The association of reproductive factors and exogenous hormone use with distal sensory neuropathy among the US postmenopausal women: results from 1999–2004 NHANES

Miss Jiayu Li

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ความสัมพันธ์ระหว่างปัจจัยทางด้านอนามัยการเจริญพันธุ์และการใช้ฮอร์โมนในสตรีวัยหมดระดูกับภาวะปลายประสาทเสื่อมโดยใช้ข้อมูลจากการสำรวจภาวะสุขภาพและโภชนาการแห่งชาติประเทศสหรัฐอเมริกา ค.ศ.1999-2004

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ปีการศึกษา 2564

Thesis Title	The association of reproductive factors and exogenous hormone use with distal sensory neuropathy among the US postmenopausal women: results from 1999–2004 NHANES
By	Miss Jiayu Li
Field of Study	Clinical Sciences
Thesis Advisor	Associate Professor Dr. UNNOP JAISAMRARN, M.D., MHS
Thesis Co Advisor	Dr. Somsook Santibenchakul, M.D., MPH, Ph.D.
	Dr. Jakkrit Amornvit, M.D.

Accepted by the FACULTY OF MEDICINE, Chulalongkorn University in Partial Fulfillment of the Requirement for the Doctor of Philosophy

..... Dean of the FACULTY OF MEDICINE
(Associate Professor CHANCHAI SITTIPUNT, M.D.)

DISSERTATION COMMITTEE

..... Chairman
(Associate Professor Dr. Kitirat Techatraisak, M.D., Ph.D.)

..... Thesis Advisor
(Associate Professor Dr. UNNOP JAISAMRARN, M.D., MHS)

..... Thesis Co-Advisor
(Dr. Somsook Santibenchakul, M.D., MPH, Ph.D.)

..... Thesis Co-Advisor
(Dr. Jakkrit Amornvit, M.D.)

..... Examiner
(Associate Professor Dr. SUKANYA CHAIKITTISILPA, M.D.)

..... Examiner
(Associate Professor Dr. SUVIT BUNYAVEJCHEVIN, M.D.)

..... Examiner
(Lecturer YUDA CHONGPISON, Ph.D.)

เจี่ยอวี๋ หลี่ : ความสัมพันธ์ระหว่างปัจจัยทางด้านอนามัยการเจริญพันธุ์และการใช้ฮอร์โมนในสตรีวัยหมดระดูกับภาวะปลายประสาทเสื่อมโดยใช้ข้อมูลจากการสำรวจ ภาวะสุขภาพและโภชนาการแห่งชาติประเทศสหรัฐอเมริกา ค.ศ.1999-2004. (The association of reproductive factors and exogenous hormone use with distal sensory neuropathy among the US postmenopausal women: results from 1999–2004 NHANES) อ.ที่ปรึกษาหลัก : รศ. ดร. อรรณพ ใจสำราญM.D., MHS, อ.ที่ปรึกษาร่วม : ดร.สมสุข สันติเบ็ญจกุลM.D., MPH, Ph.D.,ดร.จักรกฤษ อมรวิทย์M.D.

บทคัดย่อ

หลักการและเหตุผล: ภาวะปลายประสาทเสื่อมจัดเป็นความผิดปกติที่พบได้บ่อยที่สุดในผู้ป่วยโรคระบบประสาทส่วนปลาย งานวิจัยนี้จึงถูกจัดทำขึ้นโดยมีวัตถุประสงค์เพื่อศึกษาความสัมพันธ์ระหว่างปัจจัยทางด้านอนามัยการเจริญพันธุ์และการใช้ฮอร์โมนในสตรีวัยหมดระดูกับภาวะปลายประสาทเสื่อม กลุ่มประชากรที่ผู้วิจัยศึกษาได้แก่กลุ่มสตรีชาวสหรัฐอเมริกาที่มีอายุตั้งแต่ 40 ปีขึ้นไป และอยู่ในวัยหมดระดู นอกจากนี้ผู้วิจัยยังศึกษาผลของอายุต่อความสัมพันธ์ข้างต้น

วิธีการวิจัย: งานวิจัยนี้เป็นการศึกษาแบบภาคตัดขวางโดยใช้ข้อมูลกลุ่มสตรีวัยหมดระดูชาวสหรัฐอเมริกาจากการสำรวจภาวะสุขภาพและโภชนาการแห่งชาติ (NHANES) ในช่วงปี ค.ศ. 1999-2004 สตรีที่มีภาวะเบาหวาน โรคหลอดเลือดสมอง มะเร็ง โรคระบบหลอดเลือดและหัวใจ โรคระบบต่อมไทรอยด์ โรคตับ ภาวะไตวาย รวมถึงสตรีที่ถูกตัดขา จะถูกคัดออกจากงานวิจัยนี้ ผู้วิจัยใช้ monofilament ขนาด 10 กรัม ตรวจเท้าของอาสาสมัครเพื่อประเมินภาวะปลายประสาทเสื่อม และใช้แบบสอบถามสัมภาษณ์อาสาสมัครเพื่อประเมินปัจจัยทางด้านอนามัยการเจริญพันธุ์และการใช้ฮอร์โมน ผู้วิจัยวิเคราะห์ข้อมูลทางสถิติโดยใช้สมการถดถอยลอจิสติกส์พหุคูณชนิดไบนารีเพื่อศึกษาความสัมพันธ์ระหว่างปัจจัยทางด้านอนามัยการเจริญพันธุ์กับภาวะปลายประสาทเสื่อม โดยแบ่งชั้นตัวอย่าง จัดกลุ่ม และถ่วงน้ำหนักการวิเคราะห์เพื่อให้เหมาะสมกับลักษณะข้อมูลของ NHANES นอกจากนี้ผู้วิจัยยังได้ทำการศึกษาปฏิกริยาร่วมของตัวแปรต่าง ๆ ต่อความสัมพันธ์ตามวัตถุประสงค์หลัก และทำการวิเคราะห์ข้อมูลเพิ่มเติมในสตรีกลุ่มเฉพาะ

ผลการศึกษา: งานวิจัยนี้รวบรวมข้อมูลจากอาสาสมัคร 1144 ราย ผลการศึกษาพบว่าสตรีที่เริ่มมีระดูที่อายุน้อยกว่าหรือเท่ากับ 11 ปี มีแนวโน้มพบภาวะปลายประสาทเสื่อมมากกว่า (เมื่อเปรียบเทียบกับสตรีที่เริ่มมีระดูที่อายุมากกว่า 11 ปี พบว่าค่า OR = 8.13, 95%CI: 1.24 - 53.28) สตรีที่มีจำนวนปีนับเริ่มจากวันที่หมดระดูจนถึงวันที่เข้าร่วมการศึกษายาวนานกว่า 20 ปี มีแนวโน้มพบภาวะปลายประสาทเสื่อมมากกว่า (เมื่อเปรียบเทียบกับสตรีที่มีจำนวนปีนับเริ่มจากวันที่หมดระดูจนถึงวันที่เข้าร่วมการศึกษาสั้นกว่า 20 ปี พบว่าค่า OR

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		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

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KEYWORD: postmenopausal women, reproductive factors, exogenous hormone use, peripheral neuropathy, distal sensory neuropathy, National Health and Nutrition Examination Survey

Jiayu Li : The association of reproductive factors and exogenous hormone use with distal sensory neuropathy among the US postmenopausal women: results from 1999–2004 NHANES. Advisor: Assoc. Prof. Dr. UNNOP JAISAMRARN, M.D., MHS Co-advisor: Dr. Somsook Santibenchakul, M.D., MPH, Ph.D.,Dr. Jakkrit Amornvit, M.D.

Background: Distal sensory neuropathy is a common disorder in the peripheral nervous system. We aimed to investigate the association between reproductive history factors and distal sensory neuropathy among the US postmenopausal women aged 40 years and over. We also explored the heterogeneity of these associations by age.

Methods: A cross sectional study was conducted with data from postmenopausal women aged 40 years and over in National Health and Nutrition Examination Survey 1999-2004. Women with diabetes, stroke, cancer, cardiovascular diseases, thyroid disease, liver disease, weak/failing kidneys, or amputation were excluded. Distal sensory neuropathy was measured via 10-gram monofilament test and all reproductive variables and exogenous hormone use were collected by interview questionnaire. A multivariable design-based binary logistic regression was used to analyze the association between the reproductive history variables and distal sensory neuropathy accounting for sample stratification, clustering, and weighting. Heterogeneity was assessed using interaction terms overall and via subgroup analysis.

Results: A total of 1144 postmenopausal women were included in this study. Women with distal sensory neuropathy tend to report age at menarche ≤ 11 years (OR = 8.13, 95%CI: 1.24 - 53.28), time since menopause > 20 years (OR = 3.18, 95%CI: 1.32 - 7.68) while those without distal sensory neuropathy tend to report history of breastfeeding (OR = 0.45, 95%CI: 0.21 - 0.99) and exogenous hormone use (OR = 0.41, 95%CI: 0.19 - 0.87). We observed that a significant interaction term of menarche with race (*p* for interaction = 0.027). Race was

Field of Study: Clinical Sciences Student's Signature .....

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Chapter 1 – Introduction

1.1 Background

Peripheral neuropathy is a common neurologic disorder faced by family physicians and neurologists[1, 2]. It is challenging to reverse established neurologic impairment[3]. According to the Foundation for Peripheral Neuropathy, an estimated 30 million Americans experience peripheral neuropathy (https://www.foundationforpn.org/). Approximately 28% of American adults with diabetes suffer from peripheral neuropathy, which takes around $10.91 billion in health care expenditure in the US[4-6]. Alcoholism, cytostatic drugs, nutrition deficiency, cardiovascular disease (CVD) and are common causes for peripheral neuropathy[7-9]. Nevertheless, sometimes, the neurologist could not confirm the particular cause in some cases, even with a careful history and exclusive assessment[10]. Approximately 5-8 million Americans are affected by idiopathic (unknown cause) peripheral neuropathy, consisting of roughly one-third of patients[10]. An increasing number of research is focusing on identifying modifiable risk factors for peripheral neuropathy.

Aging is one of the most important risk factors for the occurrence and progression of peripheral nerve damage[8]. The overall prevalence of peripheral neuropathy appears to be around 1% in the general population, up to 7% in the elderly, with a greater prevalence in western countries, lower socioeconomic status and unhealthy lifestyle[11, 8]. The prevalence of peripheral neuropathy increases as aging among males, but it peaks in the 45-54 age group among women[12]. Around this age, the estrogen levels decrease following menopausal transition among women[13]. Postmenopausal status has been identified as a risk factor for peripheral neuropathy in non-diabetic population, which might be related to the deficiency of estrogen[14-17, 10]. Life expectancy for women has increased from 50 to 80 years, but the age of menopause remains around 50 years. Therefore, women may experience in low estrogen levels during postmenopausal phase for a third of their lives[16]. Several studies shown that women are more likely to suffer from peripheral neuropathy than males after controlling age, with a ratio of 1.5-2.0: 1[8].

Distal sensory neuropathy is one of the most common subtype of peripheral neuropathy, usually characterized by symmetric, distal foot or toe numbness, tingling, with/without neuropathic pain, or loss of sensation[18]. Ignoring the mild paresthesia or negative symptoms may eventually put peripheral neuropathy patients at the risk of various diseases or threaten their life[19, 3]. Hence, identifying the risk factor and preventive factor is essential for preventing the greater occurrence of peripheral neuropathy and slow down its development. Peripheral neuropathy always coexists with central nervous system diseases[20, 21]. The widely fluctuated hormone levels in each reproductive stage and the cumulative lifetime estrogen exposure have a substantial impact on women's central nervous system in their later life[22]. However, there is no result in the literature

regarding whether these reproductive history factors could be associated with the prevalence of peripheral neuropathy among postmenopausal women.

Our study was designed to explore the association between peripheral neuropathy and the reproductive history factors, including age at menarche, pregnancy, breastfeeding, age at menopause, time since menopause, total reproductive lifespan, and history of exogenous hormone use. Menarche, pregnancy, breastfeeding, and menopause are major reproductive factors being able to reflect women's lifetime endogenous estrogen exposure, while using exogenous hormone also could contribute to the cumulative lifetime estrogen exposure[22]. This cross-sectional study was applied with the publicly released, de-identified data from National Health and Nutrition Examination Survey (NHANES) 1999-2004. The results of this study are expected to investigate the unknown etiology of idiopathic peripheral neurologic disorders among women, provide relevant explanations for high prevalence of peripheral neuropathy in postmenopausal women, and contribute to future peripheral neuropathy management guideline making.

1.2 Research gap

More recent research has occurred in the field of identifying modifiable risk factors for peripheral neuropathy; however, these findings did not account for whether female reproductive history factors influence the occurrence of distal sensory neuropathy.

1.3 Research questions

1.3.1 Primary research questions

- Is distal sensory neuropathy associated with age at menarche among the postmenopausal women aged 40 years and over?
- Is distal sensory neuropathy associated with gravidity among the postmenopausal women aged 40 years and over?
- Is distal sensory neuropathy associated with breastfeeding history among the postmenopausal women aged 40 years and over?
- Is distal sensory neuropathy associated with age at menopause among the postmenopausal women aged 40 years and over?
- Is distal sensory neuropathy associated with time since menopause among the postmenopausal women aged 40 years and over?
- Is distal sensory neuropathy associated with total reproductive lifespan among the postmenopausal women aged 40 years and over?

- Is distal sensory neuropathy associated with the history of exogenous hormone use among the postmenopausal women aged 40 years and over?

1.3.2 Secondary research questions

- Whether age is an effect modifier for the association between distal sensory neuropathy and reproductive history?

1.4 Research objectives

1.4.1 Primary research objectives

- To investigate the association between age at menarche and distal sensory neuropathy among postmenopausal women aged 40 years and over;
- To investigate the association between gravidity and distal sensory neuropathy among postmenopausal women aged 40 years and over;
- To investigate the association between breastfeeding history and distal sensory neuropathy among postmenopausal women aged 40 years and over;
- To investigate the association between age at menopause and distal sensory neuropathy among postmenopausal women aged 40 years and over;
- To investigate the association between time since menopause and distal sensory neuropathy among postmenopausal women aged 40 years and over;
- To investigate the association between total reproductive lifespan and distal sensory neuropathy among the postmenopausal women aged 40 years and over?
- To investigate the association between history of exogenous hormone use and distal sensory neuropathy among postmenopausal women aged 40 years and over.

1.4.2 Secondary research objectives

- To explore the effect modification by age for the association between distal sensory neuropathy and reproductive history.

1.5 Research hypothesis

1.5.1 Primary research hypothesis

- There is a negative association between age at menarche and distal sensory neuropathy among postmenopausal women aged 40 years and over;
- There is a negative association between gravidity and distal sensory neuropathy among postmenopausal women aged 40 years and over;
- There is a negative association between breastfeeding and distal sensory neuropathy among postmenopausal women aged 40 years and over;

- There is a negative association between age at menopause and distal sensory neuropathy among postmenopausal women aged 40 years and over;
- There is a positive association between time since menopause and distal sensory neuropathy among postmenopausal women aged 40 years and over;
- There is a negative association between total reproductive lifespan and distal sensory neuropathy among postmenopausal women aged 40 years and over;
- There is a negative association between a history of exogenous hormone use and distal sensory neuropathy among postmenopausal women aged 40 years and over.

1.5.2 Secondary research hypothesis

- Age is an effect modifier for the association between distal sensory neuropathy and reproductive history among postmenopausal women aged 40 years and over;

1.6 Conceptual framework

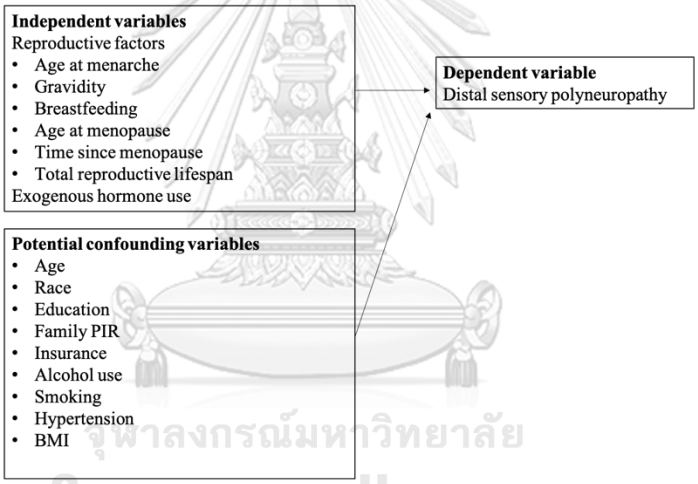


Figure 1: Conceptual framework

1.7 Operational definitions

1.7.1 Outcome

Distal sensory neuropathy was defined as having at least one insensate site on either foot as determined by a 10-gram monofilament[23]. The insensate site was determined when participants were unable to respond correctly to filament pressure at plantar sites (first metatarsal head, fifth metatarsal head, and hallux)[24].

1.7.2 Exposure

- Age at menarche was defined as the age when the first menstrual period occurred;

- Gravidity was defined as the sum number of pregnancies, including current pregnancy, live births, miscarriages, stillbirths, tubal pregnancies, or abortions;
- Breastfeeding history was defined as ever breastfed any of your children;
- Age at menopause was defined as the age at the last menstrual period;
- Time since menopause was calculated by age at interview minus age at last menstrual period;
- Total reproductive lifespan was defined in years from the onset of menarche to the onset of menopause;
- History of exogenous hormone use was defined as either use of any contraceptives including birth control pills and contraceptive injection or any type of menopausal hormone therapy including pills, cream, patches, and injectables.

1.7.3 Confounding variables

- Age was defined as the age in years of the sample person at the time of the household interview;
- Race was derived according to race and Hispanic origin;
- Education was defined as the highest degree received;
- Income was defined as a ratio of family income to the poverty threshold;
- Insurance was defined as covered by health insurance or some other kind of health care plan;
- Alcohol use was defined as at least 12 drinks of any type of alcohol (including liquor, beer, wine, wine coolers, and any other type of alcoholic beverage) in entire life. A 12 oz. beer, a 4 oz. glass of wine, or an ounce of liquor is seen as a drink;
- Smoking was defined as smoked at least 100 cigarettes in life or smoking at the time of the interview.
- Hypertension was defined according to an average systolic blood pressure ≥140 mmHg, an average diastolic blood pressure ≥90 mmHg, or self-reported currently taking prescribed medication for high blood pressure;
- Body mass index (BMI) was calculated by weight in kilograms divided by height in meters squared.

Chapter 2 - Literature Review

In this chapter, more details about the general background of distal sensory neuropathy, reproductive factors, exogenous hormone use, and their potential association were described. We focused on the potential plausibility of how female reproductive events and the related hormone levels affect the conditions in the peripheral nervous system.

2.1 Distal sensory neuropathy

The literature on topics about the general background of distal sensory neuropathy and pathophysiology of peripheral neuropathy were shown in this part.

2.1.1 General background of distal sensory neuropathy

Peripheral neuropathy is a frequent disorder that can cause various symptoms, and it's common in conditions that affect the whole body. Impaired glucose tolerance, obesity, hypertension, and dyslipidemia can directly damage peripheral nerves or perpetuate and prolong damage by impairing nerve recovery through a variety of mechanisms[10]. Due to the different measurements, study population, and study design, the prevalence of peripheral neuropathy demonstrated a great variety in different study areas worldwide[8]. Several door-to-door screening studies were applied based on the World Health Organization (WHO) two-stage protocol[25]. The prevalence rate of distal sensory neuropathy has been estimated as 0.8 per 1000 persons in Saudi Arabia, 1.4 - 2.5 per 1000 persons in Nigeria, and 7.3 per 1000 in Spain[8]. distal sensory neuropathy is a common complication of diabetes, and its morbidity rates increase as aging[26]. The higher prevalence was found in European countries; however, this finding might result from more older participants (> 50 years) being included in study[8]. A more precise estimate of distal sensory neuropathy prevalence was shown as 7% among Italian elderly (aged 65-94 years) in a population-based cohort study[27].

