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# Relationship between peripheral neuropathy and cognitive performance in the elderly population

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**Abstract**

There are only a few studies that have shown an association of peripheral neuropathy with cognitive impairment in elderly individuals. Therefore, we investigated the relationship between cognitive performance and peripheral neuropathy.

From the database of the National Health and Nutrition Examination Survey (NHANES, 1999–2002), each participant completed a household interview, physical performance test, questionnaire regarding personal health, and Digit Symbol Substitution Test (DSST) to evaluate cognitive performance. The severity of peripheral neuropathy was assessed based on the number of insensate areas in both feet during monofilament examination. We used the multivariate linear regression to analyze the association of the DSST findings with insensate areas of the worse foot.

There were 828 participants in our study from NHANES 1999 to 2002; their mean age was 69.96 ± 7.38 years, and 51.3% were male. The β coefficients of the number of insensate areas associated with the DSST findings were all negative values, and the absolute value increased as the number of insensate areas increased. After adjustment for pertinent variables, the correlations remained significantly negative (all $P$ for trend $<.001$). In addition, subgroup analysis showed no gender differences in the negative association, but this association was not significant in obese participants ($P > .05$).

Our study provides evidence that the severity of peripheral neuropathy is significantly negatively correlated with cognitive performance.

**Abbreviations:** CI = confidence interval, DSST = Digit Symbol Substitution Test, MCI = mild cognitive impairment, NHANES = National Health and Nutrition Examination Survey, SBP = systolic blood pressure.

**Keywords:** cognitive impairment, cognitive performance, dementia, elderly, peripheral neuropathy

## 1. Introduction

Dementia is a disease that affects individuals worldwide. Its global prevalence is up to 7% among elderly individuals, varying from 5% in developing countries to 8% to 10% in developed countries.[1,2] Patients with dementia may present with memory loss, cognitive impairment, functional decline, and eventual interferences in activities of daily living. Gait velocity decreases and the ability to multitask while walking is impaired as cognition declines, which leads to an increased risk of falls.[3] Mild cognitive impairment (MCI) presents as modest cognitive decline that does not interfere with the activities of daily living and is widely regarded as a symptomatic pre-dementia state.[4] Individuals with MCI have a higher risk of progressing to dementia and have higher mortality rates than those in individuals with normal cognition.[5] According to a cross-sectional study including 1174 elderly patients, cognitive dysfunction accompanied with oral frailty substantial aggravated the presence of aspiration pneumonitis.[6] According to the National Vital Statistics report published by the Centers for Disease Control and Prevention of the United States, dementia contributed to a total of 261,914 deaths from 2001 to 2017. The mortality rate increases with age from 56.9 deaths per 100,000 among individuals aged 65 to 74 years to 2707.3 deaths per 100,000 among individuals aged 85 years and older.[7] The early diagnosis and treatment of cognitive dysfunction or dementia is an important issue to prevent elderly individuals from experiencing further impairments.

Polyneuropathy is a distal symmetrical sensorimotor polyneuropathy of diabetes mellitus.[8] It is characterized by symmetrical distal numbness and paresthesia and may also be accompanied by pain and weakness. The overall prevalence in the general population is approximately 1%, which rises to 7% in elderly individuals.[9] Besides diabetes, polyneuropathy is a multifactorial disease that includes alcohol abuse, toxic agents, nutritional deficiencies, immune-mediated causes and hereditary factors.[9] A cohort study including 5229 subjects indicated that

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increased height is associated with an increased peripheral insensate neuropathy prevalence among individuals with and without diabetes, which may be due to the greater axon surface exposure to any localized injury.[10] Emerging evidences have shown that microvascular complications are the main cause of peripheral neuropathy in patients with diabetes.[11]

