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Sensory and Motor Peripheral Nerve Function and Longitudinal Changes in Quadriceps Strength

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Background. Poor peripheral nerve function is common in older adults and may be a risk factor for strength decline, although this has not been assessed longitudinally.

Methods. We assessed whether sensorimotor peripheral nerve function predicts strength longitudinally in 1,830 participants (age = 76.3 ± 2.8, body mass index = 27.2 ± 4.6 kg/m^2, strength = 96.3 ± 34.7 Nm, 51.0% female, 34.8% black) from the Health ABC study. Isokinetic quadriceps strength was measured semiannually over 6 years. Peroneal motor nerve conduction amplitude and velocity were recorded. Sensory nerve function was assessed with 10-g and 1.4-g monofilaments and average vibration detection threshold at the toe. Lower-extremity neuropathy symptoms were self-reported.

Results. Worse vibration detection threshold predicted 2.4% lower strength in men and worse motor amplitude and two symptoms predicted 2.5% and 8.1% lower strength, respectively, in women. Initial 10-g monofilament insensitivity predicted 14.2% lower strength and faster strength decline in women and 6.6% lower strength in men (all $p < .05$).

Conclusion. Poor nerve function predicted lower strength and faster strength decline. Future work should examine interventions aimed at preventing declines in strength in older adults with impaired nerve function.

Key Words: Aging—Strength—Muscle weakness—Peripheral nerve function—Sensory function—Motor neurons.

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POOR strength in late-life contributes to poor physical function (1), mobility disability (2), hospitalization (3), and mortality (4). Given its major role in late-life outcomes, investigating risk factors for strength decline in older adults is essential. Although age-related muscle atrophy plays a major role in declining strength, maintaining or gaining muscle mass does not guarantee prevention of strength loss with age (5), suggesting that other factors must contribute. One proposed contributing factor to strength decline is poor peripheral nerve function (6).

Estimated motor unit loss using surface electromyography (sEMG) is cross-sectionally associated with lower strength in older adults (age ≥60 years) (7). Moreover, strength gains occurring during early phases of training prior to increases in muscle size are associated with increased amplitude measured using sEMG (8). This technique assesses the sum of motor unit potentials, providing a global measure of neuromuscular activity. Nerve Conduction Studies (NCS) allow direct stimulation of the nerve and measurement of the signal magnitude and the speed of response across the nerve. This method is considered the clinical gold standard to measure the degree of nerve damage and to distinguish between demyelination and axonal degeneration (9).

Small clinical studies have found cross-sectional associations between motor axon loss or axonal degeneration, estimated using NCS, and muscle weakness in patients with Charcot-Marie-Tooth disease (10) and chronic inflammatory demyelinating polyradiculoneuropathy (11). In a large cohort of older adults, the Health, Aging, and Body Composition Study found that both motor peripheral nerve function

measured using NCS and sensory peripheral nerve function were related to lower quadriceps and ankle dorsiflexion strength cross-sectionally, independent of lean mass (6). Clinically, early identification of changes in nerve function that may be able to predict strength decline may lead to timely intervention and help prevent resulting disability. Therefore, we utilized standard clinical assessments to evaluate the relationship between nerve function and strength loss. Our primary aim was to investigate the longitudinal relationship between clinical measures of sensorimotor nerve function and subsequent change in quadriceps strength over 6 years. We hypothesized that poor sensory and motor nerve function would be associated with both lower quadriceps strength and faster declining strength. As an exploratory aim, we also examined the relationship between concurrent change in sensorimotor nerve function and quadriceps strength.

Methods

Study Participants

Health ABC is a prospective study of well-functioning older adults (n = 3,075; 48.4% male; 41.6% black, ages 70–79 years at baseline) established in 1997–1998 to investigate body composition and disability changes in older age. A random sample of white medicare beneficiaries and all black community residents eligible by age were recruited through mailings. Eligibility included having no difficulty walking a quarter of a mile, walking up to 10 steps, or performing activities of mobility-related daily living, having no life-threatening cancers with active treatment within the past 3 years, and planning to remain within the study area for ≥3 years. Informed consent was approved by the institutional review boards at the participating institutions. The first nerve function exam occurred 4 years after baseline, and this analysis includes covariates from the baseline exam, and therefore to distinguish baseline from the first nerve exam, nerve function measures from the first nerve exam will be referred to as "initial" measures. Quadriceps strength and ≥1 nerve function component were measured in 2,096 participants at the initial nerve exam, which occurred during Year 4 (2000–2001) of the study. Strength was measured during Years 4, 6, 8, and 10. Participants who had ≥2 measures of strength were included in the analysis. Strength was measured in 1,079 participants at four time points, in 357 at three time points, and in 343 at two time points. For the exploratory concurrent change analysis (nerve function at Years 4 and 11), strength was measured in 927 at four time points, in 162 at three time points, and in 38 at two time points. For a more detailed description of number of participants with each study measures see Supplementary Figure 1.

