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RESEARCH ARTICLE

Associations of Lower Extremity Peripheral Nerve Impairment and Risk of Dementia in Black and White Older Adults

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Abstract

Background and Objectives

Peripheral nerve impairments and dementia are common among older adults and share risk factors. However, few studies have examined whether peripheral nerve function and dementia are associated. We evaluated whether lower extremity peripheral nerve impairments were associated with higher incidence of dementia and whether associations differed by comorbidity subgroups (diabetes, low vitamin B_{12}, and *APOE* ε4 allele carriers).

Methods

We studied Black and White Health, Aging, and Body Composition Study participants 70 to 79 years of age and without dementia at enrollment. Lower extremity sensory and motor peripheral nerve function was measured at year 4 (the analytic baseline of this study). Sensory nerve impairments were measured with monofilament (1.4 g, 10 g) and vibration threshold of the toe. Monofilament insensitivity was defined as unable to detect monofilament (3 of 4 touches), and vibration detection impairment was defined as >130 μm. Fibular motor impairments were defined as <1 mV compound motor action potential (CMAP) amplitude and slow nerve conduction velocity <40 m/s. Incident dementia over the following 11 years was determined from medical records, cognitive scores, and medications. Cox proportional hazard models adjusted for demographics and health conditions assessed associations of nerve impairments with incident dementia.

Results

Among 2,174 participants (52% women, 35% Black), 45% could not detect monofilament 1.4 g, 9% could not detect monofilament 10 g, 6% could not feel vibration, 10% had low CMAP amplitude, and 24% had slow conduction velocity. Monofilament 10 g (hazard ratio [HR] 1.35, 95% CI 0.99–1.84) and vibration detection insensitivity (HR 1.73, 95% CI 1.24–2.40) were associated/borderline associated with a higher risk of dementia after covariate adjustment. Estimates were elevated but not significant for monofilament 1.4 g, CMAP amplitude, and conduction velocity ($p > 0.05$). Increasing number of peripheral nerve impairments was associated with higher risk of dementia in a graded fashion; for ≥3 impairments, the HR was 2.37 (95% CI 1.29–4.38). In subgroup analyses, effect estimates were generally higher among those with diabetes, low vitamin B_{12}, and *APOE* ε4 allele except for vibration detection.

Discussion

Peripheral nerve impairments, especially sensory, were associated with a higher risk of dementia even after adjustment for age and other health factors. These associations may represent a shared susceptibility to nervous system degeneration.

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Editorial
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From the Departments of Psychiatry and Behavioral Sciences (W.D.B., K.Y.), Epidemiology (W.D.B., K.Y.), Biostatistics (W.D.B., K.Y.), and Neurology (K.Y.), University of California San Francisco, San Francisco; Department of Neurology (N.M.R.), Geisel School of Medicine, Dartmouth, Hannover, NH; Department of Epidemiology (E.S.S.), University of Pittsburgh, PA; and San Francisco VA Medical Center (K.Y.), CA.

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Glossary

AD = Alzheimer disease; **CMAP** = compound motor action potential; **CV** = conduction velocity; **HbA1c** = hemoglobin A1c; **Health ABC** = Health, Aging, and Body Composition; **HR** = hazard ratio; **3 MS** = Modified Mini-Mental State Examination.

Lower extremity peripheral nerve impairments are common among older adults[1] and are associated with physical limitations and an increased risk of mortality.[1-3] Sensory peripheral nerve function (e.g., touch) may be impaired in up to 50% of older adults.[4] Preliminary evidence suggests that peripheral nerve impairments may also be more common in those with cognitive impairment.[5,6] Peripheral nerve impairments and dementia share risk factors, including age, diabetes, and vascular disease. Despite this, few studies have rigorously evaluated whether sensory or motor peripheral nerve function is associated with incident dementia.

