Journal of Health, Population and Nutrition

RESEARCH

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Association between life's simple 7 and peripheral neuropathy among U.S. adults, a cross-sectional study

Xi Gu[1†], Fanfan Zhu[1†], Ping Gao[1†], Ying Shen[1*] and Leiqun Lu[1*]

Abstract

Background Peripheral neuropathy (PN) is a common disease among adults that can lead to severe clinical outcomes; Life's Simple 7(LS7) is recommended to reduce the risk of cardiovascular disease and stroke. However, the association between LS7 and PN has not been well studied yet.

Methods We enrolled 4634 adults aged 40 to 85 years from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. We used univariable and multivariable logistic regression models to evaluate the association between the LS7 score and PN. The LS7 score was treated as a continuous variable and divided into three groups: inadequate (0–7), average (8–10), and optimal (11–14). Subgroup analyses were also performed.

Results The average age of the participants was 55.28(0.24) years, and 684(11.59%) of those were diagnosed with PN. In three models, the inverse associations between LS7 and PN were found. In Model 3, a point increase in the LS7 score was associated with a 9% decreased incidence of PN, the odds ratio (OR) was 0.91, and the 95% confidence interval (CI) was 0.86 to 0.97. Compared with the inadequate LS7 score group, participants in the average and optimal groups were less likely to have PN, and the OR and 95%CI were 0.75(0.59,0.96) and 0.47(0.28,0.79), respectively. No significant interactions were found in the subgroup analyses.

Conclusion An increased LS7 score is inversely associated with the likelihood of PN. This benefit was observed predominantly in participants who had the optimal LS7 score.

Keywords Life's simple 7, Peripheral neuropathy, National health and nutrition examination survey, Cross-sectional study, U.S. Adults

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Background

Peripheral neuropathy (PN) is a common but complicated disease owing to the lack of methods for early diagnosis and effective management [1]. The prevalence of PN has exceeded 20 million people in the U.S., according to previous work [2], and this figure might be underestimated. PN can lead to many symptoms, such as muscle weakness, loss of touch and temperature sensation in the hands or feet, and pain sensation disorder, resulting in an overall poor quality of life [3–5]. Additionally, PN increases the risk of falling, amputations, and movement limitation [6–8], and is significantly associated with both all-cause and cardiovascular mortality [9]. Therefore, it is important to prevent and control PN on time.

Life's Simple 7(LS7), which was defined by the American Heart Association in 2010, consists of three health factors and four health behaviors [10]. The components of LS7 are physical activity, healthy eating index (HEI)-2015, body mass index (BMI), smoking status, total cholesterol, hemoglobin A1c (HbA1c), and blood pressure. A higher LS7 score has been recommended by the committee to reduce cardiovascular disease and stroke, and many studies have identified its benefits in macrovascular diseases [11]. Recently, some studies found that LS7 was not only associated with macrovascular disease but also with other health conditions, such as Nonalcoholic Fatty Liver Disease [12], depression [13], cancer [14], dementia [15], etc. Interestingly, LS7 was also considered to be associated with hearing loss and diabetic retinopathy [16, 17], both are microvascular diseases. Therefore, we wondered whether LS7 was associated with PN, another disease related to the microvasculature [18].

Therefore, we conducted a cross-sectional study of U.S. adults to test our hypotheses. Using the National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2004, we hypothesized that a higher LS7 score could reduce the likelihood of PN.

Methods

Data source and study population

According to the introduction of the NHANES online, the survey has been conducted continuously since 1999, and relevant data have been released every two years. The survey selected approximately 5,000 participants each year to represent the national health conditions. It plays an important role in disease control and prevention in the United States. The main contents of the NHANES include demographic, dietary, examination, laboratory, and questionnaire data. Most survey data are available online (https://www.cdc.gov/nchs/nhanes/index.htm). All participants' personal information was kept confidential and protected by public law. This study was approved by the National Center for Health Statistics Ethics Review Board. The protocol number was Protocol #98 – 12. This cross-sectional study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

9145 participants who underwent lower extremity disease examinations between 1999 and 2004 were initially included in our study. First, we excluded those who did not have data on the PN section. Second, we excluded participants with missing metrics to calculate the LS7 score, including physical activity, HEI, BMI, smoking status, total cholesterol, HbA1c, blood pressure, and anti-diabetes drugs. Third, we excluded those with missing data on education level and diagnosis of diabetes. Ultimately, 4634 participants aged 40 to 85 years were included in the final analysis (shown in Fig. 1).

