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ORIGINAL RESEARCH

Association of Lower Extremity Performance With Cardiovascular and All-Cause Mortality in Patients With Peripheral Artery Disease: A Systematic Review and Meta-Analysis

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***Background*—**Peripheral artery disease (PAD) is associated with impaired mobility and a high rate of mortality. The aim of this systematic review was to investigate whether reduced lower extremity performance was associated with an increased incidence of cardiovascular and all-cause mortality in people with PAD.

***Methods and Results*—**A systematic search of the MEDLINE, EMBASE, SCOPUS, Web of Science, and Cochrane Library databases was conducted. Studies assessing the association between measures of lower extremity performance and cardiovascular or all-cause mortality in PAD patients were included. A meta-analysis was conducted combining data from commonly assessed performance tests. The 10 identified studies assessed lower extremity performance by strength tests, treadmill walking performance, 6-minute walk, walking velocity, and walking impairment questionnaire (WIQ). A meta-analysis revealed that shorter maximum walking distance was associated with increased 5-year cardiovascular (unadjusted RR=2.54, 95% CI 1.86 to 3.47, $P<10^{-5}$, n=1577, fixed effects) and all-cause mortality (unadjusted RR=2.23 95% CI 1.85 to 2.69, $P<10^{-5}$, n=1710, fixed effects). Slower 4-metre walking velocity, a lower WIQ stair-climbing score, and poor hip extension, knee flexion, and plantar flexion strength were also associated with increased mortality. No significant associations were found for hip flexion strength, WIQ distance score, or WIQ speed score with mortality.

***Conclusions*—**A number of lower extremity performance measures are prognostic markers for mortality in PAD and may be useful clinical tools for identifying patients at higher risk of death. Further studies are needed to determine whether interventions that improve measures of lower extremity performance reduce mortality. **(*J Am Heart Assoc*. 2014;3:e001105 doi: 10.1161/JAHA.114.001105)**

Key Words: lower extremity performance • mortality • peripheral artery disease

Peripheral artery disease (PAD) is an athero-occlusive disease of the lower limb arterial tree and is a common cause of morbidity and mortality in Western countries. Worldwide, it is estimated that over 200 million people are affected by PAD.[1] Approximately one third of these individuals experience intermittent claudication and subsequent impairment of mobility.[2] PAD patients demonstrate impaired performance on a range of lower extremity performance tests including poorer walking endurance, slower walking velocity, and reduced lower limb strength associated with impaired health-related quality of life.[3,4] Randomized controlled trials suggest that exercise therapies aimed at improving lower extremity performance, including supervised exercise programs, home-based walking interventions, and resistance training improve lower limb symptoms and quality of life among PAD patients.[5,6]

Observational studies demonstrate that PAD presence is a strong independent predictor of coronary and cerebrovascular events.[7] Even with current best medical therapy, the risk of cardiovascular and all-cause mortality remains ≈3 times higher in PAD patients compared to those without PAD.[7] More effective interventions for PAD management are required to reduce cardiovascular and all-cause mortality among this

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high-risk population. It is suggested, although unproven, that interventions that improve lower extremity performance may reduce cardiovascular risk among PAD patients.[8] If true, this would provide a rationale for interventions, such as exercise therapy, beyond the benefit they provide in reducing symptoms. Currently no randomized trials have examined the effect of such interventions on long-term cardiovascular risk; however, a number of observational studies have assessed the association between lower extremity performance measures and cardiovascular and all-cause mortality. We conducted a systematic review and meta-analysis to summarize current evidence for the association between lower extremity performance measures and mortality in PAD patients.

Methods

Literature Search

This systematic review was performed according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[9,10] A literature search was conducted to identify studies investigating the association between measurements of lower extremity performance and mortality in patients with PAD. The MEDLINE (1966), EMBASE (1980), SCOPUS (1996), Web of Science (1965), and Cochrane Library databases (1992) were searched from inception to March 16, 2014 with no language restrictions. The following search terms were applied: (Peripheral artery disease OR Peripheral arterial disease OR PAD OR Claudication OR limb ischaemia OR limb ischemia)[Title] AND (Muscle OR Walk* OR Strength OR Exercise OR Treadmill OR Physical activity)[Title/Abstract] AND (Mortality OR Death OR Outcome OR Prognos*)[Title]. Titles and abstracts were screened by 1 author (D.R.M.) to identify potentially relevant studies. If the suitability of an article was uncertain, the full text was assessed. All potentially eligible studies were subsequently evaluated in detail by 1 reviewer (D.R.M.) through consideration of the full text. Inclusion required assessment of a lower extremity performance measure in PAD patients, and analysis for association with either cardiovascular mortality or all-cause mortality on follow-up. Studies were excluded if the cohort was defined by the presence of PAD and an additional confounding disease process (eg, chronic renal failure), if the cohort underwent a revascularization procedure as part of the study, or if PAD specific results could not be distinguished from those of a larger population consisting of individuals without PAD. Studies investigating the association between physical activity during daily life and mortality were not considered eligible. Physical activity was defined as any bodily movement produced by skeletal muscles that results in energy expenditure, and may be influenced by factors other than lower extremity performance.[11] Database searches were supplemented by hand searching the reference lists of included studies and utilizing the related articles function in PubMed.

