From the Society for Vascular Surgery

Preliminary evidence that low ankle-brachial index is associated with reduced bilateral hip extensor strength and functional mobility in peripheral arterial disease

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Objective: **Peripheral arterial disease (PAD) has been associated with skeletal muscle pathology, including atrophy of the affected muscles. In addition, oxidative metabolism is impaired, muscle function is reduced, and gait and mobility are restricted. We hypothesized that greater severity of symptomatic PAD would be associated with lower levels of muscle mass, strength, and endurance, and that these musculoskeletal abnormalities in turn would impair functional performance and walking ability in patients with PAD.**

Methods: **We assessed 22 persons with intermittent claudication from PAD in this cross-sectional pilot study. Outcome assessments included initial claudication distance and absolute claudication distance via treadmill protocols and outcomes from the 6-minute walk (6MW). Secondary outcomes included one repetition maximum strength/endurance testing of hip extensors, hip abductors, quadriceps, hamstrings, plantar flexors, pectoral, and upper back muscle groups, as well as performance-based tests of function. Univariate and stepwise multiple regression models were constructed to evaluate relationships and are presented.**

Results: **Twenty-two participants (63.6% male; mean [standard deviation] age, 73.6 [8.2] years; range, 55-85 years) were studied. Mean (standard deviation) resting ankle-brachial index (ABI) was 0.54 ([0.13]; range, 0.28-0.82), and participants ranged from having mild claudication to rest pain. Lower resting ABI was significantly associated with reduced bilateral hip extensor strength ($r = 0.54$; $P = .007$) and reduced whole body strength ($r = 0.32$; $P = .05$). In addition, lower ABI was associated with a shorter distance to first stop during the 6MW ($r = 0.38$; $P = .05$) and poorer single leg balance ($r = 0.44$; $P = .03$). Reduced bilateral hip extensor strength was also significantly associated with functional outcomes, including reduced 6MW distance to first stop ($r = 0.74$; $P = .001$), reduced 6MW distance ($r = 0.75$; $P < .001$), and reduced total short physical performance battery score (worse function; $r = 0.75$; $P = .003$).**

Conclusions: **Our results suggest the existence of a causal pathway from a reduction in ABI to muscle atrophy and weakness, to whole body disability represented by claudication outcomes and performance-based tests of functional mobility in an older cohort with symptomatic PAD. Longitudinal outcomes from this study and future trials are required to investigate the effects of an anabolic intervention targeting the muscles involved in mobility and activities of daily living and whether an increase in muscle strength will improve symptoms of claudication and lead to improvements in other functional outcomes in patients with PAD. (J Vasc Surg 2013;57:963-73.)**

Intermittent claudication is a potentially disabling symptom of peripheral arterial disease (PAD), which is characterized by, but not limited to, calf pain that limits walking. Intermittent claudication has been shown to lead to skeletal muscle injury, characterized by a loss of muscle fibers and mild atrophy of the affected muscles.[1] In addition, although research is limited, it has been shown that oxidative metabolism is impaired,[2,3] gait and mobility restricted, and muscle function reduced[4-7] in patients with PAD. This potentially leads to loss of musculoskeletal and cardiovascular fitness, physical inactivity, impaired functional performance, and thereby reduced quality of life. Evidence suggesting that a lower ankle-brachial index (ABI), a measure of lower extremity ischemia, is related to lower physical activity levels, slower walking speed, shorter 6-minute walk distance (6MWD), and poorer tandem stand performance in PAD[5] has ignited interest as to whether PAD is associated with reduced muscle

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REPAIR IT has been funded in part by the Tom Penrose Community and Service Grant of the ESSA and was carried out at Exercise, Health and Performance, Faculty of Health Sciences, University of Sydney.

Author conflict of interest: none.

Presented at the 2012 Vascular Annual Meeting of the Society for Vascular Surgery, National Harbor, Md, June 7-9, 2012.

Additional material for this article may be found online at www.jvascsurg.org.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214/$36.00

http://dx.doi.org/10.1016/j.jvs.2012.08.103

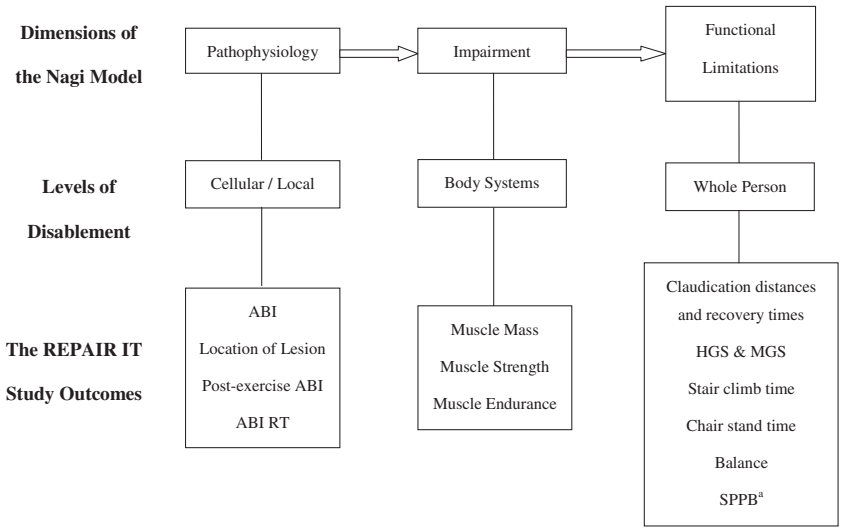

Fig 1. Nagi disablement model tailored to the Regular Exercise for Peripheral Arterial Ischemia: a Randomized Controlled Intervention Trial (*REPAIR IT*) pilot study hypotheses and outcomes. *ABI,* Ankle-brachial index; *HGS,* habitual gait speed; *MGS,* maximal gait speed; *RT,* recovery time; *SPPB,* short physical performance battery. [a]The SPPB[20] is a measure of lower extremity mobility[14] and pools the results from the repeated chair stand, standing balance, and habitual gait speed. A lower score equals poorer function.

mass, strength, and endurance, and whether muscle weakness is causally related to the functional impairment and reduced walking ability imposed by PAD.

Therefore, as represented in the Nagi disablement model (Fig 1), this study aimed to first test the hypothesis that more severe PAD would be associated with *both* lower muscle mass, strength, and endurance (proximate mediators), as well as more impaired mobility and functional performance (distal outcomes). We hypothesized that this relationship would be present despite the multiple comorbidities present among a cohort with PAD that may affect both the proximal mediators and distal outcomes. Second, we hypothesized that those musculoskeletal impairments would also be directly associated with reduced walking ability and more impaired functional performance. Finally, we hypothesized that controlling for musculoskeletal impairments would attenuate or eliminate the relationship between PAD severity and distal outcomes of mobility and function, suggesting that they mediate these relationships despite the presence of mobility limitations from other comorbidities. The cross-sectional characteristics of this cohort and testing of the hypothesized relationships among these characteristics are presented.

