Research Article

Evaluation of the Bidirectional Relations of Perceived Physical Fatigability and Physical Activity on Slower Gait Speed

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Received: July 10, 2020; Editorial Decision Date: October 30, 2020

Decision Editor: Jay Magaziner, PhD, MSHyg

Abstract

Background: Lower physical activity levels and greater fatigability contribute independently to slower gait speed in older adults. To fully understand the bidirectional relations between physical activity and fatigability, and to inform potential intervention strategies, we examined whether physical activity or fatigability explains more of the other factor's association on slower gait speed.

Methods: Two generations (probands and offspring) of older adults ($N = 2079$, mean age 73.0 ± 10.0 years, 54.2% women, 99.7% White) enrolled in the Long Life Family Study were assessed at Visit 2 (2014–2017). Self-reported physical activity was measured with the Framingham Physical Activity Index and perceived physical fatigability using the Pittsburgh Fatigability Scale. Statistical mediation analyses were conducted separately by generation with linear mixed-effect models accounting for family relatedness and adjusted for demographics, health conditions, and field center.

Results: Greater perceived physical fatigability explained the association of lower physical activity on slower gait speed via a 22.5% attenuation of the direct association (95% confidence interval [CI]: 15.0%–35.2%) for the probands and 39.5% (95% CI: 22.8%–62.6%) for the offspring. Whereas lower physical activity explained the association of greater perceived fatigability on slower gait speed via a 22.5% attenuation of the direct association (95% CI: 13.4%–32.8%) for the probands and 6.7% (95% CI: 3.8%–15.4%) for the offspring.

Conclusions: Our findings suggest that the impact of greater perceived physical fatigability on the association between lower physical activity and slower gait speed differs between younger-old and middle-to-oldest-old adults, indicating perceived physical fatigability as a potential mediator in the disablement pathway.

Keywords: Epidemiology, Fatigue, Physical function, Physical performance

Declining levels of physical activity and worsening fatigability often occur concurrently among older adults, contributing to slower gait speed (1,2). Gait speed is an important predictor of many health out-

comes, especially disability and mortality (3,4); thus, understanding the mechanisms for worsening gait speed is essential. Although physical inactivity and fatigability are known risk factors of slower gait

speed, the relations between lower levels of physical activity and greater fatigability with gait speed have not been studied in concert.

Physical activity and fatigability have been considered to influence each other in a bidirectional cycle, often making it difficult to translate for interventions aiming to slow or ameliorate the age-related disablement process. Some researchers postulate that a decline in physical activity levels precedes the onset of fatigue, particularly in observational studies conducted in clinical populations (5–10). Conversely, others have proposed the directionality of higher fatigue preceding lower total physical activity levels (11), subsequent daily physical activity (12,13), and altered patterns of physical activities accumulated throughout a day (14). One common limitation with the aforementioned work is the use of a subjective, global measurement of fatigue, making it difficult to distinguish between physical performance deterioration and lack of motivation (15). Measuring perceived physical fatigability—whole-body tiredness anchored to standardized tasks or activities of a specific intensity and duration—is more sensitive than traditional global measures of fatigue (2,16). Perceived physical fatigability overcomes self-pacing bias and ensures meaningful comparisons between participants and across studies.

In this article, we examined the independent associations of physical activity and perceived physical fatigability on gait speed—an important index in the disablement pathway. Specifically, we evaluated the direct and indirect associations of two plausible pathways related to slower gait speed: (a) lower physical activity explains the association of greater perceived physical fatigability on slower gait speed (dominant pathway: greater perceived physical fatigability → lower physical activity → slower gait speed) versus (b) greater perceived physical fatigability explains the association of lower physical activity on slower gait speed (dominant pathway: lower physical activity → greater perceived physical fatigability → slower gait speed). According to the framework proposed in the Fifth Bedside-to-Bench Conference *Idiopathic Fatigue and Aging* (17), fitness level—which could be trained and improved through appropriate physical activity—determines the total energy available, while physical activity utilizes the extra energy left beyond performing activities of daily living. The closer individuals are to their energy limit, the greater the perceived physical fatigability. It seems that physical activity is the fundamental determinant in this vicious cycle. Thus, we hypothesized that the bidirectionality is not symmetric and that greater perceived physical fatigability will explain more of the association of lower physical activity on slower gait speed, serving as a potential mediator.