Identifying an association between peripheral nerve impairment and dementia could inform clinical care and management of patients with dementia or peripheral neuropathy and help identify patients at particularly high risk of poor health outcomes. Such work is also important because it could help uncover shared mechanisms of peripheral and central neurodegeneration. A number of chronic conditions affect peripheral nerve function, including diabetes, vascular disease, vitamin B_{12} deficiency, and kidney disease.[2,7-9] Poor peripheral nerve function may also lead to poor physical function and mobility independently of chronic health conditions.[1-3] These comorbid conditions and consequences are also commonly associated with dementia.[10-13] One small study suggests that peripheral neuropathy in the context of diabetes is not associated with dementia risk.[14] However, data are limited on the association between peripheral nerve impairments and risk of dementia in the general older adult population and other comorbidity subgroups.

Here, we investigated whether lower extremity peripheral nerve impairments were associated with risk of developing dementia in Black and White older adults. We examined measures of lower extremity peripheral sensory and motor nerve function that have previously been associated with worse physical function and disability.[1-3] We also examined whether associations differed across 3 risk factors that differed on the basis of pathophysiology: comorbid diabetes status, low vitamin B_{12}, and *APOE* ε4 allele.[2,7,8]

Methods

Study Population

Health, Aging, and Body Composition (Health ABC) is a longitudinal cohort study of Black and White older adults, described in more detail eslewhere.[15] Briefly, 3,075 participants 70 to 79 years of age at enrollment were recruited in 1997 to 1998 from a random sample of White age-eligible Medicare beneficiaries and all Black age-eligible Medicare beneficiaries living within selected zip codes in Pittsburgh, PA, and Memphis, TN. Participants were excluded for several reasons: if they reported difficulty walking ¼ mile, climbing 10 stairs, or conducting activities of daily living; if they had active cancer treatment; and if they planned to move from the study area in the next 3 years. No other exclusions were made, but participants were generally healthy at baseline. Participants were followed up with approximately annual or biannual clinical examinations up to year 11, 6-month phone calls, and medical records review for major incident health events for up to 16 years.

Our current analysis focused on the 2,174 Health ABC participants who had at least 1 valid measure of peripheral sensory or motor nerve function, were without prevalent dementia in year 4, and had at least 1 additional follow-up visit.

Standard Protocol Approvals, Registrations, and Patient Consents

Health ABC was approved by the institutional review boards at each clinical site and the study coordinating center. All participants gave signed informed consent.

Peripheral Nerve Impairments

Peripheral nerve function was assessed as lower extremity sensory and motor nerve function measured by a trained examiner at the year 4 examination[16]; measures, cut points, and terminology were defined according to prior research on peripheral nerve impairments and poor health outcomes Health ABC.[1,3,7,8,17,18]

Sensory nerve function was measured with the vibration detection threshold in microns on the bottom of the large toe with a VSA-3000 Vibratory Sensory Analyzer (Medoc, Ramat Yishai, Israel), and monofilament was tested with a standard 10-g and light 1.4-g monofilament.[19] Fibular compound motor action potential (CMAP) amplitude was measured in millivolts, recording over the extensor digitorum brevis muscle and stimulating at the popliteal fossa, fibular head, and ankle with the NeuroMax 8 (XLTEK, Oakville, Ontario, Canada).[16,19] Nerve conduction velocity (CV) was measured in meters per second after measurement of distances.

We defined impairment in each measure on the basis of prior Health ABC studies of clinically meaningful impairments.[1,3,7,16,18] Sensory nerve impairments were defined as vibration detection threshold of >130 μm or inability to detect 3 of 4 touches with monofilament. Motor nerve impairment was defined as <1-mV fibular CMAP amplitude stimulating at the ankle and <40-m/s CV between popliteal fossa and fibular head. We examined each

measure separately in primary analyses. We also examined overlap of impairments, first by categorizing impairments as sensory only (vibration detection or monofilament impairment), motor nerve impairment only (amplitude and CV), or both sensory and motor nerve impairments. Second, we summed the number of impairments (0, 1, 2, or ≥3).

