

The Relationship of Reduced Peripheral Nerve Function and Diabetes With Physical Performance in Older White and Black Adults

The Health, Aging, and Body Composition (Health ABC) Study

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diabetic and nondiabetic adults. The impact of peripheral nerve function on incident disability should be evaluated in older adults.

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OBJECTIVE — Poor peripheral nerve function is prevalent in diabetes and older populations, and it has great potential to contribute to poor physical performance.

RESEARCH DESIGN AND METHODS — Cross-sectional analyses were done for the Health, Aging, and Body Composition (Health ABC) Study participants ($n = 2,364$; 48% men; 38% black; aged 73–82 years). Sensory and motor peripheral nerve function in legs/feet was assessed by 10- and 1.4-g monofilament perception, vibration detection, and peroneal motor nerve conduction amplitude and velocity. The Health ABC lower-extremity performance battery was a supplemented version of the Established Populations for the Epidemiologic Studies of the Elderly battery (chair stands, standing balance, and 6-m walk), adding increased stand duration, single foot stand, and narrow walk.

RESULTS — Diabetic participants had fewer chair stands (0.34 vs. 0.36 stands/s), shorter standing balance time (0.69 vs. 0.75 ratio), slower usual walking speed (1.11 vs. 1.14 m/s), slower narrow walking speed (0.80 vs. 0.90 m/s), and lower performance battery score (6.43 vs. 6.93) (all $P < 0.05$). Peripheral nerve function was associated with each physical performance measure independently. After addition of peripheral nerve function in fully adjusted models, diabetes remained significantly related to a lower performance battery score and slower narrow walking speed but not to chair stands, standing balance, or usual walking speed.

CONCLUSIONS — Poor peripheral nerve function accounts for a portion of worse physical performance in diabetes and may be directly associated with physical performance in older

Diabetes is associated with self-reported and objective physical performance measures of functional limitation in U.S. adults (1). Poor peripheral nerve function may play a role in reduced physical function in older diabetic adults (2,3). The incidence (4) and prevalence of poor peripheral nerve function are higher in older adults, even among those without diabetes (4–7). In the U.S. for 1999–2000, 28% of adults aged 70–79 years and 35% of adults aged ≥ 80 years had peripheral neuropathy based on a simple screen for reduced sensation at the foot (7). We previously found that diabetes was associated with subclinical functional limitation and physical performance in our cohort, although peripheral nerve function measures were not completed then (8).

To our knowledge, the relationship of combined sensory and motor peripheral nerve function to objective physical performance has not been investigated in ambulatory, community-dwelling older adults. We evaluated the distribution of sensory and motor peripheral nerve function in older diabetic and nondiabetic adults and the relationship of peripheral nerve function to objective physical performance. We hypothesized that sensory and motor peripheral nerve function explained the relationship of poor physical performance in an older community-based population, both with and without diabetes.

RESEARCH DESIGN AND METHODS

Participants were from well-functioning older white and black adults ($n = 3,075$; 48.4% male; 41.6% black), aged 70–79 years at the 1997–1998 baseline examination, in the Health,

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Table 1—Descriptive characteristics by diabetes status and sex

