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Review Article

Mobility-Related Consequences of Reduced Lower-Extremity Peripheral Nerve Function with Age: A Systematic Review

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ABSTRACT: The objective of this study is to systematically review the relationship between lower-extremity peripheral nerve function and mobility in older adults. The National Library of Medicine (PubMed) was searched on March 23, 2015 with no limits on publication dates. One reviewer selected original research studies of older adults (≥65 years) that assessed the relationship between lower-extremity peripheral nerve function and mobility-related outcomes. Participants, study design and methods of assessing peripheral nerve impairment were evaluated and results were reported and synthesized. Eight articles were identified, including 6 cross-sectional and 2 longitudinal studies. These articles investigated 6 elderly cohorts (4 from the U.S. and 2 from Italy): 3 community-dwelling (including 1 with only disabled women and 1 without mobility limitations at baseline), 1 with both community-dwelling and institutionalized residents, 1 from a range of residential locations, and 1 of patients with peripheral arterial disease. Mean ages ranged from 71-82 years. Nerve function was assessed by vibration threshold (n=2); sensory measures and clinical signs and symptoms of neuropathy (n=2); motor nerve conduction (n=1); and a combination of both sensory measures and motor nerve conduction (n=3). Each study found that worse peripheral nerve function was related to poor mobility, although relationships varied based on the nerve function measure and mobility domain assessed. Six studies found that the association between nerve function and mobility persisted despite adjustment for diabetes. Evidence suggests that peripheral nerve function impairment at various levels of severity is related to poor mobility independent of diabetes. Relationships varied depending on peripheral nerve measure, which may be particularly important when investigating specific biological mechanisms. Future research needs to identify risk factors for peripheral nerve decline beyond diabetes, especially those common in late-life and modifiable. Interventions to preserve nerve function should be investigated with regard to their effect on postponing or preventing disability in older adults.

Key words: peripheral nerve function, mobility limitation, disability, sensory function, older adults, aging

Sensorimotor peripheral nerve function impairments are common in late-life. These impairments are an important risk factor for falls in both diabetic and nondiabetic individuals [1-5] and increasing evidence shows that they are associated with mobility limitations and disability. The National Health and Nutrition Survey found that reduced sensation at the foot is highly prevalent among those with and without diabetes, increasing from 8.1% at ages 40-49 to 34.7% after age 80 [6]. This is likely an underestimate of nerve impairment in the population due

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to the use of less sensitive screening measures, limited to 10-g monofilament screening and self-reported symptoms [7]. Clinical neuropathy rates also increase with age [8]. A population-based study of Italian elders showed the incidence of distal symmetric neuropathies (DSN) increased in participants without diabetes, from 4.6 to 8.8 new cases per 1,000 person years, among those 65-79 to 80-84 years of age, respectively. Incidence rates in participants with diabetes were higher, increasing from 13.7 to 52.5 new cases per 1,000 person years from the 65-79 to the 75-79 age groups, then dropping to 48.4 new cases within the 80-84 age group, likely due to a survival effect. Diabetes accounted for only 39.2% of prevalent neuropathy cases and 49% of incident cases [8], emphasizing the need to identify other etiologic pathways, particularly in non-diabetic older adults. Clinical peripheral neuropathy is an important risk factor for disability and mobility limitations, particularly in older adults with diabetes [8-11] (www.cdc.gov/mmwr/preview/mmwrhtml/mm5446a4.htm). Subclinical peripheral nerve impairments are also associated with mobility limitations in older adults both with and without diabetes [12-15].

We describe existing evidence on impaired lower-extremity peripheral nerve function as a risk factor for mobility limitations with age. Evaluation of methods and findings available on this topic has important implications for designing interventions aimed at postponing or preventing disability in older adults. The aim of this systematic review is to evaluate the literature on lower-extremity peripheral nerve function and mobility in studies of older adults, to identify knowledge gaps and provide recommendations for future research.

MATERIALS AND METHODS

The National Library of Medicine (PubMed) was searched on March 23, 2015 with no limits on publication dates. Figure 1 illustrates the search strategy, combining Medical Subject Heading (MeSH) terms and key words describing peripheral nerve function and mobility. We limited the search to "Aged: 65+ years" due to the dramatic increase in mobility limitations for this age group (www.cbo.gov/sites/default/files/108th-congress-2003-2004/reports/04-26-longtermcare.pdf), the English language, and humans, yielding 127 articles. We evaluated the titles and abstracts of these and excluded articles that included: no lower-extremity peripheral nerve function assessment (n=52), no mobility-related outcome (n=10), neither of these (n=15), no statistical evaluation of the relationship between these measures (n=12), no original research (n=3 reviews, n=2 commentaries), case reports (n=4), and only rare conditions (n=11; see Fig. 1). Diabetic neuropathy is a well-recognized risk factor for mobility limitation [8-11] (www.cdc.gov/mmwr/preview/mmwrhtml/mm5446a4.htm), so we excluded studies of diabetes only (n=11) in order to focus our review on more representative cohorts of older adults. We evaluated references from 7 articles and from review articles found during the search, resulting in 1 additional article. Eight articles were included.