Incident Dementia

Dementia was determined through a combination of criteria established previously in Health ABC and described elsewhere in detail.[20,21] Briefly, dementia was defined as meeting 1 or more of the following: (1) recorded hospitalization with dementia as a primary or secondary diagnosis; (2) self-reported hospital admissions collected every 6 months, hospital records reviewed for a primary or secondary dementia diagnosis, and dementia medications collected at annual visits (Modified Mini-Mental State Examination[22] [3 MS] was administered in years 1, 3, 5, 8, 10, and 11; 3 MS decline of >1.5 SDs from baseline race-stratified mean); or (3) documented use of prescribed dementia medication. Most cases were based on hospitalizations either alone (40%) or in combination with other sources (36%); date of diagnosis was defined as the first date at which the participant met at least 1 of the above criteria.

Other Clinical Characteristics

Sex, race, and educational attainment were self-reported and recorded at study baseline. History of health conditions was assessed cumulatively through year 4 and defined on the basis of a combination of participant interview, medical record review, medications, and baseline laboratory values. These included diabetes, cardiovascular disease (myocardial infraction, congestive heart failure, etc.), cerebrovascular disease (stroke, TIA), hypertension, and history of cancer that was not active at time of enrollment (as a proxy for cancer treatment/drugs that may cause peripheral nerve impairments[23]). Additional clinical factors measured at year 4 included age, ankle-brachial index (for peripheral arterial disease), depressive symptoms (Center for Epidemiologic Studies Depression Short Form),[24] and body mass index, calculated as height and weight (kilograms per meter squared). Biological assays were obtained at year 4 unless otherwise noted and included renal function (cystatin-C, milligrams per deciliter), vitamin B_{12} levels (<260 pmol/L defined as low), thyroid-stimulating hormone (measured in year 2), hemoglobin A1c (HbA1c) as a proxy for severity of diabetes, and inflammation (C-reactive protein). *APOE* genotype was assessed with serum assay; *APOE* ε4 allele status was defined as ≥1 ε4 allele vs none. Participants were also asked about alcohol consumption and smoking. Alcohol consumption was assessed at year 1 only; frequent alcohol consumption (yes, no) was defined as >1 drink per day. We categorized smoking status at year 4 as never, current, or former.

Statistical Analyses

We used multivariable Cox proportional hazard models to assess the relationship between peripheral nerve impairments and time to dementia diagnosis. We included each peripheral nerve impairment measure as the primary predictor separately. Participants were followed up from year 4 (study baseline) until dementia diagnosis; participants who did not develop dementia were followed up until death, dropout, or year 15. For each outcome, we ran 3 models with increasing adjustment for covariates. The first model included demographics; the second model (our primary model) additionally included cardiometabolic conditions and health behaviors; and the third model had additional adjustment for cancer/cancer treatment history, biological assays, *APOE* ε4 allele, and baseline cognition (3 MS score from year 3).

We conducted several sensitivity and exploratory analyses. We reran models for sensory peripheral nerve impairments excluding participants with CMAP amplitude <1 mV to parse out whether individuals with significant neuropathy drove the results. Participants missing peripheral nerve or other measurements who were excluded from the analytic sample were older on average and more likely to be Black and to have comorbid health conditions than those included in analyses ($p < 0.05$). To account for these differences and to generalize results to the full Health ABC sample, we reran our primary model using inverse probability weights for missing data or study exclusion.[25] First, we used a logistic regression with demographics and dementia status as predictors of missing data/study exclusion; next, weights were calculated as the inverse of predicted values of this regression and included in our primary model (model 2). We calculated 95% CIs from 1,000 bootstrapped replications.[26]

To explore potential pathologic mechanisms and important comorbidity subgroups, we examined models stratified by several conditions associated with either peripheral neuropathy (diabetes, low vitamin B_{12}) or dementia (*APOE* ε4 allele carriers) and a reference group without these conditions. These were chosen because of their divergent etiologic relationship with peripheral nerve impairment or dementia, as well as sample size considerations for subgroup testing. We limited these analyses to sensory and motor peripheral nerve impairments that were significantly (or borderline) associated with risk of dementia in primary models. Last, we explored associations between multiple peripheral nerve impairments and risk of dementia to see whether having multiple impairments was associated with higher risk of dementia than a single impairment alone.

