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Research Article

Association of Muscle Endurance, Fatigability, and Strength With Functional Limitation and Mortality in the Health Aging and Body Composition Study

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Abstract

Background: Mobility limitation is highly prevalent among older adults and is central to the loss of functional independence. Dynamic isokinetic muscle fatigue testing may reveal increased vulnerability to disability and mortality beyond strength testing.

Methods: We studied community-dwelling older adults enrolled in the Health Aging and Body Composition study (age range: 71–82) free of mobility disability and who underwent isokinetic muscle fatigue testing in 1999–2000 (n = 1,963). Isokinetic quadriceps work and fatigue index was determined over 30 repetitions and compared with isometric quadriceps maximum torque. Work was normalized to leg lean mass accounting for gender-specific differences (specific work). The primary outcome was incident persistent severe lower extremity limitation (PSLL), defined as two consecutive reports of either having a lot of difficulty or being unable to walk 1/4 mile or climb 10 steps without resting. The secondary outcome was all-cause mortality.

Results: There were 608 (31%) occurrences of incident PSLL and 488 (25%) deaths during median follow-up of 9.3 years. After adjustment, lower isokinetic work was associated with significantly greater risks of PSLL and mortality across the full measured range. Hazard ratios per standard deviation lower specific isokinetic work were 1.22 (95% CI 1.12, 1.33) for PSLL and 1.21 (95% CI 1.13, 1.30) for mortality, respectively. Lower isometric strength was associated with PSLL, but not mortality. Fatigue index was not associated with PSLL or mortality.

Conclusions: Muscle endurance, estimated by isokinetic work, is an indicator of muscle health associated with mobility limitation and mortality providing important insight beyond strength testing.

Keywords: Mobility—Muscle—Fatigue—Strength—Sarcopenia

Mobility is central to the functional independence and quality of life of older adults. Mobility disability affects an estimated 13% of the U.S. adult population and accounts for 35% of all disability (1). Decreased skeletal muscle mass (sarcopenia) and strength (dynapenia) precede mobility disability, contribute to age-related declines in gait speed, and are consistently associated

with disability, morbidity, and mortality across populations (2–6).

Most human studies of skeletal muscle function have focused on isometric measurements of muscle strength and imaging assessments of muscle size and composition (7–10). However, isometric tests are limited by static assessment of muscle strength at maximal contraction. This procedure may not adequately capture skeletal muscle function in older individuals, who may have conditions that may affect their range of motion. In contrast, isokinetic muscle fatigue testing measures function across the entire functional range of joint movement over repetitive contractions, permitting the calculation of total contractile work, an important measure of muscle endurance. Previous studies of isokinetic muscle testing are limited by assessment of maximal strength over an incomplete functional range (60°/s) and by use of only single repetitions.

The unique clinical and physiological advantages of isokinetic testing with repetitive contractions suggest that this method may provide important insights into muscle endurance and related functional capacity in older adults. We evaluated the importance of isokinetic muscle work and fatigue in a community-based cohort study of 1,963 ambulatory older adults. We determined associations of isokinetic testing and standard measurements of isometric torque with the development of validated persistent severe lower extremity limitation events and death over long-term follow-up.

Methods

Study Population

The Health ABC cohort included 3,075 men and women aged 70–79 years, who were recruited from Medicare listings in Pittsburgh, Pennsylvania and Memphis, Tennessee. Original exclusion criteria were self-reported difficulty walking one-quarter mile, climbing 10 steps, or performing activities of daily living, treatment for cancer in the previous 3 years, or plans to move out of the area. All participants provided informed consent; consent forms and protocols were approved by the institutional review boards at each field center. For the present study, we evaluated 1,963 Health ABC participants who completed the third study examination and participated in isokinetic fatigue testing (Figure 1). This third study examination (Year 3 visit) was the only year that measured simultaneous isometric maximal strength, performed isokinetic fatigue testing, and had dual energy x-ray absorptiometry (DXA) assessment of body composition. The Health ABC study excluded participants from muscle testing if they had a history of heart attack, angioplasty, heart surgery, chest pain, shortness of breath, fainting or angina within the past 3 months, brain aneurysm or cerebral hemorrhage within past 6 months, knee replacement or knee pain precluding testing, an abnormal electrocardiogram at baseline (Year 1), or markedly elevated blood pressure at the time of the study visit (systolic >199 mm Hg or diastolic >109 mm Hg). We excluded participants who developed persistent severe lower extremity limitation prior to the third examination and had mobility disability at the Year 3 visit.