	Men		Women	
	Diabetes	No diabetes	Diabetes	No diabetes
<i>n</i>	273	869	210	1,012
Age (years)	76.8 ± 2.7	76.7 ± 2.9	76.1 ± 2.8	76.5 ± 2.9
Black race (%)	41.0*	31.0	65.7†	37.8
Diabetes duration (years)	11.3 ± 11.1	—	11.0 ± 11.2	—
Diabetes duration >5 years (%)	54.8	—	55.4	—
A1C (%)	7.1 ± 1.4†	5.3 ± 0.4	7.1 ± 1.5†	5.4 ± 0.4
A1C ≥7% (%)	45.1†	0.3	45.7†	0.3
Lifestyle characteristics				
Current smoker (%)	5.4	7.3	6.5	7.2
Drinking frequency >1/week (%)	59.6	61.7	26.7†	47.6
Physical activity (kcal · kg ⁻¹ · week ⁻¹)	2.0*	3.4	0.5†	1.8
Body composition and physical ability				
Height (cm)	173.1 ± 6.6	172.6 ± 6.7	159.1 ± 5.2	158.8 ± 63.4
BMI (kg/m ²)	28.2 ± 4.0†	26.8 ± 4.0	30.0 ± 5.5†	27.2 ± 5.3
Bone free lean mass (kg)	56.7 ± 7.4†	53.5 ± 6.7	42.6 ± 6.3†	38.7 ± 5.5
Total fat mass (kg)	25.7 ± 7.8†	23.3 ± 7.1	30.7 ± 9.0†	27.5 ± 9.0
Quadriceps strength (Nm)	113.5 ± 31.1*	118.4 ± 31.7	75.6 ± 22.7	72.8 ± 20.8
Recurrent falls in past year (%)	9.2	7.4	11.0	8.0
Comorbidities				
Cardiovascular disease history (%)	25.5	22.1	19.6†	10.4
Cerebrovascular disease history (%)	8.2	6.0	7.2	6.9
Peripheral arterial disease history (%)	7.6	4.9	4.5	3.1
Ankle-arm index <0.9 (%)	23.7†	14.4	24.7†	14.6
Hypertension (%)	78.0*	69.4	83.8†	73.0
Systolic blood pressure (mmHg)	140.2 ± 21.4	138.3 ± 20.5	145.5 ± 23.8	142.1 ± 21.8
Diastolic blood pressure (mmHg)	73.4 ± 11.3	75.0 ± 10.7	73.1 ± 11.2	74.0 ± 11.4
Cholesterol (mg/dl)	177.9 ± 36.7*	181.6 ± 31.6	198.5 ± 38.8	202.8 ± 38.3
Retinal disease/retinopathy (%)	6.6	6.9	9.0	6.1
Glaucoma (%)	15.8	12.0	22.1†	9.7
Cataracts (%)	44.2	39.7	58.0	53.6
Cystatin-C (mg/l)	1.1 ± 0.3*	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.2
Creatinine ≥1.5 men/1.3 women (%)	12.2*	7.2	9.3†	3.2
CES-D depression index	6.3 ± 6.1*	5.4 ± 5.8	8.3 ± 7.2*	6.9 ± 6.7
Knee pain, most days/month (%)	23.4*	15.9	22.9	23.6
Osteoarthritis (%)	7.0	8.3	7.7	12.3

Data are means ± SD for continuous values and medians for those with large ranges. **P* ≤ 0.05; †*P* ≤ 0.001 for diabetic vs. nondiabetic participants within sex groups.

Aging, and Body Composition (Health ABC) Study, with a follow-up examination in 2000–2001. Health ABC is an ongoing prospective cohort study investigating changes in body composition as a common pathway by which multiple diseases contribute to disability. Participants were recruited from mailings in Pittsburgh, Pennsylvania, and Memphis, Tennessee, to 1) a random sample of white Medicare beneficiaries and 2) all age-eligible black community residents. A telephone interview determined eligibility, defined as no difficulty in walking a quarter of a mile (400 m), climbing 10 steps, or performing activities of daily living; free of life-threatening cancers with no active treatment within the past 3

years; and planning to remain within the study area for ≥3 years. Participants provided informed consent before examinations, approved by institutional review boards at the University of Pittsburgh and the University of Tennessee Health Science Center. Of 3,075 participants at baseline, 2,479 of 2,493 (99.4%) with a clinic or home 2000–2001 examination had ≥1 component of the physical performance battery. The remaining cohort had telephone follow-up (*n* = 282), were deceased (*n* = 187), withdrew (*n* = 11), or missed the examination (*n* = 102). We excluded participants missing all peripheral nerve function measures (*n* = 87) or fasting blood glucose results (*n* = 23) or with diabetes onset at ≤20 years of age

(*n* = 5). We included 2,364 participants (761 white men, 381 black men, 701 white women, and 521 black women), representing 76.9% of baseline participants and 94.8% of those with a 2000–2001 examination.