All tests were 2 sided with $\alpha = 0.05$; we report 95% CIs. Analyses were conducted in R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria).

Data Availability

Health ABC data are available for approved research proposals.[27]

Results

There were 2,174 participants with at least 1 peripheral nerve function test. Prevalence of sensory and motor peripheral nerve impairments ranged from ≈6% to 24% (Table 1): nearly

Table 1 Prevalence of Nerve Impairments by Diabetes Status

Nerve impairment	Nonmissing, n	No. (%)
Sensory		
Monofilament 1.4 g	2,077	977 (45.3)
Monofilament 10 g	2,073	182 (8.5)
Vibration detection	2,040	126 (5.9)
Motor		
Amplitude <1 mV	1,894	197 (10.4)
Velocity <40 m/s	1,607	391 (23.6)

half (45%) could not detect monofilament 1.4 g; 9% could not detect monofilament 10 g; 6% could not feel vibration; 10% had low-amplitude CMAP; and 24% had slow CV. Of the 1,647 participants who had completed sensory and motor nerve function tests, 35% had 1 impairment, and 15% had multiple impairments. In terms of more moderate/severe peripheral nerve impairments, 6% had only sensory peripheral nerve impairments (of monofilament 10 g or vibration detection), 12% had only motor peripheral nerve impairments (amplitude or CV), and 4% had both sensory and motor peripheral nerve impairments. Nerve function tests were mild to moderately correlated with each other (Pearson correlation range 0.08–0.36, all $p < 0.001$, χ^2 test).

Those with sensory or motor peripheral nerve impairments tended to be older and more likely male, to have less than high school education, to have more comorbid conditions, and to have a lower prevalence of the *APOE* ε4 allele (Table 2). Trends were relatively similar when we examined sensory and motor nerve impairments separately: those with monofilament 1.4 g impairment only (mild sensory impairment) were similar to those without impairments except for a higher prevalence of low vitamin B_{12} (eTable 1, links.lww.com/WNL/B876). Participants with motor peripheral nerve impairments were more similar in age to those without motor impairments, but trends were otherwise similar to those with sensory impairments (eTable 2, links.lww.com/WNL/B876).

In multivariate analyses, sensory peripheral nerve impairments were associated with risk of dementia, and borderline associations were noted with CV but not amplitude (Table 3). In adjusted models, impairment in monofilament 1.4 g detection was borderline significantly associated with a 17% higher risk of dementia (hazard ratio [HR] 1.17, 95% CI 0.97–1.42), monofilament 10 g was borderline associated with a 35% higher risk of dementia (HR 1.35, 95% CI 0.99–1.84), and vibration detection impairment was associated with close to 73% higher risk of developing dementia (HR 1.73, 95% CI 1.24–2.40). CMAP impairment was not associated with increased risk of dementia (HR 1.09, 95% CI 0.78–1.52), but slow CV was borderline associated (HR 1.18, 95% CI 0.91–1.54). These associations remained similar in additional models even after additional inclusion of cancer history/treatment, biomarkers (vitamin B_{12} levels, cystatin-C, C-reactive protein, thyroid-stimulating hormone, HbA1c, and *APOE* ε4 allele), and baseline cognition (Table 3). Results for sensory tests were similar after exclusion of those with impaired CMAP (data not shown). There were no significant interactions by sex or race (all $p > 0.05$). Model findings remained similar after inclusion of inverse probability weights to account for missing data and potential selection bias into the analytic sample (eTable 3, links.lww.com/WNL/B876).