Measurements of Skeletal Muscle Function, Size, and Quality

Isokinetic quadriceps muscle fatigue testing

Isokinetic fatigue testing measures maximal muscle tension throughout a range of motion set at a constant angular velocity (180°/s). Health ABC study personnel performed isokinetic fatigue testing at Year 3 as previously described (11). In brief, participants were asked to perform 30 knee extensions at their maximum strength. Total work was calculated as the total muscular force output for up to a maximum of 30 knee extensions (Force × Distance). The isokinetic fatigue index was calculated as (final torque/initial peak torque) × 100, where final and initial torques represent the minimal and maximal torques from the 30 repetitions. Fatigue index was calculated among those who had complete isokinetic testing defined as completion of greater than 90% of the task (>28 reps out of a total of 30). Estimated maximal strength was also derived from peak isokinetic torque. Maximal quadriceps strength, however, was determined from isometric quadriceps maximal strength testing.

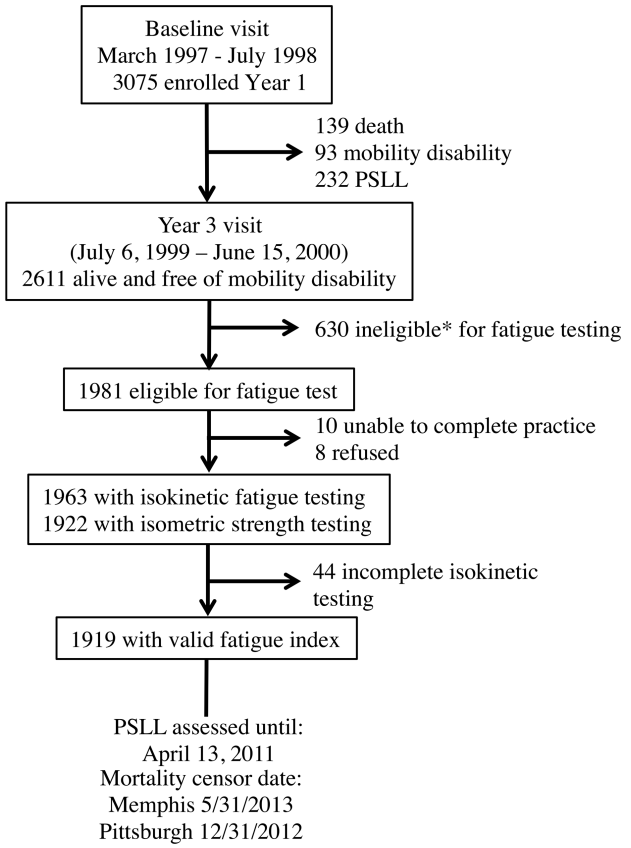

Figure 1. Participant flow diagram. Timelines for data collection and follow-up are listed in the figure. *Reasons for ineligibility included meeting prespecified criteria including history of heart attack, angioplasty, heart surgery, chest pain, shortness of breath, fainting or angina within the past 3 months, brain aneurysm or cerebral hemorrhage within past 6 months, knee replacement or knee pain precluding testing, an abnormal electrocardiogram at baseline (Year 1), or markedly elevated blood pressure at the time of the study visit (systolic >199 mm Hg or diastolic >109 mm Hg).

Isometric quadriceps maximal strength

Health ABC study personnel performed maximal isometric strength testing using a portable isometric chair (Lightweight Isometric Torque Evaluator for the Knee [LITEK, Biologic]) at Year 3 of Health ABC. The participant was positioned with the middle of the thigh placed at the end of the chair and their knee at a 90° angle. A demonstration and practice run was first performed at 50% effort and then three isometric knee extensions were performed at maximal effort with each extension lasting at least 4 seconds. Each attempt was separated by

25 seconds to allow for complete relaxation. Standard encouragement was provided during the test. We defined maximal isometric strength as the maximum value from the three trials as per previous analyses (6,7,12). The isometric test was specifically designed to measure maximal quadriceps strength. Given the modest correlation between maximal isometric strength measures and estimated maximal strength from isokinetic peak torque, we used isometric maximal strength in our primary analysis. Use of isometric measures of maximal strength also eliminated the possibility of self-pacing during the isokinetic fatigue testing leading to submaximal peak torque estimates.

Muscle quality

Given large sex-specific differences in skeletal muscle characteristics, we created standardized variables of specific work, defined as the ratio of isokinetic work to DXA leg lean mass, and specific strength, defined as the ratio of maximal isometric torque to DXA leg lean mass. These specific values in prior studies have been used as measures of muscle quality (6).

Dual energy x-ray absorptiometry

Leg lean mass and body composition were measured using DXA (Hologic QDR 4500, software version 8.21; Waltham, MA) at the Health ABC Year 3 visit (6).