The diverse presentations of peripheral neuropathy depend on the severity and the types of nerve fiber (sensory, motor, or autonomic) involved[28]. Distal sensory neuropathy could lead to disability and is independently associated with lower-limb complications: 20.4% of patients developing to ulcers and 4.1% to amputations[29]. According to the Foundation of Peripheral Neuropathy, more than 50,000 diabetic patients have amputations each year; however, 75% of these amputations are preventable. Almost half of elderly distal sensory neuropathy patients suffer from pain or discomfort, and one-third might experience numbness or restless legs, but most of them fail to completely relieve pain with symptomatic treatment[30]. Some patients also suffer from depressive symptoms, because of the direct effect of burning and tingling on their

mood and sleep[31]. However, cognitive and language impairment sometimes make it difficult for the elderly to report their symptoms[26].

The reduced peripheral sensation and motor coordination could lead to impaired balance and a higher risk of falls, especially among the elderly[32]. Those prone to falls often present with limited mobility and lower extremity symptoms such as leg cramps, restless legs syndrome, and nonspecific leg pain[30]. They have to use walking sticks; rely on assistive devices; or ask for assistance from others to maintain daily activities[29]. The limited activity could decrease muscle mass, physical activity, and sunlight exposure among distal sensory neuropathy patients, which has been related to osteoporosis and fractures[33, 34]. Consistently, patients with peripheral neuropathy show lower bone mass, and chronic inflammatory neuropathy could develop into osteoporosis within three years[33, 35].

Small fiber neuropathy is common among Parkinson's patients, shown as abnormal gait and balance parameters and more frequent falls[20]. The severity of peripheral nerves impairment (number of insensate areas) is independently correlated with lower cognitive ability among the US elderly, after adjusting for age[36]. The reduced nerve conduction in peripheral nervous system is associated with impaired cognition among Chinese Alzheimer's disease patients[21]. In addition, those with CVD are more likely to experience disorders in the peripheral nervous system[37]. The insensate foot of peripheral neuropathy is also related to all-cause and CVD mortality regardless of diabetes among US adults[38].

A comprehensive review of medical history, medications, and occupational exposures help reveal the causes of distal sensory neuropathy[9]. Diabetes is the most common cause of distal sensory neuropathy, and diabetic distal sensory neuropathy is mostly irreversible[9]. Reviewing the cardiovascular risk factors among patients also could help identify diabetic distal sensory neuropathy, such as age, smoking, hemoglobin A1c, hypertension, and triglyceride[11]. The prevalence of peripheral neuropathy in people with diabetes ranges from 7.5 to 83.4 percent[39]. Approximately 11.8% of non-diabetic adults aged ≥40 years suffer from distal sensory neuropathy[23]. Prediabetes and obesity are major causes for cryptogenic sensory polyneuropathy before the onset of frank diabetes (ranging from 2% to 77%)[40, 3]. The economic burden for pre-diabetes is more than $43 billion in US[40].

Hypertension and BMI have been reported as risk factors for peripheral nerve impairment among both middle-aged and elderly population[23]. Both general and abdominal obesity is related to distal sensory neuropathy in both diabetic and non-diabetic individuals[41]. Distal sensory peripheral neuropathy was found in 11.6% of severely obese women who had no diabetes or typical dietary deficits, and a higher prevalence was found among postmenopausal women and

the elderly[15]. A stronger association was found between more components of metabolic syndrome and peripheral neuropathy[42]. In addition, liver disease, chronic renal failure, hypothyroidism, and hyperthyroidism are also metabolic drivers for peripheral neuropathy[19].

The peripheral nerves are more likely to be influenced among those with poor nutrition caused by an unbalanced diet and alcoholism. Approximately 2.2% to 8% of distal sensory neuropathy patients have been found concurrent with vitamin B12 deficiency[7, 9]. Nearly 30% of American adults have excessive or heavy alcohol consumption, while 11% to 66% of them are at high risk of alcohol-induced peripheral nerve damage[43]. People exposed to toxic agents (like chemotherapy medication, industrial agents, or heavy metals) are at higher risk of peripheral nervous system disease[44, 9]. Distal sensory neuropathy also could be a complication of infections, autoimmune diseases, and cancers in various ways[19]. Additionally, distal sensory neuropathy could arise from genetic etiology. More than 100 genes have been confirmed to lead to peripheral neuropathy, with a prevalence of 1:2,500 worldwide[45].

The most reliable diagnosis of distal sensory neuropathy is combining findings from clinical history, symptoms, neurological examination, and electrophysiological examination. The clinical history and symptoms could help distinguish the peripheral neuropathies and central nervous system diseases (such as stroke) and may reflect the underlying cause of peripheral neuropathy[46]. In addition, family history information can help diagnose inherited neuropathies[47]. Different neurological examination tools work for assessing different types of deficits in the peripheral nervous system: 128 Hz tuning fork for vibration sensation; appropriate reflex hammer for muscle stretch reflexes, and monofilament for the sensitivity to touch/pressure. In addition, skin biopsy and peripheral nerve ultrasound examination are also new alternative measurement tools[48, 49].

American Diabetes Association's position statement has recommended that the annual monofilament screening (at least) should be provided for type 1 diabetic patients with ≥5-year duration and all type 2 diabetic patients[50]. In a primary care practice-based study, 71% of US elderly suffer from at least one deficit in the peripheral nervous system. Among those with the deficits, the absence of ankle reflexes is most common (accounting for 83%); insensitivity to touch accounts for 31%, and insensitivity to vibration for 15%[30]. However, such assessments are not routinely applied among the general population, which has led to the underestimated prevalence worldwide.

Causal treatment and symptomatic treatment are two primary goals of distal sensory neuropathy management. Firstly, causal treatment could prevent the progression of neuropathy, or sometimes improve the symptom, via controlling the underlying causes. Blood sugar control is a vital approach for preventing or delaying the onset and development of diabetic neuropathy.

The earlier treatment is implemented, the more effectively we can prevent the peripheral nerve impairment[51, 52]. Vitamin supplements are recommended for correcting the nutrition deficiency, because vitamins B1, B6, B12, and E have been reported to halt the progression of neuropathy[9]. Removing the exposure to toxic agents or stopping the toxic drugs and alcohol consumption helps avoid further peripheral nerve damage and relieve the symptoms[53, 9]. Secondly, the treatment for relieving the symptoms could significantly improve patients' quality of life. Antidepressants and pain relievers help alleviate neuropathic pain[54]. Lastly, a healthy lifestyle (proper foot hygiene and footwear, physical therapy, gait training, and weight loss) and care support are essential for distal sensory neuropathy patients[54, 19].

2.1.2 Pathophysiology of peripheral neuropathy

The pathophysiology of peripheral neuropathy is mainly determined by the underlying disease, with impaired glucose tolerance, hypertension, and dyslipidemia, as well as autoimmune and microvascular mechanisms, all playing important roles[10]. Although the exact pathophysiology of specific neuropathy has not been determined, the mechanisms of peripheral nerve damage frequently follow a similar pattern. Peripheral nervous system damage includes not only neuronal cells but also nerve supporting cells (such as satellite cells and myelin cells) and connective tissues surrounding neuronal axons[55]. Cells other than neurons play an important role in maintaining the physiological properties of peripheral nerve cells. Schwann cells, a type of glial cell, encase nerves in the myelin sheath and provide nutritional support by secreting important neurotrophic substances like nerve growth factor[55].

Peripheral nerves run parallel to blood vessels. Ischemia associated with vascular changes can also lead to nerve damage through the thickening of the vessel wall. Ultimately, vascular occlusion may occur, resulting in compromised vascular permeability and intraneural blood flow. Ischemia and inflammation are inextricably linked, and both play important roles in nerve injury and recovery[56]. Moreover, degeneration of axons or nerve supporting cells could activate a cascade of chemical processes that enter the blood circulation as degradation products, causing injury to normally healthy nerve cells, Schwann cells, local vasculature, and even further afield nerve cells[57].

2.2 Hormones in female reproductive life

The literature review in this part was on the topic of hormone changes during the reproductive cycle and the effect of hormones on the peripheral nervous system. More recent research has occurred in the field of neuroprotection of estrogen and progestogen. Oxytocin and prolactin are also included in this part because they are important for pregnancy and breastfeeding.

2.2.1 Hormone in female reproductive life

The menstrual cycle is central to various stages of female reproductive life cycle, starting from menarche and ending at the menopause. As a hormonal-driven cycle, the menstrual cycle is regulated by hypothalamic-pituitary-ovarian axis, and endometrium is the end organ of gonadal steroids[58]. A normal menstrual cycle usually starts within the first 1-3 years after menarche in puberty and recurs every 25 to 35 days, with an average of 28 days[59, 60]. Follicle-stimulating hormone (FSH), estrogens, progesterone, and luteinizing hormone (LH) are main types of hormones regulating the menstrual cycle[58].

In the first few years after menarche, the menstrual cycles are irregular, and the levels of estrogen and progesterone tend to be low and variable[61]. The secretion of FSH and LH starts at the beginning of puberty by the pituitary gland. Increased FSH works for recruiting follicles and regulating the production of gonadal hormones, such as estrogen and progesterone. Estrogens could cause the endometrium to proliferate, moreover, it is a positive feedback signal before ovulation and leads to the LH and FSH peaking the 1-2 day before ovulation. After ovulation, progesterone acts as a negative feedback signal on the pituitary, decreasing the FSH and LH. The new menstrual cycle and bleeding occur if the pregnancy is absent, and this process continues until perimenopause[61, 62].

Women will not have a menstrual period and ovulation if they get pregnant[58]. Estrogen and progesterone are largely secreted during pregnancy, but their levels dropped dramatically during the postpartum period and throughout breastfeeding[63]. Estrogen levels reach normal levels about 6 months after delivery or when the women stop lactating[64]. The progesterone usually forms again as the resumption of ovulation after the cessation of lactation, in the second half of a menstrual cycle[63]. Prolactin and oxytocin are two main hormones for breastfeeding[63]. The levels of prolactin increase significantly during pregnancy, but the milk secretion is blocked by high levels of estrogen and progesterone. After delivery, the milk secretion begins with reduced levels of estrogen and progesterone. Oxytocin increases more rapidly than prolactin, which helps milk flow in the breast for the feed[65].

Menopause marks the end of the reproductive phase in a woman's life. The earliest hormonal evidence of ovarian aging is the overexpressed serum or urinary FSH levels[62]. The high FSH levels occur before the irregular menstrual cycle and probably play a role to maintain or even increase estrogen levels[66, 67]. FSH concentrations stay stable from two to eight years after the final menstrual period, and the changes in LH are similar to FSH [68, 69]. The estrogen levels remain normal or increase during perimenopause, reach a nadir in the first two years after the final menstrual period and remain low and stable since then[16, 69]. Similarly, the progesterone levels

decrease as the poorly functioning ovaries of menopause. Additionally, anti-Mullerian hormone levels and inhibin B decrease in the early cycle and cannot be detected in the postmenopausal phase[58].

2.2.2 Female hormones and peripheral nervous system: molecular mechanisms

- **Neuroprotection of estrogen**

The complexities of estrogen levels, types, and neurological conditions must be considered when discussing estrogen's neuroprotective effects. Estrogen can exert neuroprotective effects via either estrogen receptor (ER)-dependent or ER-independent mechanisms. Most current research has focused on the role of estradiol (E2), as it is the most biologically active and potent endogenous estrogen. Physiological levels of E2 require ER-mediated mechanisms to protect nerves, whereas pharmacological levels appear to protect via non-ER-mediated mechanisms. Through the ER-ERK1/2 signaling pathway, E2 has been shown to directly promote differentiation and further myelination of Schwann cells[17]. Estrogen also protects neurons from death caused by mitochondrial dysfunction, glucose metabolism, nitric oxide production, or the administration of beta(β)-amyloid peptides, excitatory amino acids, free radicals, and glycoproteins[14, 16, 10]. Estrogen could cause vasodilation in nitric oxide synthase family members, improving blood flow to damaged nerves[70, 56].

In animal model, estrogen contributes to the maintenance of normal β-cell function, insulin-induced glucose transport, and hepatic glucose export. Reduced estrogen levels promote insulin resistance, which is one of the leading causes of peripheral nerve damage[14, 16]. Obesity, hypertension, hypercholesterolemia, and impaired glucose metabolism are all associated with oxidative stress as risk factors for peripheral neuropathy. Oxidative stress can not only cause direct damage to peripheral nerves, but it can also perpetuate and prolong this damage by impairing neural resilience[10]. Vitro studies have shown that estrogen has long-term neuroprotective effects against oxidative stress and hypoxia[16]. Estrogen does not always exert beneficial effects, and specific negative effects will be introduced in the section on exogenous hormone use further below.

- **Neuroprotection of progesterone**

Progesterone is an essential female reproductive hormone for pregnancy implantation and maintenance. Progesterone and its metabolites have neuroprotective and neurotrophic effects similar to estrogen[71]. But the related mechanisms may be different. Estrogen stimulates neuronal excitability, whereas progesterone could inhibit neuronal activity. Particularly in neuronal populations that are especially vulnerable to excitotoxicity and ischemic injury. These fragile

neurons are often characterized by high metabolic activity and abundant excitatory. Progesterone may exert neuroprotective effects by reducing neural activity[72].

Decreased mitochondrial function is a major component of the normal aging process and neurodegeneration[73]. Toxic byproducts of mitochondrial energy production pathways cause oxidative stress and disrupt lipid, protein, and nucleic acid metabolism. Progesterone up-regulates the expression of anti-apoptotic proteins located in the outer mitochondrial membrane, such as b-cell lymphoma 2 (Bcl-2), to protect neurons from multiple necrotic injuries[74]. Furthermore, progesterone can reduce inflammation by inhibiting microglia activation and cytokine production, increasing neurotrophic factor expression, and protecting neurons from glucose deprivation and β-amyloid peptide toxicity[71]. In addition, Schwann cells can express intracellular progesterone receptors and can also synthesize progesterone. Therefore, progesterone may be part of an autocrine regulatory mechanism involved in myelination[75]. Progesterone also improves axonal transport by preserving or restoring myelin integrity, which is essential for the efficient communication of neurons[76]. Natural progesterone may offer a better benefit-risk ratio than synthetic progestins[71].

- **Neural effects of other hormones**

The two main hormones required for breastfeeding are oxytocin and prolactin. Increased prolactin and oxytocin during breastfeeding might be involved in peripheral neuroprotection of breastfeeding. Inflammation and oxidative stress play crucial roles in peripheral neuropathy[3]. As a mediator of inflammation, tumor necrosis factor (TNF-α) could cause peripheral nerve injury directly and influence peripheral nerves via causing endothelial dysfunction and vascular thickening[77]. Oxytocin act as a neuroprotective factor by preventing ischemia-induced inflammation and oxidative stress, via regulating NF-**κ**B, TNF-α, interleukin-1β (IL-1β), microglial activation[78-80]. In addition, oxytocin might prevent the inflammation in peripheral nervous system by reducing the production of norepinephrine, which has been positively associated with aggravation of symptoms in neuritis [78, 81]. Meanwhile, prolactin also could provide strong neuronal protection as a neuropeptide via anti-apoptotic, anti-inflammatory, and antioxidant properties[82, 83]. The neuroprotective effect of prolactin is mainly reflected in the resistance to excitotoxic injury. Prolactin may protect against neural excitotoxicity by restoring intracellular calcium homeostasis and mitochondrial activity, as well as mechanisms of anti-apoptotic effects that may be mediated by NF-**κ**B activity[84]. In addition, prolactin may exert neuroprotective effects by increasing the anti-apoptotic proteins Bcl-2[83].

Before the final menstrual period, women experience a period when estrogen levels are relatively undisturbed, but serum FSH rises sharply. FSH and LH could increase the expression of pro-inflammatory cytokines IL-1 and IL-6[85]. Biopsy revealed LH receptor expression in myenteric neurons and glial cells, neutrophils, endothelial cells, and mast cells. LH antagonizes gastrointestinal motility in rats, by interacting with LH receptors[86].

2.3 Potential association of peripheral neuropathies with reproductive history factors

The underlying mechanism of the association between reproductive history factors and distal sensory neuropathy among non-diabetic postmenopausal women remains unclear. Prediabetes and metabolic syndrome components (besides diabetes) have been reported to be the major causes of non-diabetic cryptogenic sensory polyneuropathy. In a normoglycemic animal model, self-reinforcing cascade of metabolic and inflammatory effects ultimately resulted in microvascular damage and peripheral nerve dysfunction[3]. In this part, literature on topics of the potential association of peripheral neuropathies with reproductive factors was reviewed, according to the sequence of epidemiology, clinical observations, and potential mechanisms in the peripheral nervous system.

2.3.1 Menarche

Menarche is the occurrence of the first menstrual bleeding in the female adolescent, following the maturation of the hypothalamic-pituitary-ovarian axis[87]. It is a marker of normal female reproductive health and wellness, associated with ovulation and reproduction[88]. Menarche is considered normal if it is onset at the age between 9 and 15 years. The average of menarche is 12.4 years but varies in different studies and population, with wealthier girls having earlier menarche than poorer girls[89]. The average age for menarche is between 14 and 16 years old in Europe, and earlier in the United States[90]. There was a decreasing trend in the average menarche age over the past 100 years, especially in developed countries. In the US, the average age of menarche was older than 14 years prior to 1900, but it decreased to 12.43 years in 1988-1994 and 11.9 years in 2013-2017[91, 89, 92]. Mexican-American girls have the fastest decline in age at menarche, according to a racial comparison in the United States[93]. Age at menarche may be linked to female fertility: age at a first child born and total number of children born[94].

Genetic, ethnic, nutritional, and environmental factors could affect the onset of menarche[95]. A total of 122 single nucleotide polymorphisms were genome-wide statistically significantly associated with early menarche; 18 of these menarche genetic variants were also associated with metabolic traits, primarily overweight and height[96]. Childhood obesity has been reported as a

predictor of early menarche. Women with higher BMI or subcutaneous fat levels during childhood (5-9 years) usually have a higher risk of early onset of menarche (<11 years) [97]. Finding from meta-analysis also demonstrated that overweight/obesity predisposes to early menarche among girls[98]. In contrast, earlier age at menarche is followed by a higher BMI among adults. Each additional one year of age at menarche could lead to reduced BMI with value of 0.38 kg/m^2 [99].

The physiological process of onset of menarche is complex. Women with early menarche have a more regular menstrual cycle and greater blood E2 concentrations during the follicular phase of the menstrual cycle than later menarche women[100, 101] The estrogen levels in the postmenopausal phase are also greater among women with early menarche[102]. Early menarche might be a sign of greater cumulative estrogen exposure during women's life; however, early menarche shows a negative effect on several health problems among postmenopausal women.

Evidence from meta-analysis showed that earlier menarche (< 12 years) could be able to identify women at higher risk of metabolic syndrome. Compared to the women with late menarche (> 15 years), those with early menarche had 1.62 times higher risk to be affected by metabolic syndrome. The risk for presenting the metabolic syndrome decreases by 8% when age at menarche increases by each additional one year[103]. In a cross-sectional study with 1,503 German women, the association between early menarche and a higher risk of diabetes was significant after controlling BMI. Since then, consistent findings have been shown in several cohort studies and meta-analysis[104]. Additionally, the association between hypertension and early menarche has been shown in meta-analysis[105]. The age at menarche might be inversely associated with distal sensory neuropathy among postmenopausal women via metabolic changes.

2.3.2 Gravidity

Gravidity is defined as the sum of several times that women have been pregnant (live births, abortions, and miscarriages)[106]. A study with three-generation (1910, 1935, and 1960) women found that at least 80 percent had a child by age 40[107]. According to 2012 worldwide data, approximately 211 million pregnancies took place in 2008 and 213 million in 2012. More than half of all pregnancies occurred in Asia and less than 5 percent in North America and Oceania[108]. Besides social-economic status, fertility rates is associated with age at menarche [94, 109]. Age at first children born is directly related to age at menarche[94]. The average number of children born among Chinese Han women increased by 0.5% when their menarche occurs later each additional month[94].