We further examined the strongest associations in sensory and motor impairments (monofilament 10 g, vibration detection, and CV) among several comorbidity subgroups (those with diabetes, low vitamin B_{12}, and *APOE* ε4 allele and a reference

Table 2 Characteristics of Participants With and Without Peripheral Nerve Impairments

	No impairments	Sensory or motor impairment
No.	1,529	645
Age, mean (SD), y	76.4 (2.8)	76.8 (2.9)
Female, n (%)	908 (59.4)	224 (34.7)
Black, n (%)	587 (38.4)	202 (31.3)
High school graduate, n (%)	1,232 (80.6)	482 (74.7)
Body mass index, kg/m^2	27.5 (4.7)	27.0 (4.7)
Hypertension, n (%)	1,199 (78.4)	530 (82.2)
Cardiovascular disease, n (%)	326 (21.3)	168 (26.0)
Ankle-brachial index <0.9, n (%)	225 (15.2)	108 (17.6)
Diabetes, n (%)	524 (34.3)	284 (44.0)
Stroke, n (%)	226 (14.8)	133 (20.6)
Cancer, n (%)	581 (38.0)	236 (36.6)
Low vitamin B_{12}, n (%)	244 (16.7)	111 (18.1)
Cystatin-C, mg/L, mean (SD)	0.9 (0.2)	1.0 (0.3)
C-reactive protein, μg/mL, mean (SD)	0.9 (0.2)	1.0 (0.3)
High thyroid-stimulating hormone, n (%)	196 (13.0)	83 (13.1)
***APOE* ε4 allele, n (%)**	412 (28.5)	150 (24.7)
Current smoker, n (%)	113 (7.4)	36 (5.6)
Frequent drinking (>1/d), n (%)	113 (7.4)	52 (8.1)
Depressive symptoms, mean (SD), n (%)	282 (18.4)	115 (17.8)
Sedentary (0 walking/wk), n (%)	282 (18.4)	115 (17.8)

Values are mean ± SD when appropriate. Missing data: vitamin B_{12} levels n = 98, cystatin-C n = 53, C-reactive protein n = 70, thyroid-stimulating hormone n = 36, *APOE* genotype n = 121.

Table 3 Association of Sensory and Motor Peripheral Nerve Impairments With Dementia Incidence

Peripheral nerve impairment	HR (95% CI)		
	Model 1[a]	Model 2[b]	Model 3[c]
Sensory			
1.4-g monofilament	1.20 (0.83–1.45)	1.17 (0.97–1.42)	1.08 (0.87–1.34)
10-g monofilament	1.36 (1.00–1.86)	1.35 (0.99–1.84)	1.39 (0.97–1.99)
Vibration detection	1.80 (1.30–2.50)	1.73 (1.24–2.40)	1.94 (1.31–2.86)
Motor			
Amplitude	1.08 (0.77–1.52)	1.09 (0.78–1.52)	1.15 (0.78–1.68)
Velocity	1.21 (0.93–1.57)	1.18 (0.91–1.54)	1.25 (0.91–1.70)

[a] Model adjusted for age, race, sex, and education.
[b] Demographic-adjusted model + hypertension, diabetes, cardiovascular disease, cerebrovascular disease, smoking status, alcohol use, sedentary lifestyle, and depressive symptoms.
[c] Demographic-adjusted model + hypertension, diabetes, cardiovascular disease, cerebrovascular disease, smoking status, alcohol use, sedentary lifestyle, depressive symptoms, cancer history, cystatin-C, C-reactive protein, hemoglobin A1c, thyroid-stimulating hormone, *APOE* ε4 allele status, and baseline cognition.

group with no conditions). Although CIs were wider given smaller sample sizes, the estimated associations tended to be higher (10%–50%) for those with diabetes, low vitamin B_{12}, or the *APOE* ε4 allele for 10-g monofilament and CV impairment. Associations for vibration detection threshold fit a different pattern whereby the highest estimated association with dementia was among the no comorbidity reference group, followed by those with *APOE* ε4 allele and diabetes. Estimates were not elevated for low vitamin B_{12} (Table 4).