Some studies have investigated the relationship between diabetic peripheral microvascular complications and cognitive function, which have shown that diabetes is associated with cognitive dysfunction, and adequate diabetic control may prevent the progression of cognitive decline.[12] However, there is no significant correlation between the existence and severity of diabetic peripheral neuropathy and cognitive impairment.[13] Yasemin et al found a high prevalence of diabetic peripheral neuropathy in patients with sarcopenia, and they finally confirmed that sarcopenia had a positive correlation with diabetic peripheral neuropathy.[14] Emerging studies have shown that sarcopenia increases the risk of cognitive dysfunction,[15] and lower muscle strength is associated with poorer performance in all cognitive tests in aging adults.[16] However, there are only a few studies that have shown the correlation between peripheral neuropathy and cognitive performance, so this study focuses on the association between peripheral neuropathy and cognitive performance in elderly individuals.

## 2. Method

### 2.1. Study population

As an observational and cross-sectional study, we used the database of the National Health and Nutrition Examination Survey (NHANES) 1999 to 2002, a population-based survey designed to collect information on the health and nutrition of the US household population. It contained a substantial family interview, followed by a comprehensive physical examination at an equipped mobile examination center.[17] In addition to medical, dental, and physiological measurements, as well as laboratory tests conducted by highly trained medical personnel,[18] some of the participants completed the Digit Symbol Substitution Test (DSST) for cognitive performance evaluation and monofilament examination to detect peripheral neuropathy. The exclusion criteria included individuals younger than 60 years of age; with a history of stroke; or with incomplete laboratory data, clinical inspection findings and DSST. In addition, individuals were excluded from the monofilament examination if they had undergone amputation of the lower limbs or had a body weight of 400 lbs. or greater. The NHANES study was approved by the National Center for Health Statistics Institutional Review Board. All informed consents had been obtained from the eligible subjects before all examinations.

### 2.2. Measurement of cognitive performance

The DSST is a paper-and-pencil cognitive test presented on a single sheet of paper that requires a subject to match symbols to numbers according to a key located at the top of the page.[19] Individuals commonly complete the test within 90 to 120s; the numbers of matched symbols represent the scores, and the maximal score is 133. Low DSST scores represent poor cognitive performance. The DSST is sensitive to both the presence of cognitive dysfunction and the changes in cognitive function across a wide range of clinical populations.[20] It provides brevity; reliability; and minimal impacts of language, culture, and education on test performance.

### 2.3. Measurement of peripheral neuropathy

As a quantitative sensory test, a monofilament was used to test a single point of light touch pressure. In the NHANES, the inspector exerted approximately a 10 g of pressure using a 5.07 Semmes–Weinstein nylon monofilament to the sole of every examinee at 3 adjacent borders between the plantar and 1st metatarsal head, 5th metatarsal head, and hallux.[21] The filament lightly touched the examinee's skin; if the individual did not detect the presence of the filament during buckling, the response was defined as loss of sensation.[22] The health technician verbalized either "A" or "B" while applying the pressure, and the examinee was asked to answer "A" or "B", respectively, when the pressure was detected. A site was considered insensate if there were:

1. 2 erroneous replies,
2. 2 indeterminable replies, or
3. 1 erroneous plus 1 indeterminable reply for a site, and the number of insensate areas represented the severity of peripheral neuropathy.

### 2.4. Assessment of covariates

Demographic information was collected through a computer-supported private interview, including age, gender, ethnicity, smoking habit, and medical history. The blood glucose level was assessed in individuals who had been starved beyond 6 h using the hexokinase enzymatic method with the Cobas Mira Chemistry System. The method used to analyze the complete blood cell count (CBC) was based on the Beckman Coulter method, composed of an automatic diluting and mixing apparatus for sample processing, and a single-beam photometer for hemoglobinometry. White blood cell count differentiation exploited volume, conductivity and scatter technology. C-reactive protein levels were quantified using latex-enhanced nephelometry with a Behring Nephelometer System (Dade Behring, Deerfield, IL). Folic acid and vitamin B12 levels were using Bio-Rad Quantaphase II commercial kit.[23] Hypertension was defined as doctor-diagnosed hypertension and/or the use of antihypertensive medications. Blood pressure was estimated 3 to 4 times in the mobile examination center or during home examinations for every participant using a mercury sphygmomanometer. Diabetes was determined either based on a self-report questionnaire (use of insulin injections or oral antidiabetic agents), or the following laboratory definitions:

1. a fasting glucose level $\geq$126 mg/dL, and
2. a random serum glucose level $\geq$200 mg/dL.