Pregnancy is a female-specific reproductive event. Women will not have menstrual period and ovulation, and progestogen and estrogen are two main hormones, during pregnancy[58]. The levels

of estrogen increase up to 300-fold during the early pregnancy and peak in the late pregnancy[110]. The production of estrogen during one pregnancy in women is higher than during other non-pregnant periods in their entire life[63]. Nulligravidity is associated with lower estrogen hormone among premenopausal women. Hence, greater gravidity might reflect that women are exposed to greater concentrations and times of estrogen and progestogen[111].

Dramatic metabolic changes occur in a woman's metabolism during pregnancy, including increased visceral fat, insulin production, insulin resistance, and circulating lipid levels[112]. The retained gestational weight gain and central adiposity are related to both poor pregnancy outcomes and the long-term risk of maternal obesity[112]. Nulligravidity is associated with a higher risk of hypertension and the following elevated mortality among women in Bangladesh[113].

The immune system strengthens throughout adulthood in preparation for a series of pregnancies. When the "expected" pregnancy does not occur, the immune system might become over-stimulated, causing autoantibodies to attack healthy cells to be released. During pregnancy, the proliferation of regulatory T cells increases. Pregnancy-associated regulatory T cell proliferation has been seen as the first line of defense against inflammatory responses[114]. Compared to healthy individuals, patients with peripheral neuropathies tend to have lower numbers of circulating T regulatory cells. The dysregulation of the circulating regulatory T cells has been proved to contribute to the immune dysfunction of the peripheral nervous system[115]. Therefore, the number of pregnancies might be related to distal sensory neuropathy via hormone fluctuation, immunity changes, and metabolic changes.

2.3.3 Breastfeeding

Several benefits from breastfeeding have been confirmed for maternal and infant health, even in the absence of early, exclusive, or continued breastfeeding[116]. Estrogen and progesterone drop rapidly after delivery, while prolactin and oxytocin increase and become major driven hormones during breastfeeding. Oxytocin increases more rapidly than prolactin, which helps milk flow in the breast for the feed[65]. Both prolactin and oxytocin are neuroprotective factors, providing strong neuronal protection. Increased prolactin and oxytocin levels during breastfeeding may be involved in the peripheral neuroprotection of breastfeeding. Inflammation and oxidative stress play crucial roles in peripheral neuropathy [3]. As a mediator of inflammation, tumor necrosis factor (TNF-α) can directly cause peripheral nerve injury and influence peripheral nerves by causing endothelial dysfunction and vascular thickening [77]. Oxytocin acts as a neuroprotective factor by preventing ischemia-induced inflammation and oxidative stress by regulating NF-**K**B, TNF-α, IL-1β, and microglial activation [78-80]. Oxytocin might prevent inflammation in the

peripheral nervous system by reducing the production of norepinephrine, which has been positively associated with the aggravation of symptoms in neuritis [78, 81]. Additionally, prolactin provides strong neuronal protection as a neuropeptide with anti-apoptotic, anti-inflammatory, and antioxidant properties [82, 83].

Breastfeeding could reset metabolic changes from pregnancy. Breastfeeding could lead to a reduced risk of diabetes, metabolic syndrome, CVD, ovarian and breast cancer among women[117]. The beneficial effect of breastfeeding on impaired insulin sensitivity and glucose tolerance was found among non-diabetic postmenopausal women[118, 119]. Animal models suggested that blood glucose and insulin levels were reduced by 20% and 35% in lactating rats, respectively [120]. Breastfeeding has a beneficial effect on hyperlipidemia, visceral fat, and central obesity [112]. Lactating animals have smaller adipocytes and lower peripheral lipoprotein lipase activity than non-lactating controls[121]. Breastfeeding enhances calorie expenditure and helps with weight loss, changing the distribution of body fat. Breastfeeding-related obesity differences were discovered in postmenopausal women[119, 112]. Additionally, among women with exclusive breastfeeding, a longer breastfeeding history might prevent peripheral nerve aging by slowing the return of ovulation after delivery and reproductive aging [122].

2.3.4 Menopause

Menopause is usually diagnosed after 12 months without any menstrual period, marking the end of the reproductive phase in a woman's life. The earliest hormonal evidence of ovarian aging is the overexpressed serum or urinary FSH levels[62]. After the final menstrual period, estrogen and progesterone decrease and remain low. In premature menopause animal models, the loss of ovarian-derived estrogen leads to the brain's bioenergetic capacity by influencing glucose metabolism and mitochondrial function. The negative effect of ovariectomy could be reserved fully or partly after the immediate estrogen treatment in these model animals[123].

- **Age at menopause**

Menopause naturally happens between the ages of around 45-55 years worldwide[124]. The age onset of natural menopause is usually categorized as premature menopause (younger than 40 years), early menopause (40-44 years), normal menopause (45-54 years), and late menopause (55 years or older)[125]. In the US, the prevalence of premature and early menopause was 1.7% and 3.4%, respectively[126]. Some women may lose their ovarian function before they reach menopause naturally. The most prevalent type of premature or early menopause is surgical menopause[127]. Both genetic and environmental factors are considered important determinants of age at natural menopause, and the related factors in the different populations vary across

ethnicities. Socio-demographics, anthropometric factors, and early life experiences have also been identified as factors in determining age at menopause, such as smoking and nutrition[128]. In addition, duration and type of contraception use could influence time of menopause[126].

Women who undergo premature or early menopause, either as a result of bilateral salpingo-oophorectomy or primary ovarian insufficiency, experience early loss of estrogen and other ovarian hormones. Early menopause harms women's health outcomes. Diabetic female patients (less than 20 years old) usually get early menopause[129]. Compared to those with normal menopause, women with early menopause have an increased risk of arterial hypertension[130]. Premature or early menopause is also a significant risk factor for CVD among women[131, 132]. Consistently, women with premature menopause have a higher risk of developing metabolic syndrome[133]. In addition, early menopause is independently associated with women with the risk of osteoporosis, venereal cancers, and even early onset of Alzheimer's disease, after adjusting for other confounding factors[134-136]. Later menopause has been reported to be associated with longer life and lower risk of fracture, and all-cause mortality, but higher bone mineral density and higher risk of breast and ovarian cancer[137].

Early natural menopause is linked to a shorter reproductive lifespan and lower cumulative estrogen exposure in women, but surgical menopause can cause an abrupt loss of estrogen and progesterone in women. Early natural menopause (45 years) and surgical menopause (43 years) have both been linked to an increased incidence of glaucoma, a glaucomatous optic neuropathy[138, 139]. In women with early menopause, shorter estrogen exposure could negatively affect the function of pancreatic β-cell and induce insulin resistance, which has shown a harmful effect on peripheral nerves[140, 141]. Early menopause and premature menopause have been found more prevalent in women with chronic inflammatory diseases. The persistent chronic inflammation could induce peripheral neuropathy by impairing the efficiency of nerve regeneration and influencing the microenvironment in the peripheral nervous system, characterized by chronic macrophage infiltration, increased cytokine expression, and pro-inflammatory gene expression[142].

The functional and electrophysiological features of peripheral neuropathy, such as nerve conduction velocity, muscular strength, sensory discrimination, autonomic responses, and intimal blood flow, are affected by aging. The decline in nerve regeneration and function after injury also occurs as aging, which may result from the changes in neuronal, axonal, Schwann cell, and macrophage responses[143, 144]. Menopause has been documented to accelerate biological aging. The earlier onset of menopause is significantly associated with the acceleration of increased

epigenetic age. Hence, earlier menopause might be positively associated with distal sensory neuropathy among postmenopausal women.

- **Total reproductive lifespan**

The term "total reproductive lifespan" refers to the time between menarche and menopause. Age at menarche and age at menopause have both been documented as indicators of cumulative endogenous estrogen exposure. However, the total reproductive lifespan might be a superior variable for indicating the duration length when exposed to endogenous estrogen[22]. The longer length of this reproductive life span has been independently related to a reduced risk of CVD among postmenopausal women[145]. Moreover, total reproductive lifespan is a stronger predictor for the elderly congnition[22]. Currently, the relationship between total reproductive lifespan and peripheral neuropathy is unclear.

- **Time since menopause**

Time since menopause usually refers to the duration from menopause to the age at interview. The main types of hormones regulating the menstrual cycle are FSH, LH, estrogens, and progesterone. The earliest hormonal evidence about ovarian aging is the overexpressed serum or urinary FSH levels[62]. FSH concentrations stay stable from two to eight years after the final menstrual period but decline by 30% by approximately age 75, while the changes of LH are similar to FSH[68, 69]. The progesterone levels decrease as the poorly functioning ovaries of menopause, and estrogen levels reached their lowest point in the first two years after final menstrual period[69]. Several symptoms and disorders in multiple systems also depend on the different sex hormone levels among postmenopausal women, related but not limited to estrogen deficiency[146]. Women with more than 20 years since menopause were at a greater risk of metabolic syndrome, CVD, and elevated blood pressure than those with less than ten years since menopause[147].

Time since menopause could reflect the time of exposure to low estrogen levels. Women with a longer time since menopause harm impaired glucose tolerance, which could induce neuropathies, mostly on the small nerve fibers[148, 149]. Similar to early menopause, the longer time since menopause also could accelerate biological aging compared to those with a shorter duration after menopause. This might be the potential explanation why postmenopausal women with earlier menopause and longer time since menopause tend to have more health problems[143]. Hence, the longer time since menopause might be positively associated with distal sensory neuropathy among postmenopausal women.

2.4 History of exogenous hormone use

Exogenous hormone use refers to the administration of various hormones or their analogs that the women's endocrine glands do not make. Some hormones or analogs, particularly anabolic steroids, are routinely used in medical treatment or as performance enhancers and have been shown to have a major impact on users' future health and fertility. In this study, we defined exogenous hormone as hormonal contraceptives or menopausal hormone therapy (MHT).

2.4.1 Hormonal contraception

Hormonal contraception refers to the use of hormones to prevent pregnancy, including combined estrogen-progesterone or progesterone only. The combined hormonal pill with estrogen and progesterone is the most commonly prescribed. Progesterone works for avoiding pregnancy and the combined estrogen for controlling menstrual bleeding. Hormonal contraception inhibits follicular growth, endogenous estradiol, and progesterone production; and prevents ovulation. Hormonal contraceptives are usually taken as pills, skin patches, vagina or uterus rings[150]. Approximately 25% of women aged 15-44 years use birth control pills in the US. Most users take birth control pills to prevent pregnancy, but 14% use them for non-contraceptive reasons[151]. Immediate benefits include relief from menorrhagia and dysmenorrhea, as well as symptoms of premenstrual dysphoric disorder and acne. The majority of birth control pill side effects are minor and go away after terminating use or switching to a different pill formulation[152]. Breakthrough bleeding is the most common adverse effect of combined oral contraceptive pills. Contraceptive use is associated with non-contraceptive health outcomes in women, such as nausea, headaches, abdominal cramping, breast tenderness, and increased vaginal discharge or decreased libido[150, 151]. Although contraception has numerous advantages beyond its primary goal of preventing pregnancy, contraceptive use was associated with a higher risk of CVD[153].

The evidence for an association between contraception and nervous system disorders is controversial[22]. Contraceptive use has been shown to improve women's mid- or late cognition in both long-term and short-term users, with a considerable improvement in verbal menory[154, 155]. Long-term contraceptive usage (at least 10 years) reduces the incidence of Parkinson's disease, but the advantage is not shown in shorter-term users[156]. Women who have used contraception for more than 5 years, on the other hand, have been linked to an increased risk of Parkinson's disease[157].

Contraceptive use could affect glucose, lipid, and insulin metabolism, as well as coagulation and inflammatory profiles among users[158]. The levels of C-reactive protein (CRP) considerably increase among female athletes who used contraception[159]. As a marker for inflammation and tissue

damage, the serum or plasma levels of CRP are increased during numerous acute and chronic inflammations. In systemic inflammatory responses, CRP has been linked to peripheral nerve damage[160]. Glaucoma (optic nerve) is more common in women over 40 who have used oral contraceptives for at least three years[161]. These contradictory results could be influenced by differences in contraceptive formulation and use, the age range of the study population, and the variety of nerve types[156]. According to the studies of existing, there isn't enough research to look into the link between hormonal contraception and distal sensory neuropathy.

2.4.2 Menopausal hormone therapy

The most effective treatment for menopausal symptoms is MHT, commonly known as hormone replacement therapy (HRT). Estrogen replacement therapy (ET, ERT) is the treatment with estrogen-only, while the combination treats estrogen-progestogen therapy (EPT) of estrogens and progestogens. Because of their differing benefit-risk ratios, ET and EPT should be distinguished[162]. EPT is required for women with an intact uterus through a continual regimen or 21-day cyclic administration and 7-day pause; ET is used for women who have no uterus[163]. All estrogen treatment should start at a low dose and gradually increase. Subsequently, treatments for women in the late menopausal transition change to progestogen-dominated combined sequential EPT, which is also recommended for postmenopausal women who never get replacement therapy[164].

Menopausal hormone therapy is beneficial for CVD, diabetes, musculoskeletal system, and quality of life[165-171]. Usage of estrogens may cause dysmenorrhea, retention of body fluids, nausea, leg cramps, and headaches, while progesterone components are associated with depression, anxiety, flatulence, and increased appetite[162]. Additionally, some contraindication should be taken into account during MHT, including active hepatopathy; active arterial thromboembolism such as coronary thrombosis, angina pectoris; current idiopathic thromboembolic disease or history such as pulmonary embolism, phlebothrombosis; known or suspected estrogen-dependent malignancies; untreated estrogen-dependent cancers such as endometrial cancer, breast cancer, endometrial stromal sarcoma; and intolerance of MHT[162].

Menopausal hormone therapy's influence on postmenopausal women's neurological systems is also currently contested. More than half of observational studies demonstrate that MHT can help postmenopausal women improve their cognition and dementia severity[172, 173]. Long-term clinical trials, on the other hand, virtually always reveal no benefit, while long-term trials tend to show harm[174]. Furthermore, the timing of treatment affected the women's long-term health results. Early MHT among postmenopausal women could reduce dementia risk but initiating later in life has no advantage or increased risk[127]. MHT users and non-users in Korean postmenopausal

women have distinct nerve conduction study parameters, but the differences are not statistically significant[175].

In animal studies, aging nerves are still sensitive to estrogen and progesterone. Estrogen could help restore memory in older mice or chronically estrogen-deficient mice if given at the proper dose. The nerve growth factor is a neurotrophic factor known to play a key protective role in the development and survival of sympathetic, sensory, and forebrain cholinergic neurons. Using EPT also could regulate the expression of nerve growth factors in peripheral organs in ovariectomized female mice[71]. Although both estrogen and progesterone are well-known neuroprotective factors, there is currently limited research on whether the history of exogenous hormone use affects peripheral nerves. In addition, the regimen, timing, and dose of exogenous hormone use should be concerned for their effects.

Chapter 3 – Research Methodology

The publicly released data from NHANES in the United States was used in this study[176]. NHANES would be briefly introduced at the beginning of this chapter. All publicly available data and related documentation about the NHANES dataset are a free download on the NHANES homepage: www.cdc.gov/nchs/nhanes.htm. The research proposal, dissertation, and related manuscript of this study were written following the RECORD statement[177] – a checklist of items, an extension based on the STROBE statement.

3.1 NHANES

Current NHANES, also known as continuous NHANES, is a national survey that is developed and used in the United States to evaluate the importance and burden of public health issues. Since the late 1990s, the National Center for Health Statistics (NCHS) has been in charge of collecting NHANES data and generating the information (including survey weight) for further analysis as a data producer. The NHANES data were collected annually and publicly released each two-year cycle. Before publicly releasing, NCHS has made a cleaned dataset, codebooks for each variable, several documents for introducing the detail about the study design and data collection/analysis, and the tutorials for using NHANES data could be found on the home page.

Thousands of analyses have been conducted by the researchers (data users) to test the hypothesis with publicly available data from NHANES. The data users could search the specific variables by the "Variable Keyword Search" link from NHANES. Or they can determine the cycle they need from the "Survey Content Brochure" which contains available components across survey cycles. By exploring these two methods, we have confirmed that the data from 1999 to 2004 could be used for our study. Because "Lower extremity disease - Peripheral neuropathy" is only possible to access from 1999 to 2004, and the other required variables are also accessible from these three cycles.

Before any data management and analysis, the NHANES-related documentations were carefully reviewed, especially the information about the survey weight and variance estimation. The general information about the sampling technique and data collection procedure was introduced under each subtitle in this part. In addition, the design variables which is necessary for complex survey data analysis were also described.

3.1.1 Sampling technique

To enroll participants, the NHANES employs a complex, multi-stage, probability sampling design, with four stages as below:

- Stage 1: Primary sampling units (PSUs) are chosen from strata specified by geography (e.g., census region), metropolitan statistical area status, and other demographics using the probability proportional to a measure of size (PPS) technique. Out of the approximately 3,000 counties in the United States, about 30 were visited throughout a two-year survey cycle.
- Stage 2: From PSUs with PPS, segments (usually city blocks or their equivalent) are selected.
- Stage 3: Dwelling units (DUs) or households are randomly selected in each segment. DUs were chosen with equal probability, at a rate comparable to the maximum within-segment sampling rate required to attain the subdomain sampling rates.
- Stage 4: For each eligible household, an average of two sample people is chosen. Individuals are drawn at random within designated age-sex-race/ethnicity screening subdomains.

3.1.2 Data collection

NHANES recruits approximately 12,000 participants every two years. Although response rates fluctuated from year to year, an average of 10,500 people agreed to participate in a household interview. About 10,000 persons participated in data collection at the mobile examination centers (MEC). Each two-year data cycle could be divided into five sections:

- Demographics: demographic variables and survey design variables (survey weights, sampling units, and strata).
- Dietary: dietary intake (foods, beverages, and dietary supplements).
- Examination: physical and dental examination.
- Laboratory: analysis of blood, urine, hair, air, tuberculosis skin test, and household dust and water specimens.
- Questionnaire: information obtained during interviews.

3.1.3 Design variables

The NHANES selected participants with a complex, multistage, probability sampling design. Ignoring the included design elements can often lead to inaccurate point estimates and/or inaccurate standard errors. The "*svyset*" command defines the design variables: weight, PSU, and strata.

- Weight

The weight of the sample person represents the number of people in the population represented by the sample person. For NHANES, each individual's weight is based on population-scale weights, with the population size determined by the sum of the weights. When an NHANES sample is weighted, it is representative of the civilian noninstitutionalized resident population in United States, taking into account the survey's complex design (including oversampling), survey non-response, and post-stratification correction to match total population counts from the Census Bureau. The variables of weight in NHANES have been generated and provided by the data producer, including weight for the interview sample, examined sample, and fasting subsample. A proper weight should be chosen according to a variable of interest in a specific study hypothesis. A weight of zero indicates that individuals were not eligible to be included in a specific sample and will be excluded from the analysis. According to the data collection procedure, part (not all) of respondents who have finished the interview in each two-year cycle did not take part in the phase of examination. The weight for these participants is a positive value for WTINT2YR but a zero value for WTMEC2YR. NHANES recommended analysis with the weight including least respondents. Hence, the weight at the examination phase (including components of questionnaire and examination, WTMEC4YR and WTMEC2YR) was chosen in our study.

- PSU and strata variables

The sample design in NAHENS 1999-2001 differs significantly from NHANES 2002-2004. Mostly, two PSUs were selected per strata. Variables of “SDMVSTRA” and “SDMVPSU” released from NHAENS are not the “true” information about PSU and strata but generated and provided by the NHANES data producer. These pseudo-variables are beneficial for a data user to combine the dataset in different cycles, reducing the disclosure risks and protecting the participants’ information, and minimizing the bias caused by altering the PSU structure. Hence, “SDMVSTRA” and “SDMVPSU” were contained in our data file. In the released dataset, there were 12 PSUs in 1999 and 15 PSUs per year from 2000. In a complex survey, the precision of the estimated variance is related to degrees of freedom which depends on the information about the first stage of the sample design (PSU and strata). These masked variables produce approximately close variances estimated from the true design variables. To determine the statistical reliability of estimates in complex sample surveys, the sampling error calculation model were considered before analysis. Taylor Series Linearization (TSL) was recommended according to the NHANES tutorial. In a complex survey, the precision of the estimated variance is related to degrees of freedom (*df*), which depends on information about the first stage of sample design (*df = #primary sampling units - #strata*). If an estimated standard error has less than eight degrees of freedom, the computed estimate may be unreliable[178].