When sensory and motor impairments were categorized jointly, the number of impairments was associated with increased risk of dementia in a graded fashion (Figure). Those with 1 impairment had an HR of 1.14 (95% CI 0.85–1.53); those with 2 impairments had an HR of 1.48 (95% CI 1.03–2.13); and individuals with ≥3 impairments had an HR of 2.37 (95% CI 1.29–4.38). The largest estimated associations with dementia were for sensory nerve impairments with or without co-occurring motor nerve impairment, although sensory + motor impairments had the lowest dementia-free survival (Figure): HR for sensory alone was 1.43 (95% CI 0.89–2.30), for sensory + motor was 1.92 (95% CI 1.29–2.88), and for motor alone was 1.10 (95% CI 0.83–1.45).

Discussion

Impairments in monofilament and vibration detection were common and independently associated with incident dementia in this large population of healthy older adults. Although motor nerve impairments were not significantly associated with dementia risk, slow CV estimates were elevated and borderline significant, especially among those with diabetes. When sensory and motor nerve impairments were combined, an increasing number of impairments were associated in a step-wise fashion and with up to a 2.4 times higher risk of dementia compared to no impairments. Combined sensory and motor impairments were associated with a nearly 2 times higher risk of dementia compared to no impairments, and sensory nerve impairments alone were associated with a 1.4 times higher risk of dementia. Stratified models showed 10% to 50% stronger associations between monofilament and CV impairments and dementia in those with diabetes, low vitamin B_{12}, and *APOE* ε4 allele. However, an inability to detect vibration remained associated with higher risk of dementia even in participants without those comorbid conditions. These findings suggest that older adults with lower extremity peripheral nerve function loss, particularly sensory impairments, may be at elevated risk for dementia. These associations also suggest that individuals who develop dementia may be more likely to have peripheral nerve impairments, a potentially important issue for patients with mild cognitive impairment or dementia because peripheral nerve impairments may exacerbate mobility issues and risk for falls.

Few studies have examined the association between peripheral nerve function and dementia risk, although there is substantial evidence that links other aspects of sensorimotor function to dementia.[12,20,21,28-33] Several small studies have shown that patients with Alzheimer disease (AD) and mild cognitive impairment have worse tactile discrimination, fine motor control, peripheral nerve CMAP amplitudes, and vibration detection than cognitive normal older adults.[5,6,34,35] In prior work, we found mixed evidence for an association with sensory peripheral nerve measures in the context of multisensory impairment,[30,36] and another study found no associations with peripheral neuropathies and cognitive decline in those with diabetes.[14] This current study clarifies and extends findings across multiple measures of sensory and motor nerve impairments by including robust adjustment for potential explanatory clinical factors and by evaluating for differences by comorbidity subgroups.

Table 4 Association of Peripheral Nerve Impairments With Dementia Incidence by Comorbidity Subgroups[a]

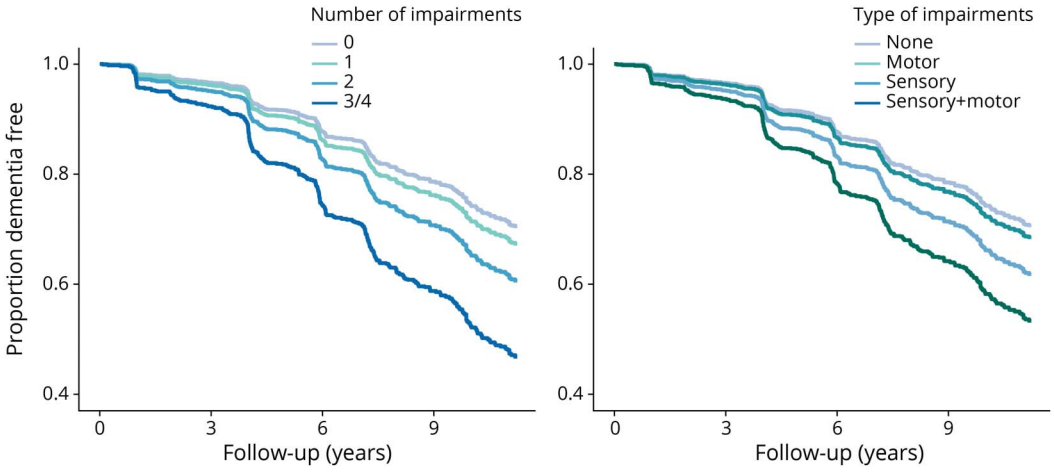
	Diabetes		Low vitamin B_{12}		*APOE* ε4 allele		No diabetes, normal B_{12}, no *APOE* ε4	
Peripheral nerve impairment	**No.**	**HR (95% CI)**	**No.**	**HR (95% CI)**	**No.**	**HR (95% CI)**	**No.**	**HR (95% CI)**
Sensory								
10-g monofilament	801	1.56 (1.02–2.37)	350	2.07 (0.90–4.73)	555	1.70 (0.95–3.04)	728	0.89 (0.41–1.96)
Vibration detection	791	1.59 (0.94–2.68)	346	1.02 (0.45–2.32)	550	1.74 (0.86–3.40)	712	1.95 (1.07–3.55)
Motor								
Velocity	587	1.48 (0.99–2.19)	263	1.64 (0.87–3.08)	418	1.29 (0.76–2.19)	588	1.07 (0.62–1.84)