METHODS

This cross-sectional study was part of a randomized, controlled pilot trial conducted by the University of Sydney, titled REPAIR IT (Regular Exercise for Peripheral Arterial Ischemia: a Randomized Controlled Intervention Trial). Ethics approval was gained on October 18, 2009, from St. Vincent's Hospital (Reference #09/079) and the University of Sydney (Reference #12334) Human Research Ethics Committees. The trial was registered with the Australia New Zealand Clinical Trials Registry (ANZCTR #12609000457246). Participants (n = 22) were recruited into the study from July 2010 via direct referral from clinics led by vascular surgeons. Written informed consent was obtained before commencement of baseline testing. Patients were included if they were older than 50 years and suffered from intermittent claudication from PAD confirmed by a vascular surgeon. Exclusion criteria included asymptomatic PAD, tissue necrosis or gangrene, significant cognitive impairment, inability to comply with study requirements, and/or current participation in regular moderate- to high-intensity exercise. Persons with specific contraindications to progressive resistance training or who were awaiting surgical intervention for PAD or other vascular disease also were excluded.

Primary outcomes. The ABI was measured twice after 10 minutes of supine rest using a LifeDop nondisplay Doppler with an 8-MHz vascular probe (Summit Doppler, Golden, Colo) per the American Heart Association (AHA) guidelines.[8] Each leg-specific ABI was then calculated and classified according to the AHA interpretation of ABI.[8] Participants whose ABI was >1.3 (n = 1) were excluded from analyses involving measurements related to PAD. Each participant's location of lesion, identified via ultrasound within 6 months of commencement of the trial, was classified as either 1 = proximal disease, where the lesion was located in the aortoiliac, iliofemoral, or common femoral region; or 2 = distal disease, where the lesion was located in the superficial femoral, popliteal, and/or tibial arteries. Multilevel disease

was classified as distal as long as one of the lesions was at the below-knee level.

Participants performed a constant workload treadmill walking test where the workload was set at the speed and grade at which the individual participant reached 80% VO_2 peak, measured during a maximum graded treadmill stress test 1 week earlier. The exercise and ABI testing protocols were conducted per AHA guidelines for treadmill testing with ABI assessments.[8] The time at which claudication pain commenced was recorded and converted to the initial claudication distance (ICD). If a participant had rest pain, then the ICD was treated as 0 or 0.01 m to allow for statistical analysis. The time at which the treadmill stopped was recorded and converted to absolute claudication distance, and the reason for stopping was also recorded. The time at which ankle pressures returned to pre-exercise levels was recorded as the ABI recovery time. In addition, the participant was asked to notify the assessor as to when the claudication pain had completely ceased. This was recorded as the claudication recovery time.

The 6MW test was performed according to Guyatt et al[9] and AHA recommendations[8] and was used to assess flat ground walking endurance. In addition, participants were asked to notify the assessor as soon as claudication commenced (6MW ICD). If participants needed to stop during the test, the distance at which they stopped for the first time was recorded as the distance to first stop. In addition, the reason why they stopped was recorded. If no stops were made during the test, the distance to first stop was recorded as the total walking distance covered at completion of the 6 minutes (6MWD) to the nearest 0.1 m. At completion of the 6 minutes, the participants were asked to sit down immediately and inform the assessor when the pain had completely gone (claudication recovery time). Each participant completed the 6MW twice at the baseline assessment, 1 week apart, with the better of the two trials used in statistical analysis. Previous randomized controlled trials from our research laboratory have reported the coefficient of variance (CV) for this test as mean of 3.0% (range, 0.0%-13.0%).[10]

Secondary outcomes and clinical characteristics. Demographic information was obtained using participant self-report and checked by the assessor during each assessment. Smoking and alcohol history, physical activity, and comorbidities affecting walking and medical history were initially obtained through interviews and confirmed through the physician screening. Comorbidity affecting walking was a self-reported mobility limitation attributed to a chronic condition. Each participant nominated the predominant cause of mobility limitation other than claudication, in his or her opinion. This was then coded as a dichotomous variable (ie, present or not). Body mass index was calculated and waist circumference was measured according to the World Health Organization Expert Committee protocols.[11] Percent body fat, skeletal muscle mass (SMM), and fat-free mass (FFM) were measured according to Lange et al.[10]

Peak dynamic muscle strength was assessed using digital K400 Keiser pneumatic resistance machines (Keiser Sports Health Ltd, Fresno, Calif). One-repetition maximum tests were performed twice at baseline, 1 week apart, according to the protocol of de Vos et al,[12] with the higher results used as the one-repetition maximum. Muscle strength was tested bilaterally on knee extension, knee flexion, chest press, and seated row. Unilateral hip abduction and hip extension strength were tested for each leg individually. Bilateral hip extension was defined as the summed unilateral hip extension. Calf muscle strength was measured in kilograms using the hack squat calf raise with range of motion carefully monitored. Previous randomized controlled trials from our research laboratory have reported a CV for these exercises as mean of 13.1% (range, 9.8%-21.7%).[10]

Dynamic muscle endurance was tested on the same day as muscle strength after resting and performed according to Lange et al.[10] Calf muscle endurance was measured by asking the participant to complete as many full-range standing calf raises as possible. Each calf raise was performed on a step, with hands placed on a horizontal bar for balance with range measured and monitored carefully. Standing balance, chair stand, stair climb, and gait speeds all were assessed as reported by Gates et al.[13] Previous trials in our laboratory have reported the CV for gait speed over two trials as mean of 4.6 (range, 0.7%-12.5%).[10] The short physical performance battery (SPPB) was scored according to McDermott et al.[14,15]

Statistical analysis. Outcomes were measured by blinded assessors and analyzed using SPSS software (PASW Statistics 18; IBM Corp, Armonk, NY). Data were inspected for normality visually and statistically and expressed as mean (standard deviation) or median (range), as appropriate. A sample was considered skewed if the standard error of the mean was ≤ -1 or ≥ 1. Non-normally distributed data were log transformed if possible for use with parametric statistics. If normalization was not possible, nonparametric statistics were substituted. Potential effects of medication usage and self-reported mobility limitation on outcomes were analyzed using independent sample *t*-tests. Relationships between potential predictors of primary and secondary outcomes were determined by simple, stepwise, and multiple regression models. Any variables identified as significant predictors of performance-related outcomes were checked for colinearity and then entered into a linear stepwise multiple regression model. Covariates specified a priori include age, gender, and severity of disease, and, if necessary, were adjusted for as appropriate. Any score of 0 was treated as 0.01 for the purpose of statistical analysis. Statistical significance was accepted at $P \leq .05$. A Bonferroni correction factor was not used, as all hypotheses were specified a priori.[16]

RESULTS

Baseline characteristics. We identified and assessed 70 participants for eligibility from the vascular clinic located at Concord Repatriation Hospital. The reasons for exclusion of 48 potential participants is outlined in Fig 2.