Quadriceps Strength

Isokinetic quadriceps strength was measured concentrically during a maximum leg extension at 60° per second using a Kin-Com dynamometer (Harrison, Tennessee). Participants performed three to six trials, and the maximal torques from the three best trials were averaged. Contraindications included history of brain aneurysm or stroke, bilateral knee replacement, severe bilateral knee pain, systolic blood pressure >199 mmHg and diastolic blood pressure >109 mmHg.

Sensory and Motor Peripheral Nerve Function

After warming the feet to 30°C, peroneal motor NC amplitude and velocity were measured using the NeuroMax8 (XLTEK, Oakville, Ontario, Canada) consistent with standard clinical protocols (12). Surface electrodes with conducting gel were placed over the anterior ankle, over the fifth metatarsophalangeal joint (lateral to long extensor tendons), and over the base of the extensor digitorumbrevis muscle (1 cm distal to calcaneous bone). The peroneal nerve was stimulated at the popliteal fossa, ~10 cm proximal to the fibular head. The motor response (CMAP, compound action potential) was recorded at the extensor digitorumbrevis muscle (12). Sensory nerve function was measured using average vibration detection threshold on the bottom of the large toe with a VSA-3000 Vibratory Sensory Analyzer (Medoc, Durham, North Carolina). Monofilament insensitivity (inability to detect 3/4 touches) was measured at the dorsum of the large toe with a standard clinical 10-g monofilament and 1.4-g monofilament. Self-reported neuropathy symptoms included: (i) numbness or tingling and (ii) sudden stabbing, burning, pain or aches, in the past 12 months on the feet or leg.

As an exploratory analysis, we also assessed the relationship between categories of nerve function change and concurrent change in quadriceps strength. Participants were categorized as: (i) "Maintained Normal"; (ii) "Normal transitioning to Poor"; (iii) "Poor transitioning to Normal"; and (iv) "Sustained Poor". Poor nerve function was defined separately for each measure. Clinical cut points of <1 mV and <40 m/s were used for motor nerve amplitude and nerve conduction velocity (NCV), respectively (13). Participants were considered to have transitioned from normal to poor or from poor to normal if they crossed the defined cut point and had a ≥5% change. For vibration threshold and 1.4-g and 10-g monofilament detection, participants transitioned if they felt the stimulation at one time point but not the other. Participants were classified as having transitioned with symptoms if they reported two symptoms at one time point and <2 at the other.

Additional Covariates

We included factors known or hypothesized to be associated with nerve function and lower-extremity strength and function. Height and weight were measured using a stadiometer and a calibrated balance beam scale. Whole body bone-free lean and fat mass were measured using dual-energy

X-ray absorptiometry (Hologic 4500A, Hologic Inc., Bedford, Massachusetts). Diabetes was defined as self-reported physician diagnosis, hypoglycemic medication use, or fasting glucose >126 mg/dL and impaired fasting glucose was defined as 100 mg/dL to <126 mg/dL after an 8-hour or longer fast (14). Hypertension was assessed by self-report, medication use, and diastolic blood pressure ≥90 mmHg or systolic blood pressure ≥140 mmHg. A >1 drink/wk cut point for alcohol consumption was used. Ankle brachial index was used to indicate peripheral arterial disease (<0.9) and stiffening (≥1.3). Depression was assessed by the Center for Epidemiologic Studies Depression Scale (15). The Modified Mini-Mental State Examination (3MSE) measured cognitive function and the Digit Symbol Substitution Test (DSST) measured attention, psychomotor speed, and executive function (16). Insufficient renal function was defined as Cystatin-C >1 mg/dL (17). Knee pain on most days in the past 12 months was self-reported. Poor vitamin B12 status was <260 pmol/L (18). Prevalent cerebrovascular disease (transient ischemic attack or stroke), cardiovascular disease (bypass or coronary artery bypass graft, carotid endarterectomy, myocardial infarction, angina pectoris, congestive heart failure), knee pain, Cystatin-C, alcohol consumption, and DSST were measured at baseline. Smoking status and 3MSE were measured at Year 3 (1999–2000). Other covariates were measured during the initial nerve exam (Year 4). Weight, total lean and fat mass, and weekly physical activity spent walking and climbing stairs (kcal/kg/wk) were included as time varying covariates from Years 4, 6, 8, and 10.