3.2 Research design

The current project is a cross-sectional study with publicly released data from NHANES 1999-2004.

3.3 Study population

Our study included women aged 40 years and over from NHANES 1999-2004.

- Exclusion criteria

Women with non-postmenopausal status were excluded. Women with stroke, cancer, diabetes, CVD, thyroid disease, liver disease, and weak/failing kidneys were excluded from the final analysis because these diseases are potential causes of peripheral neuropathy[19]. Women with amputation or insufficient information about eligibility and outcome in the released dataset were excluded. Amuputation could be a severe consequence of peripheral neuropathy that may make it difficult for monofilaments to detect foot sensation[29].

3.4 Data sources and dataset management

Dataset was generated with the standard software package (Stata/SE 15.1 for Mac, StataCorp). The data from NAHENS 1999-2004 was used in this study. Each variable would be introduced in detail as following, including related data files, data collection procedure, measurement tools, and the name, label, value, and value label of original variables. After confirming the data file required in this study, the related URLs were imported. Only related variables and sequence numbers were kept in our data file and saved as "Stata.dta files". We made the contents of data files in the same way, including sequence numbers, the names and labels of each variable. If the variable name and value differed in different cycles, the related variable would be mentioned explicitly for each cycle in this part. After saving each required data file, we used the Stata command "*append*" to combine data in the different cycles. The next step was to "*sort*" each data file by the sequence number and "*merge*" data files from various components. Only design variables, dependent variables, independent variables, confounding variables, and indicator variables (used for screening the eligible individuals) were contained in the final data set. The management of these variables could be found with detail as follows:

3.4.1 Design variables

According to the NHANES tutorial, the combined 6 years examination weight (WTMEC6YR) was generated based on WTMEC4YR and WTMEC2YR, because both interview and physical examination data from 1999 to 2004 were used in this study. The following original variables could be found in "Demographic Variables & Sample Weights" in the Demographics Data file:

WTMEC4YR - Full Sample 4 Year MEC Exam Weight; WTMEC2YR - Full Sample 2 Year MEC Exam Weight; SDMVSTRA - Masked Variance Pseudo-Stratum; SDMVPSU - Masked Variance Pseudo-PSU. In addition, the variable "SDDSRVYR - Data Release Number" also remained in our data file, which could provide information about the distribution of the sample in each cycle.

3.4.2 Outcome

Data about distal sensory neuropathy could be found in "Lower Extremity Disease - Peripheral Neuropathy" in the Examination data file. During 1999-2004, NHANES invited adults over the age of 40 to test the foot sensation with a monofilament. Those with amputation on both feet, weight > 400 pounds, or reason of participant refusal, equipment failure, or technical error were excluded from the exam. Participants were asked to lie on the exam table to receive the sensation of the touch test. Well-trained technicians applied slight pressure to plantar-first metatarsal head, plantar-fifth metatarsal head, and plantar-hallux of participants' each foot without sequential order. There were three tests at most for each of the three sites. If the participant's response was correct at the first test or answers correct for two out of three tests, it could be defined as sensate. The insensate site was defined when participants were unable to respond correctly to the filament pressure. With each site defined as sensate or insensate, the total number of insensate areas were counted and recorded for each foot[23].

According to the codebook from "Lower Extremity Disease - Peripheral Neuropathy" file, the variable LEALPN represents the number of insensate areas on the left foot. In contrast, LEARPN represents the number of the insensate regions on the right foot. Both LEALPN and LEARPN have six categories: no insensate areas, 1 insensate area, 2 insensate areas, 3 insensate areas, not enough information to collect, and missing. If the test could not be conducted because of the technician's error or some physical limitations from examinee, "not enough information to collect" was entered by the health technician. Data of participants excluded from the 10-gram monofilament test was recorded as "missing". In this study, distal sensory neuropathy was a binary variable(with distal sensory neuropathy and without distal sensory neuropathy), defined as at least one insensate sitting on either foot[23]. Variable PNEXAM will be generated for distal sensory neuropathy based on LEALPN and LEARPN.

3.4.3 Exposure

Data about the history of menstrual period, pregnancy, breastfeeding, and hormone use could be found in "Reproductive Health" in the Questionnaire data file. Female participants aged ≥ 12 years were invited to join the private face-to-face interview in the MEC. The questionnaire for reproductive health contains a complex and detailed set of questions based on the specific age

group. There were some skip patterns according to the responses to reproductive health conditions among participants. All data were self-report data in this part, so some remaining inconsistencies of reactions should be taken care of during data analysis.

- Age at menarche

Variable of “RHQ010 - Age when first menstrual period occurred” was used for defining age at menarche. This numerical data was collected with the question “How old were you when you had your first menstrual period?” and entered in “year”. It was coded as “0” if the participants have not started yet, “777” for participants' refusal, “999” for “do not know,” and “missing” for those did not receive a response for any reason. In this study, the age at menarche was a binary variable: ≤ 11 years and > 11 years[179].

- Gravidity

Variable of “RHD130 - Ever been pregnant?” and “RHQ160 - How many times have been pregnant?” will be used for defining gravity. The numerical data was collected from those answered “yes” for RHD130, with the question “How many times have you been pregnant, including current pregnancy, live births, miscarriages, stillbirths, tubal pregnancies, or abortions?”, and entered as the sum number of all pregnancies. The value of “77” was coded for participants' “refusal”, “99” for “do not know”, and “missing” for those did not receive a response for any reason. In this study, the gravidity will be binary with two categories: <4, and ≥4[180, 181].

- Breastfeeding history

Variable of “RHQ210 - Breastfed any of your children?” will be used for breastfeeding history, with the question “Did you breastfeed any of children?”. The data was entered as follows: “yes” was coded as 1, “no” as 2, “refused” as 7, and “do not know” as 9. In this study, breastfeeding history was the binary data: ever and never.

- Age at menopause

Variable of “RHQ060 - Age at last menstrual period” will be used for age at menopause, with the question “how old were you when you had your last menstrual period?”. The data was entered age in years, and “777” for refused, “999” for do not know, and “missing” for those did not receive a response for any reason. In this study, the age at menopause was the categorical data with three categories: <45; 46-55; ≥ 56 years[125].

- Time since menopause

Time since menopause was calculated by age at interview minus age at last menstrual period, with two categories: ≤20 and >20 years[147]. Variable of "RHQ060 - Age at last menstrual period" and "RIDAGEYR - Age at Screening Adjudicated" were required.

- Total reproductive lifespan

Time since menopause was calculated by age at menopause minus the age at menarche. The median cutoff point of total reproductive lifespan among our sample was 35 years old. Hence, we define total reproductive lifespan as binary variable: ≤ 35 and > 35 years.

- History of exogenous hormone use

"RHQ420 - Ever taken birth control pills?" with the question "have you ever taken birth control pills for any reason?", "RHQ510 - Used Depo-Provera or injectables?" with the question "have you ever used Depo-Provera or injectables to prevent pregnancy?" and "RHQ540 - Ever use female hormones?" with the question "have you ever used female hormones such as estrogen and progesterone? Please include any forms of female hormones, such as pills, cream, patches, and injectables, but do not include birth control methods or use for infertility" this was used for history of exogenous hormone use. RHQ540 was collected from females aged ≥ 20 years. Females with the answer yes were coded as 1, no as 2, refused as 7, and do not know as 9. Others as missing if the data was failed collected from them. The history of exogenous hormone use was binary data in this study: ever or never.

3.4.4 Confounding variables

Age, race, education, and income could be achieved from "Demographic Variables & Sample Weights" in the Demographics Data file. All participants would have demographic data records if they received the household interview. Participants aged ≥ 16 years were interviewed directly, while a proxy for those aged < 16 years or could not answer questions themselves. The demographic data was collected before the health examination. Insurance information could be found in "Health Insurance" in the Questionnaire data file. Alcohol use information could be found in "Alcohol Use" in the Questionnaire data file. Smoking information could be found in "Smoking - Cigarette/Tobacco Use - Adult (SMQ)" in the Questionnaire data file. Hypertension information should be obtained from both "Blood Pressure (BPX)" in the Examination data file and "Blood Pressure & Cholesterol (BPQ)" in the Questionnaire data file. BMI could be found in Body Measures (BMX)" in the Examination data file.

- Age

Age could be obtained from the variable “RIDAGEYR - Age at Screening Adjudicated”, entered as the age in years. Data was obtained from all participants, but those aged 85 years or over were recorded as ≥ 85 years. In this study, age was binary data:40-70 years and >70 years[23].

- Race

Race could be obtained from the variable of “RIDRETH1 - Race/Ethnicity”, entered according to the self-reported race and ethnicity information: Mexican American, Other Hispanic, non-Hispanic white, non-Hispanic Black, and other races (including the multi-racial). Data was collected from all participants. In this study, the race was binary data: Hispanic, and Non-Hispanic.

- Education

Education could be obtained from variable of “DMDEDUC – Education”, with the questions “What is your highest grade or level of school completed or the highest degree received?” Data for education is available among both males and females aged ≥ 6 years. The answer of “Less Than High School” was coded as 1, “High School Diploma (including GED)” as 2, “More Than High School” as 3, while 7 for “refused” and 9 for “do not know”; others could not be achieved as missing. Education was a binary variable in this study: less than high school and high school or over.

- Income

Income will be obtained from the “INDFMPIR - Family PIR” variable among all participants. The poverty income ratio (PIR) represents family income to the poverty threshold. This variable was calculated by dividing family income by the poverty guidelines, according to family size, a specific year, and state. The data was entered as a continuous number, but values at 5 or over were coded as 5 or more because of the disclosure concerns. Values were not calculated for missing data. Income was binary data in this study: PIR ≤2.00, PIR > 2.00.

- Insurance

Insurance will be obtained from the “HID010 - Covered by health insurance” variable. All participants were interviewed with the question, “Are you covered by health insurance or some other kind of health care plan?”. In this study, insurance was binary data: covered or not.

- Alcohol use

In this study, the variable of “ALCOHOL” will be generated according to variables of “ALQ100 - Had at least 12 alcohol drinks/1 yr?” and “ALQ110 - Had at least 12 alcohol drinks/lifetime?”, with two categories: never; and ever.

- Smoking

In this study, the variable of "SMOKING" will be generated according to variables "SMQ020 - Smoked at least 100 cigarettes in life" and "SMQ040 - Do you now smoke cigarettes", with two categories: never; and ever.

- Hypertension

Self-report hypertension information could be obtained from "BPQ020 - Ever told you had high blood pressure" and "BPQ040A - Taking prescription for hypertension", among participants aged ≥ 16 years. Blood pressure could be found in "BPXSAR - SBP average reported to examinee" and "BPXDAR - DBP average reported to examinee", among participants aged ≥ 8 years. The detailed calculation of averages of blood pressure could be found on the codebook page of "Blood Pressure (BPX)". In this study, hypertension was binary data: yes or no.

- BMI

BMI information could be obtained from the "BMXBMI - Body Mass Index (kg/m^2)" variable. BMI data is available among all participants aged ≥ 2 years. All body measures were obtained by trained health technicians in the body measures room in MEC. In this study, BMI was binary data: underweight/normal(<25 kg/m^2), and overweight/obese(≥25 kg/m^2) [182].

3.4.5 Variables about eligible criteria

Eligible participants should be identified by the "indicator" variable, which will be used with the "*subpop*" command in the analysis. The eligible observation, without disease, female, and postmenopausal status, will be coded as 1 in the "indicator" variable. Each required variable will be generated as follows.

- Female

In this study, the variable "FEMALE" was obtained from variables of "RIAGENDR – Gender". Females was coded as 1.

- Postmenopausal status

Variable "POSTMENOPAUSE" was generated for confirming the menopausal status of our study population. The postmenopausal status was defined according to "RHQ040 - Reason not having regular periods", "RHQ050 - When did SP have last period?", "RHQ060 - Age at last menstrual period", "RHD280 - Had a hysterectomy?", "RHQ290 - Age when had hysterectomy", "RHQ310 - Were both ovaries removed or only one?". The confirmed postmenopausal status was coded as 1.

- Without amputation

A new variable (NOAMPUTATION) was generated according to “LEALAMP - Left amputation” and “LEARAMP - Right amputation” from “Lower Extremity Disease - Peripheral Neuropathy” in the Examination data file. Non-amputation was coded as 1.

- Without diabetes

The new variable (NONDM) was confirmed according to a variable of “DIQ010 - Doctor told you have diabetes” in "Diabetes (DIQ)" in the Questionnaire data file and coded as 1 when participants answer “no” for DIQ010.

- Without kidney disease

The new variable (NONKID) was defined based on “KIQ020 - Ever told you had weak/failing kidneys” in "Kidney Conditions (KIQ)" and coded as 1 when participants answer “no” for KIQ020.

- Without Cancer

Cancer information could be obtained from “MCQ220 - Ever told you had cancer or malignancy” in "Medical Conditions (MCQ)" in Examination data file. The new variable (NONCANCER) was coded as 1 when participants answer “no” for MCQ220.

- Without CVD

Variables of “MCQ160B - Ever told had congestive heart failure”, “MCQ160C - Ever told you had coronary heart disease”, “MCQ160D - Ever told you had angina/angina pectoris”, and “MCQ160E - Ever told you had heart attack” was used for identifying participants without CVD. Non-CVD was coded as 1 when patients report “no” for all questions above.

- Without Stroke

“MCQ160F - Ever told you had a stroke” was used for defining participants without stroke. A new variable (NONSTRK) was generated and coded as 1 when participants answer “no” for MCQ160F.

- Without liver disease

“MCQ160L - Ever told you had any liver condition” was used for defining liver disease. A new variable (NONLIVER) was generated and coded as 1 when participants answer “non” for MCQ160L.

- Without Thyroid disease

"MCQ160I - Ever told you had thyroid disease" was used for thyroid disease. A new variable (NONTHYRIOD) was generated and coded as 1 when participants answer "non" for MCQ160I.

- Indicator variable for screening the eligible participants

The "indicator" variable for screening the eligible participants was generated and the eligible participants will be coded as 1. As this is the analysis with complex survey data, no observation could be dropped from the dataset, using "*subpop*" command with "indicator" variables instead. After generating new variables, the eligible participants were confirmed.

The codes or algorithms for all steps above were validated.

3.5 Study subjects and sample size

3.5.1 Screening the eligible participants

Once the indicator variable was confirmed, the number of study participants could be confirmed.

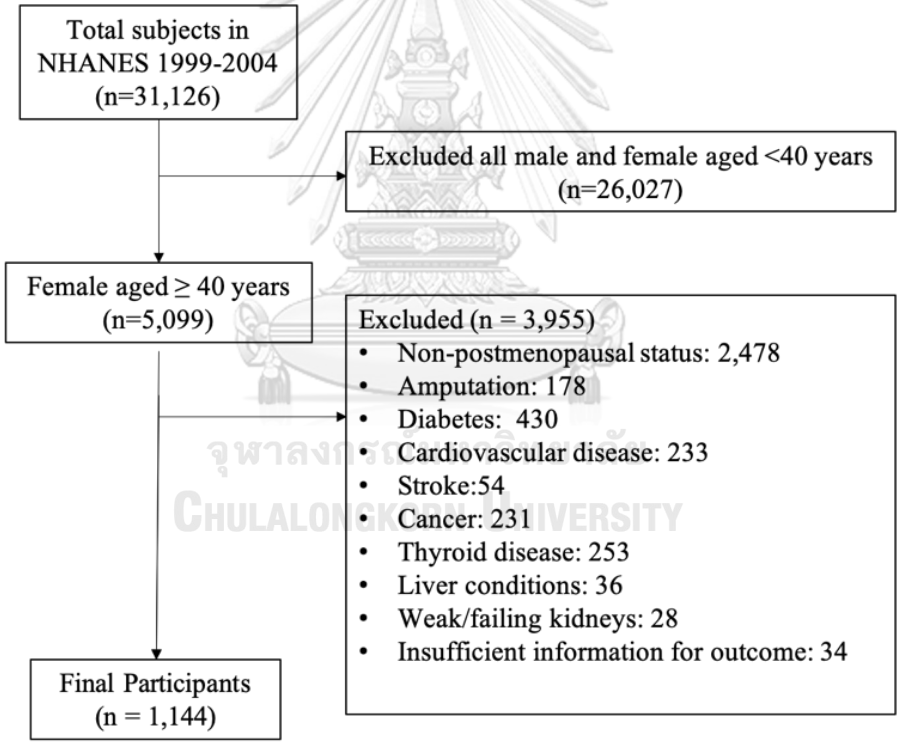


Figure 2. Flow diagram for eligible participants (NHANES 1999–2004 cycle)

3.5.2 Sample size

An adequate sample size is important for detecting the estimates and an efficient statistical difference. The minimum sample size is usually predetermined with power analysis, according to error level (alpha, α); power; and effect size. Statistical power refers to the probability to find a significant relationship, which increases with an increased sample size. In secondary data analysis,

the data has been gathered and the sample has been determined. The sample size could be confirmed whether adequate via power analysis before and after data collection. This type of calculation requires setting value for error level (usually at 0.05), power (usually 80%), and effect size (an estimated clinical difference according to the research hypothesis)[183]. However, we did not know the minimal clinical difference among the US population according to previous studies.

- To our knowledge, the present study is the first study for exploring the association between distal sensory neuropathy and reproductive factors. Current available information was not enough for conducting the predetermined power analysis. Recent publication has recommended that power calculations are not required for causal analyses of existing databases. Important research questions are recommended to be conducted and published, and then further meta-analysis could provide a more precise pooled effect estimate[184]. Hence, we used all eligible participants in the final analysis, which is also benefical for avoiding the selection bias.
- NHANES recommended sample sizes based on the design effect and specified proportion[185]. Moreover, they also recommended: 1) using at least 4 years (two cycles), and 2) collapsing the subdomains[185]. This is also the reason why we defined most of our variables as binary variables.

3.6 Data preparation

All data management and cleansing were performed with the Stata/SE 15.1 for Mac, StataCorp. Once the data file has been generated with all required variables, the data cleansing should be done as the next step. In our data file, the design variables are numerical data, and all variables of interest are categorical data. The categories were sited and recoded by our research team under consideration of literature review and reliability of estimates. The distribution and missing data for each variable were checked before data analysis.

3.6.1 Design variables

In NHANES, design variables about the first stage of sample design (SDMVSTRA, and SDMVPSU), and the weight (WTMEC4YR and WTMEC2YR) were generated and cleaned by the data producer before release. Generally, the scaling, distribution, extreme values, and the missing data should be concerned for the survey weight. The weight in NHAENS is a population scale weight, and the sum of weights is the population size. The distribution of weight could influence the precision of estimates, and the extreme values may produce the standard error for the complete or the subgroup of the sample. The missing data of weight reflects an error, and the zero value refers to a specific feature of the dataset. The combined 6 years examination weight (WTMEC6YR) was

generated based on the weight variables (WTMEC4YR and WTMEC2YR) provided in the original NHANES dataset 1999-2004. The precision of values in WTMEC4YR and WTMEC2YR was checked by the data producer (NCHS) before release. There was no missing and no zero value for WTMEC6YR in the final data file. The value of WTMEC6YR was non-normal distributed.

There was no missing data and zero value for the variables of SDMVSTRA, and SDMVPSU, so we used them directly. Before data analysis, commands (*svyset* and *svydescribe*) were used to define the sample design variables for the data set and check the distribution and sample sizes in each stratum and cluster.