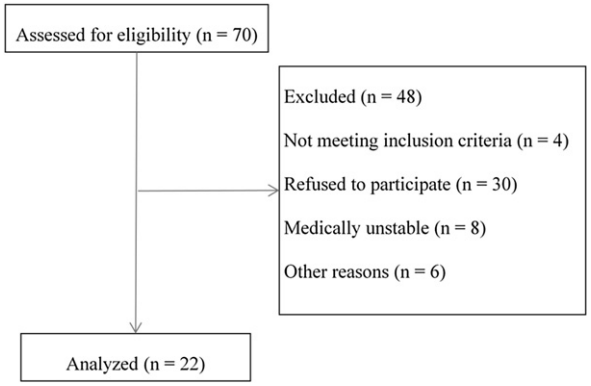

Fig 2. REPAIR IT (Regular Exercise for Peripheral Arterial Ischemia: a Randomized Controlled Intervention Trial) CONSORT (Consolidated Standards of Reporting Trials) flowchart. n = sample size.

Twenty-two participants completed baseline testing. A summary of characteristics of participants is presented in Table I . Mean (standard deviation) age of the 22 participants was 73.6 (8.2) years, and 14 participants (63.6%) were men. On average, most men were overweight with an average body mass index of 29.34 (4.47). Women on average were within the healthy weight range, with body mass index of 23.89 (3.12). Men, on average, had a larger median waist circumference of 105.9 cm (range, 89.8-120.7 cm) than the current recommendation of ≤94 cm for men with cardiovascular disease.[11] Women's median waist circumference of 80.8 cm (range, 72.0-88.7 cm) was only slightly larger than the recommended ≤80 cm. Fifty-five percent of the cohort drank alcohol on most days of the week, with consumption averaging 12 (12) drinks per week. In total, 73% of the cohort had a smoking history, 23% were current smokers, and 50% ex-smokers. Average smoking consumption was a mean 38 (30) pack-years (packs per day × years smoked). Almost half (45.5%) of the cohort was sedentary, with an average of six of the nine lifestyle and nonmodifiable risk factors for cardiovascular disease (6.0 [1.1]).[8,17] The Framingham 10-year risk score was 16.8% (9%) on average.

Comorbidity associated with PAD was relatively common, with 63.6% of the cohort having coronary artery disease, including 13.6% who had experienced a previous myocardial infarction. Only 13.6% of the cohort had cerebrovascular disease. However, almost all participants (95.5%) had hypercholesterolemia. In addition, most of the cohort (81.8%) had hypertension and 18.2% had diabetes, which is higher than the Australian national age-specific prevalence of diabetes in 2004 to 2005 of approximately 11.6%.[18] Almost 70% of the cohort had one or more chronic diseases, such as osteoarthritis, which could have influenced habitual activity levels including walking. Comorbidities affecting walking ability included osteoarthritis of the lower limb (36.4%), lower back pain (18.2%), stroke (4.5%), toe amputation (4.5%), and chronic obstructive pulmonary disease (4.5%). The majority of participants (81.8%) were being treated with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) and were taking antiplatelet medications (68.2%) or warfarin (22.7%). Almost half of the cohort (45.5%) was taking fish oil, with 9.1% taking vitamin E. No participants were taking cilostazol or pentoxifylline.

The characteristics of participants according to the severity of PAD are summarized in Table II. The duration

Table I. Baseline characteristics

Characteristic	*Total cohort*
Sample size, n	22
Age, years	73.6 (8.2)
Male, %	63.6
Body composition	
Body mass index, kg/m^2	
Men	29.34 (4.47)
Women	23.89 (3.12)
Waist circumference, cm	
Men	105.9 (89.8-120.7)
Women	80.8 (72.0-88.7)
Body fat, %	
Men	31.79 (3.60)
Women	35.00 (5.03)
Alcohol frequency (standard drinks[a] per week)	12 (12)
Current smoker, %	22.7
Ex-smoker, %	50.0
Smoking, pack-years	38 (30)
Overweight, %	50.0
Sedentary,[b] %	45.5
Risk factors for peripheral arterial disease, n	6 (1)
Framingham 10-y risk, %	16.8 (8.9)
CAD with MI, %	13.6
CAD without MI, %	40.9
Hypertension, %	81.8
Cerebrovascular disease, %	13.6
Hypercholesterolemia, %	95.5
Diabetes, %	18.2
Self-reported mobility limitation other than peripheral arterial disease, %	68.2
Osteoarthritis of lower limb	36.4
Lower back pain	18.2
Stroke	4.5
Chronic obstructive pulmonary disease	4.5
Amputation	4.5
Statin, %	81.8
Nitrate, %	31.8
Warfarin, %	22.7
Antiplatelet agent, %	68.2
β-blocker, %	22.7
Cilostazol/pentoxifylline, %	0.0
Vitamin E, %	9.1
Fish oil, %	45.5

CAD, Coronary artery disease; *MI,* myocardial infarction.

Data are reported as mean (standard deviation) for normally distributed continuous variables and as median (range) for non-normally distributed variables.

[a]Standard drink was defined as 1.5 standard drinks = 1 × 375 mL of beer or 1 × 150 mL of wine.[21]

[b]Sedentary living was defined as a lifestyle that requires minimal physical activity and that encourages inactivity through limited choices, disincentives, and/or structural, physical, or financial barriers.[22]

Table II. Baseline description of indexes of PAD severity

Characteristic	*Total cohort*
Sample size, n	22
Disease duration (months)	18 (5-240)
American Heart Association ABI classification,[a] %	
Noncompressible	4.5
Mild-to-moderate PAD	90.9
Severe PAD	4.5
Location of claudication, %	
Buttock	4.5
Thigh	4.5
Calf	81.8
Multilevel	9.1
Location of PAD lesions, %	
Proximal	40.9
Distal	59.1
Unilateral	40.9
Bilateral	59.1
Resting lowest ABI (either leg)	0.54 (0.13)
Reason for stopping during walking tests	
Claudication	100%
One-min postexercise ABI (lowest leg)	0.25 (0.18)
Drop in ankle pressure postexercise, %	66.6 (28.1)
ABI recovery time, s	901.1 (536.6)

ABI, Ankle-brachial index; *PAD,* peripheral arterial disease.

