Research Article

Longitudinal Association Between Energy Regulation and Fatigability in Mid-to-Late Life

Jennifer A. Schrack, PhD,^{1,2,*} Amal A. Wanigatunga, PhD, MPH,^{1,2} Vadim Zipunnikov, PhD,³ Pei-Lun Kuo, MD, MPH,^{1,4} Eleanor M. Simonsick, PhD,⁴ and Luigi Ferrucci, MD, PhD⁴

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland. ²Center on Aging and Health, Johns Hopkins University, Baltimore, Maryland. ³Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland. ⁴Intramural Research Program, National Institute on Aging, Baltimore, Maryland.

*Address correspondence to: Jennifer A. Schrack, PhD, 615 N Wolfe St, E7144, Baltimore, MD 21205. E-mail: jschrack@jhu.edu

Received: June 25, 2019; Editorial Decision Date: January 1, 2020

Decision Editor: Anne Newman, MD, MPH

Abstract

Background: Deficits in energy production and utilization have been linked to higher fatigue and functional decline with aging. Lesser known is whether individuals with a combination of low peak energy capacity and high energy costs for mobility (eg, impaired energy regulation) are more likely to experience the onset and progression of high fatigability with aging.

Methods: Participants in the Baltimore Longitudinal Study of Aging ($n = 651$, 49.0% male, mean age 71.9, range 50–94) with ≥ 2 visits who completed fatigability (Borg rating of perceived exertion [RPE] after a 5-minute 1.5 mph treadmill walk), slow walking energy expenditure (VO_2 mL/kg/min), and peak walking energy expenditure (VO_2 mL/kg/min), testing between 2007 and 2018. The longitudinal association between each measure of energy expenditure, a ratio of energy cost-to-capacity (cost ratio), and perceived fatigability was modeled using mixed effects models adjusted for age, body composition, and comorbidities. Time to higher perceived fatigability ($\text{RPE} \geq 10$) was modeled using Cox proportional hazards models.

Results: In continuous analyses, higher slow walking energy expenditure ($p < .05$) and a higher cost ratio ($p \leq .001$) were associated with greater perceived fatigability over time. Cox proportional hazards models using tertiles of the cost ratio suggest that, compared to those in the lowest tertile, those in the middle and highest tertiles had 1.89 (95% confidence interval [CI]: 1.57–5.16) and 2.85 (95% CI: 1.05–3.40) times greater risk of developing higher fatigability, respectively.

Conclusion: Findings suggest that strategies to prevent fatigability should consider methods to improve energy regulation by targeting both the independent and combined effects of declining peak capacity and rising energy costs for mobility with aging.

Keywords: Walking efficiency, Peak capacity, Energy cost, Fatigue

The ability to produce and utilize energy changes with aging. VO_2 peak, a measure of energy capacity, declines gradually throughout midlife and accelerates in late life (1), with approximately 55%–60% of peak energy capacity lost during this time (2). Less recognized is an increase in the energetic demands for daily tasks such as walking, contributing to the development of an “energy deficit” with aging (3–5). The underlying mechanisms contributing to these changes are often multifactorial, including age- and disease-related alterations in metabolism, biomechanics, and neuromotor control, which reduce energy capacity and effi-

ciency of movement, and increase the energetic cost of mobility in older adults (6–8).

Usual-paced walking is typically performed at a threshold below 50% of peak capacity; a level of energy expenditure that can be maintained for an extended period of time without overexertion (2). With aging, a combination of declining peak capacity and rising energetic costs lead to impaired energy regulation where the energy costs of mobility approach nearly 100% of energy capacity in very old age (2–7,9). This phenomenon has been linked with slow and declining gait speed (8), and may help explain why fatigue is so

common in older persons, especially among those in poor health who are most likely to have a critical combination of low peak capacity and high energy costs (7,10).

Perception of fatigue plays a role in the frequency, duration, and intensity of daily physical activities (11–13). As perceived fatigue rises, daily activities may be performed less often and more slowly, triggering a vicious cycle leading to further fitness reductions and the emergence of compensatory mechanisms to redirect energy to the most critical tasks (7,11). Although reported “tiredness” and “low energy” are often linked to a low energy/high fatigue phenotype (14–16), the true magnitude of the association between fatigue and energy regulation is not well understood as individuals typically equilibrate the intensity and/or duration of activities to avoid or delay fatigue onset.