3.6.2 Variables of interest

All key analysis variables are categorical data in our study. The coding errors, missing data, and strategy for handling the missing data should be concerned.

- Coding errors

Coding error was checked for each variable with the command "*codebook*".

- Missing data

The missing data is not avoidable in research. Numerous reasons could lead to missing data; mostly from the non-response. The rate, pattern, and mechanism of missing data should be checked. The commands "*mdesc*" and "*misstable summarize*" were used for confirming the rate of missing data. The rate of missing data in subgroups should not be ignored. In our study, we explored the effect modification by age, hence, the missing value of each variable by age group should be concerned. Missing data patterns provide information about the distribution of missingness. Command "*misstable patterns*" was used for determining the patterns. The output from Stata shows no specific trend in the missing data structure ("generalized pattern"). The missing data mechanism is related to the causes of missingness. Analyzing a dataset with missing data of missing at random or not missing at random will result in biased parameter estimates. More missingness was found in the older age group.

The bias increases when the rate of missing data increases and the difference in characteristics between respondents and non-respondents grows. The potential bias is the difference between the population means for respondents and the true population mean. If the missing data is around 10% for the main analysis variable among the eligible participants, the complex case analysis could be continued without further adjustment[185]. In addition, we also compared the missingness in the codebook of our final dataset with the codebook from the NAHENS home page confirming that we generated this final dataset in the right way.

- Indicator

The indicator variable was generated and confirmed that coding "1" means the eligible subgroup member. The command "*subpop*" was used with an indicator for analysis of the eligible participants in the NHANES dataset.

3.6.3 Description of the cleaned dataset

A total of 1144 observations were included in the final dataset, 390 individuals in NHANES 1999-2000, 387 in 2002-2003, and 367 in 2003-2004. The NHANES sampling error calculation model has 43 sampling error strata and 87 sampling error computation units (two PSUs per stratum), yielding 44 design-based degrees of freedom. Among 12 variables with missing data, BREASTFED shows the most missing value (11.45), following INDFMPIR (10.14), while the missingness for other variables is less than 10% (Supplemental table 1).

3.7 Data analysis

The standard software package (Stata/SE 15.1 for Mac, StataCorp) was used for data analysis. The "*svyset*" was submitted once in Stata, and the prefix "*svy:*" was used for each later individual analysis. The descriptive analysis, logistic regression, and effect modification analysis were conducted according to our research questions.

3.7.1 Descriptive analysis

All variables were categorical in our final cleaned dataset. The weighted median with interquartile range (Q1, Q3) was reported for the numerical data. All data were summarized as proportion with 95% confidence interval (CI). According to the Module 6: Sample Code of NHANES tutorial, the Stata command "*svy: mean*" could be used to explore the prevalence of variables. However, the command "*svy: tab*" or "*svy: prop*" is a better alternative when the proportion of interest is extreme (close to 0 or 1)[186]. According to the codebook of our final dataset, 89 among 1144 were diagnosed with distal sensory neuropathy, while 1,055 were without distal sensory neuropathy. Our outcome is rare. Hence, we will use "*svy: tab*" and "*svy: prop*" to determine the estimate of proportion for each variable.

Generally, the effective sample size, the width and relative width of CI, and the degrees of freedom should be concerned for the reliability of proportion. Since 2007, NCHS has recommended using the postestimation command "*kg_nchs*" following "*svy: prop*" to access Korn-Graubard CI (KG-CI), which could provide information for judging the reliability of estimate and the presentation standards of proportion[187].

3.7.2 Logistic regression

The design-based binary logistic regression was conducted following NHANES tutorials and recommendations from Book of "*Applied survey data analysis*" and "*Applied Logistic Regression*" [188, 186, 189]. The results were presented using odds ratios (OR) with 95% CI. If the odds ratio was lower than one, the variable of interest would be a protective factor. If the odds ratio was equal to one, the variables would not be associated with peripheral neuropathy. If the odds ratio was more than one, the variables would be a risk factor for peripheral neuropathy. The design-based binary logistic regression with purposeful selection of covariates was conducted as follows:

1) Since all the candidate predictors were categorical data, the crosstabulation with the command "*svy: tab*" was conducted for exploring the bivariate association between each factor with distal sensory neuropathy, requesting the row percentages. The dependent variables were listed following predictor variables. Row percentages are appropriate when row variable is explanatory, answering the questions "If the woman was exposed in the exposure, how likely was she to be distal sensory neuropathy?". Design-adjusted Rao–Scott F-test statistic with *p*-value was used as evidence for the hypothesis testing to select the potential predictor variable candidates.
2) The variables with *p*-value < 0.25 in stage 1 would be included in initial multivariable analysis. If the covariates were not significant at the 0.05 alpha level, they were removed from the initial multivariable model. Only the confounders and the covariates with *p*-value ≤ 0.05 were kept with outcome and target exposure in the model. The initial multivariable model was generated with command "svy: logistic". The dependent variable was listed before predictor variables. We use modifier "ib#." to indicate the value # as reference category among multinomial variables. By default, "i.#" means the first category will be the reference category. Stata output will include adjusted odds ratio estimates and 95% CIs for the adjusted odds ratios. Wald test will be used to test the contribution of each predictor to the multivariable model. The adjusted Wald tests in Stata for the multinomial variable in the initial model are generated by using the "*test*" command statement (eg. test 1.ageatmeno 3.ageatmeno; while the level of 2.ageatmeno is reference category). This postestimation command statement was only used for categorical variables with at least 3 categories, with "test" following k-1 variables (k means the number of categories). For the binary variables, the t-test output for each predictor was equivalent to Wald test in Stata.

3) Each dropped covariate in step 2 was added back to the model one at a time. Confounders (a change of 15% in any parameter estimate compared to the initial multivariable model) and covariates with *p*-value ≤ 0.05 were retained in the model. Next, the iteractive process of removing, refitting, and verifying as in step 1 and step 2 was conducted and ended until all clinically and statistically important variables were contained in the model.
4) Variables not selected in initial multivariable model (*p*>0.25 in stage 1) were added individually to the model obtained in Step 2. The similar process as in Step3 was conducted for the variables that were additionally added. We referred the model at this step as preliminary main effects model.
5) As age at menopause, age, and time since menopause might be correlated, Pearson correlation with command "*pwcorr*" was conducted. Generally, when the simple correlation coefficient between two predictors > 0.8 or 0.9 (equal to 1 or -1), multicollinearity would be a serious problem. The collinearity was diagnosed with variance inflation factors(VIF) exceeding 10 with the command "*collin*"[190, 191]. There was no highly correlated independent variable in our preliminary main effects model.
6) Next, we checked the possible interaction, which was based on both clinical and statistical considerations. A # sign was used to specify the two-way interaction (for example "i.var1#i.var2") which was listed after all important variables in the model obtained preliminary main effects model one at a time. Design-adjusted Wald test was used for testing whether these interactions influence the fit of model, with a significance at 0.05. In our model, interaction term of race with menarche was significant. We received a preliminary final model at this step.
7) The goodness of fit with command "estat gof" was used to test the final model and preliminary main effects model, with a significance at 0.05.

3.7.3 Effect modification

Before assessing the effect modification via subgroup analysis, we also checked the missingness of each variable in subgroups. Effect modification of above association between reproductive history factors and distal sensory neuropathy by age was assessed using interaction terms overall and via subgroup analysis. Subgroup analysis for the effect modification analysis was conducted using the final model with adjustment of other confounding variables (excluded the modifier and related interaction) as mentioned in part 3.7.2. The goodness of fit for the subgroup model was assessed. Subgroup anlysis by race was also conducted because we found a significant interaction term between race and menarche in part 3.7.2.

3.8 Ethical consideration

NHANES is approved by National Center for Health Statistics Research Ethics Review Board. All participants provided informed consent. This study was exempted by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (No. 0422/65).

Chapter 4 Results

4.1 Characteristics of the study participants

Characteristics of all participants were summarized as weighted prevalence estimates in Table 1. Total of 1,144 participants were included in the final dataset, 390 individuals from NHANES 1999-2000 cycle, 387 from 2002-2003 cycle, and 367 from 2003-2004 cycle. Of these, 89 (6.26%) participants were diagnosed as distal sensory neuropathy. The median age (Q1, Q3) was 63 (55-73) years old, with 798 (77.26%) were in 40-70 years group. The vast majority of participants (851/1,144, 89.79%) were Non-Hispanic. Approximately 745 (76.97 %) of participants completed education from high school or more than high school. As of the income status, 436 (29.65%) of participants were from lower income status group (PIR ≤ 2) and 592 (60.84 %) were from higher income status group (PIR > 2). The majority of participants (979/1,144, 89.05 %) were covered by health insurance or health care plan.

Table 1: Characteristics of study participants (NHANES 1999–2004 cycle, N = 1,144)

Variables	N (%)
Age	
40-70 y	798(77.26)
>70 y	346(22.74)
Race/Ethnicity	
Hispanic	293(10.21)
Non-Hispanic	851(89.79)
Education	
Less Than High School	397(22.93)
High School and above	745(76.97)
Income status	
PIR ≤ 2.00	436(29.65)
PIR > 2.00	592(60.84)
Insurance	
Not covered	154(10.33)
Covered	979(89.05)
Alcohol use	
Never	293(22.03)
Ever	850(77.70)
Smoking	
Never	678(55.84)

Variables	N (%)
Ever	464(44.09)
Hypertension	
No	435(46.45)
Yes	688(51.70)
BMI	
Underweight/normal	356(32.71)
Overweight/Obese	767(65.86)
Age at menarche	
> 11 y	951(81.90)
≤ 11 y	179(16.69)
Gravidity	
<4	628(63.13)
≥4	516(36.87)
Breastfeeding history	
Never	440(41.34)
Ever	573(45.74)
Age at menopause	
≤45 y	409(37.12)
46-55 y	597(53.17)
≥56 y	133(9.11)
Time since menopause	
≤ 20 y	662(66.08)
> 20 y	411(28.74)
Total reproductive lifespan	
<=35 y	558(50.46)
>35 y	493(41.90)
History of exogenous hormone use	
Never	359(22.83)
Ever	783(76.77)
DSN	
Non-DSN	1055(93.74)
DSN	89(6.26)

NOTE: Number (N) of participants with weighted percentage (%). Column percentages for sample totals which do not add up to 100% are a result of missing data. DSN, distal sensory neuropathy; PIR, prescribed investor rate; BMI, body mass index; y, years.

A total of 464 (44.09 %) of participants reported that they were or had been smoking (including the tobacco use), and 850 (77.70 %) participants reported that they were or had been drinking alcohol. The proportion of participants with health conditions of hypertension and overweight/obese were 51.70 % and 65.86 %, respectively. Among all participants, 951 (81.90 %) experienced their first menstrual period after age 11years, 516 (36.87%) had 4 or more pregnancies, and 573 (45.74%) had breastfed their children. Age at menopause groups corresponded to 37.12%, 53.17%, and 9.11% of the participants from the early/premature menopause (<45 years) group, normal menopause(46-55 years) group, and late menopause (≥56 years). Around a third of participants had their final menstrual period 20 years ago, and a half of participants experienced a shorter total reproductive lifespan (≤ 35 years). The number of exogenous hormone users was as high as 783, accounting for 76.77% of all participants, which was more than three times the number of women who had never used any exogenous hormone.

4.2 Distal sensory neuropathy and associated factors

Characteristics of social-demographic, lifestyle, medical conditions and reproductive factors of all participants were compared between distal sensory neuropathy group and non-distal sensory neuropathy group for addressing potential predictor variable candidates (Table 2). Age (p = 0.05), education (p = 0.01), time since menopause (p = 0.05) and history of exogenous hormone use (p = 0.03) were significantly different between distal sensory neuropathy group and control group. In addition, the race/ethnicity, income status, alcohol use, age at menarche, breastfeeding history, age at menopause were different between two groups, with $p < 0.25$. Hence, these variables were selected as potential predictor variable candidates for the later logistic regression model.

Table 2: Characteristics of study participants by distal sensory neuropathy (NHANES 1999–2004 cycle, n= 1,144)

Variables	Non-DSN, n= 1055		DSN, n= 89		p-value
	%	(95% CI)	%	(95% CI)	
Age					0.05*
40-70 y	94.71	92.57 - 96.39	5.29	3.61 - 7.43	
> 70 y	90.43	85.68 - 94.02	9.57	5.98 - 14.32	
Race/Ethnicity					0.13*
Hispanic	90.32	82.89 - 95.27	9.68	4.73 - 17.11	
Non-Hispanic	94.13	92.28 - 95.65	5.87	4.35 - 7.72	
Education					0.01*
Less Than High School	89.75	84.89 - 93.46	10.25	6.54 - 15.11	
High School and	94.92	93.00 - 96.44	5.08	3.56 - 7.00	

Variables	Non-DSN, n= 1055		DSN, n= 89		p-value
	%	(95% CI)	%	(95% CI)	
above					
Income status					0.14*
PIR ≤ 2.00	91.95	87.52 - 95.19	8.05	4.81 - 12.48	
PIR > 2.00	95.16	92.62 - 97.02	4.84	2.98 - 7.38	
Insurance					0.67
Not covered	94.79	87.46 - 98.50	5.21	1.50 - 12.54	
Covered	93.69	91.92 - 95.16	6.31	4.84 - 8.08	
Alcohol use					0.23*
Never	91.58	86.82 - 95.04	8.42	4.96 - 13.18	
Ever	94.33	92.00 - 96.14	5.67	3.86 - 8.00	
Smoking					0.85
Never	93.59	91.38 - 95.38	6.41	4.62 - 8.62	
Ever	93.92	90.72 - 96.27	6.08	3.73 - 9.28	
Hypertension					0.76
No	93.30	89.55 - 96.02	6.70	3.98 - 10.45	
Yes	93.95	91.42 - 95.91	6.05	4.09 - 8.58	
BMI					0.37
Underweight/normal	95.12	91.65 - 97.45	4.88	2.55 - 8.35	
Overweight/Obese	93.32	90.85 - 95.30	6.68	4.70 - 9.15	
Age at menarche					0.10*
> 11 y	94.58	92.75 - 96.06	5.42	3.94 - 7.25	
≤ 11 y	91.04	84.98 - 95.24	8.96	4.76 - 15.02	
Gravidity					0.79
<4	93.92	91.20 - 96.00	6.08	4.00 - 8.80	
≥4	93.43	90.75 - 95.53	6.57	4.47 - 9.25	
Breastfeeding history					0.20*
Never	93.45	90.42 - 95.76	6.55	4.24 - 9.58	
Ever	95.45	93.13 - 97.16	4.55	2.84 - 6.87	
Age at menopause					0.08*
≤45 y	93.58	90.54 - 95.88	6.42	4.12 - 9.46	
46-55 y	94.78	92.10 - 96.75	5.22	3.25 - 7.90	
≥56 y	87.94	79.01 - 94.02	12.06	5.98 - 20.99	
Time since menopause					0.05*
≤ 20 y	95.27	93.11 - 96.91	4.73	3.09 - 6.89	
> 20 y	92.28	89.17 - 94.72	7.72	5.28 - 10.83	
Total reproductive lifespan					0.63
<=35 y	94.06	91.56 - 96.01	5.94	3.99 - 8.44	

Variables	Non-DSN, n= 1055		DSN, n= 89		p-value
	%	(95% CI)	%	(95% CI)	
>35 y	95.00	91.64 - 97.30	5.00	2.70 - 8.36	
History of exogenous hormone use					0.03*
Never	90.16	85.74 - 93.57	9.84	6.43 - 14.26	
Ever	94.77	92.61 - 96.45	5.23	3.55 - 7.39	

NOTE: Values are weighted row percentage with 95% confidence interval (CI). DSN, distal sensory neuropathy; PIR, prescribed investor rate; BMI, body mass index; y, years. *variables with p < 0.25 vs. the values of non-distal sensory neuropathy group were included in initial multivariable analysis.

4.3 Association of distal sensory neuropathy with reproductive factors and exogenous hormone use

We observed a significant association of distal sensory neuropathy with age at menarche, breastfeeding history, time since menopause factors and exogenous hormone use (Table 3). Total of 835 participants from 43 stratas were included in the preliminary main effects model (Model 1 in Table 3). Age, race, education, income status, BMI, age at menarche, breastfeeding history, time since menopause, and history of exogenous hormone use were included in the preliminary main effects model. In the interaction assessment with the preliminary main effects model, the two-way interaction of menarche with race made a significant contribution to the fit of model (*p* for interaction = 0.027), so we added this interaction term as a source for confounding into the final model (Model 2 in Table 3). After adjusting for confounding variables, postmenopausal women with early menarche (≤ 11 years) experienced 8.13 times higher risk of distal sensory neuropathy than those with age at menarche > 11 years (OR = 8.13, 95%CI: 1.24 - 53.28, *p* = 0.03). Postmenopausal women had a longer duration after menopause (>20 years) were 3.01 times more likely to develop distal sensory neuropathy than those with shorter duration after menopause (OR = 3.01, 95%CI: 1.29 - 7.02, p = 0.012), after adjusting for other confounding variables. Postmenopausal women who ever breastfed any of their children experienced a reduction of 55% in the odds of having distal sensory neuropathy compared to those without any breastfeeding history (OR = 0.45, 95%CI: 0.21 - 0.99, p = 0.047)); and exogenous hormone users experienced a reduction of 59% in the odds of having distal sensory neuropathy than non-users(OR = 0.41, 95%CI: 0.19 - 0.87, p = 0.022). However, gravidity, total reproductive lifespan, and age at menopause were not included in the final model.

Table 3: Association of distal sensory neuropathy with reproductive factors and exogenous hormone use (NHANES 1999–2004 cycle)

Variables	Crude OR (95%CI)	*p*-value	Model 1[a] Adjusted OR (95%CI)	*p*-value	Model 2[b] Adjusted OR (95%CI)	*p*-value
Age at menarche (≤ 11 vs > 11y)	1.72(0.89, 3.30)	0.100	1.46(0.54, 3.99)	0.447	8.13(1.24, 53.28)	0.030*
Breastfeeding (Ever vs Never)	0.68(0.38, 1.23)	0.197	0.41(0.18, 0.93)	0.033*	0.45(0.21, 0.99)	0.047*
Time since menopause (> 20 vs ≤ 20 y)	1.69(1.00, 2.85)	0.049*	3.01(1.29, 7.02)	0.012*	3.18(1.32, 7.68)	0.011*
History of exogenous hormone use (Ever vs Never)	0.51(0.27, 0.94)	0.031*	0.48(0.23, 1.00)	0.051	0.41(0.19, 0.87)	0.022*

Values are crude odds ratio (OR) and adjusted OR with 95% confidence interval (CI). [a] Adjusted for age, race, education, income, body mass index (BMI), menarche, breastfeeding, time since menopause, and exogenous hormone use, n = 835 from 43 stratas; [b] Adjusted for age, race, education, income, BMI, menarche, breastfeeding, time since menopause, and exogenous hormone use and interaction term of race with menarche (*p* for interaction = 0.027); n = 835 from 43 stratas. y, years. *$p < 0.05$ vs. the values of non-distal sensory neuropathy group.

4.4 Subgroup analysis

4.4.1 Subgroup analysis by age

The subgroup analysis by age was shown in Table 4. Total of 607 participants from 43 stratas were included in women aged 40-70 years group. Breastfeeding (OR = 0.29, 95%CI: 0.10 - 0.86, *p* = 0.026) and time since menopause (OR = 3.53, 95%CI: 1.23, 10.17, *p* = 0.021) were independently associated with distal sensory neuropathy, after controlling age, race, education, income, body mass index (BMI), menarche, breastfeeding, time since menopause, and exogenous hormone use. However, association of distal sensory neuropathy with age at menarche and exogenous hormone use was not observed. A total of 228 participants from 42 strata was included in women aged > 70 years subgroup, with *p* - value for goodness of git < 0.05. Moreover, the large amount of missingness rate in this elderly subgroup was not good enough for receiving reliable estimates(supplemental table 1). For further exploring the association between reproductive history factors (including hormone use) and distal sensory neuropathy among women aged 40-70 years, we conducted another analysis with the currently available data as

mentioned in part 3.7.2. All results in women aged 40-70 years were shown in supplemental Table 2-4, and Supplemental Figure 1.