Measurements of Outcomes

Functional outcomes were serially assessed during Health ABC 6-month follow-up telephone calls and scheduled in person examinations. Health ABC investigators defined persistent severe lower extremity limitation (PSLL) as two consecutive reports of either having a lot of difficulty or being unable to walk 1/4 mile or climb 10 steps without resting. The two consecutive reports were required to involve the same functional limitation (ie, climbing 10 steps). The date of PSLL was defined as the date of the first of two successive reports. Deaths in Health ABC were ascertained by informant interviews and death certificates. The date of death was abstracted from death certificates or as reported by persons informing the clinic of death when death certificates were not available. Assessment of PSLL is current through April 13, 2011; mortality data are current through May 31, 2013, at the Memphis site and December 31, 2012, at the Pittsburgh site.

Measurements of Other Covariates

We estimated the glomerular filtration rate (GFR) from serum cystatin C measurements using the CKD-EPI 2012 cystatin C equation (13). Serum cystatin C and serum creatinine provide comparable estimates of directly measured GFR; we prefer cystatin C in studies of muscle function due to potential interdependence of creatinine and muscle mass. Prevalent diabetes, cerebrovascular disease, and coronary artery disease status was determined by self-report and with confirmation by medication use. Depression was defined as history of depression or treated depression. Cognitive function was assessed using modified mini-mental state exam on a 100-point scale (14). Physical activity was assessed by self-report as total kilocalories per week spent walking and exercising. Smoking status was assessed by questionnaire and participants were classified as current, past, or never smokers. Education was categorized into three groups: less than high school, high school graduate, and postsecondary school.

Statistical Analysis

We constructed kernel density plots to describe the distributions of isokinetic work, maximal isometric torque, specific work, and specific torque. We used the standardized variables of *specific work*, defined as the ratio of isokinetic work to DXA leg lean mass, and *specific torque*, defined as the ratio of maximal isometric torque to DXA leg lean mass, to account for sex-specific differences in muscle characteristics and as measures of muscle quality (6). We used Pearson's correlation coefficient to describe interrelationships among isokinetic work, isometric torque, and fatigue index and body composition variables. We used a discrete cumulative incidence function covariate competing risks regression (15) with death as the competing event to evaluate associations of each muscle variable with the time to PSLL. We used Cox proportional hazards models to determine associations with all-cause mortality. The censoring date for PSLL was April 13, 2011, and censoring dates for mortality were May 31, 2013, for the Memphis site and December 31, 2012, for the Pittsburgh site. To account for potential confounding, we constructed a base model that adjusted for age, race, sex, study site, education, height, and weight (continuous). A second model added smoking status (never, current, or former), diabetes (yes or no), coronary heart disease (yes or no), cerebrovascular disease (yes or no), estimated GFRcysc (eGFRcysc; continuous), depression (yes or no), physical activity (continuous), systolic blood pressure (continuous), and statin use (yes or no). We performed a parallel analysis with estimated maximal strength measured by isokinetic peak torque from the isokinetic fatigue testing protocol. We performed sensitivity analyses adjusting for leg lean mass and maximum isometric torque, excluding the 44 participants who had incomplete isokinetic fatigue testing (<28 repetitions) and subgroup analysis restricted to participants who had normal gait speeds (usual gait speed >1 m/s (16); (n = 1,610). Given the strong association of gait speed with mortality, we further adjusted for gait speed in our cox models. We used STATA 13.1 (Statacorp, College Station, TX) and R for all analyses.

Results

Characteristics of the Cohort

There were 1,963 Health ABC participants who were free of mobility disability at the Year 3 visit and completed isokinetic testing; 1,922 of these participants also completed isometric strength testing. The mean age of the study population was 75.5 ± 2.8 years; 49% were female and 36% were black. Mean values ± *SD* for isokinetic work, isometric maximal torque, isokinetic peak torque, and isokinetic fatigue index were 1,058.3 ± 450.2 J, 119.6 ± 56 Nm, 78.9 ± 29 Nm, and 76 ± 22.9% respectively. The distributions of isokinetic work and isometric torque muscle were considerably lower among women compared to men (Supplementary Figure 1). Normalization of these muscle parameters to leg lean mass yielded similar distributions of specific work and specific torque by gender. Participants who had lower quadriceps isokinetic work tended to be older, had lower body mass index and eGFRcysc, slower gait speed, and a greater prevalence of comorbidities (Table 1).