Perceived fatigability assesses perception of fatigue in relation to a standardized activity and may thus be a more reliable and discriminating indicator of health and risk of functional decline, disability, and death in older adults than traditional subjective ratings of fatigue (14–17). The cross-sectional associations between slow gait (14), the energetic cost of walking (18,19), peak walking capacity (18), and fatigability have been explored, but the longitudinal, independent, and combined effects of low peak capacity and high energy costs on the development and progression of fatigability have not been evaluated. Accordingly, this research examined the longitudinal association between the energy cost of walking, peak walking energy expenditure, and a ratio of energy cost-to-capacity (“cost ratio”) and perceived fatigability using 651 participants from the Baltimore Longitudinal Study of Aging (BLSA) aged 50–94 years. We hypothesized that the combined effects of declining peak walking capacity and rising energetic cost of walking synergistically create a low energy reserve phenotype that contributes to the emergence and progression of fatigability with aging.

Methods

Participants

The BLSA is a study of normative human aging, established in 1958 and conducted by the National Institute on Aging Intramural Research Program. Briefly, the BLSA is a continuously enrolled cohort of community-dwelling volunteers who pass comprehensive health and functional screening evaluations and are free of major chronic conditions and cognitive and functional impairment at the time of enrollment. Once enrolled, participants are followed for life and undergo extensive testing every 1–4 years depending on age (<60 every 4 years, 60–79 every 2 years, ≥ 80 every year).

The sample for the current study consists of 651 men and women with two or more BLSA clinic visits (mean 3.0 years follow-up, range 2–8) between August 2007 and September 2018. Trained and certified technicians administered all assessments following standardized protocols. The Institutional Review Board of the National Institute of Environmental Health Sciences approved the study protocol and participants provided written informed consent at each study visit.

Measures

Peak walking energy expenditure

Peak walking energy expenditure (mL/kg/min) was assessed during the 400-m segment of the long-distance corridor walk; a two-part, self-paced endurance walking test and a validated measure of cardiorespiratory fitness in older adults (20,21). The test was performed on a 20-m course in an uncarpeted corridor marked by cones at

both ends, with the participant wearing a portable metabolic analyzer, the Cosmed K₄b² (Cosmed, Rome, Italy). Participants were instructed to walk “as quickly as you can over the full 10 laps” (one lap equaled 40 m). Standardized encouragement was given with each lap along with the number of laps remaining. Split times for each lap and total time to walk 400 m were recorded. To calculate average peak walking energy expenditure per kilogram of body weight (peak VO₂ mL/kg/min), readings from the first 1.5 minutes of the test were discarded to allow the participant to adjust to the workload and the remaining readings were averaged to arrive at a single measure of the average energy expended (mL/kg/min) during 400 m of peak sustained walking (5,7).

Energetic cost of slow walking

The energetic cost of slow walking (mL/kg/min) was assessed via indirect calorimetry (Medical Graphics Corp, St Paul, MN) during 5 minutes of slow treadmill walking at 0.67 m/s (1.5 mph), zero percent grade. A single speed was used for all participants, providing a standardized measure by which to gauge age-related changes in energy expenditure (eg, walking efficiency) during a low-demand task that minimizes participant exclusion at the higher end of the age spectrum (5,7). To calculate the average volume of oxygen consumed per kilogram of body weight (mL/kg/min) during the walking task, energy expenditure readings from the first 2 minutes of testing were discarded to allow the participant to adjust to the workload. The final 3 minutes were averaged to derive a single measure of the average VO₂ (mL/kg/min) consumed, or the average energetic cost of a slow standardized walking task (5,7).

A ratio of the energetic cost of slow walking to peak walking energy expenditure (“cost ratio”) (5) was used to define the percentage of peak walking capacity needed for mobility:

$$\frac{\text{Energetic cost of slow walking (ml/kg/min)}}{\text{Peak Walking Energy Expenditure (ml/kg/min)}}$$

Perceived fatigability

Perceived fatigability was assessed immediately after the 5 minute, 1.5 mph (0.67 m/s) standardized treadmill walk by asking participants to rate their perceived exertion using the Borg rating of perceived exertion (RPE) scale. The scale ranges from 6 to 20, where higher exertion levels represent higher perceived fatigability (14). Fatigability was examined as a continuous measure and as a categorical measure with higher fatigability defined as an RPE of 10 or higher (14).