Table 4: Association of distal sensory neuropathy with reproductive factors and exogenous hormone use by age (NHANES 1999–2004 cycle)

Variables	Age 40-70 y				Age > 70 y			
	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI) [a]	*p*-value	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI) [b]	*p*-value
Age at menarche (≤ 11 vs > 11 y)	2.44(1.13, 5.25)	0.020	1.69(0.55, 5.13)	0.350	0.63(0.13, 3.05)	0.554	0.41(0.04, 4.44)	0.456
Breastfeeding (Ever vs Never)	0.44(0.20, 0.95)	0.034	0.29(0.10, 0.86)	0.026*	1.65(0.60, 4.51)	0.319	0.89(0.27, 2.91)	0.846
Time since menopause (> 20 vs ≤ 20 y)	1.85(0.89, 3.84)	0.091	3.53(1.23, 10.17)	0.021*	1.05(0.22, 5.16)	0.947	1.90(0.28, 12.79)	0.502
History of exogenous hormone use (Ever vs Never)	0.65(0.28, 1.51)	0.302	0.41(0.15, 1.13)	0.086	0.56(0.21, 1.47)	0.225	0.56(0.17,1.87)	0.341

Values are crude odds ratio (OR) and adjusted OR with 95% confidence interval (CI), after controlling race, education, income, body mass index (BMI), menarche, breastfeeding, time since menopause, and exogenous hormone use. [a] n = 607 from 43 stratas; [b] n = 228 from 42 stratas, *p*-value for goodness of fit = 0.0047. y, years. *$p < 0.05$ vs. the values of non-distal sensory neuropathy group

4.4.2 Subgroup analysis by race

Since we observed a joint presence of interacting risk for distal sensory neuropathy from two-way interaction of menarche and race, we also conducted subgroup analysis by race(Table 5). A higher odds of distal sensory neuropathy among women reported early menarche (<11 years) were seen only in Hispanic group(OR = 6.24, 95%CI: 1.23 - 31.76, p = 0.028). No significant association between age at menarche and distal sensory neuropathy was found among non-Hispanic women group (OR = 0.56, 95%CI: 0.15 - 2.13, p = 0.384). Although the association between distal sensory neuropathy and breastfeeding history was observed among Hispanic women(OR = 0.22, 95%CI: 0.06 - 0.84, p = 0.028), no association was observed among non-Hispanic women(OR = 0.61, 95%CI: 0.25 - 1.47, p = . 0.259). The association of distal sensory neuropathy and time since menopause was also affected by race: the higher odds of distal sensory neuropathy among women with longer time since menopause(>20 years) was seen among non-Hispanic women(OR = 3.91, 95%CI: 1.48 - 10.37, p = 0.007), but distal sensory neuropathy was not associated with time since menopause among Hispanic women(OR = 1.98, 95%CI: 0.43 - 9.04, p = 0.369). The association between distal sensory neuropathy and exogenous hormone use was observed among non-Hispanic women(OR = 0.38, 95%CI: 0.15 – 0.94, p = 0.036), but distal sensory neuropathy was not associated with exogenous hormone use among Hispanic(OR = 0.50, 95%CI: 0 .13 - 1.97, p = 0.310).

Table 5: Association of distal sensory neuropathy with reproductive factors and exogenous hormone use by race (NHANES 1999–2004 cycle)

Variables	Hispanic				Non-Hispanic			
	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI) [a]	*p*-value	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI) [b]	*p*-value
Age at menarche (≤ 11 vs > 11 y)	3.41(0.72,16.01)	0.102	6.24(1.23, 31.76)	0.028*	1.37(0.68, 2.77)	0.367	0.56(0.15, 2.13)	0.384
Breastfeeding (Ever vs Never)	0.25(0.07, 0.88)	0.024*	0.22(0.06, 0.84)	0.028*	0.79(0.39, 1.62)	0.520	0.61(0.25, 1.47)	0.259
Time since menopause (≥ 20 vs ≤ 20 y)	0.97(0.24, 3.93)	0.959	1.98(0.43, 9.04)	0.369	1.93(1.13, 3.29)	0.016*	3.91(1.48, 10.37)	0.007*
History of exogenous hormone use (Ever vs Never)	1.23(0.35, 4.37)	0.740	0.50(0.13, 1.97)	0.310	0.44(0.22, 0.91)	0.025*	0.38(0.15, 0.94)	0.036*

Values are crude odds ratio (OR) and adjusted OR with 95% confidence interval (CI), after controlling age, education, income, body mass index (BMI), menarche, breastfeeding, time since menopause, and exogenous hormone use. a n = 219 from 36 stratas; b n = 616 from 43 stratas. *p < 0.05 vs. the values of non -distal sensory neuropathy group

Chapter 5 Discussion

5.1 Summary of the findings

In this cross-sectional study, we observed inverse associations of distal sensory neuropathy with history of breastfeeding and exogenous hormone use; and positive associations of distal sensory neuropathy with age at menarche and time since menopause, among US postmenopausal women aged > 40 years, after adjusting for potential confounders and a joint presence of interacting risk factor (two-way interaction of menarche and race), using the NHANES 1999-2004 database. However, our study did not find the links between distal sensory neuropathy and gravidity, age at menopause or total reproductive lifespan. In subgroup analysis by age, breastfeeding and time since menopause were independently associated with distal sensory neuropathy among postmenopausal women aged 40-70 years; however, the related associations were not possible to be reported among postmenopausal women aged > 70 years, as the larger missingness rate in older group. We also observed a significant effect modification by race on the association of distal sensory neuropathy with age at menarche, breastfeeding history, time since menopause, and history of exogenous hormone use.

5.2 Context in the literature

5.2.1 Age at menarche and distal sensory neuropathy

Our finding showed that the age at menarche ≤ 11 years is an independent risk factor for distal sensory neuropathy after controlling the other variables among postmenopausal women aged 40 years and over. However, the association was only observed among Hispanic women when we conducted subgroup analysis by race.

Women with age at menarche ≤11 years are more likely to have a higher BMI or subcutaneous fat levels in childhood (5-9 years)[97]. The weight gain may persist throughout adulthood, resulting in a range of metabolic problems[99]. The higher frequency of peripheral neuropathy in women with early menarche may be due to metabolic causes such as impaired insulin response and increased insulin resistance, as well as mitochondrial damage and elevated chemokines[192, 41]. Additionally, age at menarche was inversely associated with peripheral vascular disease[193]. Peripheral nerves run parallel to blood vessels. Ischemia associated with vascular changes can also lead to nerve damage through the thickening of the vessel wall. Ultimately, vascular occlusion may occur, resulting in compromised vascular permeability and intraneural blood flow. Ischemia and inflammation are inextricably linked, and both play important roles in nerve injury and recovery[56].

The association of age at menarche with disorders in peripheral nervous system has been reported in previous studies; however, the findings of exist is not consistent. A prospective cohort study shown that the later menarche is substantially related with nephropathy in type 1 female diabetes patients, but not with retinopathy or distal sensory neuropathy[194]. In this cohort, 27 of the 315 women had early menarche (< 11 years), and 77.8% of the women had menarche at least a year after the beginning of Type 1 diabetes. The participants were tracked for up to 25 years in this cohort study. However, their sample size was small, and they did not provid information on sample size calculations. In our study, all diabetes patients were excluded, so our study populations are quite different from this previous cohort study.

A case-control study showed that women affected by the motor neuron disease had a later menarche and earlier age at menopause[195]. For the following reasons, our results contradict findings in this case-control study. Firstly, the duration from menarche to menopause is an indicator of women's cumulative endogenous hormone exposure throughout her life. The pathogenesis of motor neuron disease might be mainly caused by the shorter reproductive lifespan. Secondly, the outcome of our investigation was distal sensory neuropathy, while this case-control study was focused on motor neuron disease. Muscle weakness (distal or proximal) with atrophy and hyporeflexia, but no sensory involvement, are common characteristics of motor neuron illness[196]. Although both studies are discussing peripheral neuropathy, the nerves involved are different. Nerve condution study is needed to determine whether motor nerves are also affected in distal sensory neuropathy. However, we only could obtain data about the foot sensation assessed by monofilaments from NHANES. Thirdly, women with malignancy and autoimmune diseases, both common causes of peripheral nerve damage, were included in this research. They also took into account the impact of occupational risk factors on peripheral nerves. The number of people with peripheral neuropathy has increased among farmers and those who have been exposed to chemical products. A relatively healthy group of women were included in our study, but we did not account for the effect of occupational factors.

Early menarche was a significant risk factor for distal sensory neuropathy only among Hispanic group. Early menarche might work with social-demographic factors and genetic factors to influence the occurrence of distal sensory neuropathy among Hispanic women. In the United States, the average age at menarche was older than 14 years prior to 1900, but it decreased to 12.43 years in 1988-1994 and 11.9 years in 2013-2017[91, 89, 92]. Mexican-American women had the fastest rates of decline at the age of menarche and highest obesity rates[93]. Mexican-Americans make up the majority of the US Hispanic population. In our study, total of 231 of 293 women in Hispanic group was Mexican-American, while another 62 were the "other Hispanic". Their obesity

and CVD risk were likewise among the highest in the population. Girls who had ealier menarche were more likely to drink and smoke. Public health strategies have been recommended for this demographic to decrease obesity and mean age at menarche[93].The socio-cultural characteristics of Mexican-Americans may be responsible for heterogeneity between the race groups. Both early menarche and distal sensory neuropathy both could arise from genetic etiology. However, our findings were unable to determine whether genetics had a role in this race difference.

5.2.2 Gravidity and distal sensory neuropathy

In this study, we did not find association between gravidity and distal sensory neuropathy among the US postmenopausal women aged 40 years and over. Although every pregnancy begins with the implantation of a fertilized egg, the bodily microenvironment of pregnant women varies at different stages of pregnancy. Complex and diverse circumstances affect pregnancy outcomes[197]. The evidence about the effect of gravidity on peripheral nerve condition is limited. More studies are being conducted on peripheral neuropathies during pregnancy and the postpartum period. These peripheral neuropathies are major caused by compression or gained weight, and their symptoms are usually temporary and reversible[198]. The levels of estrogen increase suddenly and dramatically (up to 300-fold) during the early pregnancy and peak in the late pregnancy, and higher gravidity might reflect a longer duration of exposure in the high levels of estrogen[110]. Our finding might suggest that the limited duration in exposure to higher levels of estrogen during premenopausal phase might not influence the occurrence of distal sensory neuropathy.

Pregnancy has a complicated influence on women's metabolism, promoting increased insulin resistance, hyperlipidemia, adipogenesis and fat accumulation[112]. The frequent pregnancies may have permanent adverse effects on the lipid and glucose metabolism. Moreover, the repeated pregnancies may lead to the excessive weight gain, greater upper fat distribution and higher prevalence of metabolic syndrome. Diabetes or obesity risk factors could exacerbate metabolism changes that occur in the normal pregnancy[199, 200]. Greater number of pregnancies has been related to the metabolic syndrome among premenopausal women, but no significant association was observed among postmenopausal women[199]. The estrogen deficiency that comes with menopause (natural ovarian failure or removal of ovaries) and aging, may have attenuated the association between gravidity and distal sensory neuropathy[199].

The complex biological mechanisms also work with demographics and lifestyle factors together to guide to the women’s health outcome. The lack of economic opportunity is one cause for young and unmarried US women to have children, while more educated women tend to delay their marriage and childbearing[201, 202]. Inverse association between alcohol intake and fecundability has been documented[203]. In our study, women with lower education and income

status tend to have higher gravidity, while drinkers reported a lower number of pregnancies. Women are inherently motivated to ensure proper nutrition and exercise during pregnancy for better maternal and neonatal outcomes. Pregnant women generally reduce energy expenditure and ensure an adequate and balanced maternal diet [204]. In addition, women with higher pregnancies might receive greater social support from the multiparous family size[180]

In our study, the number of gravidities was counted according to all types of pregnancy, including current pregnancy, live births, miscarriages, stillbirths, tubal pregnancies, or abortions. Future studies may examine whether other pregnancy indicators (such as live births) or a specific type of pregnancy are associated with peripheral nerve changes in postmenopausal women.

5.2.3 Breastfeeding and distal sensory neuropathy

In this study, postmenopausal women who had breastfed any of their children experienced a lower risk of distal sensory neuropathy than those without breastfeeding hisotry. In subgroup analysis, this association was observed among women aged 40-70 years and Hispanic women. Several benefits from breastfeeding have been confirmed for maternal health, even in the absence of early, exclusive or continued breastfeeding[116]. In central nervous system, longer breastfeeding duration could help prevent dementia among elderly women[22]. Compare with those who never breastfed, postmenopausal women who had ever breastfed show a lower risk of stroke and multiple sclerosis after adjustment of other factors[205, 79]. The breastfeeding also show a long-term benefits for cognitive performance among postmenopausal women aged 50 years and over[206]. Our study provides evidence that breastfeeding might be a potential beneficial factor for peripheral nerves among postmenopausal women; however, the specific mechanism remains unknown.

Breastfeeding may impact peripheral nervous system for the following reasons, in addition to the direct neuroprotective activity of prolactin and oxytocin[82, 83, 207, 80]. Firstly, breastfeeding could help reverse metabolic changes occurred during pregnancy, such as visceral fat, insulin resistance[199, 200]. Lactating animals have smaller adipocytes and lower peripheral lipoprotein lipase activity than non-lactating controls[121]. Breastfeeding enhances calorie expenditure and helps with weight loss, changing the distribution of body fat. Breastfeeding-related obesity differences were discovered in postmenopausal women[119, 112]. Secondly, reproductive aging may influence the cellular, tissue, organ, and system aging of organisms. Exclusive breastfeeding slows the return of ovulation after delivery and may slow the depletion of ovarian pool, which might slow down the reproductive aging[208, 122]. Lastly, among part of women with exclusive breastfeeding, longer breastfeeding history might prevent nerve aging via slowing down the return of ovulation after delivery and reproductive aging[122].

Subgroup analysis results showed that race seemed to modify the effect of breastfeeding on distal sensory neuropathy. Specifically, in our study, lower odds of distal sensory neuropathy among breastfeeding women were observed in Hispanic women. Hispanic women were more likely to be overweight or obesity according to BMI in our study. Overweight or obese women suffer from more metabolic disorders and inflammation than underweight and normal weight women [3, 209]. Therefore, the results of the subgroup analysis might support that lactation exerts a stronger protective effect on peripheral nerves among those with more metabolic and inflammatory issues. The protection of breastfeeding may work by regulating metabolism and inflammation.

5.2.4 Age at menopause, total reproductive lifespan and distal sensory neuropathy

Distal sensory neuropathy was not significantly associated with age at menopause and total reproductive lifespan. Several reasons may contribute to the absence of associations of distal sensory neuropathy with age at menopause and total reproductive lifespan. Firstly, exogenous hormone use may influence the associations[210]. In our research, 409 women experienced menopause before the age of 45 years, 133 women reported late menopause (56 years), and 597 women reported normal menopause (45-56 years). Exogenous hormone users accounted for 39.76 of the those with early menopause. Women with shorter reproductive lifespan (≤ 35 years) are more likely to receive a higher education and tend to be hormone users. Secondly, earlier studies have shown that surgical menopause and natural menopause have inconsistent effects on women's health outcomes. Premature or early natural menopause is usually a gradual process; by contrast, surgical removal of both ovaries causes an abrupt loss of ovarian hormones, including estrogen, progesterone, and testosterone, as well as damage of the hypothalamus-pituitary-gonadal axis[127]. However, our study did not differentiate between natural and surgical menopause. Finally, our finding might also be affected by genetic factors. ApoE-**ε**4 is hypothesized to be involved delayed age at menopause as well as longer reproductive period [211, 212]. ApoE 4 could also inhibit neurite outgrowth and preferentially slows nerve regeneration in the peripheral nervous system. Although associations of distal sensory neuropathy with age at menopause and total reproductive lifespan were not found in our study, the specific populations should be considered in future studies when exploring association of distal sensory neuropathy with age at menopause and total reproductive lifespan.

5.2.5 Time since menopause and distal sensory neuropathy

In our study, time since menopause > 20 years was an independent risk factor for distal sensory neuropathy, after controlling the other variables. In subgroup analysis, this association was only observed among women aged 40-70 years and non-Hispanic women.

The time since menopause could be used as a marker of estrogen deficiency. Longer time since menopause harms impaired glucose tolerance among women, which could induce neuropathies, mostly on the small nerve fibers[148, 149]. In postmenopausal women, BMI is positively related to circulating total and free E2. When ovarian estrogen synthesis stops during menopause, adipose tissue aromatizes androstenedione to E2 and estrone, becoming the major source of estrogen production[213]. Longer time since menopause could accelerate biological aging compared to those with a shorter duration after menopause[143]. Time since menopause, rather than age itself, is an independent risk factor for distal sensory neuropathy suggests that biological aging might work with hypoestrogenism together to promote the development of peripheral neuropathy in postmenopausal women[143].

A similar finding was found in bone disease. Time since menopause, not age, is associated with an increased risk of osteoporosis[214]. Compared with serum FSH or E2 levels, time since menopause is a stronger predictor for osteoporosis[215]. Bone is highly innervated by sensory and autonomic nerve fibers, and disruption of innervation can accelerate pathological conditions of osteoporosis. Moreover, nerve damage can affect bone through proinflammatory cytokines[216]. Longer interval since menopause was associated with a higher prevalence of fractures in women[217, 218]. Women with more than five years postmenopausal duration have a higher prevalence of osteoporosis than those with shorter postmenopausal time[219].

In the United States, Mexican-Americans have the highest rates of overweight and obesity, and Hispanic postmenopausal women show more favorable estrogen profiles[220, 221]. Adipocytes produce estrogens through aromatase activity, and obese women have higher levels of circulating estrogens than other women during postmenopausal phase[222]. Hence, the difference of estrogen levels and BMI between different race group might potentially lead to the race-difference of the association between time since menopause and distal sensory neuropathy.

5.2.6 Exogenous hormone use and distal sensory neuropathy

Our study found that the history of exogenous hormone use is a protective factor for distal sensory neuropathy among postmenopausal women aged 40 years or over. The association of distal sensory neuropathy with exogenous hormone use was only found in non-Hispanic group. In our study, exogenous hormone users more tend to be non-Hispanic women, with the younger

age (40-70 years) and the time since menopause < 20 years. The race-difference of the association between exogenous hormone use and distal sensory neuropathy might be caused by these different basic characteristics among study participants.

In our study, the exogenous hormones refer to either MHT or contraceptive use, including the exogenous estrogen and progesterone, both of which are well-known neuroprotective factors[14, 71]. In animal studies, aging nerves are still sensitive to estrogen and progesterone. Using estrogen and progesterone could regulate the expression of nerve growth factors in peripheral organs in ovariectomized female mice. The nerve growth factor is a neurotrophic factor known to play a key protective role in the development and survival of sympathetic, sensory, and forebrain cholinergic neurons[71]. Consistently, our findings suggest that the use of exogenous hormones may have potentially beneficial effects on peripheral nerves among postmenopausal women.

The influence of exogenous hormones use on postmenopausal female neurological systems is currently contested. These contradictory results could be influenced by differences in hormone formulation and use, the age range of the study population, and the variety of nerve types[156]. The timing of MHT could affect the women's long-term health results. Early MHT could reduce dementia risk among postmenopausal women but initiating later in life has no advantage or increased risk[127]. Furthermore, contraception has numerous advantages beyond its primary goal of preventing pregnancy; however, the evidence for an association between contraception and central nervous system disorders is controversial[22]. Long-term contraceptive usage (at least 10 years) reduces the incidence of Parkinson's disease, but the advantage is not shown in shorter-term users[156].