Definition of life's simple 7 score

The LS7 score consists of seven cardiovascular health metrics: physical activity, HEI-2015, BMI, smoking status, total cholesterol, HbA1c, and blood pressure [19]. We determined the intensity of physical activity by a questionnaire. Participants were asked the following questions: Over the past 30 days, how often they did activity, on average, how long they did activity each time, and what vigorous/moderate activities they did. The HEI-2015 comprised 13 foods: total vegetables, greens and beans, total fruit, whole fruit, whole grains, total dairy, total protein foods, seafood, and plant protein, fatty acid ratio, sodium, refined grains, saturated fat, and added sugar [20]. We extracted the total nutrient intake of the 13 foods on the first day and summed each component's point to obtain the HEI-2015 score. Higher HEI-2015 scores indicate better dietary quality. BMI was calculated as weight(kg) divided by the squared height(m). Body measurements were conducted at a mobile examination center (MEC). Smoking status was assessed during the interviews. Smoking status was classified as never smoker (less than 100 cigarettes smoked in a lifetime), former smoker (more than 100 cigarettes smoked in a lifetime but no longer smoked), or current smoker (more than 100 cigarettes smoked in a lifetime and smoked presently). Total cholesterol and HbA1c values were obtained from laboratory data. The mean blood pressure was calculated according to the NHANES data analytic notes [21]. Each metric was divided into three categories: inadequate (0 points), average (1 point), and optimal (2 points). The detailed scoring methods are listed in an additional file (see Additional file1: Table S1). Each participant's LS7 score was the sum of seven metric points, it's ranging from 0 to 14 points. Based on previous studies [22], we further divided participants into three groups according to their LS7 scores: inadequate (0–7 points), average (8–10 points), and optimal (11–14 points).