Correlations of Work, Isometric Maximal Torque, Isokinetic Peak Torque, and Fatigue Index

There was a strong correlation of quadriceps isokinetic work with isokinetic peak torque (ρ = 0.87), modest correlation with maximum isometric torque (ρ = 0.51, p < .0001), and modest correlation with leg lean mass (ρ = 0.55; p < .0001; Supplementary Table 1). Only a modest correlation was observed between peak isokinetic torque and maximal isometric torque (ρ = 0.53). There were no meaningful correlations of isokinetic fatigue index with body composition

measures. Usual 20-m gait speed was more strongly correlated with isokinetic work (ρ = 0.35, $p < .0001$) than with isometric torque (ρ = 0.19), isokinetic torque (ρ = 0.25), or fatigue index (ρ = –0.01).

Associations of Muscle Characteristics With PSLL

During a median follow-up of 9.3 years (interquartile range 5.1, 10.5 years), there were 608 occurrences of persistent lower extremity limitation (31%) and there were 488 deaths (25%) that occurred prior to PSLL. Unadjusted incidence rates of PSLL were highest among study participants who had the lowest values of isokinetic work and isometric torque (Table 2). After adjustment, the lowest sex-specific tertile of isokinetic work was associated with an estimated 34% greater risk of PSLL (95% CI 9%–65% greater). Associations of isokinetic work with incident PSLL tended to be linear across the full measured range and were of similar magnitude among men and women (Figure 2A and B). Associations of isometric maximal torque with PSLL were generally similar to those of isokinetic work; however, CIs for continuous associations of isometric torque with PSLL did not exclude the null hypothesis among men or women. Associations of isokinetic peak torque with PSLL were consistent with isokinetic work (Supplementary Table 2). There was no association of isokinetic fatigue index with PSLL.

Associations of isokinetic work with PSLL were not materially altered by further adjustment for leg lean mass and isometric maximal strength or by exclusion of 44 participants who had incomplete testing. After further adjustment for leg lean mass and maximum strength hazard ratios for PSLL per 1-unit *SD* lower isokinetic work were 1.17 (95% CI 1.02, 1.34) for men and 1.32 (95% CI 1.09, 1.59) for women (Table 2). Restricting analyses to 1,610 participants who had normal gait speed (>1 m/s), fully adjusted hazard ratios for PSLL per 1-unit *SD* lower isokinetic work were 1.24 (95% CI 1.06, 1.44) among men and 1.17 (95% CI 0.95, 1.44) among women.

Associations of Muscle Characteristics With Mortality

There were 999 deaths (51%) during a median follow-up of 12.6 years (interquartile range 8, 13.2 years). Lower values of isokinetic work, analyzed as sex-specific tertiles or continuously, were associated with all-cause mortality (Table 3 and Figure 3). After

Table 1. Characteristics of the Year 3 Health ABC Cohort by Sex-Specific Tertile of Isokinetic Work From Fatigue Testing

			Isokinetic Work (Joules)			
		Overall	Lowest Tertile	Middle Tertile	Highest Tertile	
	Missing	*N* = 1,963	*N* = 655	*N* = 655	*N* = 653	*p* Value
Men (min, max)	0		(83, 1,075)	(1,075, 1,500)	(1,505, 3,500)	
Women (min, max)	0		(26, 682)	(682, 931)	(931, 1,774)	
Demographics, no. (%)						
Age	0	75.5 ± 2.8	76 ± 2.8	75.6 ± 2.8	74.7 ± 2.7	<.001
Female	0	968 (49)	323 (49)	322 (49)	323 (49)	
Black	0	713 (36)	260 (40)	215 (33)	238 (36)	.226
Site	0					.9
Memphis		950 (48)	309 (47)	330 (50)	311 (48)	
Pittsburgh		1013 (52)	346 (53)	325 (50)	342 (52)	
Smoking	3					.2
Never		890 (46)	308 (47)	290 (44)	297 (46)	
Current		150 (8)	63 (10)	48 (7)	39 (6)	
Former		915 (47)	282 (43)	317 (48)	316 (49)	
Physical exam, mean ± *SD*						
BMI (kg/m^2)	1	26.9 ± 4.5	26.2 ± 4.8	26.5 ± 4.4	28.1 ± 4.2	<.001
SBP (mm Hg)	0	134.6 ± 19	134.1 ± 19	136 ± 20	133.8 ± 18	.78
Modified Mini-Mental Score	3	90.3 ± 8.5	88.8 ± 10	90.5 ± 8	91.6 ± 7	<.001
Labs, mean ± *SD*						
eGFRcysc (mL/min per 1.73 m^2)	47	86 ± 19	82.7 ± 21	86.5 ± 18	88.9 ± 17	<.001
Hemoglobin (g/dL)	12	13.7 ± 1.3	13.6 ± 1.3	13.7 ± 1.3	13.8 ± 1.3	<.001
Bicarbonate (mmol/L)	186	25.3 ± 2.1	25.4 ± 2.2	25.2 ± 2.2	25.3 ± 1.9	.56
Comorbidity, no. (%)						
Diabetes	1	369 (19)	139 (21)	110 (17)	120 (18)	.2
Prevalent CAD	27	396 (20)	147 (23)	131 (20)	118 (18)	.04
Prevalent stroke	18	126 (6)	58 (9)	41 (6)	27 (4)	<.001
Medications, no. (%)						
Any statin use	1	388 (20)	121 (18)	138 (21)	129 (20)	.55
Body composition, mean ± *SD*						
Total lean body mass (kg)	15	46.4 ± 10	44.8 ± 9.6	45.5 ± 9.7	48.9 ± 10.2	<.001
Leg lean mass (kg)	19	7.4 ± 1.7	7.1 ± 1.6	7.2 ± 1.7	7.8 ± 1.7	<.001
Total body fat (kg)	15	26.3 ± 8.3	25.1 ± 8.8	25.5 ± 8.1	28.1 ± 7.8	<.001
Total leg fat (kg)	19	4.7 ± 1.7	4.6 ± 1.8	4.6 ± 1.6	5 ± 1.7	<.001
Physical performance, mean ± *SD*						
20-m usual walk speed (m/s)	2	1.18 ± 0.2	1.11 ± 0.19	1.19 ± 0.19	1.25 ± 0.2	<.001