Method

Study Sample

The Long Life Family Study (LLFS) is a family-based multicenter, international cohort study designed to evaluate the genetics and familial components of longevity and healthy aging. A general description of the cohort and recruitment has been previously described elsewhere (18). Briefly, baseline eligibility and exceptional survival were evaluated using the Family Longevity Selection Score (19). Long-lived probands, their siblings, their offspring, and spouse controls for both generations ($N = 4953$) were enrolled between 2006 and 2009 through 4 field centers (Boston University, Columbia University, University of Pittsburgh, and University of Southern Denmark). The eligible sample for the current study consisted of 2425 participants (330 proband generation; 2095 offspring

generation) who had available and valid data at Visit 2 (2014–2017) for perceived physical fatigability, physical activity, and gait speed. Participants with missing data on body mass index (BMI; $n = 15$) and the Center for Epidemiologic Studies-Depression scale ($n = 43$) were excluded. The sample was further limited to those at least 60 years old because the instrument to measure perceived physical fatigability was validated in this age range (20), resulting in a final analytic sample of 2079 participants (295 proband generation—including 46 spousal controls; 1784 offspring generation—including 461 spousal controls). The LLFS protocol was approved by the institutional review boards at each field center, and all participants provided written informed consent. Data in the current article were collected at Visit 2, unless otherwise stated.

Independent Variables

Physical activity

Self-reported physical activity was measured using the Framingham Physical Activity Index (21). Participants were asked to determine the number of hours spent in 5 specific activity levels (sleep, sedentary, slight, moderate, and heavy) for a typical day over the past year. The number of hours for all activity always totaled 24 hours. First, we multiplied the hours spent in each activity by its weighted metabolic equivalent (MET) of the activity. The MET for each activity was assigned as sleep (weighing factor [WF] = 1.0), sedentary (WF = 1.1), slight (WF = 1.5), moderate (WF = 2.4), and heavy (WF = 5.0) (22). Then, we calculated the Framingham Physical Activity Index total score as the sum of the MET-hours/day (hrs/d) across the 5 activity levels. The resulting continuous physical activity scores (rescaled to 5 MET-hrs/d) were used when continuous variables were included in analyses. Physical activity scores were also divided into generation-specific quartiles to facilitate an easier interpretation of the independent impact of physical activity on gait speed by generation.

Perceived physical fatigability

Perceived physical fatigability was measured using the Pittsburgh Fatigability Scale (PFS)—a validated, self-administered 10-item scale for older adults (20). The PFS was collected for the first time in the LLFS at Visit 2. Participants rated on a scale (0 “no fatigue” to 5 “extreme fatigue”) how much fatigue “they expected to feel immediately after completing each task/activity.” Higher PFS Physical scores indicate greater perceived physical fatigability (range from 0 to 50). PFS Physical scores were imputed ($n = 103$) when there was 1–3 missing of the 10 items (23). Given that a 5-point increment in the PFS Physical score was associated with clinical meaningful decline in gait speed (2), we rescaled the PFS Physical score variable in our analyses to 5 points.

Outcome Measure

Gait speed

The outcome was the faster of 2 usual-paced timed 4-m walks, completed as part of the Short Physical Performance Battery (24). If a 4-m course was not available, we instead conducted the gait speed measure with a 3-m course ($n = 101$). Given the potential ceiling effect of the Short Physical Performance Battery among high-functioning participants (25), we chose not to use it as the functional outcome.