Data Extraction

Two investigators (D.R.M., A.J.R.) extracted data using a predefined form. All data were cross-checked in a consensus meeting and discrepancies were resolved through discussion. Data extracted included the sample size, number of cardiovascular and all-cause deaths, length of follow-up, baseline demographic information, characteristics of the study population, method of diagnosis of PAD, detailed descriptions of the lower extremity performance tests, adjustment factors, and primary results. In addition, we recorded the number of participants in each group and estimated the corresponding 5-year mortality rate from Kaplan–Meier survival curves. Authors of eligible studies were contacted where additional information was required, all of whom replied.

Quality Assessment

Methodological quality and potential bias of included studies were assessed by 2 investigators (D.R.M., A.J.R.). A quality assessment form was devised using elements of the Newcastle Ottawa scale and Cochrane collaboration tool for assessing risk of bias.[12,13] Quality measures included (1) whether data were collected prospectively or retrospectively; (2) description of the inclusion and exclusion criteria for PAD participants; (3) assessment of PAD severity at baseline (according to ankle–brachial index [ABI] or angiographic scoring); (4) reporting of vascular risk factors at baseline; (5) follow-up time (mean or median $\geq$4 years); (6) comprehensive mortality assessment (either searched Social Security death register or contacted proxies of study participants); (7) percentage of the cohort analyzed at follow-up ($\geq$90% considered acceptable); and (8) results adjusted for multiple confounding variables (age, sex, and $\geq$2 vascular risk factors). We did not exclude any studies due to poor methodological quality.

Statistical Analysis

Meta-analyses were performed for lower extremity performance measures that were evaluated in at least 3 separate cohort studies. Both unadjusted and maximally adjusted risk ratios (RR) comparing the highest with the lowest-performance quantiles were combined using fixed-effects and random-effects models. Unadjusted RRs for cardiovascular and all-cause mortality were derived from Kaplan–Meier survival curves at 5 years follow-up as described by Parmar et al[14] Maximally adjusted RRs calculated using Cox proportional-hazards analysis were transcribed directly from

published data tables. The Cochrane Q statistic and I^2 index were used to assess the degree of heterogeneity across studies.[12] I^2 values of >50% were accepted to denote statistical heterogeneity. Sensitivity analyses were conducted using the one–study-remove approach to assess the impact of each study on the combined effect.[12] Funnel plots of the effect size versus the standard error of the log-transformed effect were constructed to assess potential publication bias. Statistical tests were considered significant if the 2-sided *P* value was less than 0.05. All computations were performed using RevMan Version 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

Results

Study Selection

Initial database searches yielded 117 potentially eligible studies after removal of duplicates (Figure 1). A total of 105 articles were excluded based on review of their titles and abstracts. The most common reasons for exclusion were absence of a lower extremity performance measure and failure to investigate cardiovascular or all-cause mortality. After evaluating 12 full-text studies, a further 2 were excluded because they investigated clinic-referred patients without a definitive diagnosis (de Liefde et al), or did not investigate the association of walking capacity with mortality (Wilson et al).[15,16] No additional studies were identified from hand searching the reference lists of included studies; therefore, 10 studies were included in this review (Table 1).[8,17–25]

Study Characteristics

The sample size of included studies ranged from 118 to 1624 participants, with a median sample size of 441 participants. Eight of the 10 studies were conducted in the United States; the remaining 2 were conducted in Japan and the Netherlands.[23,25] All studies were hospital-based and recruited either vascular inpatients or individuals presenting to a vascular clinic or noninvasive vascular laboratory. Eight of the 10 studies comprised patients with both symptomatic and asymptomatic PAD; however, 2 studies only assessed