Note: BMI = body mass index; CAD = coronary artery disease; eGFRcysc = estimated glomerular filtration rate from serum cystatin C; SBP = systolic blood pressure.

Table 2. Associations of Sex-Specific Tertiles of Muscle Parameters With Persistent Severe Lower Extremity Limitation

	Persistent Severe Lower Extremity Limitation Events				
	Number of Events	Rate per 100 Person-Years	Model 1 SubHR (95% CI)	Model 2 SubHR (95% CI)	Model 3 SubHR (95% CI)
Isokinetic work					
Men continuous (per 450 J lower)	278	3.7	1.26 (1.11, 1.44)	1.18 (1.03, 1.35)	1.17 (1.02, 1.34)
Women continuous (per 450 J lower)	330	4.4	1.36 (1.15, 1.60)	1.34 (1.12, 1.61)	1.32 (1.09, 1.59)
Highest sex-specific tertile	180	3.3	Reference	Reference	Reference
Middle sex-specific tertile	197	3.8	1.14 (0.93, 1.40)	1.12 (0.90, 1.38)	1.08 (0.87, 1.33)
Lowest sex-specific tertile	231	5.1	1.47 (1.20, 1.79)	1.34 (1.09, 1.65)	1.29 (1.04, 1.60)
Isometric torque					
Men continuous (per 56 Nm lower)	273	3.7	1.19 (1.01, 1.40)	1.14 (0.96, 1.34)	1.14 (0.96, 1.35)
Women continuous (per 56 Nm lower)	321	4.3	1.22 (0.93, 1.60)	1.22 (0.92, 1.62)	1.24 (0.93, 1.65)
Highest sex-specific tertile	192	3.7	Reference	Reference	Reference
Middle sex-specific tertile	179	3.6	1.05 (0.85, 1.29)	0.99 (0.80, 1.22)	0.99 (0.80, 1.22)
Lowest sex-specific tertile	223	4.7	1.45 (1.18, 1.78)	1.37 (1.11, 1.69)	1.38 (1.11, 1.70)
Fatigue index					
Men continuous (per 23% lower)	274	3.7	0.99 (0.89, 1.10)	0.98 (0.88, 1.10)	0.98 (0.87, 1.09)
Women continuous (per 23% lower)	317	4.3	0.94 (0.83, 1.06)	0.93 (0.82, 1.05)	0.93 (0.82, 1.06)
Highest sex-specific tertile	198	4	Reference	Reference	Reference
Middle sex-specific tertile	193	3.8	0.93 (0.76, 1.13)	0.93 (0.76, 1.14)	0.92 (0.75, 1.13)
Lowest sex-specific tertile	200	4.1	0.94 (0.77, 1.15)	0.93 (0.75, 1.14)	0.92 (0.74, 1.13)

Note: Model 1 adjusts for age, race, education, height, weight, and study site. Model 2 adds adjustment for smoking, estimated glomerular filtration rate from serum cystatin C, diabetes mellitus, coronary artery disease, cardiovascular disease, depression, cognitive function, physical activity, systolic blood pressure, and statin use. Model 3 adds leg lean mass and isometric torque (for isokinetic work). *SD* for Work is 450 J and *SD* for Torque is 56 Nm and *SD* for 23% for fatigue index. SubHR = subdistribution hazard ratio.