Covariates

Covariates including age, sex, smoking status, and history of health conditions were obtained through self-reported questionnaires. Age

was verified by official forms of identification such as a birth certificate or driver's license and was further validated through linkage to early-life census records (26). Smoking status was classified as current smokers versus past/never smokers. For the medical history, participants were asked, at Visit 1 and then updated during the annual telephone follow-ups, and again at Visit 2, to report whether they were ever told by a physician that they had any of the following conditions: heart disease, stroke (including stroke, mini-stroke, or transient ischemic attack), lung disease, cancer (except skin cancer), and arthritis. Centrally trained research assistants measured sitting blood pressure using an automated blood pressure machine 3 times, following a standard protocol. Using the average across the 3 readings, hypertension was defined as systolic blood pressure at least 130 mmHg and/or diastolic blood pressure at least 80 mmHg according to the American College of Cardiology/American Heart Association (AHA/ACC) 2017 guidelines (27). Blood samples were taken after a minimum of 6-hour fast, and the central laboratory at the University of Minnesota measured hemoglobin A1c (HbA1c) (26). Diabetes mellitus was defined as HbA1c at least 6.5 according to the 2018 criteria from the American Diabetes Association (28). Depressive symptoms were assessed using the 30-point Center for Epidemiologic Studies-Depression scale (29). Height and weight were measured in light clothing using a Handi-stat set square (Perspective Enterprises, Portage, MI) and an electronic digital scale (SECA 841, Hanover, MD), respectively. BMI was calculated as mass in kilograms divided by height in meters squared (kg/m^2) (26). Given the special study design, family structure and field center were also included as covariates.

Statistical Analyses

Descriptive characteristics of participants were reported as mean $\pm$ SD or frequencies (percentages). Due to the potential survival bias of the probands with exceptional longevity, comparisons were examined by generation (probands vs offspring) using 2-sample *t* tests for continuous variables and χ^2 tests for categorical variables. Given the significant differences of their characteristics by generation, all analyses were conducted separately for probands and offspring. Alpha was set to 0.05 and 2-sided *p* values smaller than .05 were considered significant. All analyses were performed using Stata version 16 (StataCorp, College Station, TX).

We first examined the contributions of lower physical activity and greater perceived physical fatigability on slower gait speed to determine whether they had independent associations. Multivariate linear mixed models with restricted maximum likelihood (REML) estimation were used with both physical activity and PFS Physical scores in the models and included successive levels of covariate adjustment. Within-family structure (relatedness) was accounted for using family as a random effect with an exchangeable correlation structure, addressing the special family-clustered study design. Progressive covariate adjustments were constructed to account for established and potential confounders based on prior literature (30). Model 1 was adjusted for age, sex, and field center. Model 2 was further adjusted for BMI, smoking status, heart disease, stroke, hypertension, diabetes mellitus, lung disease, cancer (except skin cancer), arthritis, and depressive symptoms.

In order to examine our bidirectional hypotheses, namely the contributions of lower physical activity on the association of greater perceived physical fatigability on slower gait speed and vice versa, we utilized a statistical mediation approach named the “ml_mediation” package in Stata to obtain direct and indirect associations,

then calculated mediation percentage. Within the package, it automatically specified 3 linear mixed models using REML estimation with the dependent variable (DV), independent variable (IV), and mediator variable (MV) we inputted: (a) the DV on the IV, (b) the MV on the IV, and (c) the DV on the MV and IV. We used the same exchangeable variance model structure as previously mentioned. Furthermore, 95% confidence intervals (95% CIs) were obtained using bootstraps. A higher mediation percentage can be interpreted when the mediator variable is explaining a greater proportion of the association of the independent variable on the dependent variable (31).

We also used linear mixed models to conduct sensitivity analyses assessing the robustness of the association of lower physical activity and greater perceived physical fatigability on slower gait speed by (a) using Framingham Heart Study recommended thresholds to categorize physical activity levels for both generations (21); (b) stratifying by sex and using sex-generation-specific thresholds to categorize physical activity quartiles given the known sex differences in the prevalence of perceived physical fatigability (29); and (c) examining the interaction terms of physical activity and PFS Physical scores with age in the overall sample and then stratifying by median (≤ 70 vs > 70 years) if interaction terms were significant.