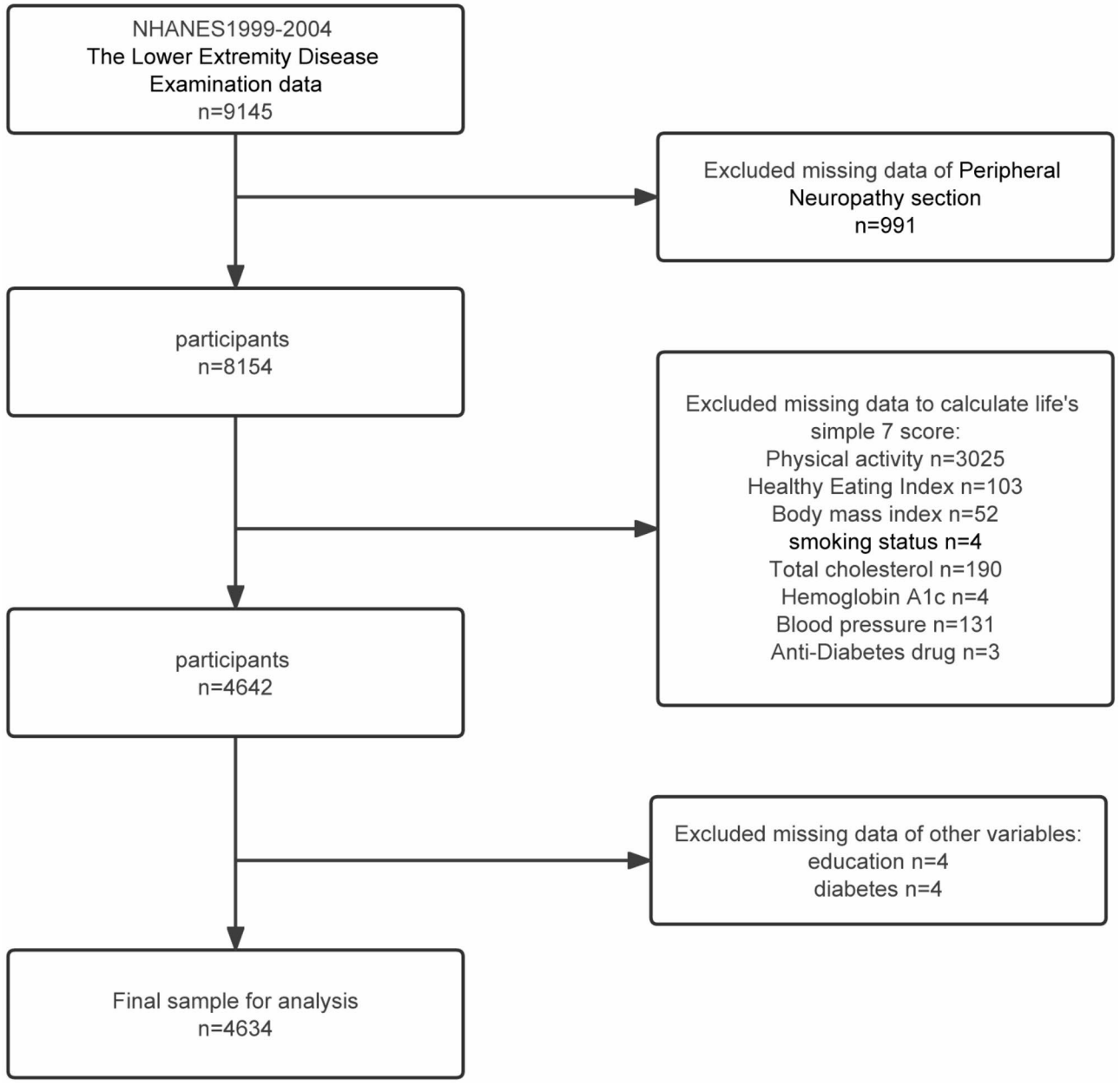

Fig. 1 Flowchart of study design
NHANES: National Health and Nutrition Examination Survey

Definition of peripheral neuropathy

According to the Lower Extremity Disease Examination protocol, well-trained health technicians used a standard monofilament to test the feelings of the participant's feet. The number of insensate foot areas was determined based on their response to monofilament testing. According to previous studies, we diagnosed if one or more of their insensate feet areas were defined [23]. The participants who reported no insensate feet areas or could not report enough information were diagnosed as having no PN.

Other variable definitions

Survey participants' demographic data (age, sex, ethnicity, educational level, and poverty income ratio) were obtained from household interviews. We categorized the poverty income ratio (PIR) into three levels: low-income (≤ 1.3), mid-level income (> 1.3 to 3.5), and high-income (> 3.5). Diabetes was diagnosed if the participants met any of the following criteria: (1) fasting plasma glucose ≥ 126 mg/dl, (2) random plasma glucose ≥ 200 mg/dl, (3) HbA1c ≥ 6.5%, (4) ever diagnosed with diabetes by doctors, and (5) use of anti-glycemic medications. Participants were considered to have hypertension if they had

one of the following three conditions: (1) systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg measured ≥ 3 times. (2) Diagnosis of hypertension by other doctors. (3) Medication for hypertension. Participants were regarded as patients with hyperlipidemia if they had either of the following conditions: (1) triglyceride ≥ 150 mg/dl, (2) total cholesterol ≥ 200 mg/dl, low-density lipoprotein (LDL) ≥ 130 mg/dl, high-density lipoprotein (HDL) < 40 mg/dl (male) or < 50 mg/dl (female), and (3) use of medication to treat dyslipidemia.