Data are reported as mean (standard deviation) for normally distributed continuous variables and as median (range) for non-normally distributed variables.

[a]Subjects were then classified according to the American Heart Association's interpretation of ABI, where 0.00-0.40 = severe PAD; 0.40-0.90 = mild-to-moderate PAD; 0.90-1.3 = normal; and >1.30 = noncompressible.[8]

participants had suffered with symptomatic PAD varied widely (median, 18 months; range, 5-240 months). Based on the AHA ABI classification scheme, the severity of PAD was mild to moderate overall.[8] Most participants experienced claudication symptoms in the calf only (81.8%). On average, 40.9% of the cohort had proximal disease, 59.1% had distal disease, and 59.1% had bilateral disease. Resting ABI in the lowest leg was on average 0.54 (0.13), and participants had a mean postexercise ABI of 0.25 (0.18), or a 66% (28%) drop in ankle pressure in this same leg postexercise. ABI returned to resting values at a mean of 901.1 (536) seconds postexercise. There were no significant relationships between location of lesion or duration of symptoms and walking ability and functional impairment.

The baseline descriptive statistics for mass, strength, and endurance are outlined in Supplementary Table I (online only). The SMM was higher on average in men (28.42 [4.84] kg) than women (15.97 [2.58] kg; $P < .001$). Men had both higher fat mass (25.78 [4.67] kg vs 20.71 [5.42] kg; $P = .03$) and higher FFM (28.42 [4.84] vs 15.97 [2.58]; $P < .001$) than women. Participants who self-reported a mobility limitation other than claudication had significantly poorer calf muscle endurance ($P = .04$), and, although not yet significant, they tended to have poorer calf muscle strength ($P = .08$). For all other muscle mass, strength and endurance outcomes values were generally similar between the two groups.

The baseline descriptive statistics for walking ability and functional performance in this cohort are outlined in Supplementary Table II (online only). For all walking and most performance-based outcomes, values were generally similar between those participants who self-reported a mobility limitation other than claudication and those who did not. Although not yet significant, participants who self-reported this limitation tended to have poorer balance ($P = .06$) and poorer performance in the SPPB ($P = .09$).

Influence of age and gender on musculoskeletal impairment and functional performance. The SMM ($r = -0.49$; $P = .02$), FFM ($r = -0.43$; $P = .04$), and whole body muscle strength ($r = -0.66$; $P < .001$) all were lower with older age, and men were stronger than women across all muscle groups ($P = .02$). Therefore, in order to assess the relationships between ABI and musculoskeletal impairment and musculoskeletal impairment and walking ability/functional performance (see Fig 1), all analytical models were adjusted for age and gender.

Influence of smoking and alcohol on walking ability in PAD. Greater smoking history ($r = 0.51$; $P = .02$; Fig 3, *A*) and greater current alcohol intake ($r = 0.57$; $P = .007$) were significantly associated with longer claudication recovery time (more severe disease). Because there was a nearly significant trend for men to have a higher alcohol intake than women ($P = .052$), gender was added to the model of alcohol and claudication recovery time. This relationship was attenuated but remained significant after controlling for gender in a multiple regression model ($r = 0.50$; $P = .03$; Fig 3, *B*).

Testing the hypotheses relating disease, impairment, and functional performance. We examined the baseline data for evidence to support the Nagi model of disability as presented in Fig 1. PAD severity was hypothesized to be directly related to distal outcome, mobility, and functional disability. One critical putative mechanism underlying this relationship is the musculoskeletal impairment caused by PAD, which in turn is hypothesized to limit mobility and functional performance. Thus, if our model is correct, the relationship between PAD severity and distal outcomes should be attenuated or eliminated once the proximate mediator, musculoskeletal impairment, is controlled for. Evidence for each of these hypotheses in this proposed pathway is examined in the following sections.

Relationship between PAD pathophysiology and musculoskeletal impairment. The relationships between ABI and body composition, muscle strength, and endurance are outlined in Table III. Lower resting ABI was significantly related to lower FFM ($r = 0.34$; $P = .04$), with a similar nearly significant trend for SMM ($r = 0.25$; $P = .07$). There was also a direct association between ABI and total lower limb strength (LLS; $r = 0.29$; $P = .05$), whole body muscle strength ($r = 0.32$; $P = .05$), and bilateral hip extensor strength (HES; $r = 0.54$; $P = .007$). The relationship between ABI and HES became even more significant after appropriately controlling for both age and gender in a multiple regression model ($r = 0.54$; $P = .004$; Fig 4).

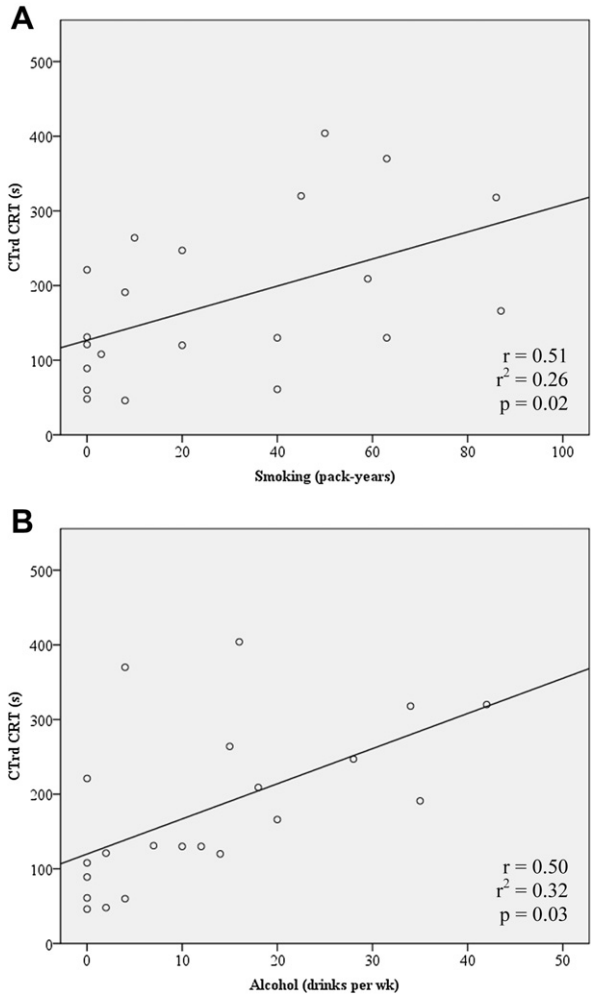

Fig 3. Relationship between smoking and alcohol consumption and indexes of peripheral arterial disease (PAD) severity. Simple linear regression between claudication recovery time (*CRT*) as an index of PAD severity and lifestyle factors. **A,** Greater smoking history was significantly associated with longer recovery time (more severe disease; r = 0.51; *P* = .02). **B,** Greater alcohol intake was also significantly associated with longer recovery time (r = 0.57; *P* = .007). Because there was a nearly significant trend for men to have a higher alcohol intake than women (*P* = .052), gender was added to the model. This relationship attenuated but remained significant after controlling for gender in a multiple regression model (r = 0.50; *P* = .03). The r and *P* values were calculated by linear regression analysis. *CTrd,* Constant treadmill protocol.