Heart disease was defined as medical history of coronary artery disease, heart failure or chest pain. Alcohol consumption was evaluated in the questionnaire by asking the examinees "Do you have at least 12 drinks within 1 year?" Smoking habits were clarified based on the response to the question "Do you currently smoke cigarettes?"

### 2.5. Statistical analyses

Analyses of all data were conducted using the Predictive Analytics Suite Workstation Statistics, v.18.0 for Windows (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean values and standard deviations, whereas categorical variables were expressed as numbers and percentages. We applied the $\chi^2$

**Table 1**

**Characteristics of study participants.**

| Variables | Number of insensate area-worse foot | | | | | |
|---|---|---|---|---|---|---|
| | 0 N = 624 | 1 N = 122 | 2 N = 43 | 3 N = 39 | total N = 828 | *P* value |
| Continuous variables* | | | | | | |
| Age (yr) | 69.22 (7.10) | 71.52 (7.86) | 74.19 (7.07) | 72.23 (8.03) | 69.96 (7.38) | <.001 |
| DSST score | 45.07 (18.63) | 39.90 (18.44) | 31.42 (17.49) | 27.28 (14.61) | 42.76 (18.97) | <.001 |
| WBC (1000 cells/uL) | 6.95 (1.80) | 6.68 (1.70) | 6.99 (1.99) | 7.14 (1.94) | 6.92 (1.80) | .396 |
| Serum folate (ng/mL) | 19.17 (10.24) | 16.62 (10.22) | 18.14 (11.23) | 20.74 (12.29) | 18.81 (10.42) | .054 |
| Vitamin B12 (pg/mL) | 686.53 (4090.96) | 661.60 (1111.27) | 644.12 (858.13) | 661.05 (771.09) | 679.45 (3585.13) | 1.000 |
| Total cholesterol | 217.19 (38.82) | 208.43 (38.58) | 208.19 (37.83) | 218.51 (49.47) | 215.49 (39.38) | .078 |
| CRP (mg/dL) | 0.52 (0.77) | 0.63 (0.88) | 0.31 (0.26) | 0.45 (0.39) | 0.52 (0.75) | .09 |
| SBP (mm Hg) | 138.03 (19.71) | 144.56 (21.58) | 149.15 (24.98) | 144.90 (24.04) | 139.85 (20.73) | <.001 |
| Categorical variables# | | | | | | |
| Male | 308 (49.4) | 68 (55.7) | 27 (62.8) | 22 (56.4) | 425 (51.3) | .205 |
| Mexican American | 133 (21.3) | 22 (18) | 9 (20.9) | 12 (30.8) | 176 (21.3) | .031 |
| Education <high school | 248 (39.8) | 55 (45.1) | 24 (57.1) | 22 (56.4) | 349 (42.3) | .030 |
| Hypertension | 408 (65.4) | 88 (72.1) | 32 (74.4) | 30 (76.9) | 558 (67.4) | .174 |
| Diabetes mellitus | 92 (14.7) | 23 (18.9) | 10 (23.3) | 11 (28.2) | 136 (16.4) | .065 |
| Heart disease | 96 (15.4) | 23 (18.9) | 9 (20.9) | 6 (15.4) | 134 (16.2) | .644 |
| Alcohol consumption >12 drinks/yr | 226 (36.2) | 51 (41.8) | 17 (39.5) | 17 (43.6) | 311 (37.6) | .554 |
| Current smoker | 73 (11.7) | 12 (9.8) | 4 (9.3) | 3 (7.7) | 92 (11.1) | .769 |

DSST = digit symbol substitution test, SBP = systolic blood pressure, WBC = white blood cell, CRP = C-reactive protein.