Sensory and motor peripheral nerve function

Peripheral nerve function measures (on right leg unless contraindicated) included monofilament testing (reduced sensation defined as inability to feel three of four touches at the great toe for both 1.4- and 10-g monofilaments), average vibration threshold in micrometers (VSA-3000 vibratory sensory analyzer; Medoc), and peroneal motor nerve conduction ampli-

Table 2—Peripheral nerve function descriptive characteristics by diabetes status and sex

	Men		Women	
	Diabetes	No diabetes	Diabetes	No diabetes
<i>n</i>	273	869	210	1,012
No 10-g monofilament detection (%)	19.2*	10.4	6.7	5.6
No 1.4-g monofilament detection (%)	61.9*	50.4	44.0	38.1
Average threshold vibration (μ)	67.8 \pm 39.4*	56.3 \pm 34.8	48.7 \pm 35.2†	42.7 \pm 31.3
CMAP (mV)	2.6 \pm 1.8*	3.0 \pm 1.9	3.5 \pm 2.1	3.6 \pm 2.0
NCV (m/s)	40.9 \pm 4.9†	42.1 \pm 5.0	43.7 \pm 4.7†	44.8 \pm 5.7

* $P \leq 0.001$; † $P \leq 0.05$ for diabetic vs. nondiabetic participants within sex groups.

tude in millivolts (compound motor action potential [CMAP]) and velocity in meters per second (nerve conduction velocity [NCV]) from the popliteal fossa and fibular head to ankle (NeuroMax 8; XLTEK).

Physical performance

The Health ABC performance battery (score range 0–12) was a supplemented version of the lower-extremity battery from the Established Populations for the Epidemiologic Studies of the Elderly (five repeated chair stands, semi-tandem and full-tandem stands for balance, and a 6-m walk for usual gait speed) (9), adding increased stand duration (30 s), a 30-s single leg stand, and a narrow walk test of balance using the same course as for usual gait speed (10). The standing balance ratio was derived by dividing summed times for all stands by maximal stand time.

Diabetes

Diabetes was defined as self-reported physician diagnosis that was not during pregnancy, hypoglycemic medication use, or fasting glucose ≥ 126 mg/dl (≥ 7.0 mmol/l) after an overnight fast (≥ 8 h). Of 2,364 participants, 20.4% (425 with diagnosed diabetes and 58 with fasting glucose ≥ 126 mg/dl) had diabetes.

Body composition and strength

Height was measured using a stadiometer. Weight was measured with a calibrated balance beam scale. Total whole-body bone mineral-free lean mass and fat mass were assessed by dual-energy X-ray absorptiometry (Hologic 4500A; Hologic) in 2001–2002. Knee extension strength (on the right leg unless contraindicated) was measured concentrically at 60°/s on an isokinetic dynamometer (125

AP dynamometer; Kin-Com) in three to six trials. Quadriceps strength was calculated as the mean maximal torque produced (Newton-meter) between 90° and 30° of knee extension from the three best trials.

Other measures

Health histories included smoking (1999–2000), alcohol consumption frequency at baseline, osteoarthritis (1999–2000), diabetes-related complications at baseline (peripheral arterial disease, cerebrovascular disease [transient ischemic attack/stroke], cardiovascular disease [bypass/coronary artery bypass graft, carotid endarterectomy, myocardial infarction, angina, or congestive heart failure], and eye diseases [1999–2000; retinopathy/retinal disease, cataracts, or glaucoma]). Medications from the prior week were inventoried in 1999–2000, coded with Iowa Drug Information System ingredient codes (11), and classified for central nervous system effects. Weekly physical activity from walking and stair climbing (kilocalories per kilogram per week), falling in the prior 12 months (none, one, or two or more), knee pain on most days in the past month, and depressive symptoms on the Center for Epidemiologic Studies Depression (CES-D) scale (12) were determined by an interviewer-administered questionnaire. Cognitive function was measured with the Modified Mini-Mental State Examination, and attention, psychomotor speed, and executive function were measured with the Digit Symbol Substitution test (13). Cystatin-C (>1 mg/dl) and serum creatinine ≥ 1.5 mg/dl for men and ≥ 1.3 mg/dl for women defined renal insufficiency at baseline. Total cholesterol was measured after a ≥ 8 -h fast. Hypertension was defined through self-reported

physician diagnosis, medication use, and/or blood pressure. Ankle-brachial index <0.9 assessed subclinical cardiovascular disease.

Statistical analyses

Differences in prevalence and univariate associations were tested separately by diabetes status and race within sex using Pearson χ^2 methods and Fisher's exact test when appropriate. For continuous variables, nonparametric one-way Mann-Whitney tests were performed for non-normal distributions.