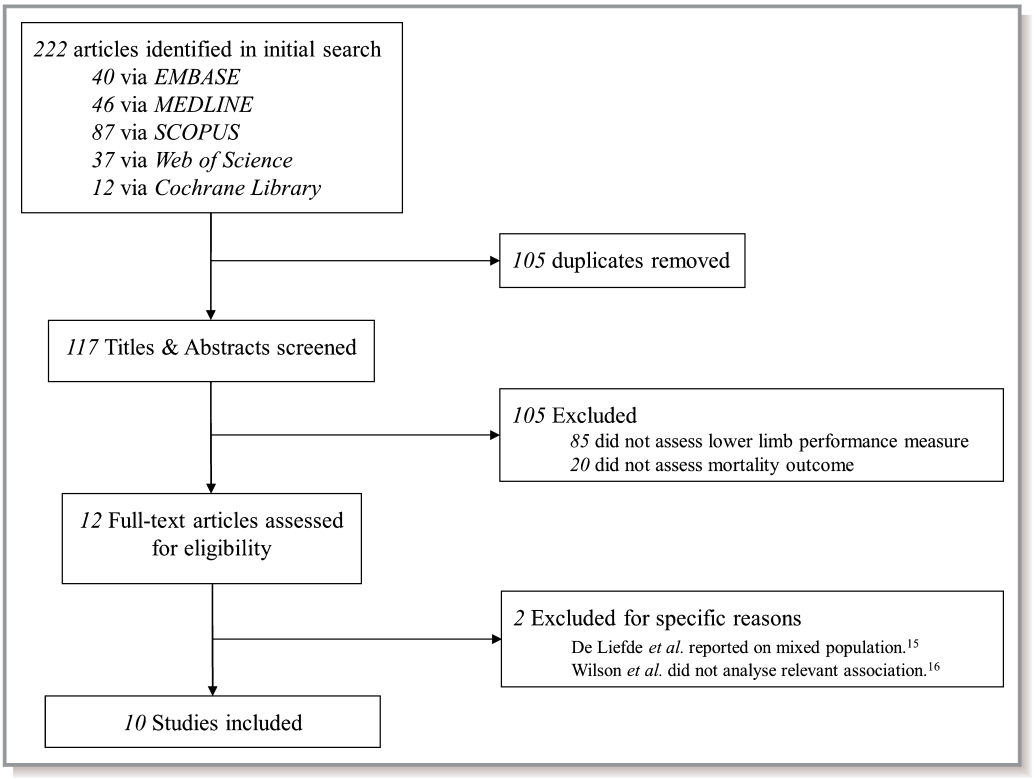

Figure 1. Outline of the study. One hundred and seventeen published studies assessing the association of lower extremity performance measures with mortality in peripheral artery disease (PAD) patients were identified by searching the EMBASE, MEDLINE, SCOPUS, Web of Science, and Cochrane Library databases. Appraisal of the abstracts identified 12 studies eligible for full-text appraisal. From these, a further 2 articles were excluded, yielding a total of 10 studies included in the review.

Table 1. Studies Assessing the Association of Lower Extremity Performance Measures and Mortality in Patients With Peripheral Artery Disease

Study	Year	Country	N_{PAD}	ABI	Claudicants	Follow-Up (y)	N_{AC} Mortality	N_{CV} Mortality*	Assessment of Lower Extremity Performance
Jain et al[8]	2013	USA	442	—	—	4.71 (2.26 to 6.24)†	123	45	2-y decline in WIQ distance, speed, and stair-climbing scores
Leeper et al[19]	2013	USA	725	—	68.4%	11.3±6.3‡	364	132	Customized symptom limited ramp treadmill protocol
Jain et al[18]	2012	USA	638	0.65±0.15‡	32.0%	4.5†	221	78	WIQ distance, speed, and stair-climbing scores
McDermott et al[21]	2012	USA	434	0.63±0.2‡	—	4.0±1.3‡	103	35	Knee extension strength, knee extension power, and plantar flexion
McDermott et al[20]	2011	USA	440	0.66±0.15‡	—	3.71 (2.17 to 6.08)†	102	39	Decline in 6-min walk, fast-paced, and usual- paced 4-metre walking velocity
Singh et al[24]	2010	USA	410	—	—	5.0±1.9‡	126	41	Isometric hip extension, hip flexion, knee extension, and knee flexion
de Liefde et al[25]	2009	Netherlands	1624	0.67±0.20‡	—	5.0‡	552	309	Treadmill total walking distance at 4 km/h
Sakamato et al[23]	2009	Japan	118	0.54±0.18‡	100.0%	5.7±3.9‡	33	16	Maximum walking distance; details not described
Gardner et al[17]	2008	USA	434	—	100.0%	5.1†	108	—	6-min walk, WIQ distance, speed, and stair-climbing scores
McDermott et al[22]	2008	USA	444	0.65‡	—	4.81 (3.13 to 5.17)†	127	55	6-min walk, fast-paced and usual-paced 4-metre walking velocity

ABI indicates ankle-brachial pressure index; AC, all-cause; CV, cardiovascular; N, number; PAD, peripheral artery disease; WIQ, walking impairment questionnaire; y, years.
*Defined as death from coronary heart disease, stroke, peripheral vascular disease, and other cardiovascular disease in 8 studies. Defined as death from cardiac causes in 1 study.[25]
†Median and interquartile range. In some cases interquartile range was not provided.
‡Mean and standard deviation. In one case standard deviation was not provided.

patients with intermittent claudication.[17,23] An ABI <0.90 was used as the diagnostic inclusion criterion for PAD in all but 1 study.[19] Baseline mean ABI ranged from 0.63 to 0.67. Follow-up ranged from an average of 3.7 to 11.3 years. All studies provided detailed baseline clinical and demographic data (Table 2).

The methodological quality of included studies is shown in Table 3. Nine studies were conducted prospectively and 1 study was performed retrospectively.[17] Inclusion and exclusion criteria were clear in all but 1 study.[19] Nine of the 10 studies had an average follow-up of ≥4 years, which was considered sufficient to detect clinically relevant differences in mortality.[20] Mortality was determined either through searching Social Security death registers (n=3), contacting proxies of study participants (n=1), or both (n=6). All of the prospective studies included ≥90% of baseline participants in their final analysis. Eight of the 10 studies adjusted their results for age, sex, and at least 2 vascular risk factors.[8,18,20–25]

Investigators examined a range of lower extremity performance measures that can be grouped into 3 general categories: (1) lower limb strength tests, (2) objectively measured walking performance, and (3) the walking impairment questionnaire (WIQ). A summary of findings is presented in Table 4.