Covariates

All participants completed a physical examination and health history assessment. Weight and height were measured according to standard protocols and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²). Total body dual-energy x-ray absorptiometry was performed using a Prodigy Scanner (GE, Madison, WI) and analyzed with version 10.51.006 software. The presence of chronic conditions was assessed by nurse practitioners and established according to information on medical history, drug treatment, and physical examination. Chronic conditions included in the analysis were reported history of: cardiovascular disease (heart disease or cardiac surgery, including myocardial infarction, congestive heart failure, angina, coronary artery bypass, and angioplasty), pulmonary disease (chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or asthma), cerebral

vascular disease (stroke or transient ischemic attack), peripheral neuropathy (diagnosis of peripheral neuropathy or nerve damage in the lower legs, feet, or hands), hypertension (diagnosis of hypertension and taking antihypertensive medications), diabetes (diagnosis of diabetes and current medication for diabetes), cancer (non-skin [squamous or basal cell] cancer), and arthritis (lower extremity arthritis pain).

Statistical Analysis

Descriptive analyses were performed to assess general characteristics of the study population, overall and by tertiles of the cost ratio. Fitted plots were created to assess trends between the energy variables, perceived fatigability, and age (Figures 1 and 2). Based on the appearance of these figures, the longitudinal association between change in each energy variable and change in perceived fatigability was modeled continuously using linear mixed effects models. To understand the independent and combined effects of changes in the energy variables, three separate models were explored to assess the effects of change in: (a) the cost ratio, (b) the energetic cost of slow walking, and (c) peak energy capacity. Time was calculated as years from baseline assessment. Longitudinal changes in the energy variables were calculated as the difference between baseline and most recent assessment for each measure. Interaction terms between the baseline energy variables and time, and change in the energy variables and time, were included in each model. Covariates included baseline age, sex, race (white vs non-white), fat mass (kg), lean mass (kg), and number of chronic conditions.

Kaplan–Meir survival curves and adjusted Cox proportional hazard models were used to estimate differences in time to high fatigability (RPE ≥ 10) by tertiles of the cost ratio. All analyses were conducted using Stata MP version 14 (Statacorp, College Station, TX).

Results

Table 1 describes baseline characteristics of study participants stratified by tertiles of cost ratio. Of the 651 participants in the analytical sample, mean baseline age was 71.7 ($SD = 9.2$) years, 51.7% were men, 69.6% were of white race, and mean BMI was 26.8 (4.3)

Figure 1. The longitudinal association between age (years) and the cost ratio, as defined by a ratio of the energetic cost of slow (mL/kg/min) walking to peak walking energy expenditure (mL/kg/min), stratified by sex. Each dot represents a participant visit, and the lines connecting the dots represent each individual's trajectory. The age-related trend (overall and per decade) is shown with blue (men) and red (women) lines.

kg/m². The cost ratio averaged 53.6% (17.6) at baseline and exceeded 50% in 346 (53.2%) of participants. Those in the highest tertile of the cost ratio tended to be older, had higher fat mass and lower lean mass, higher perceived fatigability, higher energetic cost of slow walking (mL/kg/min), and lower peak walking energy expenditure (mL/kg/min). They were also more likely to report a history of pulmonary disease, hypertension, and lower extremity arthritis pain.

The energetic cost of slow walking increased an average of 0.03 mL/kg/min per year, and did not differ as a function age. Peak walking energy expenditure decreased -0.24 mL/kg/min per year from age 50–85 and -0.30 mL/kg/min thereafter. The cost ratio increased exponentially with age (Figure 1), averaging a 0.8% increase per year from age 50 to 70 years, 1.1% from age 70 to 85 years, and 1.5% thereafter. Table 2, row (a) describes the continuous longitudinal association between the cost ratio and perceived fatigability (Models 1–3) with successive covariate adjustment. The significant interaction term in Model 1 shows that for each 0.10 (10%) annual increase in the cost ratio, perceived fatigability increased by 0.03 RPE ($p < .001$). The magnitude of this effect remained unchanged with progressive adjustment for demographics, comorbid conditions (Model 2), and body composition (Model 3).