RESULTS

The 8 articles on 6 separate cohorts included 6 cross-sectional and 2 longitudinal analyses. Study details are summarized in Table 1. Five studies were conducted in 4 U.S. populations, 3 of these community-dwelling, including 1 of disabled women (the Women's Health and Aging Study - WHAS) and 2 from a population with no mobility limitations at baseline (the Health, Aging and Body Composition Study - Health ABC). The other 2 U.S. studies recruited subjects from various residential facilities (e.g. subsidized senior housing, retirement communities/homes within the Rush Memory and Aging Project) and patients with peripheral arterial disease (PAD) (the Walking and Leg Circulation Studies - WALCS/WALCS II). Three Italian studies included: 2 from the same study of community-dwelling elderly (InCHIANTI); and 1 of both community-dwelling and institutionalized elderly (the Italian Longitudinal Study of Aging – ILSA). Mean ages across the studies ranged from 71-82, with all participants aged ≥65 years, except for one study (aged ≥59 years). Studies assessed sensory and/or motor nerve function using varied techniques including: vibration detection threshold only (n=2) [12, 16]; sensory measures and clinical signs and symptoms of neuropathy (n=2) [14, 17]; motor nerve conduction only (n=1) [18]; and a combination of both sensory measures and motor nerve conduction (n=3) [15, 19, 20]. While 3 studies measured both sensory and motor peripheral nerve function, only 2 of these presented the results separately [15, 20]. Mobility outcomes were diverse and included: standing balance scores/ratios (n=3) [12, 15, 16]; usual-paced (n=5) [12, 14-16, 19], fast-paced (n=1) [12], and narrow walking speed (n=1) [15]; chair stand ability/performance (n=2) [12, 15]; self-reported difficulty walking (n=1) [14]; physical performance battery score (n=3) [15, 17, 19]; self-reported walking and stair-climbing scores (n=1) [18]; the 36-Item Short Form Health Survey (SF-36) physical function scores (n=1) [18], and walking or stair-climbing difficulty/inability (n=1) [20].

A variety of methods that capture different domains of nerve function, such as sensory nerve function, which may be responsible for key somatosensory feedback for mobility postural control, and motor nerve function, which may provide information on muscle enervation,

were included. These common assessment techniques are described below.

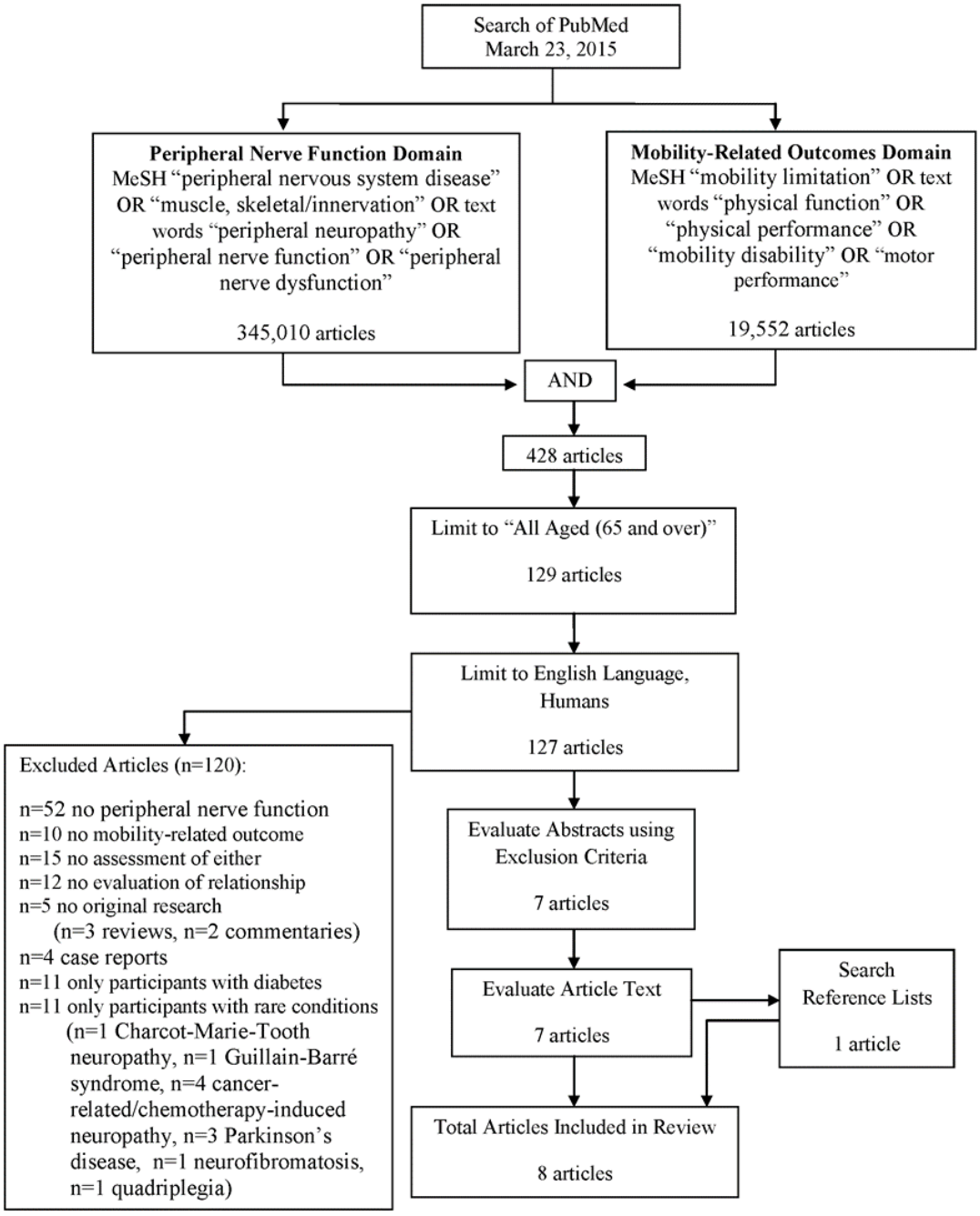

Figure 1. Flow diagram of search strategy for finding articles on the relationship between nerve function and mobility-related outcomes in older adults.