Lower Limb Strength

Singh et al (N=410) and McDermott et al (N=434) assessed the association of lower extremity performance and mortality by a range of strength tests, including isometric hip flexion, hip extension, knee flexion, knee extension, plantar flexion, and knee extension power.[21,24] Both studies were conducted on 2 related cohorts (WALCS I and WALCS II, respectively) recruited from Chicago, with results adjusted for age, sex, race, body mass index, ABI, smoking, and comorbidities.[21,24] Poor isometric strength for hip extension, knee flexion, knee extension power, and plantar flexion were independently associated with increased cardiovascular and all-cause mortality in both studies.[21,24] Conversely, no significant associations were found for hip flexion strength, which was investigated by Singh et al only.[24] Knee extension strength was not associated with mortality in the total sample of

Table 2. Characteristics of Included Studies

Study	Year	Location	Sample	Follow- Up	Mortality	$Mortality_{CV}$	Age (y)	% Males	ABI	BMI	Smoking	HTN	DM
Jain et al[8]	2013	USA	442	4.71 (2.26 to 6.24)*	123 (27.8%)	45 (10.2%)	†	†	†	†	†	†	†
Leeper et al[19]	2013	USA	725	11.3±6.3	364 (50.2%)	263 (36.3%)	62.0±9.1	97.7%	—	27.7	67.0% (ever)	64.6%	15.6%
Jain et al[18]	2012	USA	638	4.5*	221 (34.6%)	78 (12.2%)	72.7±8.3	56.6%	0.65±0.2	27.7±5.1	18.1%	—	31.8%
McDermott et al[21]	2012	USA	434	4.0±1.3	103 (23.7%)	35 (8.06%)	75±8.2	53.7%	0.63±0.2	27.9±5.1	15.2%	73.5%	32.3%
McDermott et al[20]	2011	USA	440	3.71 (2.17 to 6.08)*	102 (23.2%)	39 (8.86%)	†	56.8%	0.66±0.15‡	27.5±5.5‡	15.7%	—	32.1%
Singh et al[24]	2010	USA	410	5.0±1.9	126 (30.7%)	41 (39%)	†	60.0%	†	†	†	†	†
de Liefde et al[25]	2009	Netherlands	1624	5.0	552 (34%)	309 (19%)	64±11	70.0%	0.67±20	26±7	35.0%	40.0%	20.0%
Sakamato et al[23]	2009	Japan	118	5.7±3.9	33 (28.0%)	16 (13.6%)	68±9	86.4%	†	†	†	†	†
Gardner et al[17]	2008	USA	434	5.33*	108 (24.9%)	—	†	87.0%	†	†	†	†	†
McDermott et al[22]	2008	USA	444	4.81 (3.13 to 5.17)*	127 (28.6%)	55 (12.4%)	71.9±8.4‡	59.9%	0.65	27.3	39.4%§	—	30.7%

Mortality is reported as number and percentage. Continuous variables are represented by mean and SD unless otherwise specified. '—' Indicates that data was unavailable. ABI indicates ankle-brachial pressure index; BMI, body mass index; CV, cardiovascular; DM, diabetes mellitus; HTN, hypertension.
*Median and interquartile range.
†Only subgroup data provided.
‡Indicates mean and SE.
§Cigarette smoking in pack-years.

participants; however, Singh et al found a significant association between knee extension strength and all-cause mortality in males (P=0.010) following subgroup analysis.[24]

Objectively Measured Walking Performance

Walking ability was assessed as a potential prognostic marker for mortality in 5 studies.[17,19,22,23,25] Two studies used the 6-minute walk test whereby patients were instructed to cover as much distance as possible along a corridor within 6 minutes.[17,22] Poor performance on the 6-minute walk test was associated with increased rates of cardiovascular (P<0.001) and all-cause mortality (P=0.001) in 1 study but was not significantly associated with higher all-cause mortality (P=0.077) in a second study.[17,22] An important difference between these studies is that Gardner et al adjusted their results for the WIQ distance score, which is closely correlated with the 6-minute walk test.[17,26] This adjustment was not included by McDermott et al, and this may account for the conflicting findings.[22] Three studies assessed maximum walking distance using symptom-limited ramp treadmill protocols, and all reported poor performance to be significantly associated with higher rates of cardiovascular and all-cause mortality (Table 4).[19,23,25]

A meta-analysis of 3 studies for the association between maximum walking distance and 5-year mortality is shown in Figure 2. Combined results represent a composite of treadmill walking tests and the 6-minute walk test. Shorter walking distance was significantly associated with increased risk of cardiovascular (unadjusted RR =2.54; 95% CI 1.86 to 3.47; $P<10^{-5}$, n=1577) and all-cause mortality (unadjusted RR =2.23; 95% CI 1.85 to 2.69; $P<10^{-5}$, n=1710) under a fixed-effects model. Random-effects meta-analysis demonstrated similar effect estimates for both cardiovascular (unadjusted RR =2.64; 95% CI 1.76 to 3.96; $P<10^{-4}$) and all-cause mortality (unadjusted risk ratios=2.23; 95% CI 1.85 to 2.69; $P<10^{-4}$). Two of the 3 studies included in the analysis were considered high quality (Table 3); however, 1 study used a sample recruited from US military veterans and may not be representative of the more general PAD population.[19] Heterogeneity between studies was not considered significant (cardiovascular mortality: I^2=31%; all-cause mortality: I^2=0%), although the potential for publication bias could not be gauged due to the small number of included studies. Sensitivity analyses demonstrated that the association remained significant after removal of any 1 study (Tables 5 and 6). Meta-analysis of maximally adjusted RRs yielded more conservative effect estimates but with greater heterogeneity (Figure 3). Included studies adjusted their RRs for a range of different covariates, potentially introducing bias into the summary-effect estimates (Table 4). Data from Gardner et al and Sakamoto et al were not included in the meta-analysis

