ 85 years = 2, hence, when adjusted for age, older participants had an increased hazard rate or risk for cardiovascular mortality, when diagnosed with PN in the left foot; however, this association was not significant ($p > .05$). When adjusted for ethnicity, other Hispanic (coded 5) had a higher hazard risk for overall mortality when diagnosed with PN in the left foot, when compared to Non-Hispanic White (coded 1), since ethnicity has a positive B coefficient (.359; HR, 1.43); however, this association was not significant ($p > .05$). Similarly, gender was coded Male = 1 and Female = 2; since gender has a positive B coefficient (7.136; HR, 1256.40), it implies that females, when compared to males, females had a higher hazard risk for cardiovascular mortality when diagnosed with PN in the left foot; however, this association was not significant ($p > .05$).

Discussion

Interpretation

There are no previous studies in the literature that have examined whether health insurance status moderated the effect of PN on cardiovascular mortality. In this study,

health insurance status did not moderate the effect of PN in the right foot on cardiovascular mortality ($p > .05$). Similarly, health insurance status did not moderate the effect of PN in the left foot on cardiovascular mortality ($p > .05$). In the complex sample cox regression analyses of each foot, it was found that health insurance status had negative coefficients; similarly, the coefficients for diabetes were also negative. This implies that participants or adults who did not suffer from diabetes but had health insurance, had a reduced hazard rate or risk for cardiovascular mortality when diagnosed with PN in either the right or left foot; however, these associations were not significant ($p > .05$).

According to Akhabue et al. (2018), health insurance status has been associated with health outcomes, particularly cardiovascular disease (CVD), and mortality. As Akhabue et al. (2018) opined, States in the United States that expanded Medicaid during the Affordable Care Act (ACA) implementation, reported significantly lower numbers of uninsured hospitalizations for serious cardiovascular events, when compared to the States that did not embrace the expansion of Medicaid. The results of this study confirm this trend. Participants who did not suffer from diabetes, but had health insurance, had a reduced hazard rate or risk for cardiovascular mortality when diagnosed with PN in either the right or left foot, although the association was not significant ($p > .05$).

In the study by Hicks et al. (2021), the authors found that the association between peripheral neuropathy and cardiovascular mortality was not statistically significant (HR, 1.27; 95% CI [0.98, 1.66]). The results of this study highlighted a similar trend. PN in the right foot was associated with an increased hazard risk of cardiovascular mortality,

although this association was not significant (HR,5.73; 95% CI [0.152, 3.338], $p > .05$). Similarly, PN in the left foot was associated with a reduced hazard risk of cardiovascular mortality and this association was not significant (HR; 0.09; 95% CI [-8.409, 3.642], $p > .05$).

The findings of this study can be interpreted or analyzed in the context of the theoretical framework of the socioecological model (Cowan et al., 2021). The constructs of the socioecological model include individual, network, community, and structural (Cowan et al., 2021). Health insurance status can be influenced by factors acting at structural levels. These factors are mediated through laws and policies as well as society and economics (Cowan et al., 2021). For example, if a government institutes universal health insurance coverage, it is likely that the most vulnerable in the population will be protected or have at least some insurance coverages, which will likely improve their health outcomes. As Akhabue et al. (2018) opined, States in the United States that expanded Medicaid during the Affordable Care Act (ACA) implementation, reported significantly lower numbers of uninsured hospitalizations for serious cardiovascular events, when compared to the States that did not embrace the expansion of Medicaid.

Limitations

This study has some limitations. One of the limitations is that there are other important causes of PN in the United States, such as AIDS/HIV and chemotherapy which were not controlled for in this study because of the sample size and availability of data constraints. In addition, trans or non-binary gender respondents were not controlled for in

this study because there was not a large enough sample size for this category of respondents.

Furthermore, the proportional hazards assumption for the complex sample Cox regression analyses for PN in the left foot was violated. Hence, the results of this study, as it relates to PN in the left foot, should be cautiously interpreted. The violation of the proportional hazard's assumptions for the complex sample Cox regression analyses for the left foot might limit the generalizability of the findings.