To understand the independent associations of the components of the cost ratio (energetic cost of walking and peak energy capacity) with perceived fatigability, additional models were run with each variable expressed independently. Table 2, row (b) describes the continuous longitudinal association between the energetic cost of walking and perceived fatigability. The significant interaction term for Model 1 shows that for each 1.0 mL/kg/min annual increase in the energetic cost of walking over time, perceived fatigability increased by 0.02 RPE ($p < .05$). This association became slightly stronger with progressive covariate adjustment ($\beta = 0.03$ RPE, $p < .05$). Table 2, row (c) describes the continuous longitudinal association between peak walking energy expenditure and perceived fatigability. The significant interaction for Model 1 shows that for each 1.0 mL/kg/min decrease in peak walking energy expenditure over time, perceived fatigability increased by 0.009 RPE ($p < .05$). However, these effects were attenuated after further adjustment for other covariates ($\beta = -0.008$ RPE, $p > .05$). Model fits were compared by examining estimated densities of the residuals and running models including terms for peak walking energy expenditure, the energetic cost of slow walking, and the cost

Figure 2. A scatterplot and lowess line describing the association between the cost ratio, a ratio of energy-cost-to-energy capacity, and perceived fatigability (RPE). RPE = Rating of perceived exertion.

Table 1. Baseline Characteristics of 651 BLSA Participants by Cost Ratio Tertile, Defined as the Energy Cost of Slow Walking to Peak Walking Energy Expenditure

	Highest Cost Ratio Tertile (0.58–1.0) N = 217		Middle Cost Ratio Tertile (0.46–0.57) N = 217		Lowest Cost Ratio Tertile (cost ratio: 0.15–0.45) N = 217		p-trend
	Mean/No.	SD (%)	Mean/No.	SD (%)	Mean/No.	SD (%)	
Age (years)	75.0	8.6	71.5	8.7	67.2	9.1	<.001
Male sex	98	(45.2)	104	(47.9)	117	(53.9)	.18
BMI (kg/m ²) ^a	27.3	4.4	27.1	4.4	26.1	4.1	.006
Fat mass (kg)	28.1	10.0	26.9	9.7	24.1	9.0	<.001
Lean mass (kg)	45.7	9.0	46.8	9.7	48.6	10.2	.007
Non-white race	69	(31.8)	68	(31.3)	62	(28.6)	.73
Ever smoked ^b	82	(37.7)	86	(39.6)	77	(35.5)	.67
Cardiovascular disease	21	(9.7)	24	(11.1)	16	(7.4)	.41
Pulmonary disease	15	(6.9)	8	(3.7)	1	(0.46)	.002
Diabetes	44	(20.3)	41	(18.9)	28	(12.9)	.10
Hypertension	114	(52.5)	110	(50.7)	87	(40.1)	.02
Stroke	7	(3.2)	6	(2.8)	2	(0.9)	.24
Cancer	28	(12.9)	26	(12.0)	25	(11.5)	.90
Peripheral neuropathy	18	(8.3)	21	(9.7)	13	(6.0)	.36
Lower extremity arthritis	95	(43.8)	72	(33.2)	70	(32.2)	.02
Perceived Fatigability (RPE) ^c	9.6	(2.2)	8.3	(2.0)	7.6	(1.8)	<.001
Energetic cost of walking ^d	9.7	(1.8)	8.7	(1.2)	7.8	(1.5)	<.001
Peak Walking VO ₂ ^e	13.6	(2.7)	17.0	(2.4)	21.5	(4.4)	<.001
Cost ratio ^f	0.73	(0.15)	0.51	(0.03)	0.37	(0.06)	<.001

Note: BMI = Body mass index; RPE = Rating of perceived exertion.

^aWeight in kilograms divided by height in meters squared.

^bReported ever smoking on a regular basis.

^cRating of perceived exertion after 5 minutes of slow treadmill walking (0.67 m/s, 0% grade).

^dAverage energy expended during 5 minutes of slow (0.67 m/s, 0% grade) treadmill walking (mL/kg/min).

^eAverage peak energy expenditure during the 400-m walk (mL/kg/min).

^fRatio of the energetic cost of slow walking to peak walking energy expenditure.

Table 2. Longitudinal mixed models of the association between: (a) the cost ratio and perceived fatigability, (b) the energetic cost of walking and perceived fatigability, and (c) peak walking capacity and perceived fatigability, with progressive covariate adjustment

Outcome:	Model 1	Model 2	Model 3
Perceived fatigability (RPE) (N = 651)	β (SE)	β (SE)	β (SE)
(a)Baseline cost ratio ^a	.48 (.05)***	.46 (.05)***	.41 (.05)***
Time (years)	-.03 (.05)	-.03 (.05)	-.04 (.05)
Change in cost ratio × time	.03 (.008)**	.03 (.008)**	.03 (.008)**
(b)Baseline energetic cost of slow walking (mL/kg/min)	.23 (.05)***	.30 (.05)***	.36 (.05)***
Time (years)	.08 (.09)	.05 (.001)	.01 (.09)
Change in energetic cost of walking × time	.02 (.01)*	.03 (.01)*	.03 (.009)*
(c)Baseline peak walking energy expenditure (mL/kg/min)	-.13 (.02)***	-.12 (.02)***	-.09 (.02)***
Time (years)	.11 (.06)	.11 (.06)	.11 (.06)
Change in peak walking energy expenditure × time	-.009 (.004)*	-.008 (.004)	-.008 (.004)

Note: RPE = Rating of perceived exertion.