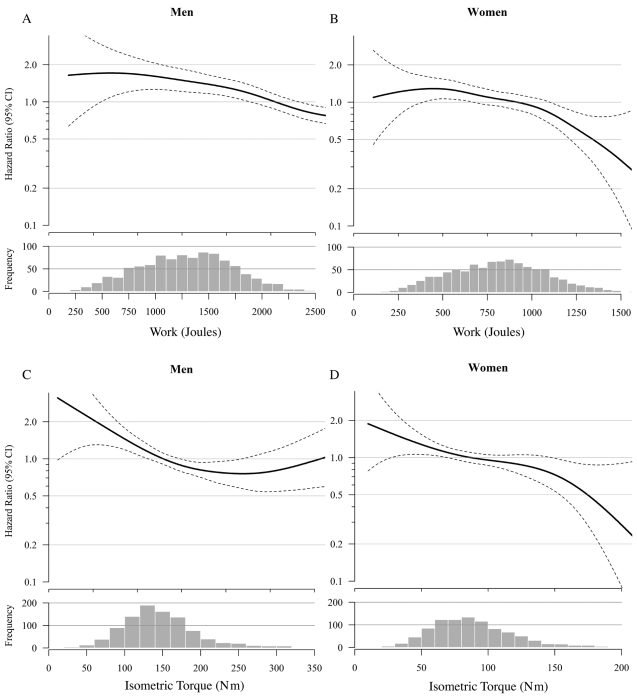

Figure 2. Spline representing the form of the sex-specific association of quadriceps isokinetic work (**A** and **B**) and maximal isometric torque (**C** and **D**) with persistent severe lower extremity limitation. Adjusted for age, race, height, weight, study site, and education.

adjustment, each 1 *SD* lower isokinetic work was associated with an estimated 27% greater risk of death among men (95% CI 16%–38% greater) and a 30% greater risk of death among women (95% CI 8%–56% greater). Isokinetic peak torque was also associated with mortality in men, but, in contrast to total isokinetic work, was not independently associated with mortality in women after adjustment (Supplementary Table 2). Further adjustment for leg lean mass and maximal isometric torque did not materially alter the size of these associations of isokinetic work with mortality. In contrast, neither isometric torque nor isokinetic fatigue index was associated with mortality. Sensitivity analysis further adjusting for usual gait speed did not substantially alter the estimates of association of isokinetic work with mortality. After further adjustment for gait speed, each 1 *SD* lower isokinetic work was associated with an estimated 21% greater risk of death among men (95% CI 10%–33% greater) and a 31% greater risk of death among women (95% CI 7%–59%).

Association of Muscle Quality With Study Outcomes

After adjustment, lower values of isokinetic specific work were also associated with incident PSLL and all-cause mortality (Table 4 and Supplementary Figure 2). Lower values of specific isometric torque were associated with a greater risk of PSLL, but not death.

Discussion

In a community-based cohort of ambulatory older adults, isokinetic measurement of quadriceps total work over repetitive contractions was associated with significantly greater risks of future persistent lower extremity disability and death over long-term follow-up. Associations with PSLL were present across the measured range of values among both men and women and were robust to adjustment for clinical risk factors and leg lean mass. In contrast to maximal strength, only isokinetic quadriceps work was associated with all-cause mortality in both men and women. Taken together, these findings underscore the clinical significance of isokinetic testing with repetitive contractions, which may provide a dynamic and provocative measurement integrating aspects of peak performance and muscle endurance.

Table 3. Associations of Sex-Specific Tertiles of Muscle Parameters With Mortality

	Mortality				
			Model 1	Model 2	Model 3
	Number of Events	Rate per 100 Person-Years	HR (95% CI)	HR (95% CI)	HR (95% CI)
Isokinetic work					
Men continuous (per 450 J lower)	567	5.8	1.36 (1.24, 1.48)	1.27 (1.16, 1.38)	1.25 (1.13, 1.37)
Women continuous (per 450 J lower)	432	4.1	1.42 (1.21, 1.69)	1.30 (1.08, 1.56)	1.35 (1.11, 1.63)
Highest sex-specific tertile	271	3.7	Reference	Reference	Reference
Middle sex-specific tertile	319	4.6	1.21 (1.03, 1.43)	1.11 (0.93, 1.32)	1.10 (0.93, 1.31)
Lowest sex-specific tertile	409	6.6	1.77 (1.51, 2.08)	1.50 (1.27, 1.77)	1.49 (1.25, 1.77)
Isometric torque					
Men continuous (per 56 Nm lower)	553	5.8	1.07 (0.98, 1.18)	1.02 (0.93, 1.14)	1.01 (0.91, 1.12)
Women continuous (per 56 Nm lower)	423	4.1	1.16 (0.93, 1.45)	1.08 (0.93, 1.25)	1.09 (0.93, 1.27)
Highest sex-specific tertile	293	4.3	Reference	Reference	Reference
Middle sex-specific tertile	316	4.7	1.16 (0.98, 1.36)	1.09 (0.92, 1.28)	1.08 (0.91, 1.28)
Lowest sex-specific tertile	367	5.7	1.35 (1.15, 1.59)	1.20 (1.02, 1.42)	1.19 (1.01, 1.41)
Fatigue index					
Men continuous (per 23% lower)	555	5.7	0.99 (0.91, 1.06)	0.96 (0.89, 1.04)	0.96 (0.89, 1.04)
Women continuous (per 23% lower)	417	4.1	1.09 (0.97, 1.23)	1.08 (0.95, 1.22)	1.08 (0.95, 1.23)
Highest sex-specific tertile	310	4.7	Reference	Reference	Reference
Middle sex-specific tertile	321	4.8	1.02 (0.87, 1.19)	0.98 (0.83, 1.14)	0.98 (0.83, 1.15)
Lowest sex-specific tertile	341	5.2	1.06 (0.91, 1.24)	1.01 (0.86, 1.20)	1.01 (0.86, 1.20)