Table 1. Summary of Studies on Peripheral Nerve Function and Mobility-Related Outcomes

Author, Year	Participants	Mean Age ± SD (years)	Design	Sensory PN Measure(s)	Motor PN Measure(s)	Other PN Measure(s)
Resnick et al., 2000[12]	894 disabled community-dwelling older women from WHAS, USA	All ≥ 65 with more than one-quarter of the sample ≥ 85 (no mean ± SD provided)	Cross-sectional	Vibration threshold (vibrating platform)		
Ferrucci et al., 2004[14]	818 community dwelling older adults with no history of neurological disease from the InCHIANTI study, Italy	All ≥ 65 (no mean ± SD provided)	Cross-sectional	4.31 (2-g) and 4.56 (4-g) monofilament; Vibration threshold (non-graduated tuning fork)		
Inzitari et al., 2006[17]	1,052 older adults from ILSA, Italy	71 ± 5; Range: 65-84	Prospective cohort with 3 year follow-up	Bilateral Achilles tendon reflex, touch and pinprick sensation*		Two phase screening for DSN: 1) symptoms, medications, brief neurologic exam (heal-to-toe gait, bilateral Achilles tendon reflex, light touch and pinprick); positive screenings proceeded to 2) extensive neurologic exam, medical history, review of medical records when available (electromyography, sural nerve biopsy, blood and spinal fluid exam)*
Strotmeyer et al., 2008[15]	2,364 black and white community dwelling older adults with and without diabetes with no mobility disability at baseline from the Health ABC Study, USA	Men with diabetes 76.8 ± 2.7; Men without diabetes 76.7 ± 2.9; Women with diabetes 76.1 ± 2.8; Women without diabetes 76.5 ± 2.9; Range: 73-82	Cross-sectional	5.07 (10-g) and 4.17 (1.4-g) monofilament; Vibration threshold (vibrating platform);	Peroneal motor NCV and CMAP amplitude	
Buchman et al., 2009[16]	629 older adults without dementia in residential facilities from the Rush Memory and Aging Project, USA	81.8 ± 7.7	Cross-sectional	Vibration threshold (graduated tuning fork)		
Evans et al., 2011[18]	462 patients with PAD from WALCS and WALCS II, USA	75.0 ± 8.3; all ≥ 59 at baseline with nerve measures at 4th annual follow-up	Cross-sectional		Peroneal motor NCV	
Chiles et al., 2014[19]	983 community dwelling older adults from the InCHIANTI study, Italy	Participants with: No diabetes 74.6 ± 7.4; Impaired fasting glucose 74.8 ± 6.8; Diabetes 75.4 ±7.5; all ≥ 65	Cross-sectional	4.31 (2-g) and 4.56 (4-g) monofilament; Vibration threshold (non-graduated tuning fork)*	Peroneal motor NCV	Neuropathy score based on: 4.31 (2-g) and 4.56 (4-g) monofilament; Vibration threshold (non-graduated tuning fork); and Peroneal motor NCV
Ward et al., 2014[20]	2,148 black and white community dwelling older adults with no mobility disability at the first nerve exam from the Health ABC Study, USA	76.5 ± 2.9; Range: all 70-79 at baseline (nerve measures occurred 3 years after baseline)	Prospective cohort with 10 year follow-up	5.07 (10-g) and 4.17 (1.4-g) monofilament; Vibration threshold (vibrating platform). Neuropathy symptoms: numbness or tingling and aching or burning pain. Sensory neuropathy score based on: 5.07 (10-g) and 4.17 (1.4-g) monofilament; Vibration threshold	Peroneal motor NCV and CMAP amplitude; Motor neuropathy score based on Peroneal motor NCV and CMAP amplitude	Neuropathy score based on: 5.07 (10-g) and 4.17 (1.4-g) monofilament; Vibration threshold (vibrating platform); Peroneal motor NCV and CMAP amplitude

*These measures were only analyzed as part of a composite measure of poor nerve function/neuropathy; SD = standard deviation; PN = peripheral nerve; PAD = peripheral arterial disease; WHAS = Women's Health and Aging Study; InCHIANTI = Invecchiare nel Chianti ; g = gram; ILSA = Italian Longitudinal Study on Aging; DSN = Distal Symmetrical Neuropathy; Health ABC Study = Health, Aging and Body Composition Study; NCV = nerve conduction velocity; CMAP = compound muscle action potential; WALCS = Walking and Leg Circulation Study.

Nerve Conduction Studies (NCS)

NCS measure both motor and sensory nerves by electrically stimulating the nerve and evaluating the response using surface electrodes. Results include compound muscle action potential (CMAP for motor nerves) and sensory nerve action potential amplitude (SNAP for sensory nerves), the size of an evoked response from electrical stimulation of the nerve; and nerve conduction velocity (NCV), the speed at which the signal propagates down the nerve. Lower amplitudes may be indicative of a smaller number of functioning axons, while slower NCV may indicate loss of myelin sheath, which insulates the axon, and/or loss of the larger, faster conducting axons [21, 22] (www.ninds.nih.gov/disorders/peripheralneuropathy/detail_peripheralneuropathy.htm).

Monofilament detection

Monofilament detection assesses sensory nerve function. Pressure is applied to the extremity (often the dorsum of the large toe since it is highly sensitive and not as prone to callous) with a thin nylon thread until the thread buckles. The participants are asked to report, often during multiple trials, if/when they feel the pressure is being applied.