As expected, within the level of musculoskeletal impairment, SMM and muscle function were themselves highly correlated. Specifically, there were significant direct relationships between SMM and FFM and bilateral HES (r = 0.69; *P* = .007; r = 0.69; *P* = .007); total LLS (r = 0.79; *P* = .02; r = 0.76; *P* = .02); and whole body strength (WBS; r = 0.85; *P* = .002; r = 0.84; *P* = .002), respectively. Therefore, we constructed a stepwise multiple regression model to determine if these factors were independent of each other with respect to their relationship to ABI. When both HES and FFM were entered into a stepwise regression model with ABI as the dependent variable, ABI was no longer significantly related to FFM (r = 0.22; *P* = .38), suggesting that the apparent relationship between ABI and FFM was largely

Table III. Baseline resting ABI as a predictor of body composition, muscle strength, and endurance

Characteristic	*Resting ABI*
Skeletal muscle mass,[a] kg	r = 0.25; *P* = .07[b,c]
Fat mass,[a] kg	r = −0.48; *P* = .04[b,c]
Fat-free mass,[a] kg	r = 0.34; *P* = .04[b,c]
Calf strength, kg	r = 0.10; *P* = .62[b,c]
Calf endurance, repetitions	r = 0.42; *P* = .12
Bilateral knee extensor strength, N	r = 0.25; *P* = .12[b,c]
Bilateral hip extensor strength, N-m	r = 0.54; *P* = .004[b,c]
Total lower limb strength, N	r = 0.29; *P* = .05[b,c]
Whole body strength, N	r = 0.32; *P* = .05[b,c]

ABI, Ankle-brachial index; *N,* newtons; *N-m,* newton-meters.
The r value represents the correlation coefficient unless otherwise stated.
[a]Skeletal muscle mass (SMM), fat-free mass (FFM), and fat mass (FM) were calculated using bioelectrical impedance analysis and the following formulas: SMM = 0.401 (height in square centimeters/resistance in ohms) + 3.825 (×1 for male or 0 for female) + age in years (−0.071) + 5.102[23] FFM = −4.03 + 0.734 (height in square centimeters/resistance in ohms) + 0.116 (body weight in kilograms) + 0.096 (reactance in ohms) + 0.984 (×1 for male or 0 for female)[24] FM = Body weight − FFM.[24]
[b]Controlled for gender.
[c]Controlled for age.

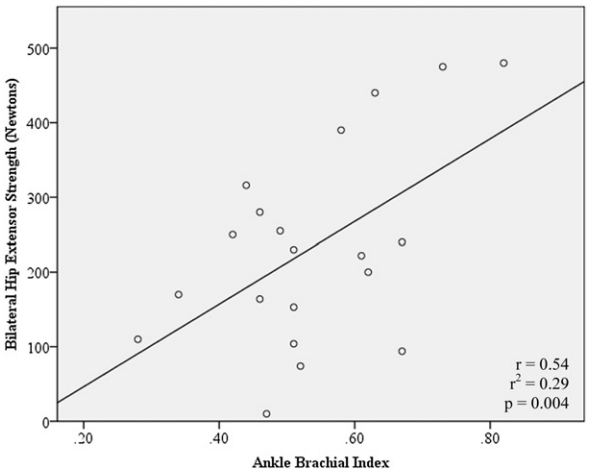

Fig 4. Relationship between ankle-brachial index (ABI) and bilateral hip extensor strength. Simple linear regression between ABI and bilateral hip extensor strength. Low ABI was significantly associated with reduced bilateral hip extensor strength (r = 0.54; *P* = .007). Because bilateral hip extensor strength reduced with age (*P* = .005) and women had weaker hip extensors than men (*P* = .04), age and gender were added to the model. This relationship remained after controlling for both age and gender in a multiple regression model (r = 0.54; *P* = .004). The r and *P* values were calculated by linear regression analysis.

Table IV. Baseline muscle mass and strength as predictors of walking ability and functional performance

Characteristic	*Skeletal muscle mass,*[a] *kg*	*Calf strength, kg*	*Bilateral hip extensor strength, N-m*
6MW ICD, m	r = 0.58; $P = .18$[d,e]	r = 0.53; $P = .10$[d,e]	r = 0.47; $P = .08$[d,e]
6MWD first stop, m	r = 0.51; $P = .04$[d,e]	r = 0.46; $P = .75$[d,e]	r = 0.74; $P = .005$[d,e]
6MWD, m	r = 0.31; $P = .34$[d,e]	r = 0.49; $P = .28$[d,e]	r = 0.75; $P < .001$[d,e]
HGS, m/s	r = 0.18; $P = .32$[d,e]	r = 0.46; $P = .08$[d,e]	r = 0.58; $P = .007$[d,e]
MGS, m/s	r = 0.23; $P = .55$[d,e]	r = 0.63; $P = .003$[d,e]	r = 0.58; $P = .01$[d,e]
Stair power,[b] W	r = 0.60; $P = .04$[d,e]	r = 0.76; $P = .006$[d,e]	r = 0.78; $P = .001$[d,e]
Five-chair stand time, seconds	r = −0.08; $P = .28$[d,e]	r = −0.41; $P = .12$[d,e]	r = −0.43; $P = .03$[d,e]
Static balance, seconds	r = −0.18; $P = .75$[d,e]	r = 0.13; $P = .58$[d,e]	r = 0.44; $P = .02$[d,e]
SPPB score[c]	r = −0.08; $P = .54$[d,e]	r = 0.36; $P = .16$[d,e]	r = 0.59; $P = .003$[d,e]

6MW, 6-Minute walk; *6MWD,* 6-minute walk distance; *ICD,* initial claudication distance; *HGS,* habitual gait speed; *MGS,* maximal gait speed; *m/s,* meters per second; *N-m,* newton-meters; *SPPB,* short physical performance battery; *W,* watts.

The r value represents the correlation coefficient unless otherwise stated.

[a]Skeletal muscle mass (SMM) was calculated using bioelectrical impedance analysis and the following formula: SMM = 0.401 (height in square centimeters/resistance in ohms) + 3.825 (sex: male = 1; female = 0) + age in years (−0.071) + 5.102.[23]

[b]Stair climb power was calculated using the following formula[25,26]: Power (in watts) = [Body weight (in newtons) × Height of stairs (in meters)]/Ascent time (in seconds).