* Values were expressed as mean (standard deviation).

# Values in the categorical variables were expressed as number (%).

test to analyze categorical data and the Mann–Whitney *U* test or Student *t* test for continuous data. Two-sided *P* values $\leq .05$ were used to represent significant differences. Linear regression analysis was applied to identify the association between the insensate areas of the foot and DSST score. Three models were applied as follows: model 1 contained age, gender, race/ethnicity, and educational background less than high school; model 2 included model 1 + white blood cell counts, C-reactive protein levels, folic acid levels, vitamin B12 levels, and systolic blood pressure (SBP); model 3 included model 2 + histories of hypertension, diabetes, heart disease, current smoking, and alcohol consumption.

## 3. Results

### 3.1. Characteristics

There were 828 individuals involved in this study. The characteristics of the participants classified by the number of insensate areas of the worse foot were illustrated in Table 1. The mean age was 69.96 ± 7.38 years, and 51.3% of the participants were male. Individuals with a higher number of insensate areas had lower DSST scores, were older, and had higher SBP than those in individuals with zero insensate areas.

### 3.2. Correlation between peripheral neuropathy and cognition

Based on the linear regression models (Table 2), the number of insensate areas were significantly negatively associated with DSST scores. The β coefficients of the DSST for model 1 to 3 were −3.208, −8.487, and −12.726, respectively, while the number of insensate areas increased after adjusting for age, gender, race/ethnicity, and educational background [95% confidence intervals (CIs), −6.244 to −0.172, −13.541 to −3.432, and −17.686 to −7.767, respectively; *P* for trend <.001]. After adjusting for additional covariates including a history of diabetes mellitus, the negative association remained, with β coefficients of −1.648, −7.573, and −12.393, respectively, while the number of insensate areas increased (95% CIs, −4.645 to 1.349, −12.517 to −2.628, and −17.241 to −7.544, respectively; *P* for trend <.001).

### 3.3. Gender and obesity differences in the relationship between peripheral neuropathy and cognition

In Table 3, gender and body mass index (BMI) were separated from the overall variables as a subgroup. Based on participants with insensate areas of the foot, we noticed that both the male or female genders showed negative associations with the DSST score; the β coefficients for models 1 to 3 were −3.742, −3.709, and −3.563, respectively, for male participants (95% CIs, −5.524 to −1.961, −5,490 to −1.927, and −5.325 to −1.802, respectively) and −4.583, −4.290, and −3.898 for female participants (95% CIs, −6.694 to −2.473, −6.383 to −2.197, and −5.973 to −1.822, respectively), with both *P* values less than .001. However, when we analyzed the BMI subgroup, only the nonobese participants showed negative correlations between insensate areas of the foot and DSST scores in models 1 to 3, with β coefficients of −5.125, −4.859, and −4.558, respectively (95% CIs, −6.697 to −3.553, −6.426 to −3.293, and −6.107 to −3.008, respectively; all *P* values <.001), whereas the obese group showed no significant associations between the insensate areas of the foot and DSST scores.

## 4. Discussion

According to our results, the severity of peripheral neuropathy is significant negatively correlated with cognitive performance in

**Table 2**

**Regression coefficients of insensate area of foot for DSST.**

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| **Variables** | **β (95% CI)** | ***P* value** | **β (95% CI)** | ***P*-value** | **β (95% CI)** | ***P* value** |
| Number of insensate area-worse foot (as the categorical variables) | −5.340 (−6.911, −3.768) | <.001 | −5.047 (−6.592, −3.502) | <.001 | −3.696 (−5.032, −2.360) | <.001 |
| Number of insensate area-worse foot (as the continuous variables) | | | | | | |
| 0 | reference | – | reference | – | reference | – |
| 1 vs 0 | −3.208 (−6.244, −0.172) | .038 | −2.149 (−5,180, 0.882) | .164 | −1.648 (−4.645, 1.349) | .281 |
| 2 vs 0 | −8.487 (−13.541, −3.432) | .001 | −7.986 (−12.992, −2.980) | .002 | −7.573 (−12.517, −2.628) | .003 |
| 3 vs 0 | −12.726 (−17.686, −7.767) | <.001 | −13.008 (−17.904, −8.112) | <.001 | −12.393 (−17.241, −7.544) | <.001 |
| *P* for trend | < .001 | | < .001 | | < .001 | |