Vibration detection threshold

Vibration detection threshold (or vibration threshold) measures sensory nerve function by resting the bottom of the large toe on a vibrating knob connected to the top of a platform. The vibration is increased until the participant reports feeling it. Another method is a quantitative tuning fork, which involves adjusting calibrated weights on the two arms of the fork, to change the vibration from a scale of 0 to 8 [23]. With this method, the participant reports when they no longer feel the vibration.

Studies with cross-sectional mobility outcomes

Results summarizing associations between peripheral nerve measures and cross-sectional mobility outcomes are presented in Table 2. Resnick and colleagues analyzed data from 894 WHAS participants, a cohort of disabled community-dwelling women aged ≥65 years at baseline [12]. Vibration threshold categorized peripheral nerve impairment based on age-specific normal values [24]: 3.43 to <4.87 vibration units (vu; 0-6.5 vu=0-20 microns; www.physitemp.com/products/VibrationSensativity/) for mild, 4.87 to <6.31 vu for moderate, and ≥6.31 vu for severe [12]. Peripheral nerve impairment was related to poor balance (inability to tandem stand), (OR [95% CI]: 2.21 [1.36-3.60], 1.95 [1.07-3.55], and 3.02 [1.65-5.51] for mild, moderate, and severe nerve impairment, respectively vs. normal nerve function; p<0.05). Slower usual-paced (means [no SD reported]: -0.08, -0.08, and -0.15 m/s for mild, moderate, and severe nerve impairment, respectively, p<0.01 for pairwise comparisons) and fast-paced walking speeds (-0.13, -0.12, and -0.24 m/s for mild, moderate, and severe nerve impairment, respectively, p<0.01 for pairwise comparisons) were present in women with all levels of impairment. Inability to stand from a chair was only worse in women with severe nerve impairment (OR [95% CI]: 3.62 [1.99-6.54]). Models were adjusted for age, self-reported diabetes, BMI, vision, arthritis, and history of stroke. Diabetes (n=165, 18.5%) was not associated with any mobility measure after adjustment for sensory impairments, suggesting that sensory impairments may partly explain the association between diabetes and mobility. Quadriceps strength (dynamometer) and poor balance attenuated 10%-28% of the association of nerve impairment with chair stand performance and 30%-60% of its association with walking speed (in terms of β), demonstrating some mediation from muscle function and balance, as may be expected. This study presented some of the first cross-sectional evidence suggesting impairments in sensory peripheral nerve function may be related to poor mobility. Limitations include that only sensory nerve function was measured, lack of longitudinal data, and evaluation of disabled women only.

Ferrucci et al. investigated whether monofilament and tuning fork detection assessed by a neurologist were related to walking speed and self-reported ability to walk 1 km in 818 Italian elders from the InCHIANTI study (≥65 years at baseline, no history of neurological disease) [14]. Adjusting for age and sex, inability to feel either the 4.31 (2-g) or 4.56 (4-g) monofilament was associated with slower walking speed compared to the study sample average (% difference [95% CI]: -12% [-19%- -6%]) and inability to walk 1 km (OR [95% CI]: 2.9 [1.4-5.9]). Average walking speed was 1.04 m/s. This percent difference corresponds to 0.12 m/s, which exceeds the magnitude of clinically meaningful change and the difference associated with important outcomes like declines in self-reported mobility [25] and decreased survival [26]. Absent/reduced vibration threshold (vibration felt for <10 seconds [14]) measured with a tuning fork set to 128 Hz [14] was not associated with either mobility outcome. However, these tuning fork measures are not be able to detect subclinical declines and are largely clinical screening tools for major loss of sensation.

Strotmeyer et al. assessed whether sensory and motor nerve function were related to mobility in 2,364 community-dwelling white and black elderly with and without diabetes from the Health ABC Study (ages 70-79

at baseline) [15]. Sensory nerve function was assessed using average vibration threshold, and standard (10-g) and subclinical (1.4-g) monofilaments. Peroneal motor NCS were performed with stimulation at the popliteal fossa and fibular head and recording at the extensor digitorum brevis (highly reproducibly in a sample of these participants [27]). Better monofilament detection (10-g/1.4-g) was associated with higher scores on a supplemented version of the lower-extremity battery from the Established Populations for the Epidemiologic Studies of the Elderly (EPESE) [28] (β=0.174, p=0.003), faster narrow walking speed (β=0.049, p=0.006), and faster 5 repeated chair stand speed (β=0.015, p=0.007). Worse vibration threshold was associated with lower performance battery score (β= -0.004, p<0.001), slower usual walking speed (β= -0.0005, p=0.005), and lower standing balance ratio (β= -0.001, p<0.001). Higher CMAP amplitude was associated with higher performance battery score (β=0.105, p<0.001), faster usual walking speed (β=0.008, p=0.004), faster narrow walking speed (β=0.029, p<0.001), and higher standing balance ratio (β=0.014, p<0.001). Motor NCV was not associated with mobility. Models were adjusted for demographics, diabetes, body composition, lifestyle factors, and chronic conditions. These findings show that varied measures of peripheral nerve function may be associated with different components of mobility, though both sensory and motor nerve impairments were associated with the performance battery, usual and narrow walking speed, and balance. Adjustment for peripheral nerve function measures attenuated a proportion of the association of diabetes with poor mobility (20.8% for usual walking speed, 26.5% for standing balance ratio, 25.1% for performance battery score, and 11.4% for narrow walking speed). The use of multiple measures of sensory and motor nerve function afforded the investigation of their varied relationships to mobility. However, sensory nerve conduction was not assessed and older adults with initial mobility limitation were not included. Nevertheless, these findings are generalizable to a racially diverse, well-functioning population at baseline.