Statistical analyses

According to the NHANES tutorials, we used weighted methods to analyze the data. The weight in our study was calculated using the following formula: sample weight = 2/3 × MEC 4-year weight (NHANES1999-2002) or 1/3 × MEC 2-year weight (NHANES2003-2004). Continuous variables are presented as mean ± standard error (SE), and categorical variables are presented as numbers and weighted percentages. The baseline characteristics of the different LS7 score groups were analyzed using one-way analysis ANOVA (normal distribution) and the chi-square test (categorical variables).

Odds ratios (ORs) and 95% confidence intervals(95%CIs) were calculated for PN with LS7 scores, using weighted logistic regression models. Both non-adjusted and multivariate-adjusted models were used. We constructed three models: (Model 1) unadjusted; (Model 2) adjusted for age and sex; and (Model 3) adjusted for age, sex, ethnicity, educational level, PIR, and alcohol consumption. We included variables as confounders based on existing literature [16] and clinical judgment. We converted the LS7 score into a categorical variable according to the cutoff value in previous studies and calculated the P for the trend to verify the results of the LS7 score as a continuous variable and to examine the possibility of nonlinearity.

Subgroup analysis was used to examine the association between the LS7 score and PN according to age (< 65 and ≥ 65 years), sex (Male, Female), ethnicity, and education level. Each stratification was adjusted for age, sex, ethnicity, education, poverty income ratio, and alcohol consumption, excluding the stratification factor itself. Tests for effect modification of subgroup indicators were followed by the likelihood ratio test.

Several sensitivity analyses were performed. First, we adjusted for diabetes, hypertension, and hyperlipidemia in the multivariable logistic regression model. Second, these same adjustments were applied in the subgroup analyses.

The missing values of PIR (continuous) were less than 8%; therefore, they were replaced with the mean values. No other imputation methods were used. Statistical analyses were performed using the statistical software package R version 4.2.1 and Free Statistics software (version 1.7.1). Statistical significance was defined as a two-sided P-value < 0.05.

Results

Weighted characteristics of participants stratified by LS7 score categories

There were 4634 participants involved in the study. Among them, the average age was 55.28(0.24) years old, 2534(52.14%) were male, and 684(11.59%) were diagnosed with PN. Participants in the optimal LS7 score group, compared to those in the inadequate score group, were younger, more likely to be female, non-smokers, and with higher income and education levels. They also exhibited lower alcohol consumption, BMI, blood pressure, HbA1c, and total cholesterol levels, along with higher physical activity time and HEI scores. Meanwhile, they had a lower risk of developing diabetes, hypertension, and hyperlipidemia. The relevant data are presented in Table 1.

Association between LS7 score and PN in adults from NHANES 1999–2004

In the univariable logistic regression model, the LS7 score was inversely associated with the incidence of PN, OR was 0.87(95%CI [0.82,0.92]). In addition, other races (compared to non-Hispanic whites), education level of college or above (compared to High School or less), and PIR greater than 3.5(compared to less than or equal to 1.3) were inversely associated with the likelihood of PN. In contrast, age, male, Non-Hispanic Black (compared to non-Hispanic white), former smokers (compared to non-smokers), and diabetes or hypertension were positively associated with PN. The detailed results are presented in an additional file (see Additional file1: Table S2). In the weighted multivariable logistic regression, Model 1 yielded similar results to the univariable regression model when LS7 was treated as a continuous variable. Besides, a point increase in the LS7 score decreased the likelihood of PN by 10% and 9% in Model 2 (OR 0.9 [95%CI:0.85,0.95]) and Model 3 (OR 0.91 [95%CI:0.86,0.97]), respectively. Additionally, when compared with the inadequate LS7 score group, the participants in average and optimal groups were less likely to have PN in all three models. In Model 1, the OR and 95%CI were 0.69(0.54,0.88) and 0.30(0.19,0.47), p for trend < 0.0001. In Model 2, the OR and 95%CI were 0.72(0.57,0.92) and 0.44(0.27,0.71), p for trend = 0.001. In Model 3, the OR and 95%CI were 0.75(0.59,0.96) and 0.47(0.28,0.79), p for trend = 0.009. Table 2 shows the results.