Means of physical performance measures were calculated with ANCOVA by diabetes status and adjusted for demographic factors and peripheral nerve function (monofilament detection, average vibration threshold, CMAP, and NCV). Separate models were used for usual walking speed, narrow walking speed, chair stands per second, standing balance ratio, and performance battery score. Each peripheral nerve function measure was entered as an individual variable, as each represented a distinct component of nerve function with modest correlation between measures ($r = 0.03$ – 0.22 , adjusted for age, sex, and race). Vibration threshold was also analyzed by quartiles because of its skewed distribution to very low or very high threshold values, although results did not change.

Stepwise multiple linear regression was performed with physical performance measures as outcomes and diabetes and peripheral nerve function as the independent variables of interest, while adjusting for demographic variables and variables detailed in OTHER MEASURES. Models met underlying assumptions and were built progressively by entering variables stepwise as follows: diabetes, demographic factors, body composition, strength, physical function risk factors, diabetes-related comorbidities, and finally peripheral nerve function. Diabetes and demographic factors were included in all models, and remaining variables were removed in a stepwise manner at $P > 0.10$. Models were run excluding diabetic participants to determine whether relationships remained consistent. Diabetes severity was assessed by replacing diabetes with dummy variables for either diabetes duration (≤ 5 years, >5 years, or no diabetes) or A1C ($<7\%$, $\geq 7\%$, or no diabetes) in the final models. Multicollinearity for independent variables was assessed using the variance inflation fac-

tor (VIF), the inverse of the proportion of variance not accounted for by other independent variables; no VIF was >10 and the mean VIF for each regression model was ≤2 (14). Percent change in performance measures due to diabetes was calculated using the formula [(unstandardized β for diabetes) (unit change in diabetes)/performance measures mean for entire sample] × 100; 95% CIs were calculated using the formula [(unstandardized β for diabetes) (unit change in diabetes) ± (SE of β for diabetes) (1.96)]/performance measures mean for entire sample] × 100. Data were analyzed using SPSS (SPSS, Chicago, IL) statistical software.

RESULTS — Black participants were more likely to have diabetes than white participants (Table 1). The mean diabetes duration was 11 years; 55% of participants had duration of >5 years and 45% had A1C ≥7%. Diabetic participants had higher BMI, higher lean mass, higher fat mass, lower physical activity, more hypertension, worse ankle-arm index, higher creatinine, and a higher CES-D depression index than nondiabetic participants. Diabetic men had higher cystatin-C levels, lower cholesterol levels, and more knee pain in the past 30 days than nondiabetic men. Diabetic women were more likely to report cardiovascular disease history, glaucoma, and less frequent drinking. Diabetic men had less 10- and 1.4-g monofilament detection, higher average threshold vibration, lower CMAP, and lower NCV than nondiabetic men (Table 2). Diabetic women had higher average threshold vibration and lower NCV than nondiabetic women.

Older adults with diabetes had slower chair stand rates, shorter standing balance times, slower usual walking speed, slower narrow walking speed, and lower physical performance battery score compared with nondiabetic adults (Table 3). After adjustment for peripheral nerve function, the mean value of each performance measure improved for both those with and without diabetes (Table 3).

In adjusted analyses, diabetes was associated with worse physical performance for all measures except chair stands (Table 4, model 1). With the addition of peripheral nerve function for model 2, diabetes was not associated with usual walking speed (from 2.1 to 1.7% lower; 20.8% β attenuation) or the standing balance ratio (from 4.6 to 3.4% lower; 26.5% β attenuation) and was attenuated, al-

though it remained significantly related to lower performance battery score (from 4.8 to 3.6% lower; 25.1% β attenuation) and slower narrow walking speed (from 11.4 to 10.1% lower; 11.4% β attenuation). Impaired monofilament detection was related to lower performance battery score, slower narrow walking speed, and fewer chair stands. Higher average vibration threshold was related to lower performance battery scores, slower usual walking speed, and shorter standing balance times. Lower CMAP was related to lower performance battery scores, slower usual and narrow walking speed, and shorter standing balance times. Lower NCV was related to fewer chair stands. When fibular head rather than popliteal fossa CMAP and NCV were included, all relationships were similar. Excluding diabetic participants did not alter associations, except for monofilament detection and the performance battery score.