Statistics

Means and frequencies of participant characteristics were compared by sex using *t*-test and chi-squared statistics. Repeated measures analysis using Proc Mixed (SAS, version 9.3, SAS Institute Inc., Cary, North Carolina) was used to assess the relationships of initial and concurrent change in nerve function with change in strength. Separate models were built for each nerve measure because some were moderately correlated. The first set of models adjusted for age, race, height, weight, study site, and the interaction between each variable and time. Sensitivity analyses adjusted for lean and fat mass instead of weight (5,19). Variables were included in models if they were related to the predictor or outcome ($p < .1$). Fully adjusted models included diabetes, blood pressure, ankle brachial index, cerebrovascular disease, cardiovascular disease, knee pain, cognition, depression, vitamin B12 status, smoking, alcohol consumption, physical activity, and renal function. Sex and nerve function interactions were tested to assess whether sex modified the relationship between nerve function and strength. Because of the role of diabetes in peripheral nerve function and strength (20), we ran a sensitivity analysis excluding participants with diabetes. Percentage of strength loss was calculated by dividing the standardized betas by the mean strength of the population. Given the initial nerve function analysis was performed separately for men and women, the sex-specific mean strength was used for this analysis. Because the exploratory concurrent change analysis was not stratified by sex, the strength of the overall study population was used for this analysis.

Results

Men had greater quadriceps strength, height, lean mass, and fat mass compared with women (Table 1). They were more likely to consume >1 drink/wk, had higher physical activity, and more diabetes, impaired fasting glucose, arterial stiffening, cardiovascular disease, and poor vitamin B12 status. Men had worse motor amplitude (3.1 ± 1.9 vs 3.7 ± 2.0 mV, $p < .0001$), conduction velocity (41.9 ± 4.9 vs 45.3 ± 5.3 m/s, $p < .0001$), and vibration threshold (57.4 ± 36.4 vs 42.7 ± 31.4 μ, $p < .0001$), and more 1.4-g and 10-g monofilament insensitivity (50.4% vs 37.7% and 10.8% vs 5.3%, both $p < .0001$). Women reported more lower-extremity numbness (10.1% vs 6.1%, $p = .002$) and pain (18.7% vs 11.8%, $p < .0001$). Significant and borderline significant interactions between sex and vibration threshold ($p = .01$) and motor amplitude ($p = .09$) were associated with strength; therefore, analyses were performed separately by sex (Tables 2 and 3). Concurrent change analyses in nerve function and strength were not stratified by sex because no significant sex interactions existed.

Initial 1.4-g and 10-g monofilament insensitivity were associated with 3.7% and 14.2% lower strength, respectively, in women and 4.1% and 6.6% lower strength, respectively, in men. In women, 10-g sensitivity was also associated with faster strength decline (time interaction). In women, one standard deviation lower initial motor amplitude and two symptoms were associated with 2.5% and 8.1% lower strength, respectively. In men, worse vibration perception threshold was associated with 2.4% lower strength.

In the exploratory analysis examining the relationship between concurrent change nerve function and quadriceps strength, "Sustained Poor" 10-g sensitivity was associated with 16.5% lower strength and faster strength decline. "Poor transitioning to Normal"10-g sensitivity and motor amplitude were associated with 12.9% and 14.7% lower strength, respectively. "Normal transitioning to Poor" and "Sustained Poor" vibration threshold were associated with 10.7% and 16.9% lower strength, respectively.

Associations remained consistent after adjusting for lean and fat mass (results not shown). Excluding participants with diabetes, associations remained largely consistent; however, 1.4-g insensitivity no longer predicted strength in men. Transitioning from reporting <2 to 2 symptoms ("Normal transitioning to Poor") was associated with lower strength, but other symptom groups were not.