Table 3. Quality Assessment of Included Studies

Study	Prospective Data Collection	Description of Selection Criteria	Assessment of Baseline PAD Severity	Detailed Population Characteristics	Follow-Up ≥4 Years	≥90% of Participants Included in Final Analysis	Comprehensive Mortality Assessment*	Adjustment for Population Stratification
Jain et al[8]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Leeper et al[19]	Yes	No	No	Yes	Yes	Yes	Yes	No
Jain et al[18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McDermott et al[21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McDermott et al[20]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Singh et al[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
de Liefde et al[25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sakamato et al[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gardner et al[17]	No	Yes	Yes	Yes	Yes	N/A	Yes	No
McDermott et al[22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

N/A indicates not applicable due to retrospective study design; PAD, peripheral artery disease.
*Considered comprehensive if mortality status was searched on a Social Security death register or if proxies of study participants were contacted.

because published RRs had very narrow confidence intervals that would not have been expected from the sample sizes included in the studies (Table 4).[17,23] Meta-analysis could not be performed for specific walking endurance tests because fewer than 3 published studies evaluated each test.

Walking velocity was investigated in 2 studies from the same cohort.[20,22] Slower fast-paced 4-metre (4-m) walking velocity was significantly associated with cardiovascular and all-cause mortality, whereas slower normal-paced 4-m walking velocity was only associated with all-cause mortality.[22] Patients with the greatest decline in the 6-minute walk test and fast-paced 4-m velocity test over 2 years had significantly increased risk of subsequent cardiovascular and all-cause mortality.[20]

Walking Impairment Questionnaire

Jain et al and Gardner et al assessed the association of lower WIQ scores with mortality in 638 and 434 PAD patients, respectively.[17,18] The WIQ is a subjective measure of patient-perceived walking performance developed for individuals with PAD. Both Jain et al and Gardner et al reported an association between lower WIQ stair-climbing score with increased mortality (Table 4).[17,18] Conversely, no associations were found for the WIQ distance score or speed score in either study. An additional study by Jain et al, conducted on the same patient cohort, showed that a significant decline in WIQ stair-climbing score, distance score, and speed score over 2 years were each associated with increased all-cause mortality.[8]

Discussion

The main finding of this systematic review was that shorter walking distance in a 6-minute walk test or a treadmill test was associated with an increased risk of cardiovascular and all-cause mortality among people with PAD. These findings were confirmed in a meta-analysis that demonstrated PAD patients in the lowest performance quantile for walking endurance had more than twice the risk of cardiovascular and all-cause mortality compared to those in the highest quantile. Moreover, this risk remained significant, although not as strong, after some studies adjusted for a range of traditional cardiovascular risk factors. Although it is well established that ambulation and survival are closely correlated in the general population, this association had not been confirmed in PAD patients.[27] Summary risk estimates generated in the present meta-analysis were similar to those seen in the general population who completed a long-distance corridor walk test, suggesting that even among patients with advanced walking impairment, limited ambulation predicts mortality.[27]

The association between lower limb strength and mortality was variable, as evidenced by conflicting findings in the literature.[21,24] Poorer hip extension strength, knee flexion strength, plantar flexion strength, and knee extension power were associated with increased cardiovascular and all-cause mortality. In contrast, poorer hip flexion and knee extension strength were not consistently associated with mortality. Reasons for these differences are unclear. One possible explanation is that some lower limb muscle groups may be more susceptible to muscle ischemia than others, and conse-

Table 4. Summary of the Association of Lower Extremity Performance Measures With Cardiovascular and All-Cause Mortality