Model 1: Adjusted for baseline age, baseline energy measure, time since baseline, and an interaction between the baseline energy measure × time.

Model 2: Model 1 + sex, race, number of comorbid conditions.

Model 3: Model 2 + fat mass (kg), lean mass (kg).

^aDefined as a ratio of the energetic cost of slow walking (mL/kg/min) to peak walking energy expenditure (mL/kg/min).

*** $p \leq .0001$; ** $p \leq .001$; * $p < .05$.

ratio. In the end, the cost ratio remained the most strongly associated with perceived fatigability.

Lastly, to provide clinical perspective, a time-to-event analysis was performed among the 486 participants free of higher fatigability at baseline (RPE < 10) to predict the development of higher fatigability according to baseline tertiles of cost ratio (see [Supplementary](#)

[Table 1](#) for participant characteristics by tertile). As shown in [Figure 3](#), the trajectories of time to high fatigability differed by tertile (log rank to compare survival distributions $p < .0001$). In Cox proportional hazards models (adjusted for age, sex, race, fat mass, lean mass, and number of comorbidities), the hazard of developing higher fatigability was 1.89 times (95% CI: 1.05–3.40) greater for those in

Time Since Baseline (years)	1	3	5	7	9
Lowest Cost Ratio Tertile					
Number at Risk	189	131	84	37	7
Cumulative Events	10	13	15	16	16
Middle Cost Ratio Tertile					
Number at Risk	173	130	86	52	13
Cumulative Events	15	26	35	39	39
Highest Cost Ratio Tertile					
Number at Risk	123	92	62	43	8
Cumulative Events	20	36	43	50	53

Figure 3. Kaplan-Meier estimates of the proportion of participants who developed high fatigability ($RPE \geq 10$) over time, stratified by tertiles of cost ratio (log rank to compare survival distributions $p < .0001$). RPE = Rating of perceived exertion.

the middle tertile of cost ratio and 2.85 times (95% CI: 1.57–5.16) greater for those in the highest tertile of cost ratio, relative to those in the lowest tertile, respectively.

Discussion

A higher cost ratio, as defined by a ratio of the energetic cost of slow walking to peak walking energy expenditure, was more strongly associated with increasing perceived fatigability over time than independent measures of peak walking energy expenditure or the energetic cost of walking in well-functioning middle- and older-aged adults. Moreover, those in the middle and highest tertiles of the cost ratio, where the energetic cost of walking ranged from 46% to 100% of peak walking capacity, had significantly greater risk of developing higher fatigability ($RPE \geq 10$) than those in the lowest cost ratio tertile after adjusting for meaningful covariates. Collectively, these results provide support for the hypothesis that a combination of declining peak walking capacity and rising energetic cost of walking work synergistically to create a low energy phenotype that contributes to the onset and progression of fatigability with aging.

Although previous work has linked high energetic cost with fatigability (19), slow gait speed (8,19,22), poor walking efficiency (7,8,22), and reduced aerobic capacity (7,18), this is the first study to examine the longitudinal association between changes in energy regulation and fatigability with aging. Our measure of energy regulation, the “cost ratio” was more strongly associated with increasing fatigability than independent measures of energetic cost and peak walking capacity, suggesting the combined effect of decreasing capacity and increasing costs should be considered in conjunction

when evaluating the risk of the development and progression of fatigability in older adults. This is consistent with previous work by our group linking impaired energy regulation with slow gait speed in older adults (5,8). When combined with other research linking fatigability with declining functional performance (15), these results further suggest that energy regulation is a key factor in the pathway between higher fatigability and reduced functional performance.

Previous research has shown that healthy persons tend to walk at a level of energy expenditure below 50% of their peak capacity (2,6), and that those who cross this threshold may have biomechanical and metabolic inefficiencies contributing to a loss of efficiency and slower gait speed, exacerbated by the aging process (2,4,5,8,22). The results from the current study add to these findings by demonstrating that higher perceived fatigability following the completion of a standardized slow walking task is more likely to occur as the energetic cost of walking approaches and exceeds 50% of peak walking capacity. To this end, high fatigability may be a sign of compromised energy regulation even among functionally independent older adults, illuminating potential mechanisms linking high fatigability with eventual poor health outcomes.