In 629 older adults from various residential facilities, the Rush Memory and Aging Project (age 81.8 ± 7.7 years) measured vibration threshold using a graduated tuning fork [16]. Gait and balance parameters were analyzed from a factor analysis of the EPESE. Gait included time and steps to walk 8 feet and turn around and balance score included a one leg stand, toe stand, and tandem walk. Adjusting for demographics, the ability to discriminate vibration at lower intensities was associated with a better balance score (β=0.067, p<0.001) and faster gait speed (β=0.045, p=0.005), although the association with gait speed was attenuated to nonsignificant when adjusting for BMI, physical activity, chronic conditions (including diabetes), and history of falls. Adjusting for diabetes alone did not affect the association between vibration threshold and balance or gait speed. Vibration threshold was not associated with leg strength measured using hand-held dynamometers. However, hand-held dynamometers may be subject to error depending on the strength of the examiner, particularly when measuring lower-extremity strength [29, 30]. This study did not include a measure of motor nerve function, though supported the association between sensory nerve function and balance.

Evans and colleagues performed peroneal motor NCS with stimulation at the popliteal fossa (recording site not reported) in 462 patients (age ≥59 years at baseline) with PAD (ankle brachial index <0.9) from WALCS/WALCS II [18]. Adjusting for age and sex, worse NCV quartile scores were associated with lower SF-36 physical function scores (worst to best: 38.8, 50.2, 53.9, 52.2, p-trend<0.001), lower Walking Impairment Questionnaire (WIQ) speed scores (worst to best: 29.0, 37.4, 35.4, 41.0, p-trend=0.003), and lower stair-climbing scores (worst to best: 36.4, 43.6, 47.3, 50.6, p-trend=0.001). Worse CMAP amplitude quartile scores were associated with lower SF-36 physical function scores (worst to best: 41.1, 48.4, 52.5, 52.6, p-trend<0.001), lower WIQ walking distance scores (worst to best: 33.4, 38.4, 43.8, 41.8, p-trend=0.03), and lower stair-climbing scores (worst to best: 35.2, 46.5, 48.8, 46.4, p-trend=0.007). Results remained consistent when adjusting for lifestyle factors, diabetes, and other chronic conditions. Importantly, persons with severe PAD typically have worse peripheral nerve function [31] and poorer lower-extremity performance [32]; however, these relationships are understudied in older adults. This study did not assess sensory nerve impairments, an important limitation since these also may affect mobility.

Chiles et al. calculated neuropathy scores in a further analysis of the InCHIANTI study [19]. Impairments on the following peripheral nerve function tests were summed, assigning 1 point for each impairment for a total possible score of 5: peroneal motor NCV <40 m/s (stimulation and recording sites not specified), CMAP amplitude <3 mV, inability to feel the 4.31 (2-g) monofilament, inability to feel the 4.56 (4-g) monofilament, and absent/reduced vibration threshold (felt for <10 seconds [14]) with a tuning fork [14]. They also evaluated NCV continuously and found that worse velocity was associated with lower SPPB scores (β=0.05, p<0.05) but not slower gait speed, while worse summed neuropathy scores were associated with both lower SPPB scores (β= -0.94 for 2 vs. 0-1; β= -2.42 for ≥3 vs. 1; both p<0.01) and slower gait speed (β= -0.10 for 2 vs. 0-1; β= -0.15 for ≥3 vs. 1; both p<0.01), adjusting for demographics, BMI, smoking status, and diabetes. The

association between diabetes and SPPB was attenuated by 8% when adjusted for NCV, by 19% when adjusted for neuropathy score, and by 33% when adjusted for both, although diabetes remained significant in all models. These findings provide additional support that peripheral nerve function may partially mediate the relationship between diabetes and poor mobility. A global neuropathy score based on clinical cut points was more strongly associated with mobility than a single peripheral nerve function measure alone, although only NCV was evaluated separately. Poor neuropathy scores may be a sign of more severely impaired nerves, which may contribute more strongly to poorer mobility.

Table 2. Summary of Results from Studies on Peripheral Nerve Function and Mobility-Related Outcomes

Peripheral nerve measures	Standing balance	Usual paced walking speed	Fast paced walking speed	Narrow walking speed	Chair stand ability, once	Chair stand speed, 5 repeated	Self-reported difficulty walking 1 km	SPPB/ PPB	WIQ walking score	WIQ stair climbing score	SF-36	Mobility disability
Neuropathy score		C[19]						C[19]				L[20]
DSN								L[17]				
Sensory measures												
Vibration threshold (vibrating platform)	C[12, 15]	C[12, 15]	C[12]	0[15]	C[12]	0[15]		C[15]				L[20]
Vibration threshold (graduated tuning fork)	C[16]	0[16]										
Vibration threshold (non-graduated tuning fork)		0[14]					0[14]					
2g/4-g monofilament detection*		C[14]					C[14]					
10-g monofilament detection	0[15]	0[15]		C[15]		C[15]		C[15]				
Sensory neuropath score												L[20]
Neuropathy symptoms												L[20]
Motor measures												
Peroneal CMAP	C[15]	C[15]		C[15]		0[15]		C[15]	C[18]	C[18]	C[18]	L[20]
Peroneal motor NCV	0[15]	0[15, 19]		0[15]		0[15]		0[15], C[19]	C[18]	C[18]	C[18]	
Motor neuropathy score												L[20]

C = significant associations found with cross-sectional mobility. L= significant associations found with longitudinal mobility. 0 = no association found. Blank cell = no association assessed. *No distinction was made between results for different monofilament forces within the manuscript. SPPB = Short Physical Performance Battery; PPB = Physical Performance Battery; WIQ = Walking Impairment Questionnaire; SF-36 = 36-Item Short Form Health Survey; DSN = Distal Symmetrical Neuropathy; NCV = nerve conduction velocity. CMAP = compound muscle action potential.