As reported in our previous study (8), greater diabetes severity was significantly associated with worse physical performance, with results for diabetic adults with less severe disease being not different from those for nondiabetic adults. Diabetes severity was related to lower performance battery scores (A1C ≥7% and duration >5 years), slower usual walking speed (A1C ≥7%), and narrow walking speed (duration >5 years), and shorter standing balance times (A1C ≥7% and duration >5 years) than those for nondiabetic adults. Relationships between diabetes severity and physical performance did not affect associations with peripheral nerve function.

CONCLUSIONS — Our results indicate that poor peripheral nerve function explains a portion of the association of diabetes with physical disability. In this population of community-dwelling older adults, both poor sensory and motor peripheral nerve function were independently associated with worse physical performance. These findings are important because studies of physical performance in older adults typically do not assess peripheral nerve function. Adjustments for lean mass and strength did not eliminate relationships, suggesting that peripheral nerve function affects physical performance directly rather than indirectly through associations with muscle.

Sensory nerve assessments were related to several performance measures. Lack of 10-g monofilament detection is

Table 3—Adjusted performance measures for diabetic and nondiabetic participants

Adjustment for variables	Chair stands (per s)		Standing balance ratio		Walking speed for usual 6-m walk (m/s)		Walking speed for narrow 6-m walk (m/s)		Performance score (0–12)	
	Diabetic	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic
None	0.31 ± 0.14*	0.35 ± 0.14	0.66 ± 0.29*	0.73 ± 0.28	1.05 ± 0.24*	1.12 ± 0.26	0.72 ± 0.50*	0.90 ± 0.53	6.09 ± 1.90*	6.77 ± 1.84
1. Sex, race, age, site	0.32 ± 0.13*	0.35 ± 0.13	0.65 ± 0.26*	0.73 ± 0.26	1.07 ± 0.24*	1.12 ± 0.22	0.74 ± 0.50*	0.90 ± 0.52	6.12 ± 1.76*	6.77 ± 1.76
2. 1 and peripheral nerve measures	0.34 ± 0.14†	0.36 ± 0.15	0.69 ± 0.26*	0.75 ± 0.26	1.11 ± 0.50†	1.14 ± 0.51	0.80 ± 0.50*	0.95 ± 0.51	6.43 ± 1.65*	6.93 ± 1.65

Data are means ± SD. *P ≤ 0.001; †P ≤ 0.05 for diabetic vs. nondiabetic participants.

Table 4—Multivariate linear regression models for the performance battery, usual walk, narrow walk, standing balance, and chair stands

	Performance battery score (0–12)		Usual walking speed (m/s)		Narrow walking speed (m/s)		Standing balance ratio		Chair stands (per s)	
	β	P value	β	P value	β	P value	β	P value	β	P value
Final model, no peripheral nerve function variables										
Diabetes	-0.332	0.001	-0.024	0.07	-0.105	<0.001	-0.034	0.04	-0.010	>0.10
Final model, with peripheral nerve function variables										
Diabetes	-0.250	0.009	-0.019	>0.10	-0.094	0.001	-0.025	>0.10	-0.007	>0.10
Monofilament detection (no/10-g/1.4-g)	0.174	0.003	—	>0.10	0.049	0.006	—	>0.10	0.015	0.007
Average vibration threshold (μ)	-0.004	<0.001	-0.0005	0.005	—	>0.10	-0.001	<0.001	—	>0.10
CMAP (mV)	0.105	<0.001	0.008	0.004	0.029	<0.001	0.014	<0.001	—	>0.10
NCV (m/s)	—	>0.10	—	>0.10	—	>0.10	—	>0.10	0.001	0.09