Category	Lower Extremity Performance Measure	Cardiovascular Mortality		All-Cause Mortality		Adjustment for Confounders	References
		Effect Estimate*	*P* Value	Effect Estimate*	*P* Value		
Strength tests	Hip extension	HR=5.00 (1.09 to 22.93)	0.029†	HR=2.0 (0.9 to 4.1)	0.013†	‡ and physical activity	24
	Hip flexion	—	0.073	—	0.069†	‡ and physical activity	24
	Knee extension	—	0.184	HR=2.91 (1.30 to 6.53)	0.010†	‡ and physical activity	24
		—	0.170	—	0.185	‡ and physical activity	21
	Knee extension power	HR=8.89 (1.86–42.43)	0.006	HR=1.9 (1.0 to 3.5)	0.046	‡ and physical activity	21
	Knee flexion	HR=4.2 (1.12 to 15.79)	0.042†	HR=2.23 (1.02 to 4.87)	0.029†	‡ and physical activity	24
	Plantar flexion	HR=3.89 (1.07 to 14.1)	0.006†	HR=3.2 (1.5 to 6.7)	0.004	‡ and physical activity	21
Exercise and treadmill tests	Symptom limited treadmill protocol	RR=2.50 (1.43 to 4.17)	<0.001	RR=2.44 (1.75 to 3.33)	<0.001	Age	19
	Maximum treadmill distance, 4 km/h	HR=1.67 (1.08 to 2.57)	<0.05	HR=1.69 (1.21 to 2.27)	<0.05	Age, gender, ABI, smoking, HTN, systolic blood pressure, comorbidities	25
	Maximum treadmill distance	RR=1.01 (1.00 to 1.01)	0.012		NA	Age, diabetes, coronary revascularization, exercise program	23
	6 minute walking distance	—	NA	—	0.077	None	17
		HR=5.59 (1.97 to 15.9)	<0.001	HR=2.36 (1.33 to 4.18)	0.001	‡	22
	Fast-paced 4-m walk	HR=3.7	0.014	HR=1.9	0.029	‡	22
	Normal- paced 4-m walk	—	0.071	HR=1.86 (1.06 to 3.29)	0.021	‡	22
Patient- reported lower extremity performance	WIQ stair-climbing score	HR=3.11 (1.30 to 7.47)	0.04	HR=1.70 (1.08 to 2.66)	0.02	‡ and physical activity, statins, ACEI	18
		—	NA	RR=1.01 (1.00 to 1.01)	0.023	None	17
	WIQ distance score	—	0.51	—	0.20	‡ and physical activity, statins, ACEI	18
		—	NA	—	0.55	None	17
	WIQ speed score	—	0.33	—	0.07	‡ and physical activity, statins, ACEI	18
		—	NA	—	0.132	None	17

Effect estimates for nonsignificant findings are not shown. ABI indicates ankle-brachial pressure index; ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; HR, hazard ratio; HTN, hypertension; NA, data not presented; RR, relative risk; WIQ, walking impairment questionnaire; 4-m, 4-metre.

*Represents hazards ratios or risk ratios and 95% CI for the lowest performance quantile compared to the reference group.

†Results significant for male subgroup only.

‡Results adjusted for age, sex, race, BMI, ABI, smoking, comorbidities.

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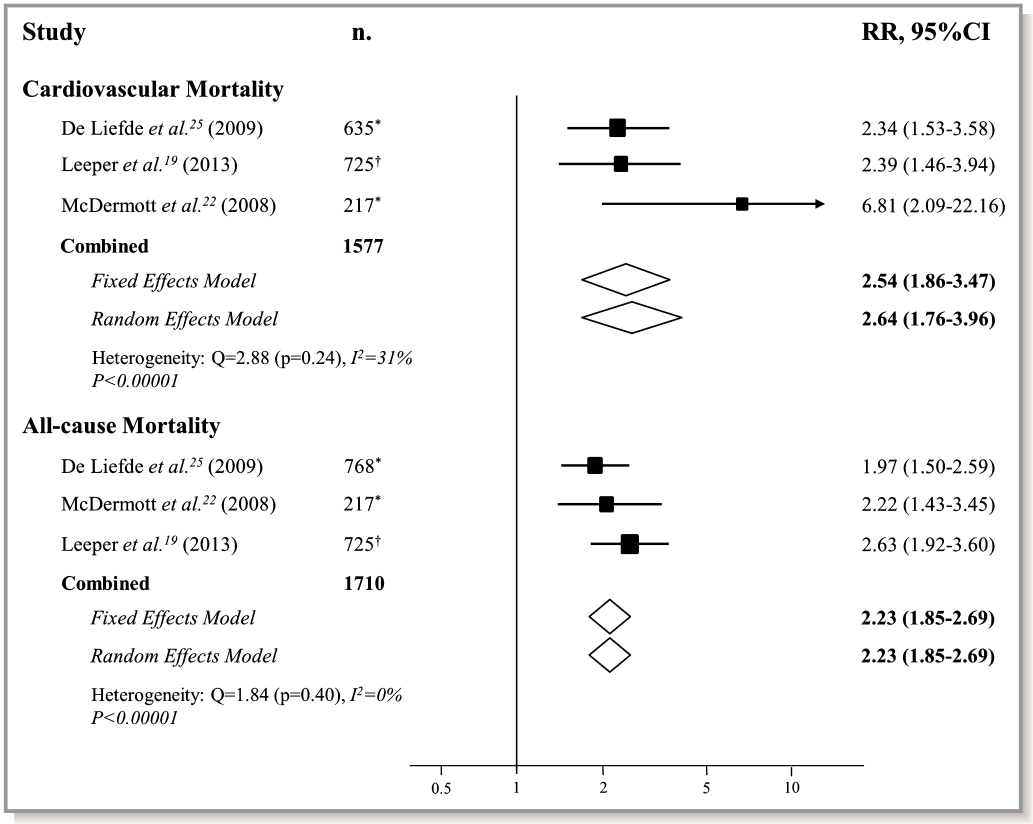

Figure 2. Meta-analysis of the association between maximum walking distance and 5-year cardiovascular and all-cause mortality. Forest plot illustrating unadjusted risk ratios (RRs) and 95% CIs for the association of shorter walking distance with cardiovascular and all-cause mortality. The diamond represents an overall RR calculated in the current meta-analysis. The number n represents the sum of patients in the highest and lowest quantiles for each study. $P<10^{-5}$ under both fixed-effects and random-effects models. *Comparison of lowest- performance quartile to highest-performance quartile.[22,25] †Comparison of patients with performance below set value compared to patients with performance above and including set value.[19]

quently, more sensitive indicators of systemic atherosclerosis. The prognostic value of lower limb strength has not been studied extensively in the general population. However, hazard ratios for lower limb strength reported in this systematic review appear to be considerably higher than those for hand grip strength in the general population, tentatively suggesting that lower limb muscle strength provides greater prognostic information in PAD patients than individuals without PAD.[28]