Results

Among the 2079 participants (99.7% non-Hispanic White) included in these analyses, probands were aged 65–107 years (92.2 ± 6.9 years) and the offspring were aged 60–93 years (69.9 ± 6.3 years; Table 1). Overall, 1127 (54.2%) were women, with a slightly higher proportion of women in the proband (62.0%) compared to the offspring (52.9%) generation ($p = .004$). Compared to the offspring, probands had lower levels of physical activity, higher PFS Physical scores, and slower gait speed (all $p < .001$; Table 1). All other related covariates, except lung disease, were significantly different between probands and offspring (Table 1).

When included in the same model, lower physical activity and higher PFS Physical scores were both significantly associated with slower gait speed for both generation models. In Model 2 (fully adjusted model), every 5 MET-hrs/d lower physical activity was independently associated with 0.05 m/s (95% CI: -0.07 to -0.03 ; $p < .001$) slower gait speed for the probands and 0.01 m/s (95% CI: -0.02 to -0.00 ; $p = .005$) for the offspring (Table 2). Additionally, every 5-point higher PFS Physical score was associated with 0.03 m/s (95% CI: -0.04 to -0.01) slower gait speed for the probands and 0.03 m/s (95% CI: -0.03 to -0.02) for the offspring (both $p < .001$; Table 2). Furthermore, probands in the lowest quartile of physical activity had a slower gait speed by 0.17 m/s (95% CI: -0.23 to -0.10 ; $p < .001$) compared to those in the highest quartile after adjustment (Model 2, Table 3). The offspring in the lowest quartile of physical activity had a slower gait speed by 0.04 m/s (95% CI: -0.06 to -0.01 ; $p = .008$).

When using the Framingham-recommended thresholds to categorize physical activity levels, the associations between greater perceived physical fatigability and slower gait speed were unchanged, but statistically significant associations were only seen between the lowest and highest physical activity groups in relation to slower gait speed (Supplementary Table 1). When stratified by sex and generation, similar associations were observed between lower physical activity and slower gait speed, but were attenuated for women in the proband and men in the offspring generation; yet the significant

Table 1. Visit 2 Characteristics by Proband and Offspring Generations: The Long Life Family Study (*N* = 2079)

Characteristics	All (<i>N</i> = 2079)	Probands (<i>n</i> = 295)	Offspring (<i>n</i> = 1784)	<i>p</i> Value
Age, years	73.0 ± 10.0	92.2 ± 6.9	69.9 ± 6.3	<.001
Women	1127 (54.2)	183 (62.0)	944 (52.9)	.004
Body mass index, kg/m ²	27.5 ± 5.2	26.2 ± 5.0	27.7 ± 5.2	<.001
Current smoker	115 (5.5)	6 (2.0)	109 (6.1)	.005
Heart disease	110 (5.3)	46 (15.6)	64 (3.6)	<.001
Stroke	69 (3.3)	25 (8.5)	44 (2.5)	<.001
Hypertension*	1277 (61.4)	205 (69.5)	1072 (60.1)	.002
Diabetes mellitus [†]	226 (10.9)	43 (14.6)	183 (10.3)	.027
Lung disease	261 (12.6)	37 (12.5)	224 (12.6)	.995
Cancer	410 (19.7)	84 (28.5)	326 (18.3)	<.001
Arthritis	604 (29.1)	128 (43.4)	476 (26.7)	<.001
Depression symptoms (CES-D), 0–30	3.2 ± 3.4	4.4 ± 3.7	3.0 ± 3.3	<.001
Physical activity [‡] , MET-hrs/d	37.0 ± 7.1	31.1 ± 5.3	38.0 ± 6.9	<.001
PFS Physical score, 0–50	13.5 ± 9.7	24.4 ± 10.6	11.7 ± 8.3	<.001
Usual-paced gait speed, m/s	1.02 ± 0.27	0.66 ± 0.23	1.08 ± 0.22	<.001

Notes: CES-D = Center for Epidemiologic Studies-Depression scale; MET = metabolic equivalent; PFS = Pittsburgh Fatigability Scale (higher scores = greater perceived fatigability); SD = standard deviation. All reported in mean ± SD or *n* (%).