Table 1 Weighted characteristics of participants stratified by life's simple 7 score categories in adults from NHANES 1999–2004 (*N* = 4634)

Variables	Total	Inadequate (0–7)	Average (8–10)	Optimal (11–14)	*p*-value
		(*n* = 2024)	(*n* = 2198)	(*n* = 412)	
Age(years)	55.28(0.24)	56.77(0.23)	55.00(0.38)	51.28(0.62)	< 0.0001
Life's Simple 7 score	8.02(0.06)	6.06(0.03)	8.82(0.02)	11.39(0.04)	< 0.0001
Alcohol consumption(g/d)	11.99(0.73)	12.38(1.09)	12.38(0.96)	8.94(1.30)	0.02
BMI (kg/m^2)	28.34(0.16)	31.19(0.16)	27.17(0.14)	23.41(0.23)	< 0.0001
Systolic BP (mmHg)	127.00(0.48)	133.60(0.57)	124.53(0.57)	114.51(0.75)	< 0.0001
Diastolic BP (mmHg)	74.07(0.29)	76.03(0.39)	73.35(0.31)	70.34(0.49)	< 0.0001
HbA1c (%)	5.56(0.02)	5.91(0.03)	5.37(0.02)	5.15(0.03)	< 0.0001
Total cholesterol(mg/dl)	211.01(1.03)	224.97(1.55)	204.62(1.10)	189.52(1.93)	< 0.0001
Physical activity(minutes/week)	272.08(10.67)	213.27(11.43)	309.18(15.60)	319.26(28.01)	< 0.0001
HEI-2015 score	51.87(0.39)	47.55(0.34)	53.42(0.40)	60.31(0.83)	< 0.0001
Sex					< 0.0001
Female	2100(47.86)	878(44.89)	965(45.53)	257(68.15)	
Male	2534(52.14)	1146(55.11)	1233(54.47)	155(31.85)	
Ethnicity					0.001
Non-Hispanic White	2855(82.87)	1157(80.60)	1396(83.32)	302(88.91)	
Mexican American	866(18.69)	410(4.10)	399(3.74)	57(2.78)	
Non-Hispanic Black	651(3.78)	352(8.73)	266(5.75)	33(3.15)	
Other Hispanic	136(3.34)	53(3.29)	73(3.67)	10(2.13)	
Other Race	126(3.36)	52(3.38)	64(3.51)	10(3.03)	
PIR					< 0.0001
≤1.3	880(11.85)	446(13.92)	388(11.31)	46(6.94)	
>1.3 to ≤ 3.5	1933(37.03)	890(41.51)	899(34.80)	144(30.87)	
>3.5	1821(51.12)	688(44.57)	911(53.90)	222(62.19)	
Education					< 0.0001
High School education or less	2329(40.61)	1157(48.88)	1048(38.34)	124(21.44)	
College education or above	2305(59.39)	867(51.12)	1150(61.66)	288(78.56)	
Smoking status					< 0.0001
never	2099(46.51)	601(29.80)	1164(52.33)	334(79.99)	
former	1678(34.14)	861(39.08)	745(33.82)	72(18.26)	
current	857(19.35)	562(31.12)	289(13.84)	6(1.75)	
Diabetes					< 0.0001
no	3901(88.51)	1442(77.48)	2049(94.96)	410(99.54)	
yes	733(11.49)	582(22.52)	149(5.04)	2(0.46)	
Hypertension					< 0.0001
no	2213(55.21)	624(36.26)	1237(62.64)	352(89.64)	
yes	2421(44.79)	1400(63.74)	961(37.36)	60(10.36)	
Hyperlipidemia					< 0.0001
no	890(19.61)	162(6.76)	508(21.86)	220(54.81)	
yes	3744(80.39)	1862(93.24)	1690(78.14)	192(45.19)	

Abbreviation: BMI, body mass index; BP: Blood pressure; HbA1c: Hemoglobin A1c; HEI: Healthy Eating Index; PIR: Poverty income ratio; NHANES, National Health and Nutrition Examination Survey

Subgroup analysis of the association between LS7 score and PN in adults from NHANES 1999–2004

Consistent results between the LS7 score and PN were observed when the analyses were stratified by age (binary classification), sex, education level, and ethnicity. No significant interactions were found after controlling for potential confounders. All *p*-values for the interaction were more than 0.05(shown in Fig. 2).