Studies with longitudinal mobility outcomes

Results summarizing associations between peripheral nerve measures and longitudinal mobility outcomes are presented in Table 2. A subsample of participants from ILSA [17] were evaluated for DSN using a two phase screening process. Participants with a self-reported diagnosis of DSN or diabetes or ≥1 sign or symptom of neuropathy during the first phase underwent a full neurological exam. Motor performance was calculated as a composite score from 0 (worst) to 14 (best) by summing the following items: time to stand from a chair, number of

times a participant could step up on a 23-cm step in 10 seconds, tandem walk, standing on one leg, walking speed, and number of steps to turn 180°, as previously described [33, 34]. Motor performance decline over three years was defined continuously and dichotomously as a score difference above the 75th percentile (decliners) or below (non-decliners). In 1052 participants (age 71 ± 5 years) with initially non-impaired motor performance (score of 14), Inzitari and colleagues found that signs and symptoms of DSN assessed during the screening phase predicted decline in motor performance score (β=0.73, p=0.001 for continuous decline; OR [95% CI]: 2.00 [1.03-3.87] for decliners vs. non-decliners) after adjusting for demographics, diabetes, chronic conditions, ADL, and IADL (instrumental ADL). Clinical DSN was associated with poor motor performance, independent of diabetes, which has clinical relevance since older adults without diabetes may be less likely to be screened or have a full clinical assessment for neuropathy. While the screening for neuropathy was quite comprehensive in this study, the adoption of this method by other large studies is unlikely since it is time intensive, expensive, and requires a physician. The effects of subclinical peripheral nerve impairments were not studied. In addition, substantial attrition occurred between the two time points (33%), which may have resulted in retention bias. This study did not evaluate the effect of changes in nerve function over time, though was important in showing that initial DSN predicted mobility decline over time.

A longitudinal analysis within the Health ABC study investigated whether sensory and motor peripheral nerve function predicted incident mobility disability, defined as two consecutive self-reports of "a lot of difficulty/ inability" to walk a one-quarter of a mile or climb 10 steps [20, 35]. Participants were 2,148 community-dwelling older adults (mean age 76.5 ± 2.9) with no mobility disability at the 2000/01 nerve exam, which occurred 3 years after baseline. Motor and sensory peripheral nerve function were measured as described within the cross-sectional study. [15] Additionally, self-reported symptoms of numbness or tingling and sudden stabbing, burning pain, or deep aching in the legs or feet were included. Counts of sensory, motor, and combined sensory and motor nerve impairments were created using clinically meaningful values of 1) <1 mV for CMAP amplitude; 2) < 40 m/s for motor NCV; [21] 3) 1.4-g or 10-g monofilament insensitivity; and 4) inability to detect vibration (threshold ≥131 μ). One standard deviation worse amplitude (HR=1.29, 95% CI=1.16–1.44) and vibration threshold (HR=1.13, 95% CI=1.04–1.23) and one (HR=1.34, 95% CI=1.11–1.63) and two symptoms (HR=1.65, 95% CI=1.26–2.17) were associated with incident mobility disability. These analyses adjusted for demographics, diabetes, body composition, chronic conditions, and lifestyle factors. Two motor (HR=2.10, 95% CI=1.43–3.09), two sensory (HR=1.91, 95% CI=1.31–2.88), and ≥3 over all peripheral nerve impairments (HR=2.33, 95% CI=1.54–3.53) were associated with even higher hazards of incident mobility disability (vs. no impairments), adjusting for demographics, height, weight, and site. These findings support that multiple nerve function impairments may have a stronger effect on disability than individual nerve impairments alone. Quadriceps strength attenuated the relationship of mobility disability to vibration threshold (4%) and having two motor impairments (8%) to nonsignificant. Strength also attenuated having ≥3 nerve impairments (5%), although it remained a significant predictor of disability. Each of these nerve function measures significantly predicted strength, [36] and strength significantly predicted disability in all models, suggesting that it may be a mediator between nerve impairment and mobility disability. The interaction between diabetes and 1.4-g monofilament detection was significantly associated with disability (HR=1.48, 95% CI=1.02–2.16). The 1.4-g monofilament is typically used to detect subclinical sensory impairment and is not often used in examining individuals with diabetes; however, these findings suggest that it may be useful for identifying individuals with diabetes at risk of developing disability. Strengths of this study include the prospective cohort design, 10 years of follow-up capturing incident mobility disability, and the assessment of multiple domains of lower-extremity peripheral nerve function. Importantly, this study shows that lower-extremity peripheral nerve function impairment precedes mobility disability. This study was limited in that nerve function was only analyzed at one time point and therefore the effects of the duration of nerve impairment were not assessed. In addition, this study did not measure sensory nerve conduction and analyses were limited to older adults with no initial mobility limitation.

DISCUSSION

This systematic review presents evidence from 8 epidemiologic studies, 6 cross-sectional and 2 longitudinal studies of older adults showing that poor sensory and motor peripheral nerve function are associated with and predict poor physical function and mobility disability. Both sensory and motor peripheral nerve function were associated with standing balance scores/ratios, [12, 15, 16] usual [12, 14-16, 19] and narrow gait speed [15], performance battery scores, [15, 17, 19] and mobility disability [20]. Older adults both with and without diabetes experience a high incidence and prevalence of poor nerve function and overt neuropathy [6, 8]. In one study of adults with a mean age of 76.5 years

and no mobility disability at baseline, 55% had ≥1 peripheral nerve impairment initially and approximately half of these individuals had no neuropathy symptoms [20]. By the end of the 10-year follow-up, 30% of this study population developed mobility disability. Findings from this review suggest that much of the impaired nerve function among older adults that may lead to mobility decline may go undetected, particularly among those without diabetes who are not considered traditionally high-risk.