[c]The SPPB[20] is a measure of lower extremity mobility[14] and pools the results from the repeated chair stand, standing balance, and habitual gait speed. A lower score equals poorer function.

[d]Controlled for gender.

[e]Controlled for age.

explained by lower strength in those with lower FFM. The remaining strength variables were not used in stepwise regression models with FFM and ABI due to colinearity (r > 0.7) with FFM (see above). Thus, ABI was associated with lower strength, independent of differences in muscle mass.

ABI as a predictor of walking ability and functional performance at baseline in PAD. Lower ABI was associated with a shorter 6MW ICD (r = 0.48; $P = .03$) and distance to first stop (r = 0.38; $P = .05$), and there was a nearly significant association between a lower ABI and a shorter 6MWD (r = 0.36; $P = .06$). Lower ABI was also associated with worse balance in single leg stance (r = 0.44; $P = .03$) and tended to be associated with lower overall functional performance via SPPB score (r = 0.36; $P = .06$).

Muscle mass, strength, and endurance as predictors of walking ability and functional performance at baseline in PAD. The relationships between muscle mass, strength, and endurance as predictors of walking ability and functional performance in patients with PAD are outlined in Table IV. Participants with lower SMM stopped significantly earlier during the 6MW (r = 0.51; $P = .04$). Participants with lower bilateral HES (r = 0.74, $P = .001$; Fig 5, *A*), lower total lower limb muscle strength (r = 0.63; $P = .008$), and lower WBS (r = 0.60; $P = .01$) also stopped significantly earlier during the 6MW. Furthermore, participants with lower bilateral HES (r = 0.75, $P < .001$; Fig 5, *B*), lower total lower limb muscle strength (r = 0.67; $P = .001$), and lower WBS (r = 0.65; $P = .001$) walked significantly less in 6 minutes, respectively. In addition, participants with lower WBS had an earlier onset of claudication during the 6MW (r = 0.45; $P = .01$). Participants with weaker calf muscles had a significantly longer claudication recovery time on a constant treadmill protocol (r = −0.61; $P = .02$). Thus, the relationships between musculoskeletal impairment and claudication outcomes were in general stronger and broader than those relating ABI to claudication directly (see above).

There was a significant direct relationship between SMM and stair climb power (r = 0.60; $P = .04$). Participants with lower calf muscle strength had a slower maximal gait speed (r = 0.63; $P = .003$) and reduced stair climb power (r = 0.76; $P = .006$). Participants with reduced bilateral HES, reduced total LLS, and reduced WBS had a slower habitual gait speed (HES, r = 0.58; $P = .007$; LLS, r = 0.47; $P = .01$; WBS, r = 0.49; $P = .04$, respectively), slower maximal gait speed (HES, r = 0.58; $P = .01$; LLS, r = 0.49; $P = .02$; WBS, r = 0.51, $P = .01$, respectively), reduced stair climb power (HES, r = 0.78; $P = .001$; LLS, r = 0.75; $P = .003$; WBS, r = 0.78; $P = .001$, respectively), reduced total static balance (HES, r = 0.44; $P = .02$; LLS, r = 0.42; $P = .007$; WBS, r = 0.42; $P = .007$, respectively), and reduced SPPB score (worse function; HES, r = 0.75; $P = .003$; Fig 5, *C*; LLS, r = 0.41; $P = .01$; WBS, r = 0.40; $P = .02$, respectively). The relationship between SMM and stair climb power was attenuated and no longer significant (r = 0.19; $P = .42$) when HES was added to the model (Table V, model 1). Thus, a variety of different measures of whole body and LLS were strongly related to every functional performance variable we measured, as hypothesized. These relationships were far broader and more significant than the few trends we observed for ABI itself to predict functional performance.

Relationship between ABI and walking ability/functional performance is attenuated once musculoskeletal impairment is added to the model. In support of our first hypothesis, as shown above, more severe PAD (lower ABI) was associated with lower FFM, lower muscle strength, and poorer walking ability (earlier claudication) and tended to be associated with poorer performance in functional performance outcomes (gait, chair stand,