The cost ratio has been proposed as a phenotypic measure of aging (9,23–25), manifesting as poor walking efficiency, low peak capacity, and high resting metabolic rate (7,10,23,24,26). The current findings support this hypothesis by showing an exponential increase in the cost ratio with age and suggesting that even small changes in perceived fatigability may be reflective of energy dysregulation across multiple levels of exertion. In addition to reduced functional performance (14,15), fatigability has been linked to altered and diminished physical activity profiles (11,27), preclinical peripheral artery disease (28), high inflammatory burden (29), excess adiposity (30,31), and cancer history (32,33). Detection of changes in fatigability, and its underlying mechanisms, may thus provide new insight into the multifaceted processes contributing to a loss of physiologic resilience with aging.

Some limitations should be noted. First, BLSA participants are healthier than the general population, thus these results may be understated compared to more clinical populations. Replication in other aging studies is warranted, especially at older age ranges and among those with higher disease burden. Second, it is possible the speed of the slow walking test (0.67 m/s) may inflate the energetic cost of walking in young and middle aged participants (3,34). However, given the average age of the study population was 71.4 years at baseline, these effects are likely minimal. Moreover, the slow treadmill speed was chosen to: (i) facilitate testing in even the oldest old, and (ii) be consistent with the minimal speed required for independent mobility (5,35–37), both of which increase the construct validity of the measure. Finally, because peak walking energy expenditure was measured during the 400 m walk, participants may not have reached as high a level of exertion, as on a treadmill test. However, the 400 m walk is a validated measure of cardiorespiratory fitness (21), and the average respiratory quotient was 0.94, indicating a high level of exertion (38).

In summary, this study found that compromised energy regulation is associated with the development and progression of perceived fatigability over time, suggesting that measures of both peak energy capacity and the energetic cost of walking should be considered when examining underlying physiological mechanisms contributing to the development and progression of fatigability in older adults. Further, these findings highlight the need for a better understanding of the loss of energy availability with aging and the underlying biological and physiological mechanisms contributing to this process.

Future research should target individuals who are either in or approaching the classification of high energy costs in relation to energy capacity to help fuel future interventions aimed at alleviating fatigability and promoting healthy longevity.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Table 1s. Baseline characteristics of the 486 participants whose perceived fatigability was <10 RPE at baseline by tertiles of energy reserves, as defined by a ratio of the energy cost of walking to peak walking energy expenditure.

Funding

This work was supported by grants R21AG053198 and P30AG021334 from the National Institute on Aging. Data used in the analyses were obtained from the Baltimore Longitudinal Study of Aging (1ZIAAG000015-61), an Intramural Research Program of the National Institute on Aging. J.S. is supported by R21AG053198, P30AG021334, U01AG0057545, and R01AG061786. A.W. and V.Z. are supported by U01AG0057545 and R01AG061786.

Conflict of Interest

E.S., L.F., and J.S. currently serve on the editorial board for the Journal of Gerontology: Medical Sciences. A.W., P.K., and V.Z. have no conflicts to disclose.