Sensitivity analyses

In the sensitivity analyses, after adjusting for diabetes, hypertension, and hyperlipidemia, the LS7 score remained inversely associated with the incidence of PN. For further details, refer to Additional File 1: Tables S3 and S4.

Table 2 Association between life's simple 7 score and peripheral neuropathy in adults from NHANES 1999–2004 (*N* = 4634)

Variable	Model 1		Model 2		Model 3	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Continuous LS7	0.87(0.82,0.92)	< 0.0001	0.90(0.85,0.95)	< 0.001	0.91(0.86,0.97)	0.003
Categorical LS7						
Inadequate (0–7)	Reference		Reference		Reference	
Average (8–10)	0.69(0.54,0.88)	0.003	0.72(0.57,0.92)	0.01	0.75(0.59,0.96)	0.02
Optimal (11–14)	0.30(0.19,0.47)	< 0.0001	0.44(0.27,0.71)	0.001	0.47(0.28,0.79)	0.01
P for trend		< 0.0001		0.001		0.009

Abbreviation: LS7, Life's Simple 7; OR, odds ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey

Model 1: no adjustment

Model 2: adjusted for age and sex

Model 3: adjusted for age, sex, ethnicity, education, poverty income ratio, and alcohol consumption

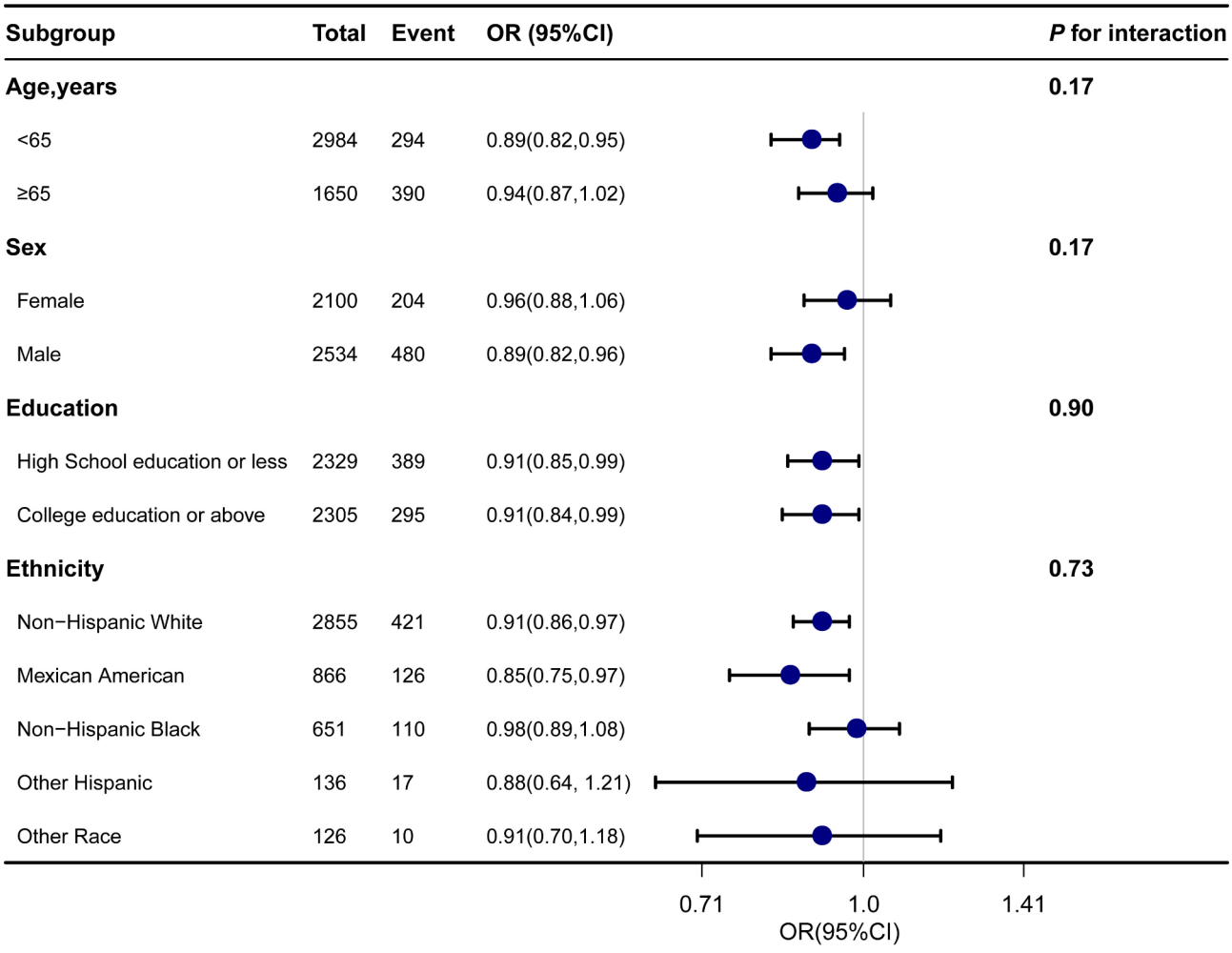

Fig. 2 Association of Life's Simple 7 with Peripheral neuropathy in various subgroups

OR: odds ratio; CI: confidence interval

Each stratification was adjusted for age(continuous), sex, ethnicity, education, poverty income ratio, and alcohol consumption, excluding the stratification factor itself

Discussion

Through this cross-sectional study, we found that a higher LS7 score was associated with a lower incidence of PN among adults in the U.S., regardless of diabetes status. The results were stable in the subgroup analysis.

Several studies have been conducted to determine one or more risk factors of PN. Our findings differed from the results reported in these studies. In the UK Prospective Diabetes Study [24], 1148 patients with diabetes and hypertension were included. The tight blood pressure control was not significantly associated with the reduced risk of neuropathy, compared to those who underwent less tight control during a median follow-up of 8.4 years. In a Steno type 2 randomized study [25], 160 patients with diabetes and microalbuminuria were included. After a mean 3.8-year follow-up, the ORs and 95%CIs for PN did not differ significantly between the intensive($n = 80$) and standard treatment($n = 80$) groups. Another randomized controlled