Table 1. Participant Characteristics by Sex

Characteristics	Women (n = 934)	Men (n = 896)	p Value
Age, years	76.2 (2.8)	76.5 (2.8)	.005
Black race, *n* (%)	367 (39.3)	270 (30.1)	<.0001
Quadriceps strength, Nm	74.0 (21.0)	119.1 (30.8)	<.0001
Body composition			
Height, cm	158.1 (15.0)	172.8 (8.8)	<.0001
BMI, kg/m^2	27.2 (5.3)	27.1 (3.8)	.56
Lean mass, kg	40.8 (6.1)	56.3 (7.2)	<.0001
Fat mass, kg	28.7 (9.1)	25.1 (7.2)	<.0001
Lifestyle characteristics			
Current smoker, *n* (%)	58 (6.5)	56 (6.5)	.99
Alcohol consumption >1/wk, *n* (%)	424 (46.1)	526 (59.7)	<.0001
Physical activity, kcal/kg/wk	5.0 (15.5)	6.9 (13.6)	.004
Chronic health conditions			
Diabetes, *n* (%)	161 (17.4)	211 (23.9)	.0006
Impaired fasting glucose, *n* (%)	118 (12.8)	174 (19.7)	<.0001
Ankle-arm index <0.9, *n* (%)	126 (14.0)	120 (13.8)	.90
Ankle-arm index >1.3, *n* (%)	30 (3.3)	63 (7.2)	.0002
Hypertension, *n* (%)	745 (80.8)	695 (78.5)	.23
Cardiovascular disease, *n* (%)	84 (9.7)	191 (23.0)	<.0001
Cerebrovascular disease, *n* (%)	53 (5.8)	45 (5.2)	.54
Knee pain most days per month, *n* (%)	153 (16.6)	124 (14.0)	.13
Poor vitamin B12, *n* (%)	128 (14.4)	177 (20.3)	.001

Notes: BMI = body mass index. Data are means (*SD*) unless otherwise specified.

Table 2. Initial Nerve Function and Longitudinal Quadriceps Strength in Women

	First Models		Second Models	
	Standardized Betas		Standardized Betas	
	Main Effect	Time Interaction	Main Effect	Time Interaction
Motor nerve function				
Amplitude, *SD* lower	−2.31‡	−0.09	−1.87†	0.11
Velocity, *SD* lower	−0.29	−0.07	0.24	−0.11
Sensory nerve function				
1.4-g monofilament insensitivity	−3.03*	0.14	−2.72*	0.12
10-g monofilament insensitivity	−10.65§	1.14*	−10.48‡	1.02*
Vibration threshold, *SD* lower	−0.03	−0.04	0.45	−0.01
Symptoms				
One	−0.64	0.52*	0.06	0.35
Two	−6.54†	0.65	−5.97†	0.44

Notes: AAI = Ankle arm index; DSST = Digit Symbol Substitution Test; CES-D = Center for Epidemiologic Studies Depression Scale; *SD* = standard deviation. Motor amplitude *SD* = 1.99 mV; motor nerve conduction velocity *SD* = 5.36 m/s; vibration threshold *SD* = 34.74 μ. First models—adjusted for age, race, height, weight, site, time interactions. Second models: *Motor nerve function*—first models + diabetes, low and stiffening AAI, knee pain, DSST, CES-D, smoking, physical activity, renal function. *Sensory nerve function*—first models + diabetes, low and stiffening AAI, knee pain, DSST, CES-D, smoking, physical activity, renal function. *Symptoms*—first models + low and stiffening AAI, knee pain, DSST, CES-D, smoking, physical activity, renal function.

*p < .05; †p < .01; ‡p < .001; §p < .0001.

Discussion

Poor sensory and motor peripheral nerve functions were associated with low quadriceps strength and greater strength decline in a large cohort of older men and women. These findings are important because quadriceps strength has been shown to subsequently contribute to poor function (1), disability (2), and major health outcomes (3,4) in older adults. To our knowledge, this is the first report of a longitudinal relationship between measures of motor and sensory nerves and strength.