Table 5. Fixed-Effects Leave-one-Out Sensitivity Analyses for the Association Between Maximum Walking Distance and Mortality

	Meta-Analysis of Unadjusted Data		Meta-Analysis of Adjusted Data	
Study Removed	RR, 95% CI	*P* Value	RR, 95% CI	*P* Value
Cardiovascular mortality				
de Liefde et al[25]	2.80 (1.77 to 4.44)	$<10^{-4}$	1.67 (1.08 to 2.58)	$<10^{-4}$
Leeper et al[19]	2.64 (1.77 to 3.95)	$<10^{-5}$	2.00 (1.34 to 2.99)	7×10^{-4}
McDermott et al[22]	2.36 (1.71 to 3.26)	$<10^{-5}$	1.95 (1.38 to 2.74)	10^{-4}
All-cause mortality				
de Liefde et al[25]	2.48 (1.92 to 3.21)	$<10^{-5}$	2.42 (1.81 to 3.23)	$<10^{-5}$
Leeper et al[19]	2.04 (1.62 to 2.57)	$<10^{-5}$	1.84 (1.38 to 2.45)	$<10^{-4}$
McDermott et al[22]	2.23 (1.81 to 2.74)	$<10^{-5}$	2.03 (1.61 to 2.57)	$<10^{-5}$

RR indicates risk ratio.

Table 6. Random Effects Leave-one-Out Sensitivity Analyses for the Association Between Maximum Walking Distance and Mortality

	Meta-Analysis of Unadjusted Data		Meta-Analysis of Adjusted Data	
Study Removed	RR, 95% CI	*P* Value	RR, 95% CI	*P* Value
Cardiovascular mortality				
de Liefde et al[25]	3.50 (1.31 to 9.38)	0.01	3.30 (1.56 to 6.98)	0.002
Leeper et al[19]	3.44 (1.26 to 9.42)	0.02	2.77 (0.86 to 8.93)	0.09
McDermott et al[22]	2.36 (1.71 to 3.26)	$<10^{-5}$	1.96 (1.33 to 2.90)	6×10^{-4}
All-cause mortality				
de Liefde et al[25]	2.48 (1.92 to 3.21)	$<10^{-5}$	2.42 (1.81 to 3.23)	$<10^{-5}$
Leeper et al[19]	2.04 (1.62 to 2.57)	$<10^{-5}$	1.84 (1.38 to 2.45)	$<10^{-4}$
McDermott et al[22]	2.25 (1.70 to 2.98)	$<10^{-5}$	2.03 (1.42 to 2.91)	10^{-4}

RR indicates risk ratio.

Participant self-report of stair-climbing ability was also associated with mortality in 2 separate studies.[17,18] Objectively measured stair-climbing ability has been shown to be a reliable substitute for peak oxygen consumption in the general population and may explain why the WIQ stair-climbing score, as opposed to the WIQ distance or speed