Implications

This study has implications for the discipline of public health, the practice of public health as a profession, and finally, for social change. The results of this study demonstrated that health insurance status did not moderate the effect of PN in either the right or left foot on cardiovascular mortality in adults without diabetes who lack health insurance. However, participants or adults who did not suffer from diabetes but had health insurance, had a reduced hazard rate or risk for cardiovascular mortality when diagnosed with PN in either the right or left foot, although these associations were not significant. These results build on existing evidence that having health insurance improves health outcomes. Walden University defines positive social change as a deliberate process of the creation and application of ideas, strategies, and actions to promote the worth, dignity, and development of individuals and societies (Walden University, 2023). For public health and public health practitioners, it serves as a reminder that there should be a renewed interest in policies that promote universal health insurance coverage, or at least some level of health insurance coverage, as these could

improve health outcomes for many in the society. These results should be considered when advocating for health insurance coverage for the most vulnerable, either at the local, state, or federal levels. The implications for social change are that adults without diabetes who have been diagnosed with PN in either foot, could enjoy better health outcomes such as reduced cardiovascular mortality, if they had some level of health insurance coverage.

Based on the findings from this study, it is evident that having health insurance mitigated the hazard risk for cardiovascular mortality among adults not suffering from diabetes in the U.S., although the association was not significant. It is therefore recommended that public health practitioners should advocate at all levels of decision making (local, state, and federal), for policies that promote widespread health insurance coverage. This is particularly important, so as to protect the most vulnerable in society such as the low-socioeconomic class or marginalized populations. Furthermore, it is recommended that adult patients not suffering from diabetes, but who present with PN in either foot, should be screened for cardiovascular disease. If cardiovascular disease is diagnosed, they should be aggressively treated and managed to prevent unnecessary cardiovascular mortality.

This study's findings have potential impact for positive social change at the individual and societal/policy levels. Detection or diagnosis of PN in the lower extremities among adults who do not suffer from diabetes, should be followed by thorough screening for markers of cardiovascular disease. If cardiovascular disease is detected, such individuals should be aggressively treated to prevent unnecessary deaths.

This will bring about positive health outcomes both for the individuals, their families, and society at large. It will also afford policy makers to institute laws or policies that will ensure targeted screening of adults not suffering from diabetes, who might present with symptoms suggestive of PN in the lower extremities.

Recommendations for Further Research

The findings of this study, within its limitations, highlight that adults who do not suffer from diabetes but lack health insurance, are at an increased risk for cardiovascular mortality when diagnosed with PN in either foot. Further research is recommended to examine whether the type of health insurance (private, health insurance obtained through employment, or government programs like Medicare and Medicaid) in adults not suffering from diabetes are also associated with cardiovascular mortality. Furthermore, future research should also aim to examine PN in its entirety (both feet), since this study only examined PN in either the right or left foot.

Conclusion

PN is associated with a substantial burden among adults not suffering from diabetes in the United States. Within this study's limitations, the lack of health insurance, as demonstrated by the results of this study, increases the hazard risk of cardiovascular mortality among these adults, especially when diagnosed with PN in either foot. Thus, in order to improve the health outcomes of these adults suffering from PN, there should be concerted effort on the part of relevant stakeholders, to advocate for and ensure widespread health insurance coverage for the most vulnerable in the society and the wider population in general.

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Part 3: Summary

Integration of the Studies

The findings in these three studies, taken together, confirmed, and highlighted useful insights about the social problem of the substantial burden of PN among adults not suffering from diabetes in the United States. Before this study, there were no previous studies in the literature on whether poverty income ratio and veteran military status moderated the effect of PN on overall mortality; similarly, there were no previous studies on whether health insurance status moderated the effect of PN on cardiovascular mortality.

Oshio (2019) highlighted that poverty and low income were associated with poor health outcomes. The results of the first study (Manuscript 1) in this series of studies confirmed this trend. Participants who did not suffer from diabetes but had reduced poverty income ratio (0–1.99), had a reduced hazard risk for overall mortality when diagnosed with PN in either the right or left foot. Dunn et al. (2019), in their study, highlighted that veterans and military personnel were at an increased risk of developing PN, either from combat-sustained peripheral nerve injuries (CSPNIs) or exposure to various neurotoxic agents known as xenobiotics (Valentine, 2020). The results of the second study in this series (Manuscript 2) confirmed this trend. Participants who did not suffer from diabetes but had veteran/military status, had an increased rate or risk of overall mortality when diagnosed with PN in either the right or left foot, although the association was not significant ($p > .05$) Furthermore, Akhabue et al. (2018) opined that lack of health insurance is associated with poor health outcomes. The results of the third

study in this series (Manuscript 3) confirmed this trend. Participants who did not suffer from diabetes but had health insurance had a reduced hazard rate or risk for cardiovascular mortality when diagnosed with PN in either the right or left foot, although the association was not significant ($p > .05$).