*Hypertension is defined by systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg.

[†]Diabetes mellitus is defined by hemoglobin A1c ≥6.5.

[‡]Physical activity was measured with the Framingham Physical Activity Index.

association of perceived physical fatigability held for sex-generation subgroups (Supplementary Table 2). The interaction between physical activity and age was significant ($p = .002$; data not shown). Age-stratified models revealed that for those aged 70 years or younger, lower physical activity was no longer significant in the model that also included PFS Physical scores, whereas, for those older than 70 years, both lower physical activity and higher PFS Physical scores were significantly associated with slower gait speed (Supplementary Table 3). The interaction between perceived physical fatigability and age was not significant ($p = .15$; data not shown).

The mediation analyses revealed that lower physical activity and greater perceived physical fatigability explained almost equally each other's association on slower gait speed among the probands, whereas greater perceived physical fatigability largely explained the association of lower physical activity on slower gait speed among the offspring (Figure 1). Specifically, every 5 MET-hrs/d lower physical activity was directly associated with 0.051 m/s (95% CI: −0.069 to 0.036) and 0.010 m/s (95% CI: −0.017 to −0.005) slower gait speed for the probands and the offspring, respectively. Greater perceived physical fatigability explained the association of lower physical activity on slower gait speed via a 22.5% attenuation of the direct association (95% CI: 15.0%–35.2%) for the probands and 39.5% (95% CI: 22.8%–62.6%) for the offspring, using the fully adjusted models (Figure 1, upper table). Every 5-point higher PFS Physical score was directly associated with 0.03 m/s slower gait speed for both the probands (95% CI: −0.034 to −0.021) and the offspring (95% CI: −0.032 to −0.021). Lower physical activity explained the association of greater perceived fatigability on slower gait speed via a 22.5% attenuation of the direct association (95% CI: 13.4%–32.8%) for the probands and 6.7% (95% CI: 3.8%–15.4%) for the offspring, using the fully adjusted models (Figure 1, lower table).

Discussion

Our findings show that perceived physical fatigability is likely a potential mediator in the disablement pathway, given that greater perceived physical fatigability largely explained the association of lower

physical activity on slower gait speed among the offspring. For the probands, both lower physical activity and greater perceived physical fatigability equally explained each other's association on slower gait speed. Together, these findings suggest that the impact of perceived physical fatigability in the disablement pathway might differ across the life span. At younger-old ages, physical activity is largely working through perceived fatigability to slower gait speed, whereas at middle-to-oldest-old ages, many other factors such as inflammation and chronic diseases may also share the mediating effect with perceived fatigability on the association between lower physical activity and slower gait speed.

Studies examining the association between physical activity and perceived physical fatigability are limited. Recent work from the Baltimore Longitudinal Study of Aging has linked physical activity with perceived fatigability showing total daily physical activity 1.3% lower for every unit increment in greater perceived fatigability measured by the Borg rating of perceived exertion (32). Our study, using the PFS—a different validated measurement of perceived physical fatigability—revealed that the probands in the lowest quartile of physical activity had 9.1 points higher PFS Physical scores, while the offspring in the lowest quartile of physical activity was 4.4 points higher compared to the highest quartile of physical activity (Supplementary Table 4). On the continuous scale, every 5 MET-hrs/day lower physical activity was associated with 2.8 and 1.2 points higher PFS Physical scores for the probands and offspring, respectively (Supplementary Table 4). Although not on the same scale, this work corroborates the inverse association between lower physical activity and greater perceived fatigability reported in the Baltimore Longitudinal Study of Aging. Beyond these confirmatory findings, to the best of our knowledge, this is the first study to carefully examine the bidirectional relation of physical activity and perceived physical fatigability.