Importantly, the relationship between nerve function and mobility appears to be mostly consistent across varied levels of peripheral nerve impairment severity [12], different populations, subgroups of older adults, and different methods of measuring of mobility [14, 15]. Of the studies that were able to assess the effects of sex [14-20] and race [15, 18, 20] on the relationship, none reported significant differences, although only the effects of white and black race were investigated. More data is needed among additional ethnic groups. Several studies indicate that peripheral nerve impairments may partially explain the association with diabetes and poor mobility [12, 15, 19]. In 6 studies, peripheral nerve function was associated with mobility independent of diabetes, emphasizing the importance of investigating additional risk factors for impaired nerve function. Clinically diagnosed peripheral neuropathy is a well-known risk factor for poor mobility in individuals with diabetes [8-11] (www.cdc.gov/mmwr/preview/mmwrhtml/mm5446a4.htm); although our review indicates that advanced age is an important risk factor for poor nerve function, independent of diabetes [6, 8]. In addition, older adults with poor peripheral nerve function in combination with certain comorbidities, such as PAD may represent important high-risk groups towards which interventions should be focused.

Findings suggest that a greater burden of sensory and motor nerve impairments may lead to worse mobility compared to individual impairments alone. Evidence also suggests that poor nerve function may even be detrimental at subclinical levels [12, 14, 15, 20], although more longitudinal data from older adults with no to minimal impairments at baseline are needed as confirmation. Two studies assessed composite neuropathy scores and found that these were positively associated with all mobility outcomes including usual paced walking speed [19], performance battery score [19], and mobility disability [20]. This is particularly important since chronic sensorimotor distal polyneuropathy, which affects both sensory and motor nerves, is recognized as one of the most common forms of neuropathy [37].

We found 3 conflicting findings in the literature upon which further examination may shed light on the effects of different methodological approaches to examining the nerve impairment-mobility relationship. First, peroneal motor NCV was related to the SPPB in one study [19] but was not related to a supplemented version of the EPESE SPPB in another study [15]. The supplemented Health ABC version of the EPESE SPPB captures a wider range of function by including additional measures to overcome the ceiling effect of the original battery. Therefore it is unlikely that the lack of relationship is due to the use of the supplemented SPPB. Perhaps the adjustment of more chronic conditions attenuated the relationship by accounting for important explanatory factors. In addition, a number of measurement and physiological factors (e.g., lower limb temperature) may influence the reliability of NCS measures [27, 38]. Some factors can be minimized, even in older populations, by using standardized clinical measurement procedures [27, 38]. Despite this, NCV may be subject to more measurement variability than CMAP amplitude due to variations in temperature and height. Moreover, more missing data may occur for NCV than for amplitude. Among adults age ≥80 years, 25% and 40% may exhibit absent NC responses at the peroneal and sural nerves, respectively [39]. Further review of an absent response is needed to determine whether it resulted from difficulty in stimulation or truly impaired nerve function [39]. Upon evidence of truly impaired nerve function, a value of 0 may be assigned to the amplitude. However, with an absent CMAP response, NCV is not able to be obtained and therefore has missing data.

Second, vibration threshold was associated with usual gait speed when assessed using a vibrating platform [15], which quantifies a wide range of sensory nerve function (e.g. ability to feel 0-131 microns) but not when using a standard non-quantitative tuning fork [14]. The relationship between vibration threshold assessed with a graduated tuning fork, which quantifies sensory nerve function using a smaller scale (0-8), and usual gait speed was attenuated to nonsignificant when adjusted for BMI, physical activity, chronic conditions, and history of falls [16]. Similarly, monofilament detection was associated with usual gait speed when using the more sensitive 2-g and 4-g threads [14], but not when using the standard 10-g thread [15]. These findings may indicate a need for more rigorous testing to detect subclinical impairments when predicting mobility decline. Sensitive methodology may become particularly important when analyzing longitudinal data in order to capture changes in nerve function.

Methods of peripheral nerve assessment vary in testing time, expense of equipment, training requirements of the examiner, and practicality of implementation in large studies. NCS are an objective and reliable method of assessing nerve function [27, 40-42] and the most quantitative method to detect peripheral neuropathy non-invasively. [7] However, equipment for NCS is expensive, measurement is relatively time consuming

(e.g. 20-30 minutes per nerve), and requires a well-trained examiner and board-certified physician to interpret certain data. Furthermore, absent responses may present analytic challenges since it is not always clear whether these results are due to difficulty in stimulation or truly impaired nerve function [39]. However, absent sural responses were associated with more severe diabetic peripheral neuropathy assessed by vibration threshold in diabetic younger adults (mean ages 44.7 ± 1.02 to 48.5 ± 1.11 years) [43]. Future work is needed to extend these findings to older adults. While NCS are considered "gold standard" measures clinically, limitations may exist to using these in older adults for longitudinal changes in nerve function.