[a]Based on models adjusted for age, race, sex, and education, hypertension, diabetes (for nondiabetes models), cardiovascular disease, cerebrovascular disease, smoking status, alcohol use, sedentary lifestyle, and depressive symptoms.

We found relatively consistent associations between sensory nerve impairments and dementia, regardless of covariate adjustments or stratification. The finding that the relationship between some peripheral nerve impairments (monofilament and CV) and dementia is stronger in those with diabetes may suggest that peripheral sensory impairments capture disease severity or susceptibility to cognitive decline not captured by other measures such as HbA1c. Although estimates were also elevated for individuals with low B_{12}, we did not find significant associations with peripheral nerve impairments and dementia, perhaps because of the small sample size and lack of measures of other vitamin B deficiencies. Deficiencies in vitamins B_{12}, B_9, and B_6 cause elevated homocysteine levels that may contribute to epigenetic factors, including effects on DNA methylation, which may increase dementia and AD risk[37] and worsen peripheral nerve function.[9,38] Vitamin B supplementation has successfully slowed cognitive decline and brain atrophy in individuals with mild cognitive impairment[39,40] and may have important implications for preventing dementia in individuals with peripheral neuropathy. Similarly, associations for *APOE* ε4 allele carriers were elevated but not significant, possibly due to the smaller sample. Associations remained for vibration detection impairment even among the low-comorbidity reference group, suggesting that the association between peripheral nerve impairments and dementia is not just due to comorbid risk factors.

The mechanisms linking peripheral nerve function and dementia are unclear but could reflect common upstream pathogenic factors such as inflammation, oxidative stress, cellular aging, genetics, epigenetic, or neurodegenerative factors. Nutritional deficiencies and medication or toxins were not completely measured in this study and may also help explain the association between peripheral nerve impairment and dementia,[23,37] as might gut-microbiome differences and the gut-brain axis.[41] Future work to identify the underlying

Figure Estimated Proportion Dementia-Free by Number Associated With Number and Type of Peripheral Nerve Impairments



Adjusted for demographics, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, smoking status, alcohol use, sedentary lifestyle, and depressive symptoms.

and cellular mechanisms that drive this association may provide new insights into shared susceptibilities of the central and peripheral nervous systems. Peripheral nerve impairments may also be associated with dementia through effects on mobility, underlying frailty, or impaired central sensory processing. Peripheral nerve impairments are independently associated with poorer quadriceps and muscle strength,[3,42] worse lower extremity physical function,[1,18,43,44] and mobility disability.[2,7] Poor physical functioning and mobility (key aspects of physical frailty) are in turn strong predictors of accelerated cognitive decline, cognitive frailty, and increased risk of dementia.[12,28,45] It is possible that peripheral nerve impairments contribute to and are influenced by physical frailty, thus increasing risk for cognitive frailty and in turn dementia.