Model 1 = Age, gender, race-ethnicity, educational background < high school. Model 2 = Model 1 + (white blood cell, C-reactive protein, total cholesterol, serum folate, vitamin B12, systolic blood pressure). Model 3 = Model 2 + (history of hypertension, diabetes mellitus, heart disease, current smoker, alcoholic consumption >12/year).

elderly individuals; even though we adjust for diabetes mellitus as a covariate, the negative association remain statistically significant. In our previous study, we found the relationship between low muscle strength of the quadriceps and cognitive impairment.[24] Emerging evidences have shown that demyelination and axonal degeneration are established hallmarks of diabetic neuropathy pathophysiology,[25] and the gradual decay of muscle intensity in type 2 diabetes patients is related to the presence and severity of diabetic peripheral neuropathy.[26] Multiple studies have demonstrated that sarcopenia in patients with diabetes is associated with peripheral neuropathy, and diabetic peripheral neuropathy may be an independent risk factor for sarcopenia.[27,28] In this study, we further provide the evidence that peripheral neuropathy is correlated with cognitive impairment.

Moreover, a growing number of epidemiological studies have linked diabetes with cognitive impairment and dementia; some have even provided information about the impact of peripheral neuropathy, and the conclusions are distinct. One cross-sectional study indicates that cognitive performance is poorer in patients with diabetes and peripheral neuropathy or elevated hemoglobin A1c levels.[29] Another retrospective cohort study including 148 participants reveals that patients with diabetes have poorer cognition, and the degeneration is not related to the severity level of diabetic peripheral neuropathy.[30] Gu et al indicates that patients with peripheral neuropathy and cognitive impairment carry a higher risk of falls compared to those with peripheral neuropathy but without cognitive impairment.[31] In a cross-sectional study including 101 participants, Tine et al discovers that a reduction in cognitive function adversely affects gait, despite the presence of peripheral neuropathy.[32] Per Lorraine et al, diabetes is associated with cognitive dysfunction, but the presence of peripheral microvascular disease does not add to cognitive decline. This result implies that cognitive impairment in diabetes may not be limited to the pathological changes of vascular system in brain.[13] However, there have been no direct discussion about the correlation between peripheral neuropathy and cognitive performance. To our best knowledge, this is the first report to propose that deteriorative peripheral neuropathy with or without diabetes confers adverse effects on cognitive function.

The mechanisms of diabetic peripheral neuropathy and dementia/cognitive impairment seem to share several similar pathophysiological aspects, including insulin dysregulation, inflammation, advanced glycation end-products, and oxidative stress.[33] In the brain, the molecular and biochemical cascades of insulin and insulin-like growth factor resistance disturb neuronal survival, energy production, gene expression, plasticity, and white matter integrity.[34] The most well-known mechanism is damage to the microvasculature. Retinopathy is a well-established microvascular complication of chronic hyperglycemia. Because retinal and cerebral arterioles have similar morphophysiological characteristics, it is believed that retinal microvascular damage may be an indicator of cerebral microvascular disease, which can impair cognitive performance.[35] Alterations in microvascular structure include vascular hypertrophy, inward vascular remodeling, and vascular rarefaction, which lead to a reduction in the oxygenated blood supply and gradual loss of normal physiological function of the host organ.[36] In our study, we find that participants with more serious peripheral neuropathy have higher SBP and worse cognitive performance. A published paper has shown that high blood pressure might accelerate the pathological changes in cerebral construction and physiological function by remodeling of vascular system, which interferes the auto-regulation and the