A common theme from the series of studies is that each of the independent variables in the three studies conducted (i.e., poverty income ratio, veteran/military status, and health insurance status, respectively) was associated with the effect of PN on the outcome variables respectively. When taken together, these findings address or inform the research problem of the entire study. Before this study, there were no published studies in the literature that had examined whether the independent variables in these series of studies (poverty income ratio, veteran/military status, and health insurance status) moderated the effect of PN on overall and cardiovascular mortality.

The findings of these studies align with the theoretical framework of the socioecological model (Cowan et al., 2021). In the first study or manuscript, poverty income ratio could be explained by factors acting at the structural level within the theoretical framework of the socioecological model (Cowan et al., 2021). These factors are mediated through laws and policies, as well as society and economics. A viable economy brought about by the right set of economic policies or laws will likely result in more gainful employment opportunities for the people, thereby reducing or improving their poverty income ratio. The findings of the first study align with this framework. Participants who did not suffer from diabetes but had reduced poverty income ratio (0–

1.99), had a reduced hazard risk for overall mortality when diagnosed with PN in either the right or left foot.

The findings of the second study also align with this framework. Veteran/military status can be explained by factors acting at the individual and community levels within the theoretical framework of the socioecological model (Cowan et al., 2021). As Inoue et al. (2021) opined, veterans and military personnel usually indulge in the use of alcohol and other drugs known to be neurotoxic; these substances are responsible for the development of PN among veterans and military personnel. At the community level, military personnel or veterans might be deployed to communities or environments where they become exposed to various chemicals such as herbicides or pesticides (Dunn et al., 2020). These situations increase their risk of developing PN. Although veteran/military status did not moderate the effect of PN on overall mortality, participants who did not suffer from diabetes, but had veteran/military status, had an increased hazard risk or rate of overall mortality when diagnosed with PN in either foot; however, this association was not significant ($p > .05$).

The findings of the third study also align with this framework. Health insurance status can be explained by factors acting at the structural level within the theoretical framework of the socioecological model (Cowan et al., 2021). According to Akhabue et al. (2018), lack of health insurance has been associated with poor health outcomes, particularly serious cardiovascular diseases, and mortality. As Cowan et al. (2021) highlighted, structural factors are mediated through laws and economic policies. For example, if a government institutes universal health insurance coverage system, it is

likely that the most vulnerable in the population will be protected or have at least some insurance coverages, which will likely improve their health outcomes. Similarly, as Akhabue et al. (2018) opined, States in the United States that expanded Medicaid during the Affordable Care Act (ACA) implementation, reported significantly lower numbers of uninsured hospitalizations for serious cardiovascular events, when compared to the States that did not embrace the expansion of Medicaid. Although health insurance status did not moderate the effect of PN on cardiovascular mortality, participants who did not suffer from diabetes, but had health insurance, had a reduced hazard risk or rate of cardiovascular mortality when diagnosed with PN in either foot; however, this association was not significant ($p > .05$).

There were some unanticipated findings or insights across the studies that may be relevant to the broader research problem of the lack of studies in the United States that have examined the socioeconomic risk factors for PN among adults without diabetes. Surprisingly, in the first study, PN in the right foot was associated with a reduced hazard risk of overall mortality, although the association was not significant (HR = 0.62; 95% CI [-2.383, 1.424] $p = .321$). Similarly, peripheral neuropathy in the left foot was associated with a reduced hazard risk of overall mortality, but the association was significant (HR = 0.21; 95% CI [-3.091, -.071] $p = .016$). What was unanticipated about these findings in the first study was the reduced hazard risk of overall mortality in participants diagnosed with PN in either foot.