Motor amplitude, but not velocity, was related to strength longitudinally. This finding is consistent with NCS in small patient populations with multiple etiologies of neuropathy (8,9) and supports and extends our earlier cross-sectional findings in this study population (10). Low motor amplitude may represent in part axonal loss or degeneration, whereas low NCV is believed to indicate demyelination (21,22). Our findings may implicate axonal degeneration in neuromuscular weakness. However, sEMG (23) and NCS (24) have shown that changes in motor amplitude may also be influenced by a number of other physiological and nonphysiological factors. Although we cannot control for all of these factors, our standardized clinical measurement protocol was designed to minimize error. Moreover, in a subsample

Table 3. Initial Nerve Function and Longitudinal Quadriceps Strength in Men

	First Models		Second Models	
	Standardized Betas		Standardized Betas	
	Main Effect	Time Interaction	Main Effect	Time Interaction
Motor nerve function				
Amplitude, *SD* lower	−1.96	0.28	−1.24	0.26
Velocity, *SD* lower	0.01	0.27	0.69	0.33
Sensory nerve function‡				
1.4-g monofilament insensitivity	−5.24†	−0.15	−4.94†	0.05
10-g monofilament insensitivity	−9.23†	0.31	−7.81*	0.50
Vibration threshold, *SD* lower	−3.75§	0.08	−2.81†	0.01
Symptoms				
One	−1.29	−0.42	0.44	−0.58
Two	−1.73	0.11	1.48	0.02

Notes: AAI = Ankle arm index; DSST = Digit Symbol Substitution Test; CES-D = Center for Epidemiologic Studies Depression Scale; *SD* = standard deviation. Motor amplitude *SD* = 1.99 mV; motor nerve conduction velocity *SD* = 5.36 m/s; vibration threshold *SD* = 34.74 μ. First models – adjusted for age, race, height, weight, site, time interactions. Second models: *Motor nerve function*—first models + low and stiffening AAI, stiffening AAI, cerebrovascular disease, knee pain, poor vitamin B12, DSST, CES-D, renal function. *Sensory nerve function*—first models + diabetes, cerebrovascular disease, knee pain, DSST, CES-D, renal function. *Symptoms*—first models + diabetes, cerebrovascular disease, knee pain, DSST, CES-D, renal function.

*$p < .05$; †$p < .01$; ‡$p < .001$; §$p < .0001$.

of participants from this cohort, we earlier found that age, body composition, diabetes, race, and gender had no significant effect on reliability of NC measures (12).

Motor amplitude has been correlated with and is believed in part to reflect muscle mass (25). Nerve impairment may lead to muscle atrophy, and in severe cases of peripheral neuropathy, muscle wasting is present (9). We investigated lean mass as a potential mediator in the relationship between peripheral nerve function and strength. Although lean mass was associated with strength, it did not mediate the relationship between nerve function and strength. Similarity, Lauretani and colleagues (21) reported that neither motor amplitude nor velocity was associated with lean mass. However, they reported a cross-sectional relationship between muscle density and motor amplitude, suggesting that future work should examine muscle density as potential mediator between motor amplitude and muscle strength.

Our results also suggest a role of sensory nerve function in the loss of lower-extremity strength with age. Like muscle strength, impairments in both cutaneous receptor function and proprioception have been implicated in poor mobility outcomes such as decreased function and increased risk of falls in older adults (26). Burke and colleagues (27) have shown that cutaneous stimulation may influence muscle activation in the lower extremity, suggesting communication between cutaneous receptors, muscle spindles, and alpha motor neuron activity. In addition, experimental studies have found that blocking afferent input in healthy individuals can lead to reduced maximal voluntary contractions (28), and that somatosensory stimulation of the hand can increase muscle strength in stroke patients (29). Supporting our findings, we found that similar measures of sensory and motor nerve function were associated with lower-extremity muscle power in a cohort of older community-dwelling men (30). Muscle power incorporates velocity of movement in addition to force (eg, strength) (30,31), although both muscle power and strength are used to assess muscle function loss in older adults. Although increasing evidence exists that both motor and sensory nerve function play a role in muscle strength, the exact mechanism of this relationship is still unclear. Our findings may be reflective of the complex interplay in which motor neurons obtain feedback from cutaneous receptors, joint receptors, spinal interneurons, and higher centers for coordinated movement involving muscle lengthening, contraction velocity, and force development (32).