Alternatively, these associations may indicate shared underlying neurodegeneration. Peripheral neuropathy sensory loss in aging follows a typical pattern (distal, bilateral, and symmetrical) due to loss of energy production in the cell bodies of the dorsal root ganglia.[46] Although common dementias such as AD have not been found to substantially affect the peripheral nervous system,[47] neurodegenerative protein deposits have been found in dorsal root ganglia.[48] This suggests that the neurogenerative processes occurring in the CNS are also occurring in the peripheral nervous system. AD-related neurodegeneration may also impair sensory processing pathways in the brain. Our sensory nerve tests were not pure nerve function tests because they incorporated sensory processing as well, which may be impaired before dementia diagnosis. However, adjustment for baseline cognitive function did not substantially attenuate this association, as would be expected if our findings were due to cognitive decline. Future studies should examine the extent to which perceptual (or central) impairments may contribute to this association. The overlap between peripheral and CNS functional decline is understudied, and our findings highlight a need for future research to clarify potential associations, underlying mechanisms, and treatment implications.

There are some important limitations in this study. Peripheral nerve function was measured only in the lower extremity of 1 limb and at 1 time point in these analyses. Future studies should examine whether findings differ if sensory and motor nerve impairments are measured on all limbs and whether changes in function over time predict dementia risk. We did not have information on whether peripheral nerve impairments were drug induced. To partly mitigate this, we included adjustment for cancer history because chemotherapy is a common cause of peripheral neuropathy. We also did not have other measures for vitamin B_{12} and related deficiencies such as homocysteine levels or more detail on upstream biological mechanisms. Future studies will be needed to determine the contribution of medications, genetics, the gut-brain axis, cellular aging, and immunologic function to this association. There may be important differences by subtype of peripheral nerve impairment, location and mechanisms of injury, and duration, which were not assessed. Dementia was based on a set of previously established criteria but was not a clinical diagnosis. Together, these measurement issues may have led to misclassification of some participants, biasing estimates likely toward the null. More missing data existed for motor nerve tests, which may have reduced our power to detect associations: effect estimates for CV impairment were borderline significant, but CIs were wider. Missing data also could lead to a biased analytic sample; however, we conducted additional sensitive analyses to account for potential selection bias due to missing data or analysis exclusion, and estimates were very similar to our primary models. Health ABC participants identified as Black or White; therefore, our findings may not apply to other racial/ethnic groups not studied in this cohort. In addition, due to enrollment criteria, participants were generally healthier than the general population of older adults at enrollment,[36] so these findings may not be generalizable to a broader population of Black and White women and men. However, it is also possible that these associations could be stronger in a sample with a greater range in health status.

Despite these limitations, the strengths of this study should be emphasized. This is among the largest prospective studies to include peripheral nerve measurements in older adults. We followed up a cohort of Black and White men and women for >10 years, used multiple objective measures for peripheral nerve impairments, had older adults both with and without diabetes, and examined both sensory and motor tests. We examined combined effects of sensory and motor nerve impairments on risk of dementia. We also used an established definition of all-cause dementia based on multiple criteria and sources; including criteria based on both in-person cognitive tests and report of medications and hospitalizations likely reduces potential for bias due to loss of follow-up of participants developing dementia.[49] We also included robust adjustments for shared risk factors and conducted exploratory analyses to examine whether associations differed by important subgroups.

Lower extremity peripheral nerve impairments were associated with up to 2.4 times higher risk of dementia in Black and White older adults in this study. These associations have implications for clinical care and management. Patients with poor sensory peripheral nerve function, in particular, may be a high-risk subgroup for dementia, especially if they have co-occurring risk factors such as diabetes, low vitamin B_{12}, and the *APOE* ε4 allele. However, individuals with poor vibration detection may also be at higher risk of dementia even without other risk factors. Likewise, individuals living with mild cognitive impairment or dementia may benefit from basic screenings for peripheral nerve impairments because co-occurring peripheral nerve impairments could exacerbate functional limitations, frailty, and risk of falls. Future studies are needed to clarify the association between motor nerve function and dementia in larger samples and to investigate the underlying mechanisms. This work highlights an intriguing but underappreciated link between the peripheral nervous system and dementia.

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Disclosure

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