Final models were additionally adjusted for age (all), race (all), sex (all), study site (all), height (chair stands), total fat mass (all), quadriceps strength (all), current smoking (performance battery and standing balance ratio), medications with central nervous system effects (performance battery, usual walking speed, standing balance ratio, and chair stands), physical activity (performance battery and usual walking speed), falls (performance battery, narrow walking speed, and standing balance ratio), osteoarthritis (standing balance ratio), knee pain (chair stands), prevalent cerebrovascular disease (performance battery, usual walking speed, narrow walking speed, and chair stands), blood pressure (performance battery, usual walking speed, standing balance ratio, and chair stands), cholesterol (narrow walking speed), cataracts (performance battery, usual walking speed, and chair stands), glaucoma (performance battery and standing balance ratio), high creatinine concentration (performance battery), high cystatin-C concentration (performance battery, usual walking speed, standing balance ratio, and chair stands), CES-D (all), Modified Mini-Mental State Examination (performance battery, narrow walking speed, and standing balance ratio), and Digit Symbol Substitution (all). Variables above and additional variables listed in RESEARCH DESIGN AND METHODS were removed from models in a stepwise manner at $P > 0.10$.

generally associated with clinical disease that is predictive of future foot ulcers (15). In addition, perception with the more sensitive 1.4-g monofilament, which detects subclinical neuropathy, and reduction in vibration threshold were related to performance.

CMAP of the peroneal motor nerve was related to all performance measures except chair stands. We are uncertain as to why NCV showed weaker relationships; however, we did not examine any nerve supplying the proximal musculature of the lower limbs. Fibular head nerve conduction results were consistent with those for the popliteal fossa, suggesting that entrapment at the knee does not explain associations with physical performance. Lower NCV was not related to fast walking speed in the InCHIANTI Study, an Italian cohort aged ≥ 60 years, although it was related to longer 400-m walk time and lower summary performance score (16). Low CMAP is related to nerve axonal damage and low NCV is related to nerve demyelination (17). Interestingly, the InCHIANTI Study showed that lower peroneal CMAP, but not NCV, was independently associated with lower calf muscle density (18). Our relationships of poor peripheral nerve function and physical performance may be similar to the relationships with muscle. Severe diabetic peripheral neuropathy is clearly

related to muscle atrophy, with neuropathy score and muscle volume being highly correlated (19,20). Proximal muscle weakness with inability to stand is usually the result of proximal motor neuropathy of the demyelinating variety, especially in older adults (21).

At the Health ABC Study baseline, diabetes, particularly with longer duration or poor control, was associated with subclinical functional limitation (8) and reduced strength (22), although we had no measure of peripheral nerve function then. Previous studies of older diabetic adults indicated that worse peripheral nerve function is related to poorer balance and slower gait speed (2,3). Our results suggest that peripheral nerve impairments affect certain types of physical functioning more than others and are consistent with those of a study of disabled women aged ≥ 65 years, which showed that lower summary performance score, poor balance, and slower gait speed were associated with worse sensory nerve function and an attenuation of diabetes and physical performance after adjustment for nerve function (3,23). In older Italian adults, distal symmetrical neuropathy was associated with a twofold increased risk of physical performance decline independent of diabetes (24).

Our study is unique in its inclusion of state-of-the-art standardized sensory and

motor peripheral nerve function assessments and objective physical performance. Peripheral nerve function measures were limited to large fiber nerves rather than small fiber nerves. Ideally, nerve conduction studies test multiple nerves to confirm polyneuropathy. The peroneal nerve, rather than the sural nerve, was selected because it is a motor nerve and more likely to have a response in older adults (5). We controlled for many factors potentially affecting both our outcome and exposure of interest, including lean mass and quadriceps strength, to account for decreased physical functioning occurring indirectly through loss of muscle mass and falls. Peripheral nerve function was probably worse in nonstudy participants and Health ABC Study participants without a follow-up; therefore, results may apply only to ambulatory community-dwelling older adults. Future studies are needed to address these associations across wider ages of older adults (including those with worse physical function) and to evaluate whether peripheral nerve function in the upper extremities contributes to upper-extremity performance. Prospective studies, which we are conducting, are needed to address causality of associations between peripheral nerve function and physical performance.

In summary, this multiethnic study of

older men and women showed consistent associations of poor sensory and motor peripheral nerve function and worse objective physical performance. Considering the high prevalence of poor peripheral nerve function in older adults, in our study and in the U.S. (7), and the current diabetes epidemic, peripheral nerve impairments are an unappreciated problem in the elderly population. Peripheral nerve function should be evaluated when one is studying physical performance in older adults. Whether poor peripheral nerve function will affect future disability in diabetic and nondiabetic older adults needs to be examined, and longitudinal data are currently being collected for our cohort.

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