Note: Model 1 adjusts for age, race, education, height, weight, and study site. Model 2 adds adjustment for smoking, estimated glomerular filtration rate from serum cystatin C, diabetes mellitus, coronary artery disease, cardiovascular disease, depression, cognitive function, physical activity, systolic blood pressure, and statin use. Model 3 adds leg lean mass and isometric torque (for isokinetic work). *SD* for Work is 450 J and *SD* for Torque is 56 Nm and *SD* for 23% for fatigue index. HR = hazard ratio.

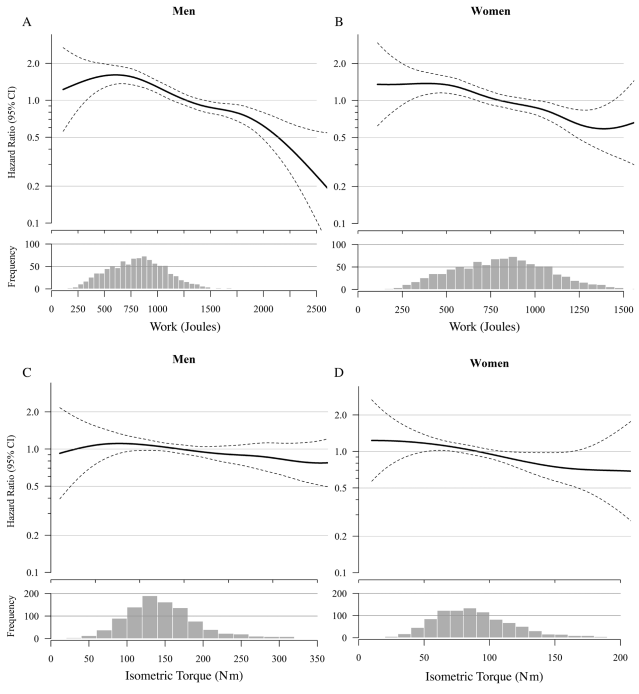

Figure 3. Spline representing the sex-specific form of the association of quadriceps isokinetic work (**A** and **B**) and isometric torque (**C** and **D**) with all-cause mortality. Adjusted for age, race, height, weight, study site, and education.

Table 4. Association of Specific Work and Specific Torque With Study Outcomes

Persistent Severe Lower Extremity Limitation Events		
	Model 1	Model 2
	SubHR (95% CI)	SubHR (95% CI)
Specific work		
Per *SD* lower (48 J/kg)	1.25 (1.15, 1.36)	1.22 (1.12, 1.33)
p value	<.001	<.001
Specific torque		
Per *SD* lower (6.5 Nm/kg)	1.17 (1.03, 1.33)	1.16 (1.02, 1.33)
p value	.017	.03
Mortality		
	Model 1	Model 2
	HR (95% CI)	HR (95% CI)
Specific work		
Per *SD* lower (48 J/kg)	1.29 (1.21, 1.38)	1.21 (1.13, 1.30)
p value	<.001	<.001
Specific torque		
Per *SD* lower (6.5 Nm/kg)	1.07 (0.99, 1.16)	1.02 (0.95, 1.09)
p value	.082	.556

Note: Model 1 adjusts for age, sex, race, education, height, weight, and study site. Model 2 adds adjustment for smoking, estimated glomerular filtration rate from serum cystatin C, diabetes mellitus, coronary artery disease, cardiovascular disease, depression, cognitive function, physical activity, systolic blood pressure, and statin use. HR = hazard ratio; SubHR = subdistribution hazard ratio.