Similar unanticipated findings were documented in the second study. In the second study, veteran/military status did not moderate the effect of PN on overall

mortality ($p > .05$). Furthermore, PN in the right foot was associated with a reduced hazard risk of overall mortality (HR = 0.47; 95% CI [-2.351, 0.851], $p = .218$); in the left foot, peripheral neuropathy was also associated with a reduced hazard risk of overall mortality (HR= 0.19; 95% CI [-3.295, -.077] $p = 0.038$).

In the third study, health insurance status did not moderate the effect of PN on cardiovascular mortality ($p > .05$). Furthermore, while PN in the right foot was associated with an increased hazard risk of cardiovascular mortality, the association was not significant (HR= 1.745; 95% CI [0.152, 3.338] p= .071). However, the finding in the left foot was similar to the unanticipated findings in the first and second manuscripts. PN in the left foot was associated with a reduced hazard risk of cardiovascular mortality, but the association was not significant (HR= 0.09; 95% CI [-8.409, 3.642], $p = .077$).

These findings are quite relevant to the broader research problem. PN has been independently linked to overall and cardiovascular mortality among adults in the United States not suffering from diabetes (Hicks et al., 2021). The findings in this study largely suggest that participants diagnosed with PN had a reduced hazard risk or rate of overall and cardiovascular mortality. These unanticipated findings could be due to the fact that this study only examined PN in either foot, in each of the three studies. Previous studies such as the study by Hicks et al. (2021) examined PN in its entirety (both feet).

This series of studies, when taken as a whole, have potential implications for positive social change. This study highlighted that adult participants who do not suffer from diabetes, but had reduced poverty income ratio, had a reduced hazard risk for overall mortality when diagnosed with PN in either foot. These findings might enable

government, policy makers, and other relevant stakeholders to institute economic policies that could reduce income inequality, poverty, and promote gainful employment. Through these measures, these patients could enjoy better health outcomes and reduced overall mortality, thus bringing about the much-desired positive social change. This study also highlighted that adult participants who do not suffer from diabetes, but had veteran/military status, had an increased hazard risk of overall mortality when diagnosed with PN in either foot, although this association was not significant ($p > .05$). These findings might enable relevant stakeholders such as military institutions, government, veterans' welfare associations, physicians, and non-governmental organizations, to institute policies that will encourage aggressive targeted screening of veterans and military personnel for PN in the feet. Those diagnosed with PN should be aggressively and adequately treated to prevent unnecessary mortality and improve the health outcomes of these individuals, thus bringing about the much-desired positive social change. Finally, this study highlighted that adult participants who do not suffer from diabetes but had health insurance, had a reduced hazard risk for cardiovascular mortality when diagnosed with PN in either foot, although this association was not significant ($p > .05$). This finding has implications for social change. Relevant stakeholders, government, and policy makers can institute policies and laws that will ensure universal or widespread health insurance coverage for the most vulnerable in society and the population in general. Such policies might prevent unnecessary cardiovascular mortalities and bring about the much-desired positive social change.

Based on these three studies, further research should investigate whether these socioeconomic factors moderate the effect PN in its entirety (both feet) on overall and cardiovascular mortality in adults not suffering from diabetes. Furthermore, the type of health insurance, such as private, government, Medicaid, and Medicare, should be studied, as it relates to cardiovascular mortality. There are important lessons that can be learned from this research study. Prior to this study, it was not known whether important socioeconomic factors such as poverty income ratio and veteran/military status moderated the effect of overall mortality; similarly, it was not known whether health insurance status moderated the effect of PN on cardiovascular mortality. However, the lessons learned from this study are that poverty income ratio moderated the effect of PN in either foot on overall mortality among adults not suffering from diabetes; veteran/military status did not moderate the effect of PN in either foot on overall mortality among adults not suffering from diabetes, and similarly, health insurance status did not moderate the effect of PN in either foot on cardiovascular mortality among adults not suffering from diabetes.

Conclusion

In summary, the results of this research have highlighted important findings and filled an important gap in literature. This study highlighted that poverty income ratio moderated the effect of PN on overall mortality among adults not suffering from diabetes in the United States; veteran/military status did not moderate the effect of PN on overall mortality among adults not suffering from diabetes in the United States, and similarly, health insurance status did not moderate the effect of PN on cardiovascular mortality

among adults not suffering from diabetes in the United States. These findings have implications for positive social change, that can improve the health outcomes of those adults who are poor or with high poverty income ratio.

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