trial, the ADDITION-Europe Study [26], also gained similar results. They included 2861 diabetes patients. Intensive treatment did not reduce the ORs of neuropathy compared to the routine care group after a five-year follow-up. Furthermore, after 13 years of diabetes diagnosis, 1256 participants without PN were selected. PN was set as the primary endpoint in the ADDITION Denmark study [27]. They found that baseline levels of HDL and LDL cholesterol were inversely related to the risk of incident diabetic polyneuropathy (DPN), whereas baseline levels of age, weight, waist circumference, and BMI were positively related to DPN.

In line with our findings, other researchers have also identified certain risk factors that were associated with PN. Several studies indicated that prediabetes patients were at a higher risk for PN than the control group [28–30]. Besides, metabolic syndrome has been identified as an essential risk factor for PN [3]. Abdominal obesity, hypertension, and lipid abnormalities have been the most significant components of incident PN in different studies [31, 32]. However, unlike these studies, cardiovascular health metrics were integrated into one metric, named LS7 in our study, and we evaluated the association between LS7 and PN. Furthermore, we converted LS7 into three categories and determined the optimal LS7 score range that would be linked to the lowest risk of PN. The participants in other studies were mostly patients with diabetes, in contrast, the participants in our survey were the general population. Thus, our results can be applied in more general fields. Similar to previous studies, we found that age, male sex, BMI, hypertension, and diabetes are positively associated with PN. Smoking also increased the incidence of PN; however, this risk was limited in participants who were former smokers. Hypertriglyceridemia is a significant risk factor for PN in patients with diabetes [33]. However, due to the abundant missing values of triglycerides, we could not obtain similar results in our study. It is pertinent to acknowledge that variances in risk factor profiles and mechanisms underlying PN across different populations hold significance in contextualizing our findings. Consequently, when drawing direct comparisons with studies involving distinct patient cohorts, such as individuals with diabetes, it is prudent to exercise caution.