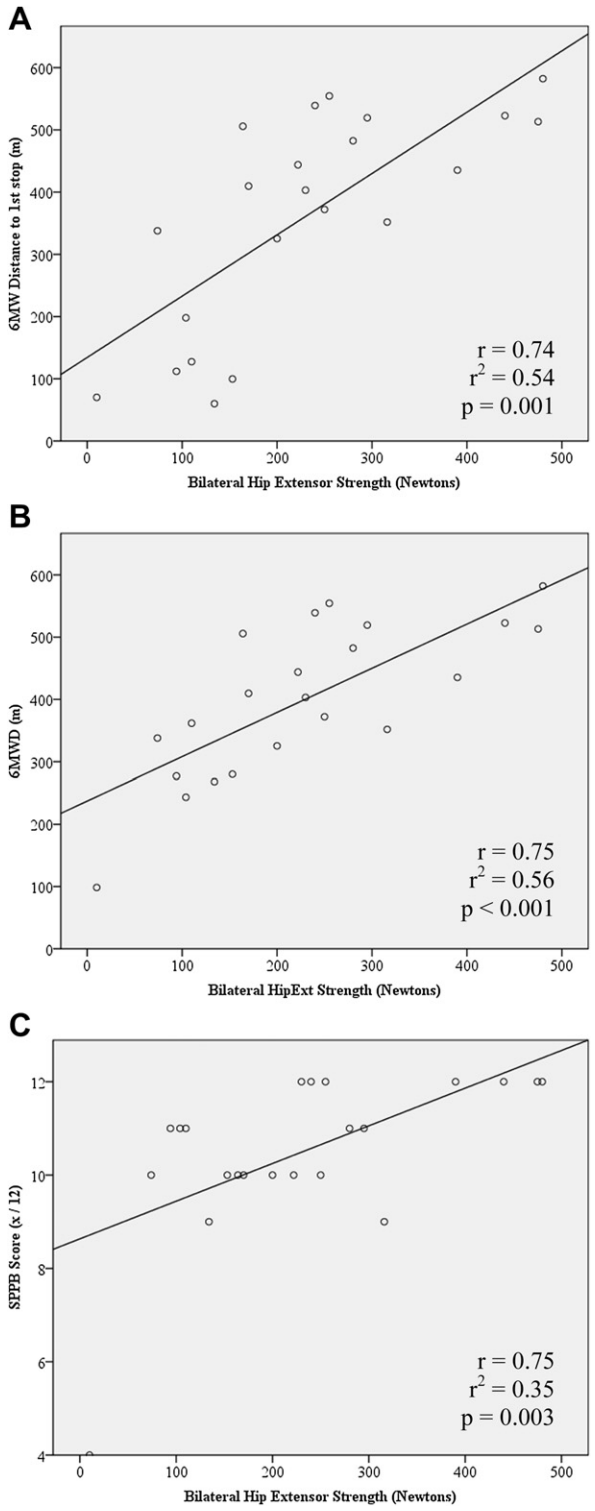

Fig 5. Relationship between bilateral hip extensor strength and walking ability and functional performance in subjects with peripheral arterial disease. **A** and **B,** Simple linear regression between bilateral hip extensor strength (HES) and the distance to first stop and total walking distance for the 6-minute walk (*6MW*). Reduced HES was significantly associated with a shorter distance to first stop during flat ground walking (**A;** r = 0.74; $P < .001$) and reduced total 6-minute walk distance (**B;** 6MWD; r = 0.75; $P < .001$). Because the distance to first stop reduced with age ($P = .02$) and men were significantly stronger than women ($P = .004$), age and gender were added to the distance to first stop model and gender to the 6MWD models. These relationship remained after controlling for age and gender in these multiple regression models (r = 0.74; $P = .001$; r = 0.75; $P < .001$ respectively). **C,** Simple linear regression between HES and short physical performance battery (SPPB) score. (The SPPB[20] is a measure of lower extremity mobility[14] and pools the results from the repeated chair stand, standing balance, and habitual gait speed. A lower score equals poorer function.) Reduced HES was significantly associated with reduced SPPB score (worse function; r = 0.59; $P = .002$). Because HES reduced with age ($P = .004$) and women had weaker hip extensors than men ($P = .04$), age and gender were added to the model. This relationship became stronger after controlling for both age and gender in a multiple regression model (r = 0.75; $P = .003$). The r and P values were calculated by linear regression analysis.

stair climb, balance, and SPPB). In addition, per our second hypothesis, greater musculoskeletal impairment, as measured by lower SMM and muscle strength, was associated with an even greater degree than ABI itself with poorer walking ability and significantly worse performance in functional outcomes. To confirm whether the relationships between ABI and walking ability or function could be explained by variation in muscle mass and/or muscle strength (hypothesis 3), we controlled for muscle mass and strength in separate stepwise multiple regression models of these outcomes.

Therefore, the independent variables ABI and bilateral HES (both predictive of 6MWD to first stop) were entered into a stepwise regression model (Table V, model 2). Only bilateral HES remained a significant predictor (r = 0.74; $P < .001$) in the model for 6MWD to first stop. Similarly, the independent variables ABI and bilateral HES (both predictive of 6MWD) were entered into a separate stepwise regression model (Table V, model 3). Only bilateral HES remained a significant predictor (r = 0.74; $P < .001$) in the model for 6MWD. Finally, the independent variables ABI and bilateral HES (both predictive of single leg balance) were entered into a separate stepwise regression model (Table V, model 4). Only bilateral hip extensor strength remained a significant predictor in the model (r = 0.48; $P = .03$) for single leg balance. Because the presence of a self-reported mobility limitation tended to affect single leg balance, we added this to the stepwise regression model. The relationship between bilateral HES and single leg balance remained unchanged once the presence of a comorbidity affecting performance was appropriately controlled for. Therefore, in all three stepwise models, the ABI relationship was attenuated and no longer significant once muscle strength was included in the model. Thus, muscle strength appears to mediate the relationship between ABI and distal walking and functional outcomes in this cohort.

Table V. Stepwise regression models relating a reduction in ABI to muscle weakness and reduced walking ability

Model	*Variables entered*[a]	*Variables removed*	*Variables remaining*	*r value*	P *value*
1	Stair climb power SMM BL HES	SMM	Stair climb power BL HES	0.78	<.001
2	6MW first stop ABI BL HES	ABI	6MW first stop BL HES	0.74	<.001
3	6MWD ABI BL HES	ABI	6MWD BL HES	0.74	<.001
4	Single leg balance ABI BL HES Comorbidity	ABI Comorbidity	Single leg balance BL HES	0.48	.03

6MW, 6-Minute walk; *6MWD,* 6-minute walk distance; *ABI,* ankle-brachial index; *BL HES,* bilateral hip extensor strength; *SMM,* skeletal muscle mass. The r value represents the correlation coefficient unless otherwise stated.
[a]Age and gender were added to all five stepwise regression models.

Thus, in full support of our hypotheses, the relationships between PAD severity and walking and functional outcomes were attenuated and no longer significant once muscle strength was taken into account. In addition, the relationships between SMM and distal outcomes all were eliminated when adjusted for strength, suggesting that it was the musculoskeletal dysfunction related to muscle atrophy itself rather than loss of muscle mass per se that was directly linked to reduced mobility and function in this cohort.

DISCUSSION

Our results confirm that greater severity of PAD (defined by a lower resting ABI) was associated with lower FFM and a similar nearly significant trend for SMM, lower muscle strength, as well as poorer walking ability and performance-based tests of function (gait, stair climbing, chair rising, and balance). Because lower muscle mass and muscle strength were themselves significantly related to poorer walking ability and performance-based tests of function, we further hypothesized that these musculoskeletal impairments might underlie the apparent effect of PAD on walking/ability and functional performance. In support of this potential mechanistic pathway, the relationships between PAD and walking ability/functional performance were no longer significant once we controlled for muscle strength. Furthermore, muscle mass differences did not explain additional variance in walking or functional outcomes beyond that attributable to muscle strength itself. Thus, our overall results suggest that sarcopenia and its related muscle dysfunction underlie a significant portion of the functional deficits observed in PAD. These relationships are consistent with the Nagi model of disability[19] (see Fig 1), wherein the active pathology, PAD (low ABI), leads to impairment of muscle mass and thereby strength, leading to limitations in walking ability and performance-based tests of function, including gait speed, chair stand, balance, stair climb, and summary SPPB score. Nagi recognized that the consequence of disease for an individual should be described at the level of both the person and society, and highlighted that such a limitation in performance of functional tasks is highly predictive of future disability, or the inability of a person to perform necessary social roles[19] and subsequently of more basic activities of daily living. Future trials should investigate whether preventing or attenuating this sarcopenia and associated muscle dysfunction would ultimately improve mobility and functional dependency in this cohort.