Other methods of assessing nerve function may be more economical and less time intensive but are limited to assessing sensory nerve function, such as monofilament detection and vibration threshold. These measures typically require the participant to report feeling the stimulation and are therefore subjective. Methods range in sensitivity, quantitative capacity, and predictiveness. Standard 10-g monofilament testing is used clinically to predict diabetic foot ulceration [44], whereas light-touch 1.4-g and 2-g monofilament testing are generally used to detect subclinical impairment [45]. Lighter touch monofilaments, e.g. up to 4-g, may be more sensitive measures capable of detecting neuropathy earlier than the 10-g monofilament [46]. Monofilament threads of varying pressure can be used in combination as a semi-quantitative measure of touch sensation [47]. Vibration threshold measured using vibrating platforms quantify wide ranges of sensory nerve function (e.g. ability to feel 0-131 microns). Some tuning forks can provide a quantitative measure of vibration threshold that has been shown to correlate with the SNAP amplitude [23]. Work by Oyer and colleagues suggests that categorizing tuning fork thresholds as 10 seconds or less can detect significant impairment in diabetic adults (ages of participants not reported) who exhibit normal 10-g monofilament detection [48]. Additionally, signs and symptoms may be used to measure poor nerve function, but may not be able to detect subclinical disease.

Values of sensitivity and specificity should be assessed for a wide range of tests in older adults, particularly since they may have poor nerve function that is asymptomatic. Compared to NCS, 10-g monofilament testing had 77% sensitivity and 96% specificity detecting DSN, while vibration threshold had 53-80% sensitivity and 98-99% specificity, although these were performed in younger to middle aged adults (ages 37.6 ± 10.4 to 57.7 ± 10.1 years) [7] with and without diabetes and/or neuropathy, not in older adults. A study of middle aged adults with diabetic peripheral neuropathy (ages 53 ± 3.6 years) and younger healthy controls (ages 33 ± 3.2 years) found that a combination of thermal sensitivity and vibration threshold had optimum values of sensitivity (92-95%) and specificity (77-86%) for detecting peripheral neuropathy when comparing thermal, vibration, and monofilament testing [49]. Thermal sensitivity, is primarily mediated by thinly myelinated or unmyelinated small nerve fibers, while the previously described tests assess peripheral nerve function that is primarily mediated by large myelinated nerve fibers and some thinly myelinated fibers [49]. However, thermal testing is uncommon in studies of older adults. Moreover, little is known on how these tests perform in older adults with cognitive impairment.

Many of the studies identified were limited to measuring sensory nerve function. These studies may not fully capture the relationship between nerve function and mobility since motor and sensory nerves may vary in their associations with measures of mobility and may be mediated by different mechanisms [15, 50, 51]. Poor motor nerve function may contribute to the observed reduction in size and number of muscle fibers, preferentially affecting type II fast twitch fibers [52] and may lead to declines in muscle density [51], a measure of muscle-fat infiltration and intracellular fat content in muscle [53]. These changes may precipitate declines in muscle strength and muscle power [54], though this has not been examined prospectively. Muscle power has been associated with peripheral nerve function in older men [50] and may be an important mechanism to assess when investigating its relationship with mobility since it captures both force and velocity, which are likely dependent on the number and firing rate of motor units [55]. Sensory nerve function may also impact mobility by affecting strength and power [50]. Evidence shows that experimentally blocking sensory input may lead to reduced maximal voluntary contractions [56], while somatosensory and cutaneous stimulation may result in short-term increases in strength and muscle activation [57, 58]. The relationships between these different components of peripheral nerve and muscle function are not fully understood. Both motor and sensory nerve function parameters have also been associated with proprioception, which involves various muscle-, joint-, and cutaneous-mechanoreceptors [59]. Loss of proprioception has been linked to impaired balance performance [60] and falls [60, 61]. Although hypothesized to be primarily controlled by the sensory system, ankle inversion and eversion proprioception showed a strong association with peroneal CMAP, demonstrating the important link between motor and sensory nerve function [59]. The most common types of age-related and diabetic neuropathies affect both sensory and motor nerves, and therefore, it may be difficult to separate out the individual effects of each [37].

This review only assessed the relationship between measures of lower-extremity peripheral nerve function and common age-related declines in mobility, not exact etiology or mechanisms for these declines. For instance, getting out of a chair may be heavily influenced by proximal neuropathies, which were not covered in this review. However, more research is needed on the potential mechanisms in which nerve impairments may lead specifically to mobility limitations and disability. Mechanisms in the relationship between peripheral nerve impairments and mobility decline may guide potential therapeutic interventions. For instance, in middle aged to older adults with a range of peripheral nerve function, greater hip strength was found in those who had better balance than would be expected from their proprioceptive threshold and age [62]. These findings suggest that future work should examine hip strengthening as potential intervention to improve balance, particularly in older adults with impaired ankle proprioception.

A number of additional gaps in the current literature need to be addressed. First, the relationships between lower-extremity peripheral nerve function and mobility in subgroups of older populations, such as different races and ethnicities, frail or institutionalized older adults and the young-old vs. the old-old, are unknown and should be assessed, particularly given the health disparities of disease-related risk factors for neuropathy. The performance of different nerve function measures should be evaluated among individuals with varying levels of cognitive impairment, particularly those that rely on more subjective assessment. Given that varied levels of severity of peripheral nerve impairment are associated with poor mobility outcomes, future work should quantify peripheral nerve function continuously rather than dichotomously. Focusing on a spectrum of impairment is particularly important for preventing the progression of nerve function decline and mobility impairments. In addition, small fiber sensory neuropathy, which manifests as a burning sensation in the feet and can be assessed by thermal sensitivity testing [49] and more advanced techniques such as corneal confocal microscopy [63], has been understudied in the context of late-life mobility decline and should be investigated. Limited longitudinal data on nerve function in older adults exists. Specifically, data from longitudinal cohort studies are needed to assess the duration effects of peripheral nerve impairment on mobility declines as well as potential mechanisms for the relationship such as muscle structure and function. Understanding the role of neuromuscular parameters in the disablement process may help identify multiple points of intervention. Interventions targeting individuals with poor and at risk for peripheral nerve function decline should be investigated, with the goal of preventing subsequent disability.

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