To our knowledge, this is the first study to evaluate muscle endurance and fatigue measurements in relation to the long-term risk of severe lower extremity limitation and the first to directly compare associations with those of standard isometric measures of muscle strength. Prior studies have demonstrated associations of static isometric muscle strength with mortality and gait speed decline (6,7,17). Since muscle strength is highly dependent on joint angle (18), repeated

dynamic testing through a range of joint angles provides additional information regarding muscle capacity providing an integrated measure of peak performance and muscle endurance that may more directly relate to the functional demands of daily living tasks, for example, descending stairs (19,20). Moreover, by providing variable resistance to movement at a constant speed throughout each repetition, isokinetic testing is a safe mechanism for testing endurance and possibly resistance training. Future studies are needed to further characterize associations of isokinetic muscle endurance testing with other important functional outcomes, such as falls or decline in gait speed.

Despite correlation of isokinetic work with leg lean mass, associations with functional limitations were independent of leg muscle mass and maximal isometric strength in our study. This suggests that muscle endurance assessed by total isokinetic work over repeated contractions may provide a window into muscle quality reflecting the efficiency of muscle mitochondrial metabolism, biomechanical function, and walking energetics (21,22). The independent association of total isokinetic work with important clinical outcomes despite controlling for usual gait speed indicates that more provocative muscle endurance testing is important in identifying older adults at high risk of functional limitations.

The association of total isokinetic work with clinical outcomes among those with normal gait speed underscores its utility among higher functioning older adults. Muscle endurance testing may identify early vulnerability to mobility decline. Our findings have potential clinical implications for early referral for isokinetic testing among higher functioning individuals with conditions associated with increased risk of mobility decline such as those with chronic kidney disease (23,24) and complicated diabetes (25,26). Among those with poor total isokinetic work levels, isokinetic resistance exercise may provide a safe (27) and controlled modality to improve isokinetic work, strength, and function. Indeed, previous trials of resistance exercise training among older adults across a range of physical performance have demonstrated that lower extremity resistance training increases total muscle work translating into improvements in stair descent and balance (28,29). Additionally measurement of total isokinetic work may safely assess effectiveness of rehabilitative interventions or efficacy of drug therapies targeting improvements in muscle-specific performance and endurance.

There are several strengths of our current study. The Health ABC study performed muscle function testing using standardized procedures and validated incident PSLL events over long-term follow-up by requiring confirmation on two separate occasions, reducing the potential for misclassification. The Health ABC also conducted detailed comorbidity assessment, facilitating adjustment for known risk factors for lower extremity disability. Finally, the community-based recruitment strategy of Health ABC enhances the generalizability of our study results.

Our study was limited by the relatively healthy cohort of older adults in Health ABC who were ambulatory and eligible to undergo functional muscle testing. Second, given the high correlation of total isokinetic work with isokinetic peak torque derived from fatigue testing, we cannot completely distinguish the role of peak performance and endurance on our study outcomes. Our study may not have precisely captured maximum dynamic strength by isokinetic testing. The modest correlation of isokinetic peak torque with maximal isometric strength compared with prior studies (30) may indicate submaximal participant effort. Despite these limitations, we observed a continuous association of isokinetic work with our study outcomes. A key potential advantage of isokinetic testing with repeated contractions is application to disease states in which range of motion may be limited. Further studies are needed to evaluate the potential utility of isokinetic tests of muscle endurance in more vulnerable populations. These studies should be designed to better distinguish the contribution of peak isokinetic performance (torque) and endurance on functional outcomes. Third, the observational nature of our study cannot prove a causal relationship between muscle function and disability due to the possibility for confounding by other characteristics that were not measured in Health ABC or by residual differences in comorbid conditions that were not captured by Health ABC procedures. Finally, measurements of muscle function were performed on a single occasion later in life; additional measurements may add further insight into the development of clinically relevant disabilities.

In summary, isokinetic quadriceps work, a dynamic test integrating aspects of muscle endurance, is associated with long-term risks of disability and death. Isokinetic tests of muscle function over repetitive contractions may provide novel insight into muscle health and reserve functional capacity beyond traditional static strength testing among older adults. Measurements of isokinetic work over multiple contractions may have the advantage of integrating aspects of peak performance and muscle endurance helping to identify older individuals who have diminished reserve capacity and greater susceptibility to future mobility limitation. Moreover, measurements of muscle endurance are a novel, safe, and relatively inexpensive method that could be used in estimating the impact of targeted interventions on functional outcomes. Given the high burden of mobility disability in an aging population, identifying cost-effective strategies of improving muscle endurance may lead to substantial improvements in functional and clinical outcomes.

Supplementary Material

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

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