References

- Fleg JL, Morrell CH, Bos AG, et al. Accelerated longitudinal decline of aerobic capacity in healthy older adults. *Circulation*. 2005;112:674–682. doi: [10.1161/CIRCULATIONAHA.105.545459](#)
- Waters RL, Mulroy S. The energy expenditure of normal and pathologic gait. *Gait Posture*. 1999;9:207–231. doi: [10.1016/S0966-6362\(99\)00009-0](#)
- Waters RL, Lunsford BR, Perry J, Byrd R. Energy-speed relationship of walking: standard tables. *J Orthop Res*. 1988;6:215–222. doi: [10.1002/jor.1100060208](#)
- Martin PE, Rothstein DE, Larish DD. Effects of age and physical activity status on the speed-aerobic demand relationship of walking. *J Appl Physiol* (1985). 1992;73:200–206. doi: [10.1152/jappl.1992.73.1.200](#)
- Schrack JA, Simonsick EM, Ferrucci L. The relationship of the energetic cost of slow walking and peak energy expenditure to gait speed in mid-to-late life. *Am J Phys Med Rehabil*. 2013;92:28–35. doi: [10.1097/PHM.0b013e3182644165](#)
- Larish DD, Martin PE, Mungiole M. Characteristic patterns of gait in the healthy old. *Ann N Y Acad Sci*. 1988;515:18–32. doi: [10.1111/j.1749-6632.1988.tb32960.x](#)
- Schrack JA, Simonsick EM, Ferrucci L. The energetic pathway to mobility loss: an emerging new framework for longitudinal studies on aging. *J Am Geriatr Soc*. 2010;58 (Suppl 2):S329–S336. doi: [10.1111/j.1532-5415.2010.02913.x](#)
- Schrack JA, Zipunnikov V, Simonsick EM, Studenski S, Ferrucci L. Rising energetic cost of walking predicts gait speed decline with aging. *J Gerontol A Biol Sci Med Sci*. 2016;71:947–953. doi: [10.1093/gerona/glw002](#)
- Kuo P-L, Schrack JA, Shardell MD, et al. A roadmap to build a phenotypic metric of aging: insights from the Baltimore Longitudinal Study of Aging. *J Intern Med*. In Press.
- Schrack JA, Knuth ND, Simonsick EM, Ferrucci L. “IDEAL” aging is associated with lower resting metabolic rate: the Baltimore Longitudinal Study of Aging. *J Am Geriatr Soc*. 2014;62:667–672. doi: [10.1111/jgs.12740](#)
- Wanigatunga AA, Simonsick EM, Zipunnikov V, et al. Perceived fatigability and objective physical activity in mid- to late-life. *J Gerontol A Biol Sci Med Sci*. 2018;73:630–635. doi: [10.1093/gerona/glx181](#)
- Gonzales JU, Wiberg M, Defferari E, Proctor DN. Arterial stiffness is higher in older adults with increased perceived fatigue and fatigability during walking. *Exp Gerontol*. 2015;61:92–97. doi: [10.1016/j.exger.2014.12.005](#)
- Appels A, Mulder P. Excess fatigue as a precursor of myocardial infarction. *Eur Heart J*. 1988;9:758–764. doi: [10.1093/eurheartj/9.7.758](#)
- Simonsick EM, Schrack JA, Glynn NW, Ferrucci L. Assessing fatigability in mobility-intact older adults. *J Am Geriatr Soc*. 2014;62:347–351. doi: [10.1111/jgs.12638](#)
- Simonsick EM, Glynn NW, Jerome GJ, Shardell M, Schrack JA, Ferrucci L. Fatigued, but not frail: perceived fatigability as a marker of impending decline in mobility-intact older adults. *J Am Geriatr Soc*. 2016;64:1287–1292. doi: [10.1111/jgs.14138](#)
- Eldadah BA. Fatigue and fatigability in older adults. *PM R*. 2010;2(5):406–413. doi: [10.1016/j.pmrj.2010.03.022](#)
- Alexander NB, Taffet GE, Horne FM, et al. Bedside-to-Bench conference: research agenda for idiopathic fatigue and aging. *J Am Geriatr Soc*. 2010;58:967–975. doi: [10.1111/j.1532-5415.2010.02811.x](#)
- Barbosa JF, Bruno SS, Cruz NS, de Oliveira JS, Ruaro JA, Guerra RO. Perceived fatigability and metabolic and energetic responses to 6-minute walk test in older women. *Physiotherapy*. 2016;102:294–299. doi: [10.1016/j.physio.2015.08.008](#)
- Richardson CA, Glynn NW, Ferrucci LG, Mackey DC. Walking energetics, fatigability, and fatigue in older adults: the study of energy and aging pilot. *J Gerontol A Biol Sci Med Sci*. 2015;70:487–494. doi: [10.1093/gerona/glu146](#)
- Simonsick EM, Montgomery PS, Newman AB, Bauer DC, Harris T. Measuring fitness in healthy older adults: the Health ABC Long Distance Corridor Walk. *J Am Geriatr Soc*. 2001;49:1544–1548. doi: [10.1046/j.1532-5415.2001.4911247.x](#)
- Simonsick EM, Fan E, Fleg JL. Estimating cardiorespiratory fitness in well-functioning older adults: treadmill validation of the long distance corridor walk. *J Am Geriatr Soc*. 2006;54:127–132. doi: [10.1111/j.1532-5415.2005.00530.x](#)
- Schrack JA, Simonsick EM, Chaves PH, Ferrucci L. The role of energetic cost in the age-related slowing of gait speed. *J Am Geriatr Soc*. 2012;60:1811–1816. doi: [10.1111/j.1532-5415.2012.04153.x](#)
- Ferrucci L, Schrack JA, Knuth ND, Simonsick EM. Aging and the energetic cost of life. *J Am Geriatr Soc*. 2012;60:1768–1769. doi: [10.1111/j.1532-5415.2012.04102.x](#)
- Ferrucci L, Cooper R, Shardell M, Simonsick EM, Schrack JA, Kuh D. Age-related change in mobility: perspectives from life course epidemiology and geroscience. *J Gerontol Biol Sci Med Sci*. 2016;71:1184–1194. doi: [10.1093/gerona/glw043](#)
- Ferrucci L, Levine ME, Kuo P-L, Simonsick EM. Time and the metrics of aging. *Circ Res*. 2018;123:740–744. doi: [10.1161/CIRCRESAHA.118.312816](#)
- Fabbri E, An Y, Schrack JA, et al. Energy metabolism and the burden of multimorbidity in older adults: results from the Baltimore Longitudinal study of aging. *J Gerontol A Biol Sci Med Sci*. 2015;70:1297–1303. doi: [10.1093/gerona/glu209](#)
- Schrack JA, Kuo P-L, Wanigatunga AA, et al. Active-to-sedentary behavior transitions, fatigability, and physical functioning in older adults. *J Gerontol A Biol Sci Med Sci*. 2019;74:560–567. doi: [10.1093/gerona/gly243](#)
- Martinez-Amezcu P, Matsushita K, Simonsick EM, Ferrucci L, Schrack JA. Fatigability and functional performance among older adults with low-normal ankle-brachial index: cross-sectional findings from the Baltimore Longitudinal Study of Aging. *Atherosclerosis*. 2018;272:200–206. doi: [10.1016/j.atherosclerosis.2018.03.037](#)
- Wanigatunga AA, Varadhan R, Simonsick EM, et al. Longitudinal relationship between interleukin-6 and perceived fatigability among well-functioning adults in mid-to-late life. *J Gerontol A Biol Sci Med Sci*. 2019;74:720–725. doi: [10.1093/gerona/gly120](#)
- Martinez-Amezcu P, Simonsick EM, Wanigatunga AA, et al. Association between adiposity and perceived physical fatigability in mid- to late life. *Obesity (Silver Spring)*. 2019;27:1177–1183. doi: [10.1002/oby.22500](#)