The novel design of this study, compared with other trials assessing muscle strength, are the specific procedures involved in muscle strength testing, including the number of muscle groups assessed as well as the precise measurement of maximum dynamic muscle strength using well-established one-repetition maximum protocols.[12] Dynamic muscle strength is far more applicable to walking and activities of daily living and has never before been used in a cohort with PAD. This randomized controlled trial assessed maximum dynamic muscle strength across seven separate muscle groups, including the calf muscle, quadriceps, hamstrings, hip abductors, hip extensors, pectorals, and upper back muscle groups. This enabled us to analyze relationships for individual muscle groups as well as combined groups to help identify the exact muscle groups with impaired muscle strength and endurance in this cohort and furthermore, which muscle groups were specifically related to walking impairment. This has never before been done in cohorts with PAD. Our results confirm that the strongest predictor of walking ability and the ability to complete performance-based tests of function was bilateral HES, when compared with other muscle groups. In addition, stronger calf muscles were associated with a quicker claudication recovery time. Because the hip extensors were such a strong mediator of walking and functional outcomes, future trials should aim to strengthen these muscles and investigate the effect this has on a person's walking ability and ability to perform activities

of daily living. Furthermore, the addition of biomechanical gait analysis in future trials would better define how strengthening the hip extensors and calf muscles may improve walking/functional ability in this cohort.

The relationships we presented all support the hypothesis that an anabolic exercise intervention aimed at improving WBS and overall muscle function could improve the functional limitations caused by the physiologic impairments imposed by PAD. Future trials should aim to compare the effects of strengthening various muscle groups, with particular focus on those we have identified as most strongly related to PAD and walking outcomes in claudicants: hip extensors and plantar flexors.

CONCLUSIONS

A lower ABI is related to lower FFM and poorer HES, WBS, and walking ability and functional performance. In addition, poor bilateral HES is significantly related to a shorter distance to first stop, reduced total walking distance, and poorer scores for performance-based tests of function. Our results suggest the existence of a causal pathway from local disease pathophysiology (reduction in ABI) to impairment of the musculoskeletal system (atrophy and weakness) to whole body disability represented by claudication outcomes and performance-based tests of functional mobility in an older cohort with symptomatic PAD. Longitudinal outcomes from the REPAIR IT study and future trials are required to investigate the effects of an anabolic intervention targeting the muscles involved in gait to test the hypothesis that an increase in lower limb muscle strength and mass will improve symptoms of claudication and lead to improvements in other functional outcomes in patients with PAD.

AUTHOR CONTRIBUTIONS

Conception and design: BP, JR, PD, RL, MS
Analysis and interpretation: BP, JR, MS
Data collection: BP, MS
Writing the article: BP, JR, MS
Critical revision of the article: JR, PD, RL, MS
Final approval of the article: RL, MS
Statistical analysis: BP, JR, MS
Obtained funding: BP, MS
Overall responsibility: BP

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Submitted Jun 4, 2012; accepted Aug 16, 2012.

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Supplementary Table I (online only). Baseline descriptive statistics for body mass, strength, and endurance and the effect of self-reported mobility limitation

Characteristic	*Total pilot cohort*	P *value*[a]
Sample size, n	22	
Skeletal muscle mass,[b] kg		
Men	28.42 (4.84)	.31
Women	15.97 (2.58)	.76
Fat mass,[b] kg		
Men	25.78 (4.67)	.96
Women	20.71 (5.42)	.90
Fat free mass,[b] kg		
Men	28.42 (4.84)	.44
Women	15.97 (2.58)	.99
Calf strength, kg	10 (10)	.08
Calf endurance, repetitions	17 (7-50)	.04
Knee flexor strength, N	393 (153)	.87
Knee flexor endurance, N	1598 (153-6435)	.80
Knee extensor strength, N	99 (57)	.24
Knee extensor endurance, N	552 (465)	.85
Bilateral hip extensor strength, N-m	231 (130)	.19
Bilateral hip extensor endurance, N	1276 (928)	.62
Total lower limb strength, N	873 (401)	.37
Total lower limb endurance, N	3703 (2534)	.96
Chest press strength, N	121 (58)	.72
Seated row strength, N	161 (64)	.80
Whole body strength, N	987 (415)	.58

N, Newtons; *N-m,* newton-meters.

Data are reported as mean (standard deviation) for normally distributed continuous variables and as median (range) for non-normally distributed variables.

[a]Between-group value for participants who self-reported a mobility limitation and those who did not.

[b]Skeletal muscle mass (SMM), fat-free mass (FFM), and fat mass (FM) were calculated using bioelectrical impedance analysis and the following formulas: SMM = 0.401 (height in square centimeters/resistance in ohms) + 3.825 (sex: male = 1; female = 0) + age in years (−0.071) + 5.102[23] FFM = −4.03 + 0.734 (height in square centimeters/resistance in ohms) + 0.116 (body weight in kilograms) + 0.096 (reactance in ohms) + 0.984 (sex: male = 1; female = 0)[24] FM = Body weight − FFM.[24]

Supplementary Table II (online only). Baseline descriptive statistics for walking ability and functional performance and the effect of self-reported mobility limitation

Characteristic	*Total pilot cohort*	P *value*[a]
Sample size, n	22	
CTrd initial claudication distance, m	119.9 (63.0)	.87
CTrd absolute claudication distance, m	447.9 (305.8)	.79
Claudication recovery time, seconds	178.8 (107.5)	.64
GTrd initial claudication distance, m	165.7 (91.8)	.86
GTrd absolute claudication distance, m	296.2 (129.6)	.74
6MW distance to first stop, m	375.9 (164.9)	.82
6MWD, m	415.7 (104.9)	.92
Habitual gait speed, m/s	1.13 (0.29)	.79
Maximal gait speed, m/s	1.54 (0.42)	.52
Stair climb power,[b] W	236.1 (108.0)	.25
Five-chair stand time, seconds	11.7 (8.0-108.0)	.36
Semitandem balance, seconds	15.0 (0.0)	.99
Tandem stand balance, seconds	15.0 (0.7-15.0)	.19
Single leg balance eyes open, seconds	15.0 (0.0-15.0)	.21
Single leg balance eyes closed, seconds	2.4 (1.3)	.06
Total static balance, seconds	76.60 (41.9-79.3)	.09
SPPB score[c]	11 (4-12)	.09

6MWD, 6-Minute walk distance; *CTrd,* constant treadmill protocol; *GTrd,* graded treadmill protocol; *m/s,* meters per second; *SPPB,* short physical performance battery; *W,* watts.

Data are reported as mean (standard deviation) for normally distributed continuous variables and median (range) for non-normally distributed variables.

[a]Between-group value for participants who self-reported a mobility limitation and those who did not.

[b]Stair climb power was calculated using the following formula[25,26]: Power (in watts) = [Body weight (in newtons) × Height of stairs (in meters)]/ Ascent time (in seconds).

[c]The SPPB[20] is a measure of lower-extremity mobility[14] and pools the results from the repeated chair stand, standing balance, and habitual gait speed. A lower score equals poorer function.