Side effects for some specific population also should be concerned in study design. Contraceptive use was associated with a higher risk of CVD[153]. Contraceptive use could increase the risk of inflammatory and coagulation disorders among users with polycystic ovarian syndrome[158]. In our study, all patients with self-reported CVD were excluded; however, information about polycystic ovarian syndrome was not available. In future study, exogenous hormone regimens, timing, dose, duration of administration, and health conditions of study population should also be concerned when exploring the association between exogenous hormone use and peripheral neuropathy.

5.3 Strengths and limitations

This study has several strengths. First, this is the first study to investigate the association between reproductive history factors and distal sensory neuropathy in postmenopausal women, with nationally representative data. Second, we utilized logistic regression with purposeful selection

strategy to assess the association between exposure and outcome. This strategy allows us to correctly identify and retain confounders at a higher rate than other selection algorithms. Next, our findings might provide more rationale for the gender difference in prevalence of distal sensory neuropathy. Last, we identified that the effect of reproductive factors and exogenous hormone use on distal sensory neuropathy is not constant by race.

Despite the strengths, the study has some limitations. First, the assessment of peripheral neuropathy was limited to monofilament test and only available in NHANES 1999-2004. We cannot judge whether our finding from NHANES 1999-2004 could be generalized among the current US postmenopausal women. Moreover, symptoms of peripheral neuropathy were not used in this study because the large amount of missing data for related variables in NHANES. Other neurological examinations, nerve conduction study, or biopsy were not available from NHANES[47]. Second, information and recall bias in assessing the exposure existed among postmenopausal women in this study; selection bias might lead to an apparent association. Third, as sample size of participants included in the fasting subsample is small, more following study participants characteristics based on blood test was not provided in this study. Our study population did not receive fasting blood tests or insulin sensitivity status. Diabetes was defined by history through interviews. Therefore, the non-diabetic status may be misclassified. Our study did not include blood cholesterol or other inflammatory biochemical markers as potential confounders which may explain the underlying mechanism of distal sensory neuropathy. Malnutrition is another common cause for distal sensory neuropathy[19]; however, participants with vitamin B12 deficiency were not specified or excluded in our study. Next, all participants were collapsed into two category levels for each variable, because the sample size is small with more specific subdomains[185]. Fifth, as this was a cross-sectional study, only the prevalence of distal sensory neuropathy was reported, and causal relationship could not be confirmed. Sixth, the study population is only postmenopausal women in the United States[223]. So future studies should be conducted among different ethnic people, and racial differences should be concerned. Last, we cannot rule out the chance that the observed association in the subgroup analysis was a random finding.

5.4 Conclusion

Age at menarche, time since menopause, breastfeeding and exogenous hormone use were associated with distal sensory neuropathy in our study. There was race-based heterogeneity in these associations among US postmenopausal women aged 40 years and over. Our findings may provide a rationale for the etiology of distal sensory neuropathy among US postmenopausal women. Reproductive factors might influence the peripheral nerve health via both hormone and

metabolism related pathway. Greater exposure to estrogen before menopause might not be able to prevent the occurrence of distal sensory neuropathy. In contrast, the estrogen deficiency might work with biological aging to cause peripheral nerve damage in postmenopausal women. The exogenous hormone use may help slow nerve damage or recover damaged nerves. Promoting breastfeeding may reduce the burden of peripheral neuropathy in middle-aged postmenopausal women. Exogenous hormone use might be useful for management of peripheral neuropathy. Further research should investigate the underlying mechanism.

Appendix

As the larging missingness among women aged > 70 years, the subgroup analysis by age could not be conducted in our study. Hence, we have conducted further analysis among to investigate the association between reproductive factors and distal sensory neuropathy. The results could be found from Supplemental Table 2-4 and Supplemental Figure 1. Next, we also provided more details about our participants (Supplemental Table 5-12). Finally, we also conducted similar analysis among women with overweight/obesity, because the metabolism related mechanism might be potential explanation for our finding (Supplemental Table 13-16 and Supplemental Figure 2). All analyses were conducted with data from NHANES 1999-2004 cycles.

Supplemental Table 1. Missingness of all variables (NHANES 1999–2004 cycle, N= 1,144)

Variables	Overall, n=1,144		Age 40-70 year, n=798		Age > 70 year, n=346		Hispanic, n=293		Non-Hispanic, n=851	
	n	%	n	%	n	%	n	%	n	%
Distal sensory neuropathy	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Age at menarche	14	1.22	7	0.88	7	2.02	0	0.00	14	1.65
Gravidity	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Breastfeeding	131	11.45	80	10.03	51	14.74	26	8.87	105	12.34
Age at menopause	5	0.44	5	0.63	0	0.00	2	0.68	3	0.35
Time since menopause	71	6.21	28	3.51	43	12.43	18	6.14	53	6.23
Total reproductive lifespan	93	8.13	43	5.39	50	14.45	22	7.51	71	8.34
History of exogenous hormone use	2	0.17	1	0.13	1	0.29	0	0.00	2	0.24
Age	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Race/Ethnicity	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Education	2	0.17	0	0.00	2	0.58	0	0.00	2	0.24
Income	116	10.14	79	9.90	37	10.69	35	11.95	81	9.52
Alcohol use	1	0.09	1	0.13	0	0.00	0	0.00	1	0.12
Smoking status	2	0.17	1	0.13	1	0.29	1	0.34	1	0.12
Hypertension	21	1.84	16	2.01	5	1.45	6	2.05	15	1.76
Body mass index	21	1.84	11	1.38	10	2.89	5	1.71	16	1.88
Insurance	11	0.96	4	0.50	7	2.02	5	1.71	6	0.71

Supplemental Table 2. Characteristics of the postmenopausal women aged 40-70 years (NHANES 1999–2004 cycle, N=798)

Variables	N	%
Age		
40-59 y	400	64.45
60-70 y	398	35.55
Race/Ethnicity		
Hispanic	225	10.83
Non-Hispanic	573	89.17
Education		
Less than high school	260	20.40
High school and above	538	79.60
Income status		
PIR ≤2.00	268	24.61
PIR >2.00	451	65.79
Insurance		
Not covered	148	13.09
Covered	646	86.55
Alcohol use		
Never	187	19.54
Ever	610	80.11
Smoking		
Never	456	52.67
Ever	341	47.30
Hypertension		
No	380	54.96
Yes	402	42.92
BMI		
Underweight/normal	228	31.62
Overweight/obese	559	67.06
Gravidity		
<4	438	64.32
≥4	360	35.68
Breastfeeding history		

Variables	N	%
Never	332	43.24
Ever	386	44.30
Time since menopause		
≤20 y	626	82.47
>20 y	144	14.22
History of exogenous hormone use		
Never	150	13.43
Ever	647	86.27
DSN		
Non-DSN	747	94.71
DSN	51	5.29

NOTE: Number (N) of participants with weighted percentages (%). Column percentages for the sample totals that do not add up to 100% are a result of missing data. DSN, distal sensory neuropathy; PIR, prescribed investor rate; BMI, body mass index; y, years.

Supplemental Table 3. Characteristics postmenopausal women aged 40-70 years by distal sensory neuropathy (NHANES 1999–2004 cycle, N=798)

Variables	Non-DSN, N=747		DSN, N=51		p-value
	%	95% CI	%	95% CI	
Age					0.49
40-59 y	95.24	91.85 - 97.51	4.76	2.49 - 8.15	
60-70 y	93.76	90.18 - 96.33	6.24	3.67 - 9.82	
Race/Ethnicity					0.045*
Hispanic	89.91	80.52 - 95.76	10.09	4.24 - 19.48	
Non-Hispanic	95.3	93.17 - 96.92	4.7	3.08 - 6.83	
Education					0.265
Less Than High School	92.5	85.79 - 96.69	7.5	3.31 - 14.21	
High School and above	95.28	92.86 - 97.07	4.72	2.93 - 7.14	
Income status					0.301
PIR ≤2.00	93.17	86.91 - 97.03	6.83	2.97 - 13.09	
PIR >2.00	95.66	92.90 - 97.58	4.34	2.42 - 7.10	
Insurance					0.994
Not covered	94.68	87.19 - 98.47	5.32	1.53 - 12.81	
Covered	94.7	92.61 - 96.33	5.3	3.67 - 7.39	
Alcohol use					0.887
Never	94.37	87.84 - 98.01	5.63	1.99 - 12.16	
Ever	94.77	91.88 - 96.87	5.23	3.13 - 8.12	
Smoking					0.152*
Never	95.93	93.62 - 97.59	4.07	2.41 - 6.38	
Ever	93.35	89.13 - 96.31	6.65	3.69 - 10.87	
Hypertension					0.402
No	93.77	89.94 - 96.46	6.23	3.54 - 10.06	
Yes	95.69	92.10 - 97.96	4.31	2.04 - 7.90	
BMI					0.378
Underweight/normal	96.38	91.99 - 98.74	3.62	1.26 - 8.01	
Overweight/obese	94.19	90.96 - 96.53	5.81	3.47 - 9.04	
Breastfeeding					0.034*

History					
Never	93.23	89.41 - 96.00	6.77	4.00 - 10.59	
Ever	96.92	94.06 - 98.65	3.08	1.35 - 5.94	
Gravidity					0.989
<4	94.69	90.41 - 97.45	5.31	2.55 - 9.59	
≥4	94.72	91.74 - 96.87	5.28	3.13 - 8.26	
Time since menopause					0.095*
≤20 y	95.35	93.33 - 96.91	4.65	3.09 - 6.67	
>20 y	91.71	84.84 - 96.14	8.29	3.86 - 15.16	
History of exogenous hormone use					0.306
Never	95.35	93.33 - 96.91	4.65	3.09 - 6.67	

NOTE: Values are weighted row percentages with 95% CI. DSN, distal sensory neuropathy; PIR, prescribed investor rate; BMI, body mass index; CI, confidence interval; y, years. * p<0.25 vs. the values of non-distal sensory neuropathy group.

Supplemental Table 4. Associations between breastfeeding and distal sensory neuropathy among postmenopausal women aged 40-70 years (NHANES 1999–2004 cycle)

Analysis strategies	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Primary analysis				
Breastfeeding (Ever vs. Never) [a]	0.44 (0.20, 0.95)	0.038*	0.29 (0.11, 0.79)	0.017*
Effect modification by BMI [b]				
Breastfeeding (Ever vs. Never) within underweight/normal group	1.12 (0,23, 5.42)	0.885	0.55 (0.09, 3.43)	0.513
Breastfeeding (Ever vs. Never) [c] within overweight/obese group	0.36 (0.14, 0.93)	0.035*	0.21 (0.06, 0.73)	0.013*

Values are weighted OR with 95% CI. [a]Adjusted for age, income, race, BMI, and time since menopause in the primary multivariable model analysis, n=613. [b]Adjusted for age, income, race, and time since menopause in the subgroup analysis multivariable model; n=169 in the underweight/normal group and n=444 in the overweight/obese group. [c]Among the 43 stratas in the primary analysis, three stratas were omitted in the underweight/normal group analysis multivariable model because they contained no subpopulation members. OR, odds ratio; CI, confidence intervals; BMI, body mass index. * $p<0.05$ vs. the values of non-distal sensory neuropathy group.

Supplemental Table 5. Characteristics of study participants by age at menarche (NHANES 1999–2004 cycle)

Variables	Age at menarche		p - value
	> 11 y N(%)	≤ 11 y N(%)	
Age			0.0737
40-70 y	655(81.72)	136(18.28)	
>70 y	296(87.66)	43(12.34)	
Race/Ethnicity			0.0553
Hispanic	237(75.56)	56(24.44)	
Non-Hispanic	714(83.94)	123(16.06)	
Education			0.2196
Less Than High School	330(79.92)	64(20.08)	
High School and above	619(84.00)	115(16.00)	
Income status			0.3932
PIR ≤ 2.00	374(85.05)	58(14.95)	
PIR > 2.00	487(82.55)	98(17.45)	
Insurance			0.4515
Not covered	129(79.45)	24(20.55)	
Covered	811(83.37)	155(16.63)	
Alcohol use			0.1007
Never	247(86.76)	42(13.24)	
Ever	703(81.97)	137(18.03)	
Smoking			0.0003
Never	583(87.72)	84(12.28)	
Ever	367(77.23)	94(22.77)	
Hypertension			0.1245
No	349(81.06)	82(18.94)	
Yes	584(84.69)	94(15.31)	
BMI			0.0338
Underweight/normal	307(87.18)	44(12.82)	
Overweight/obese	628(81.35)	130(18.65)	
Number of pregnant			0.6943

Variables	Age at menarche		p - value
	> 11 y N(%)	≤ 11 y N(%)	
<4	523(83.53)	95(16.47)	
≥4	428(82.30)	84(17.70)	
Breastfeeding history			0.0844
Never	359(81.66)	76(18.34)	
Ever	491(86.36)	75(13.64)	
Age at menopause			0.9259
≤45 y	340(83.12)	66(16.88)	
46-55 y	497(82.60)	95(17.40)	
≥56 y	109(84.51)	18(15.49)	
Time since menopause			0.0734
≤ 20 y	543(81.46)	113(18.54)	
> 20 y	354(86.71)	54(13.29)	
Total reproductive life			0.0012
<=35 y	490(87.16)	68(12.84)	
>35 y	394(77.58)	99(22.42)	
History of exogenous hormone use			0.0633
Never	307(87.45)	45(12.55)	
Ever	642(81.68)	134(18.32)	

NOTE: Number (N) of participants with weighted row percentages (%). PIR, prescribed investor rate; BMI, body mass index; y, years.

Supplemental Table 6. Characteristics of study participants by gravidity (NHANES 1999–2004 cycle)

Variables	Gravidity		p - value
	<4 N(%)	≥4 N(%)	
Age			0.1869
40-70 y	438(64.32)	360(35.68)	
>70 y	190(59.09)	156(40.91)	
Race/Ethnicity			0.0202
Hispanic	114(50.72)	179(49.28)	
Non-Hispanic	514(64.54)	337(35.46)	
Education			0.0000
Less Than High School	140(43.94)	257(56.06)	
High School and above	487(68.87)	258(31.13)	
Income status			0.0000
PIR ≤ 2.00	193(50.31)	243(49.69)	
PIR > 2.00	374(69.23)	218(30.77)	
Insurance			0.0025
Not covered	61(45.73)	93(54.27)	
Covered	563(65.17)	416(34.83)	
Alcohol use			0.0124
Never	139(54.44)	154(45.56)	
Ever	488(65.46)	362(34.54)	
Smoking			0.8936
Never	374(63.36)	304(36.64)	
Ever	253(62.83)	211(37.17)	
Hypertension			0.1363
No	249(66.12)	186(33.88)	
Yes	368(60.32)	320(39.68)	
BMI			0.4593
Underweight/normal	205(65.20)	151(34.80)	
Overweight/obese	411(62.30)	356(37.70)	
Breastfeeding history			0.0002

Never	266(65.82)	174(34.18)	
Ever	233(50.69)	340(49.31)	
Age at menopause			0.0604
≤45 y	244(68.68)	165(31.32)	
46-55 y	316(59.50)	281(40.50)	
≥56 y	65(59.77)	68(40.23)	
Time since menopause			0.3084
≤ 20 y	367(64.13)	295(35.87)	
> 20 y	223(60.43)	188(39.57)	
Total reproductive life			0.0574
<=35 y	328(66.23)	230(33.77)	
>35 y	251(59.64)	242(40.36)	
History of exogenous hormone use			0.1180
Never	181(56.99)	178(43.01)	
Ever	446(64.99)	337(35.01)	

NOTE: Number (N) of participants with weighted row percentages (%). PIR, prescribed investor rate; BMI, body mass index; y, years.

Supplemental Table 7. Characteristics of study participants by breastfeeding history (NHANES 1999–2004 cycle)

Variables	Breastfeeding history		p - value
	Never N(%)	Ever N(%)	
Age			0.0646
40-70 y	332(49.39)	386(50.61)	
>70 y	108(40.78)	187(59.22)	
Race/Ethnicity			0.0310
Hispanic	83(36.35)	184(63.65)	
Non-Hispanic	357(48.78)	389(51.22)	
Education			0.2533
Less Than High School	123(43.30)	244(56.70)	
High School and above	317(48.85)	327(51.15)	
Income status		0.8970	
PIR ≤ 2.00	157(47.36)	232(52.64)	
PIR > 2.00	237(46.86)	281(53.14)	
Insurance			0.0290
Not covered	58(57.46)	77(42.54)	
Covered	380(46.27)	489(53.73)	
Alcohol use			0.0167
Never	95(38.62)	176(61.38)	
Ever	344(49.98)	397(50.02)	
Smoking			0.0240
Never	238(42.66)	369(57.34)	
Ever	202(53.87)	202(46.13)	
Hypertension			0.2253
No	170(49.72)	208(50.28)	
Yes	264(45.79)	353(54.21)	
BMI			0.0511
Underweight/normal	129(41.34)	185(58.66)	
Overweight/obese	304(50.36)	379(49.64)	
Age at menopause			0.3105

Variables	Breastfeeding history		p - value
	Never N(%)	Ever N(%)	
≤45 y	155(50.49)	198(49.51)	
46-55 y	235(46.86)	302(53.14)	
≥56 y	48(40.46)	71(59.54)	
Time since menopause			0.8657
≤ 20 y	268(47.82)	323(52.18)	
> 20 y	148(48.64)	215(51.36)	
Total reproductive life			0.2750
<=35 y	215(49.69)	273(50.31)	
>35 y	188(44.99)	257(55.01)	
History of exogenous hormone use			0.0713
Never	116(40.91)	196(59.09)	
Ever	324(49.68)	375(50.32)	

NOTE: Number (N) of participants with weighted row percentages (%). PIR, prescribed investor rate; BMI, body mass index; y, years.

Supplemental Table 8. Characteristics of study participants by age at menopause (NHANES 1999–2004 cycle)

Variables	Age at menopause			p - value
	≤45 y N(%)	46-55 y N(%)	≥56 y N(%)	
Age				0.0000
40-70 y	303(38.25)	425(55.41)	65(6.35)	
>70 y	106(34.29)	172(47.03)	68(18.68)	
Race/Ethnicity				0.9495
Hispanic	108(38.59)	147(52.39)	36(9.02)	
Non-Hispanic	301(37.20)	450(53.62)	97(9.18)	
Education				0.0718
Less Than High School	136(37.76)	198(49.05)	62(13.19)	
High School and above	272(37.20)	398(54.82)	71(7.98)	
Income status			0.0004	
PIR ≤ 2.00	172(43.93)	199(43.73)	64(12.34)	
PIR > 2.00	203(33.50)	333(59.19)	52(7.30)	
Insurance				0.1802
Not covered	69(46.54)	69(45.91)	16(7.55)	
Covered	335(36.27)	525(54.43)	114(9.30)	
Alcohol use				0.3113
Never	114(41.51)	139(48.25)	39(10.24)	
Ever	295(36.30)	457(54.80)	94(8.90)	
Smoking				0.0256
Never	239(34.96)	345(53.66)	90(11.38)	
Ever	169(40.29)	251(53.32)	43(6.40)	
Hypertension				0.0017
No	169(40.77)	232(53.29)	30(5.94)	
Yes	231(34.05)	353(53.58)	103(12.36)	
BMI				0.3891
Underweight/normal	118(34.85)	188(57.05)	47(8.10)	
Overweight/obese	281(38.47)	401(51.99)	83(9.54)	

Variables	Age at menopause			p - value
	≤45 y N(%)	46-55 y N(%)	≥56 y N(%)	
Time since menopause				0.0000
≤ 20 y	166(28.58)	437(65.39)	59(6.03)	
> 20 y	243(63.43)	160(34.68)	8(1.89)	
Total reproductive life				NA
<=35 y	402(72.15)	156(27.85)	0(0)	
>35 y	0(0)	429(89.59)	64(10.41)	
History of exogenous hormone use				0.0001
Never	106(29.90)	189(53.92)	63(16.18)	
Ever	303(39.76)	406(53.12)	70(7.12)	

NOTE: Number (N) of participants with weighted row percentages (%). PIR, prescribed investor rate; BMI, body mass index; y, years.