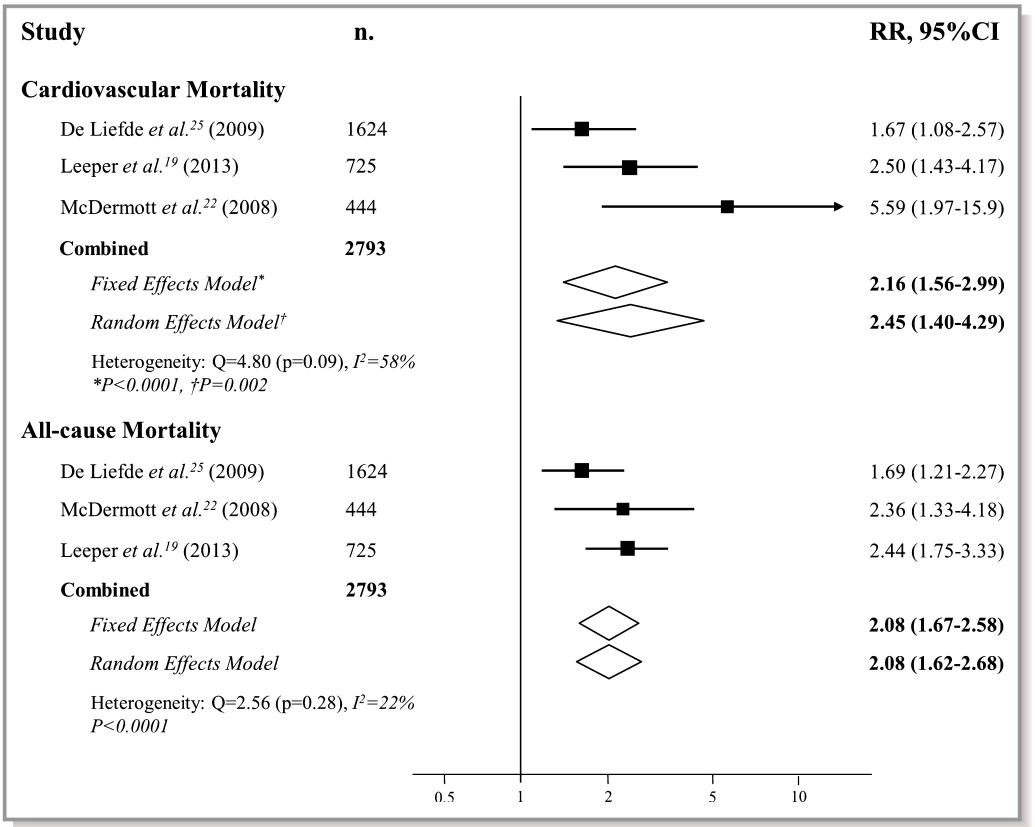

Figure 3. Meta-analysis of maximally adjusted risk ratios (RRs) for the association between maximum walking distance and mortality in peripheral artery disease. Forest plot illustrating maximally adjusted RRs and 95% CIs for the association of shorter walking distance with cardiovascular and all-cause mortality. Covariates included in multivariate analyses for individual studies are listed in Table 4. The diamond represents an overall RR calculated in the current meta-analysis. The number n represents the combined sum of patients in each study. **P* value calculated according to fixed-effects model. †*P* value calculated according to random-effects model.

scores, was associated with mortality.[29] Alternatively, it may be possible that patients have more accurate recall of their stair-climbing capacity because it is potentially easier to quantify than walking distance and speed. The findings of this review for the WIQ differ from that of the general population. Nead et al found that the WIQ distance, speed, and stair-climbing categories independently predicted cardiovascular and all-cause mortality in a large cohort with normal ABI.[30] Moreover, WIQ stair climbing appeared to be the weakest predictor of mortality of all 3 WIQ categories. Further studies are required to reconcile these inconsistencies.

Several possible explanations exist for the association between reduced lower extremity performance and mortality in PAD patients. First, individuals with PAD suffer multiple comorbidities that may limit mobility and reduce survival. Two of the three studies included in our meta-analysis of adjusted RRs (Figure 3) thoroughly adjusted their results for confounding chronic diseases. As expected, adjusted RRs were not as strongly associated with mortality as unadjusted RRs, and we cannot exclude the possibility that the association between walking distance and mortality would not exist after comprehensive, uniform adjustment of comorbid conditions. Secondly, the lower extremity performance measures we investigated may possibly reflect the degree of peripheral atherosclerosis. Several of these performance measures have previously been shown to be associated with ABI, which is a marker of systemic atherosclerosis and cardiovascular risk.[4,7,31] Two of the three studies included in our maximally adjusted risk estimates for cardiovascular and all-cause mortality adjusted their results for ABI. Finally, there is some evidence to suggest that skeletal muscle itself has functional roles that may act to reduce cardiovascular risk. Preclinical studies demonstrate that healthy skeletal muscle secretes an array of anti-inflammatory and cardioprotective cytokines.[32] It is possible that the association between poor lower extremity performance and mortality is in part mediated by loss of healthy skeletal muscle, which has beneficial anti-inflammatory or other effects.[33] Further work is required to explore these hypotheses.

This review supports the use of corridor-walking tests, such as the 6-minute walk, for patients with PAD. These tests can feasibly be applied in the clinical setting to identify individuals at high risk of cardiovascular events. In comparison with other prognostic tests, the corridor-walking tests are relatively inexpensive, do not require special equipment, and can be undertaken efficiently by members of the nursing and allied health teams. There are few other physical or biological markers that have been shown to have comparable mortality prediction in PAD patients. The ABI has previously been used for cardiovascular risk prediction in PAD; however, 2 studies in this review reported strong associations between walking distance and mortality after adjusting for ABI. This suggests that lower extremity performance measures provide prognostic information beyond that of the ABI and comorbidities. Overall, the findings of this review emphasize the importance of measuring lower extremity performance in PAD patients both in the clinical setting and in research studies. Further investigation is needed to determine whether interventions that improve walking ability, such as supervised exercise programs, also reduce mortality.

This study has several limitations. First, data from individual studies were observational and do not imply a causal association. Interventional studies are required to elucidate whether improvement in lower extremity performance prolongs life. Second, there was variation in the methods used to assess walking performance. Heterogeneity analyses were conducted to assess interstudy variation and random-effects meta-analysis was calculated for all comparisons, taking into account interstudy variation. We were unable to investigate differences in effect estimates across different walking tests due to the limited number of studies available. Third, analyses conducted to assess potential publication bias were underpowered, and we cannot rule out the possibility that unpublished studies exist. Finally, meta-analysis of maximally adjusted RRs incorporated both hazard ratios and RRs and combined data that were adjusted for different and correlated confounders. We cannot exclude the possibility that these associations no longer exist after comprehensive, uniform adjustment. It is likely that the results may have been influenced by residual confounding that we could not adjust for.

In conclusion, this systematic review suggests that poorer walking performance, assessed by the 6-minute walk or on a treadmill, is associated with increased cardiovascular and all-cause mortality in patients with PAD. These tests may provide useful prognostic information for patients with PAD. Interventional trials are required to elucidate whether exercise programs and other interventions that improve functional performance reduce mortality in PAD patients.

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Disclosures

None.

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