Motor and sensory nerve function measured predicted strength longitudinally in women, whereas only sensory nerve function predicted strength in men. Because men tend to have significantly higher muscle strength than women (33), possibly women, lacking higher strength, are more susceptible to the negative effects of poor motor nerve function. Future studies are needed to investigate these sex differences, particularly with regard to late-life disability. We also found that 10-g monofilament insensitivity, which is predictive of diabetic foot ulceration (34), was associated with faster strength decline. Earlier, we found that poor 1.4-g monofilament detection, which is used to detect subclinical sensory impairment, was associated with loss of muscle power in men. This evidence suggests that these simple sensory monofilament tests may be potentially useful in predicting future decline in muscle function (30).

This epidemiologic study cannot substitute comprehensive neurophysiologic evaluation of sensorimotor function in individual subjects; however, it has a number of strengths. This study provides valuable new insights on changes of different indicators of sensorimotor function over time and their association with quadriceps strength. Findings are more generalizable than in-depth clinical studies of individual patients. Sensory and motor nerves were assessed using

standard clinical methodology. These motor NC measures are used in clinical practice and are highly reproducible gold standard measurements that we validated in this cohort (12). Our measure of quadriceps strength has been validated and is related to poor function and health outcomes in older adults (1–4). We chose these specific assessments of nerve function and strength because of their reliability in studies of older adults (12,35).

We used prospective data from a large, multiethnic, well-characterized cohort of older adults. We were able to adjust for a number of health conditions and behaviors that are known to contribute to peripheral nerve impairment. This allowed us to assess the extent to which the effects of poor nerve function are due to these underlying factors. Although we observed some attenuation due to these factors, our results suggest that older adults with poor sensory and motor nerve function have faster declines in strength, even when taking into account many of these traditional risk factors in old age (eg, diabetes). This suggests that novel risk factors and interventions to address these impairments with age should be explored.

We measured nerve function distally and strength proximally along the leg, in accordance with standard measures in epidemiologic studies. This study was designed to assess the relationship between overall lower-extremity nerve function and quadriceps strength in a large epidemiologic cohort and, therefore, not designed to elucidate specific mechanisms. For example, the association of poor sensorimotor nerve function and quadriceps strength may reflect abnormal function in both extensor digitorumbrevis innervated by the sciatic and peroneal nerve and quadriceps innervated by the femoral nerve. Future work is critical to elucidate specific mechanisms for the association of peripheral nerve function and strength decline in older adults.

Although we observed larger decreases in strength associated with nerve function change groups when compared with initial nerve function measures, our concurrent change analysis was exploratory given we only had two time points for nerve function measures and we may have had insufficient statistical power to detect some associations due to small numbers in some nerve function change groups. In addition, findings from this analysis showing that those who improved to normal motor amplitude and experienced reduced symptoms had worse strength seem somewhat counterintuitive. These findings may be evidence of the negative longitudinal effects of early nerve function impairments— even if reversed— and suggest the importance of early prevention and intervention for nerve impairments, such as better glycemic control or supplementation for a vitamin B12 deficiency (11). These results could also indicate the complexity of the age-related loss of muscle strength whereby multiple physiologic mechanisms may act simultaneously or sequentially with each other. That said, we were not able to rigorously evaluate these pathways with our data, given that we were limited to only two time points and do not know when these improvements occurred. Although exploratory, these results suggest that future work on the timing of interventions for improving nerve function is crucial.

Furthermore, participants returning for follow-up clinic visits were healthier, resulting in some inevitable retention bias (36). Our results were mostly consistent when we excluded individuals with diabetes, suggesting that the relationships were not driven by diabetes alone. This is consistent with what has been found cross-sectionally (6) and underlies the importance of the high prevalence of impaired nerve function in older adults without diabetes (37).

In conclusion, poor motor and sensory nerve function contribute to poor and declining strength in older adults. Given the high incidence and prevalence of subclinical and overt neuropathy in older adults (37,38), and the current and projected diabetes epidemic (39), identifying and preventing impairments associated with poor nerve function such as declines in strength is essential. Poor sensory and motor nerve function may accelerate strength decline. Future work should focus on how impairments in nerve and muscle function interact and lead to poor mobility outcomes in older adults. Modifiable risk factors and interventions for neuromuscular decline in late-life are understudied and should be investigated.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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