The underlying pathophysiology of PN remains poorly understood. Hyperglycemia, dyslipidemia, and obesity can lead to mitochondrial dysfunction in patients with diabetes. Subsequently, energy loss and nerve axon injury may occur [34, 35]. Insulin resistance is common among patients with metabolic syndrome and can cause insufficient glucose uptake in the nervous system [36]. In animal studies, researchers have found that high-fat feeding could harm the mitochondrial and nervous systems through various pathways, including energy depletion [37], oxidative stress [38], endoplasmic reticulum stress [39], etc. Longer-chain saturated fatty acids are another risk factor for neuronal mitochondrial damage [40].

Our study has several strengths. First, we extracted the data from the NHANES database and performed data analysis using the weighted method, so that the results could represent the general U.S. population. Second, unlike other studies, LS7 integrates risk factors for PN. The LS7 score can be used to analyze the association between cardiovascular health metrics and PN more comprehensively. This may help us identify the best lifestyle behavior and determine clinical treatment more accurately in future studies. Third, we expanded the range of the surveyed population rather than being limited to patients with diabetes.

Our study had some limitations. First, we could not determine the causal relationship between LS7 and PN through a cross-sectional study. Prospective studies are recommended for future research endeavors to investigate the potential causal connections between LS7 scores and PN. Second, sleep conditions were not included as covariables in our study. Therefore, we were unable to determine whether PN and sleep disorders were related. However, the questionnaire on sleep was available only after 2005 in the NHANES database. Third, we defined PN using a 10-gram filament force to examine foot sensation. This method may not be accurate for the diagnosis of small fiber neuropathy. However, the participants in the NHANES did not undergo skin biopsy. In addition, the sensitivity and specificity of monofilament testing range from 57 to 93% and 75–100%, respectively [41]. In future studies, alternative methods such as nerve conduction velocity, electromyography, and skin biopsy should be considered for a more accurate diagnosis of PN.

Conclusion

In this study, we found that increased LS7 score was inversely associated with PN incidents among U.S. adults. This benefit was observed primarily in participants who had the optimal LS7 score. More prospective studies are needed in the future to identify whether the improvement of comprehensive cardiovascular health metrics could reduce the risk of PN.

Abbreviations

PN	Peripheral neuropathy
LS7	Life's Simple 7
NHANES	National Health and Nutrition Examination Survey
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
HEI	Healthy eating index
BMI	Body mass index
HbA1c	Hemoglobin A1c
MEC	Mobile examination center
PIR	Poverty income ratio
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
ORs	Odds ratios
CIs	Confidence intervals
DPN	Diabetic polyneuropathy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41043-025-00864-9.

Supplementary Material 1

Acknowledgements

We gratefully thank Jie Liu of the Department of Vascular and Endovascular Surgery, Chinese PLA General Hospital for his contribution to the statistical support, study design consultations, and comments regarding the manuscript.Thanks to Zhang Jing (Second Department of Infectious Disease, Shanghai Fifth People's Hospital, Fudan University) for his work on the NHANES database.His outstanding work, nhanesR package and webpage, makes it easier for us to explore NHANES database.We thank the funding support for co-author FanFan Zhu's study. The funding organization is the Shanghai Municipal Huangpu District Commission (HLQ202205).

Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Xi Gu, Fanfan Zhu, and Ping Gao. The first draft of the manuscript was written by Xi Gu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

No funding was received to assist with the preparation of this manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Approval was obtained from the NCHS Research Ethics Review Board. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate

Written informed consent was obtained for participation in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 2 December 2023 / Accepted: 3 April 2025
Published online: 15 April 2025

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