**Table 3**

**Regression coefficients of insensate area of foot for DSST in gender and obesity subgroup.**

| | | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|---|
| **Variables** | | **β (95% CI)** | ***P* value** | **β (95% CI)** | ***P* value** | **β (95% CI)** | ***P* value** |
| Number of insensate area | Male | −3.742 (−5.524, −1.961) | <.001 | −3.709 (−5,490, −1.927) | <.001 | −3.563 (−5.325, −1.802) | <.001 |
| | Female | −4.583 (−6.694, −2.473) | <.001 | −4.290 (−6.383, −2.197) | <.001 | −3.898 (−5.973, −1.822) | <.001 |
| | Nonobesity | −5.125 (−6.697, −3.553) | <.001 | −4.859 (−6.426, −3.293) | <.001 | −4.558 (−6.107, −3.008) | <.001 |
| | Obesity | −1.682 (−4.286, 0.923) | .205 | −1.734 (−4.365, 0.897) | .195 | −1.628 (−4.281, 1.026) | .228 |

Obesity: BMI > 30 (kg/m$^2$). Model 1 = Age, (gender), race-ethnicity, educational background < high school. Model 2 = Model 1 + (white blood cell, C-reactive protein, total cholesterol, serum folate, vitamin B12, systolic blood pressure). Model 3 = Model 2 + (history of hypertension, diabetes mellitus, heart disease, current smoker, alcoholic consumption >12/year).

cerebral circulation.[37] It is tempting to speculate that microvascular pathological changes may play an important role in explaining the association between peripheral neuropathy and cognitive impairment.

Our study finds a negative correlation between peripheral neuropathy and cognitive performance only in nonobese individuals, this correlation is not significant in obese individuals. Various studies have shown that obesity have adverse effects on cognitive function. Anthropometric measurements of obesity are also associated with reduced neural integrity, such as gray and white matter atrophy and weaker verbal and working memory, motor speed, attention, and executive functions.[38,39] Wang et al indicates that obesity might affect brain structure, the leptin/insulin physiological imbalance, oxidative free radicals, cerebrovascular function, the blood–brain barrier, and inflammation, all of which play significant roles in the degeneration of cognitive and motor functions.[40] A review article summarizes that mid-life obesity is associated with cognitive decline, but this association is not significant in late life.[41] Furthermore, a systemic review including 20 randomized control trials that reveals that purposeful weight loss among obese/overweight individuals is related to advancements in performance across diverse cognitive domains (memory, attention, executive functions, language, and motor speed).[42] Horie et al points out that intentional weight loss through dieting is associated with cognitive improvement in obese elderly individuals with MCI.[43] In summary, this study additionally finds the negative correlation between peripheral neuropathy and cognitive performance only exists in the nonobese group.

Our study has some limitations. First, the NHANES dataset is the result of a cross-sectional assessment that evaluates DSST scores and the severity of peripheral neuropathy at a single time point. Hence, longitudinal repeated interactions between cognitive function and peripheral neuropathy are not available. Next, the NHANES database is composed of US citizens; thus, our findings may not appropriately apply to other ethnicities. Furthermore, some of the covariates such as a history of diabetes or other chronic diseases are obtained by self-report questionnaires, which may be influenced by the bias of human factors. Finally, the test to diagnose peripheral neuropathy is a monofilament examination in the NHANES dataset, which is based on the subjective responses of all participants during the examination. The nerve conduct velocity test may have been a better substitute examination because of its objectiveness, which may have helped reduce the interference of human factors.

## 5. Conclusions

Our study emphasize that the severity of peripheral neuropathy has a significantly negative association with cognitive performance in elderly individuals. In the future, more studies are required to investigate whether the examination to detect peripheral neuropathy can directly predict the risk of cognitive impairment, which may help us connect the damage of peripheral nerve system with the dysfunction of central nerve system.

## Author contributions

**Conceptualization:** Wei-Liang Chen.
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