31. Cooper R, Popham M, Santanasto AJ, Hardy R, Glynn NW, Kuh D. Are BMI and inflammatory markers independently associated with physical fatigability in old age? *Int J Obes*. 2019;43:832–841. doi:[10.1038/s41366-018-0087-0](https://doi.org/10.1038/s41366-018-0087-0).
32. Gresham G, Dy SM, Zipunnikov V, et al. Fatigability and endurance performance in cancer survivors: analyses from the Baltimore Longitudinal Study of Aging. *Cancer*. 2018;124:1279–1287. doi: [10.1002/cncr.31238](https://doi.org/10.1002/cncr.31238)
33. Wanigatunga AA, Gresham GK, Kuo PL, et al. Contrasting characteristics of daily physical activity in older adults by cancer history. *Cancer*. 2018;124:4692–4699. doi: [10.1002/cncr.31745](https://doi.org/10.1002/cncr.31745)
34. Ralston HJ. Energy-speed relation and optimal speed during level walking. *Int Z Angew Physiol*. 1958;17:277–283. doi: [10.1007/bf00698754](https://doi.org/10.1007/bf00698754)
35. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332:556–561. doi: [10.1056/NEJM199503023320902](https://doi.org/10.1056/NEJM199503023320902)
36. Fried LP, Bandeen-Roche K, Chaves PH, Johnson BA. Preclinical mobility disability predicts incident mobility disability in older women. *J Gerontol A Biol Sci Med Sci*. 2000;55:M43–M52. doi: [10.1093/gerona/55.1.m43](https://doi.org/10.1093/gerona/55.1.m43)
37. Bhasin S, Cress ME, Espeland MA, et al. Functional outcomes for clinical trials in frail older persons: time to be moving. *J Gerontol Biol Med Sci*. 2008;63A:160–164. doi: [10.1093/gerona/63.2.160](https://doi.org/10.1093/gerona/63.2.160)
38. McArdle WD, Katch FL, Katch VL. *Exercise Physiology: Energy, Nutrition, and Human Performance*. 3rd ed. Philadelphia, PA: Lea & Febiger; 1991.