Supplemental Table 9. Characteristics of study participants by time since menopause (NHANES 1999–2004 cycle)

Variables	Time since menopause		p - value
	≤ 20 y N(%)	> 20 y N(%)	
Age			0.0000
40-70 y	626(85.29)	144(14.71)	
>70 y	36(11.75)	267(88.25)	
Race/Ethnicity			0.0320
Hispanic	186(78.29)	89(21.71)	
Non-Hispanic	476(68.70)	322(31.30)	
Education			0.0038
Less Than High School	202(61.22)	160(38.78)	
High School and above	460(72.21)	249(27.79)	
Income status		0.0000	
PIR ≤ 2.00	212(57.76)	190(42.24)	
PIR > 2.00	382(75.17)	185(24.83)	
Insurance			0.0188
Not covered	120(81.92)	29(18.08)	
Covered	539(68.35)	376(31.65)	
Alcohol use			0.0000
Never	139(54.99)	132(45.01)	
Ever	522(73.70)	279(26.30)	
Smoking			0.0233
Never	374(66.47)	254(33.53)	
Ever	287(73.69)	156(26.31)	
Hypertension			0.0000
No	321(82.56)	97(17.44)	
Yes	329(57.60)	305(42.40)	
BMI			0.4309
Underweight/normal	191(71.75)	132(28.25)	
Overweight/obese	463(69.11)	267(30.89)	
Total reproductive life			0.0000

Variables	Time since menopause		p - value
	≤ 20 y N(%)	> 20 y N(%)	
<=35 y	278(59.55)	280(40.45)	
>35 y	369(81.46)	124(18.54)	
History of exogenous hormone use			0.0000
Never	142(49.96)	180(50.04)	
Ever	519(75.36)	230(24.64)	

NOTE: Number (N) of participants with weighted row percentages (%). PIR, prescribed investor rate; BMI, body mass index; y, years.

Supplemental Table 10. Characteristics of study participants by total reproductive lifespan (NHANES 1999–2004 cycle)

Variables	Total reproductive lifespan		p - value
	<=35 y N(%)	>35 y N(%)	
Age			0.1049
40-70 y	420(56.23)	335(43.77)	
>70 y	138(48.75)	158(51.25)	
Race/Ethnicity			0.5399
Hispanic	145(51.46)	126(48.54)	
Non-Hispanic	413(55.00)	367(45.00)	
Education			0.4227
Less Than High School	191(57.44)	165(42.56)	
High School and above	366(53.84)	327(46.16)	
Income status		0.0183	
PIR ≤ 2.00	228(60.02)	167(39.98)	
PIR > 2.00	275(50.31)	279(49.69)	
Insurance			0.0595
Not covered	93(63.60)	54(36.40)	
Covered	458(53.33)	437(46.67)	
Alcohol use			0.8150
Never	146(55.42)	118(44.58)	
Ever	411(54.24)	375(45.76)	
Smoking			0.3206
Never	323(52.80)	292(47.20)	
Ever	234(56.86)	200(43.14)	
Hypertension			0.0151
No	234(58.66)	175(41.34)	
Yes	313(50.67)	308(49.33)	
BMI			0.5349
Underweight/normal	191(71.75)	132(28.25)	
Overweight/obese	463(69.11)	267(30.89)	
History of exogenous			0.0946

Variables	Total reproductive lifespan		p - value
	<=35 y N(%)	>35 y N(%)	
hormone use			
Never	152(48.28)	164(51.72)	
Ever	405(56.53)	328(43.47)	

NOTE: Number (N) of participants with weighted row percentages (%). PIR, prescribed investor rate; BMI, body mass index; y, years.

Supplemental Table 11. Characteristics of study participants by history of exogenous hormone use (NHANES 1999–2004 cycle)

Variables	History of exogenous hormone use		p - value
	Never N(%)	Ever N(%)	
Age			0.0000
40-70 y	150(13.47)	647(86.53)	
>70 y	209(55.16)	136(44.84)	
Race/Ethnicity			0.0723
Hispanic	113(33.50)	180(66.50)	
Non-Hispanic	246(21.71)	603(78.29)	
Education			0.0000
Less Than High School	178(37.94)	218(62.06)	
High School and above	179(18.37)	565(81.63)	
Income status		0.0000	
PIR ≤ 2.00	190(36.75)	245(63.25)	
PIR > 2.00	127(15.37)	464(84.63)	
Insurance			0.3475
Not covered	46(19.40)	108(80.60)	
Covered	308(23.29)	669(76.71)	
Alcohol use			0.0027
Never	119(31.31)	174(68.69)	
Ever	239(20.25)	609(79.75)	
Smoking			0.0002
Never	233(27.56)	444(72.44)	
Ever	125(16.97)	338(83.03)	
Hypertension			0.0008
No	100(16.29)	334(83.71)	
Yes	256(29.15)	431(70.85)	
BMI			0.1735
Underweight/normal	103(20.42)	251(79.58)	
Overweight/obese	246(23.78)	521(76.22)	

NOTE: Number (N) of participants with weighted row percentages (%). PIR, prescribed investor rate; BMI, body mass index; y, years.

Supplemental Table 12. Characteristics of study participants.

Variables	Non-DSN, N= 1055	DSN, N= 89
Age, y *	63(55,72)	68(60,78)
Race/Ethnicity		
Mexican American	199(86.15)	32(13.85)
Other Hispanic	57(91.94)	5(8.06)
Non-Hispanic White	573(93.17)	42(6.83)
Non-Hispanic Black	187(94.92)	10(5.08)
Other Race	39(100.00)	0(0.00)
Education		
Less Than High School	347(87.41)	50(12.59)
High School Diploma	290(94.77)	16(5.23)
More Than High School	416(94.76)	23(5.24)
Income (PIR) *	2.46(1.29,4.45)	1.65(0.99,3.02)
Insurance		
Not covered	140(90.91)	14(9.09)
Covered	906(92.54)	73(7.46)
Alcohol use		
Never	259(88.40)	34(11.60)
Current	529(94.63)	30(5.37)
Former	266(91.41)	25(8.59)
Smoking		
Never	623(91.89)	55(8.11)
Current	161(93.60)	11(6.40)
Former	269(92.12)	23(7.88)
Hypertension		
No	407(93.56)	28(6.44)
Yes	629(91.42)	59(8.58)
BMI		
Underweight	8(80.00)	2(20.00)
Normal weight	319(92.20)	27(7.80)
Overweight	360(93.51)	25(6.49)
Obese	350(91.62)	32(8.38)
Age at menarche, y *	13(12,14)	13(12,14)

Variables	Non-DSN, N= 1055	DSN, N= 89
Number of pregnant *	4(2,6)	4(2,5)
Breastfeeding history		
Never	409(92.95)	31(7.05)
Ever	529(92.32)	44(7.68)
Age at menopause, y *	48(43,51)	45.5(40,50)
Time since menopause, y *	15(6,26)	23(12.5,31)
Total reproductive life, y *	35(30,39)	33(28,37)
History of exogenous hormone use		
None	317(88.30)	42(11.70)
Menopausal hormone therapy only	504(94.38)	30(5.62)
Hormonal contraceptives use only	226(93.39)	16(6.61)
Both	6(85.71)	1(14.29)

NOTE: Number (N) of participants with unweighted row percentages (%). *Median with interquartile range. PIR, prescribed investor rate; BMI, body mass index; y, years.

Supplemental Table 13. Missingness of all variables by obese status (NHANES 1999–2004 cycle, N= 1,144)

Variables	Overweight/obese, N=767		Underweight/normal, N=356	
	n	%	n	%
DSP	0	0.00	0	0.00
Age at menarche	9	1.17	5	1.4
Gravidity	0	0.00	0	0.00
Breastfeeding	84	10.95	42	11.8
Age at menopause	2	0.26	3	0.84
Time since menopause	37	4.82	33	9.27
Total reproductive life	51	6.65	40	11.24
History of exogenous hormone use	0	0	2	0.56
Age	0	0.00	0	0.00
Race/Ethnicity	0	0.00	0	0.00
Education	0	0.00	2	0.56
Income	64	8.34	51	14.33
Alcohol use	0	0	1	0.28
Smoking status	1	0.13	1	0.28
Hypertension	11	1.43	7	1.97
Insurance	4	0.52	7	1.97

Supplemental Table 14. Association of distal sensory neuropathy with reproductive factors and exogenous hormone use by obese status (NHANES 1999–2004 cycle)

	Model 1[a]				Model 2[b]			
Variables	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*p*-value	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*p*-value
Age at menarche (≤ 11 vs > 11 y)	2.03(0.90, 4.58)	0.088	13.51(1.37, 132.81)	0.027*	1.19(0.22, 6.35)	0.837	1.85(0.14, 25.34)	0.636
Breastfeeding (Ever vs Never)	0.50(0.24, 1.02)	0.058	0.32(0.11, 0.91)	0.034*	1.75(0.57, 5.38)	0.321	0.95(0.23, 3.98)	0.941
Time since menopause (> 20 vs ≤ 20 y)	1.52(0.84, 2.75)	0.159	5.62(1.81, 17.49)	0.004*	1.37(0.42, 4.42)	0.595	0.59(0.09, 3.85)	0.572
History of exogenous hormone use (Ever vs Never)	0.58(0.27, 1.23)	0.151	0.33(0.11, 0.96)	0.043*	0.32(0.09, 1.18)	0.085	0.61(0.19, 1.99)	0.402

Values are crude odds ratio(OR) and adjusted OR with 95% confidence interval (CI), after controlling race, education, income, menarche, breastfeeding, time since menopause, and exogenous hormone use and interaction term of race with menarche. [a] n = 592 from 43 stratas; [b] n = 222 from 40 stratas, *p*-value for goodness of fit = 0.0047. y, years. *$p < 0.05$ vs. the values of non-distal sensory neuropathy group

Supplemental Table 15. Characteristics postmenopausal women with overweight/obesity by distal sensory neuropathy (NHANES 1999–2004 cycle, N= 767)

Variables	Non-DSN, N = 710		DSN, N = 57		p-value
	%	95%CI	%	95%CI	
Age					0.185*
40-59 y	0.94	0.91 - 0.97	0.06	0.03 - 0.09	
60-70 y	0.90	0.83 - 0.95	0.10	0.05 - 0.17	
Race/Ethnicity					0.323
Hispanic	0.90	0.80 - 0.97	0.10	0.04 - 0.20	
Non-Hispanic	0.94	0.91 - 0.96	0.06	0.04 - 0.09	
Education					0.018*
Less Than High School	0.88	0.81 - 0.93	0.12	0.07 - 0.19	
High School and above	0.95	0.92 - 0.97	0.05	0.03 - 0.08	
Income status				0.089*	
PIR ≤ 2.00	0.91	0.84 - 0.95	0.09	0.05 - 0.16	
PIR > 2.00	0.95	0.92 - 0.97	0.05	0.03 - 0.08	
Insurance					0.997
Not covered	0.93	0.83 - 0.98	0.07	0.02 - 0.17	
Covered	0.93	0.91 - 0.95	0.07	0.05 - 0.09	
Alcohol use					0.375
Never	0.91	0.84 - 0.96	0.09	0.04 - 0.16	
Ever	0.94	0.91 - 0.96	0.06	0.04 - 0.09	
Smoking					0.982
Never	0.93	0.90 - 0.96	0.07	0.04 - 0.10	
Ever	0.93	0.88 - 0.97	0.07	0.03 - 0.12	
Hypertension					0.336
No	0.92	0.86 - 0.96	0.08	0.04 - 0.14	
Yes	0.94	0.91 - 0.97	0.06	0.03 - 0.09	
Age at menarche					0.083*
> 11 y	0.95	0.92 - 0.96	0.05	0.04 - 0.08	
≤ 11 y	0.89	0.80 - 0.95	0.11	0.05 - 0.20	

Variables	Non-DSN, N = 710		DSN, N = 57		p-value
	%	95%CI	%	95%CI	
Gravidity					0.847
<4	0.93	0.89 - 0.96	0.07	0.04 - 0.11	
≥4	0.94	0.89 -0.97	0.06	0.03 - 0.11	
Breastfeeding history					0.054*
Never	0.93	0.89 - 0.96	0.07	0.04 - 0.11	
Ever	0.96	0.94 - 0.98	0.04	0.02 - 0.06	
Age at menopause					0.351
≤45 y	0.93	0.89 - 0.95	0.07	0.05 - 0.11	
46-55 y	0.95	0.91 - 0.97	0.06	0.03 - 0.09	
≥56 y	0.89	0.75 - 0.97	0.11	0.03 - 0.25	
Time since menopause					0.157*
≤ 20 y	0.95	0.92 - 0.97	0.05	0.03 - 0.08	
> 20 y	0.92	0.88 - 0.95	0.08	0.05 - 0.12	
Total reproductive life					0.220*
<=35 y	0.93	0.90 - 0.95	0.07	0.05 - 0.10	
>35 y	0.96	0.91 - 0.98	0.04	0.02 - 0.09	
History of exogenous hormone use					0.147*
Never	0.90	0.84 - 0.95	0.10	0.05 - 0.16	
Ever	0.94	0.91 - 0.96	0.06	0.04 - 0.09	

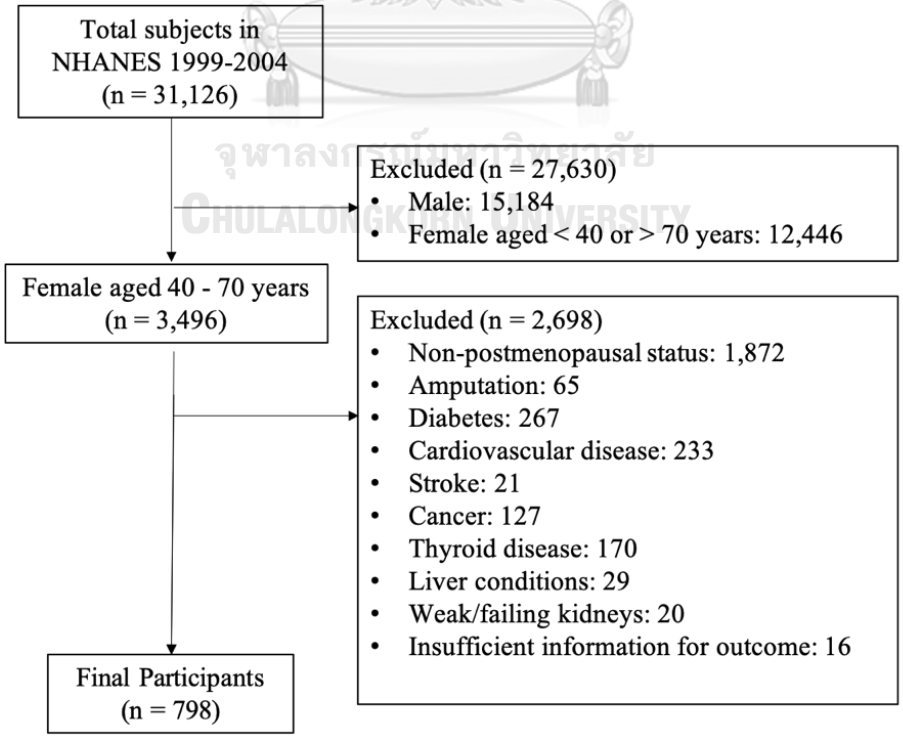
NOTE: Values are weighted row percentage with 95% confidence interval (CI). DSN, distal sensory neuropathy; PIR, prescribed investor rate; y, years. * Variables with p < 0.25 vs. the values of non-distal sensory neuropathy group were included in initial multivariable analysis.

Supplemental Table 16. Associations between breastfeeding and distal sensory neuropathy among postmenopausal women with overweight/obesity (NHANES 1999–2004 cycle)

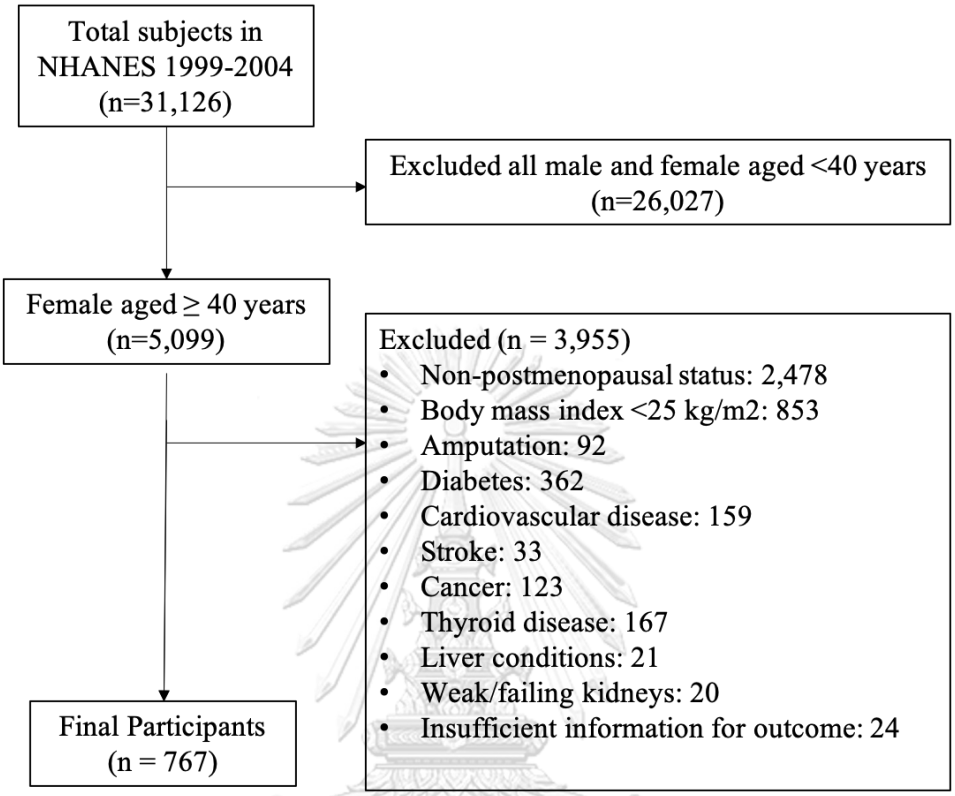
Variables			Model 1[a]		Model 2[b]	
	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*p*-value
Age at menarche (≤ 11 vs > 11 y)	2.03(0.90, 4.58)	0.088	1.51(0.50, 4.56)	0.449	8.30(1.33, 51.83)	0.025*
Breastfeeding (Ever vs Never)	0.50(0.24, 1.02)	0.058	0.27(0.10, 0.76)	0.014*	0.08(0.02, 0.34)	0.001*
Time since menopause (> 20 vs ≤ 20 y)	1.52(0.84, 2.75)	0.159	3.70(1.56, 8.76)	0.004*	4.51(1.83, 11.13)	0.002*
History of exogenous hormone use (Ever vs Never)	0.58(0.27, 1.23)	0.151	0.47(0.18, 1.19)	0.107	0.37(0.14, 0.97)	0.044*

Values are crude odds ratio(OR) and adjusted OR with 95% confidence interval (CI). [a]Adjusted for age, race, n = 645 from 43 stratas; [b]Adjusted for age, race, interaction term of race with menarche (*p* for interaction = 0.0391) and interaction term of race with breastfeeding (*p* for interaction = 0.0199); n = 835 from 43 stratas. y, years. *$p < 0.05$ vs. the values of non-distal sensory neuropathy group.

Supplemental Figure 1. Flow diagram for postmenopausal women aged 40-70 years (NHANES 1999–2004 cycle)



Supplemental Figure 2. Flow diagram for postmenopausal women with overweight/obesity (NHANES 1999–2004 cycle)



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VITA

NAME	Jiayu Li
DATE OF BIRTH	17 June 1993
PLACE OF BIRTH	Heilongjiang Province
INSTITUTIONS ATTENDED	Faculty of Medicine, Chulalongkorn University
HOME ADDRESS	Room 832 Ashton Chula Silom, ถนน พระรามสี่ ๔, Si Phraya, Bang Rak, Bangkok 10500