In general, the biological basis for the potential mediating effect of perceived physical fatigability in the disablement pathway related to gait speed is poorly understood. Greater perceived physical fatigability is associated with poorer aerobic capacity (ie, fitness) (33,34) which may further lead to subsequent functional decline

Table 2. Associations Between Lower Physical Activity (Continuous Measure) and Greater Perceived Physical Fatigability on Slower Gait Speed (m/s): The Long Life Family Study

Probands (<i>n</i> = 295)			Offspring (<i>n</i> = 1784)		
Variables	β Coefficient	<i>p</i> Value	Variables	β Coefficient	<i>p</i> Value
<i>Model 0</i>			<i>Model 0</i>		
PA/5 MET-hrs/d	−0.07 (−0.09, −0.05)	<.001	PA/5 MET-hrs/d	−0.01 (−0.02, −0.01)	.001
PFS Physical score/5pts	−0.04 (−0.05, −0.03)	<.001	PFS Physical score/5pts	−0.04 (−0.05, −0.03)	<.001
<i>Model 1</i>			<i>Model 1</i>		
PA/5 MET-hrs/d	−0.05 (−0.07, −0.03)	<.001	PA/5 MET-hrs/d	−0.01 (−0.02, −0.00)	<.001
PFS Physical score/5pts	−0.03 (−0.04, −0.02)	<.001	PFS Physical score/5pts	−0.04 (−0.04, −0.03)	<.001
<i>Model 2</i>			<i>Model 2</i>		
PA/5 MET-hrs/d	−0.05 (−0.07, −0.03)	<.001	PA/5 MET-hrs/d	−0.01 (−0.02, −0.00)	.005
PFS Physical score/5pts	−0.03 (−0.04, −0.01)	<.001	PFS Physical score/5pts	−0.03 (−0.03, −0.02)	<.001

Notes: MET = metabolic equivalent; PA = physical activity; PFS = Pittsburgh Fatigability Scale. Physical activity was measured with the Framingham Physical Activity Index and rescaled to every 5 MET-hrs/day. Perceived physical fatigability was measured with the Pittsburgh Fatigability Scale (PFS, range 0–50) and rescaled to every 5 points. All models accounted for family structure. Model 0 adjusted for field center. Model 1 adjusted for age, sex, and field center. Model 2 adjusted for Model 1 + body mass index, smoking status, heart disease, stroke, hypertension, diabetes mellitus, lung disease, cancer (except for skin cancer), arthritis, and depressive symptoms.

Table 3. Associations Between Physical Activity Quartiles and Greater Perceived Physical Fatigability on Slower Gait Speed (m/s): The Long Life Family Study

Probands (<i>n</i> = 295)			Offspring (<i>n</i> = 1784)		
Model 0	β Coefficient	<i>p</i> Value	Model 0	β Coefficient	<i>p</i> Value
PA Quartiles (MET-hrs/d)			PA Quartiles (MET-hrs/d)		
QI (24.4 to <26.9)	−0.23 (−0.30, −0.16)	<.001	QI (25.0 to <33.0)	−0.05 (−0.07, −0.02)	.001
QII (26.9 to <30.0)	−0.09 (−0.15, −0.03)	.004	QII (33.0 to <37.1)	−0.00 (−0.03, 0.03)	.941
QIII (30.0 to <33.9)	−0.05 (−0.11, 0.01)	.075	QIII (37.1 to <42.3)	−0.01 (−0.04, 0.02)	.423
QIV (33.9 to 55.8)	Ref		QIV (42.3 to 71.7)	Ref	
PFS Physical score/5pts	−0.04 (−0.05, −0.03)	<.001	PFS Physical score/5pts	−0.04 (−0.05, −0.03)	<.001
Model 1	β Coefficient	<i>p</i> Value	Model 1	β Coefficient	<i>p</i> Value
PA Quartiles (MET-hrs/d)			PA Quartiles (MET-hrs/d)		
QI (24.4 to <26.9)	−0.18 (−0.25, −0.11)	<.001	QI (25.0 to <33.0)	−0.05 (−0.08, −0.02)	<.001
QII (26.9 to <30.0)	−0.06 (−0.12, 0.00)	.055	QII (33.0 to <37.1)	−0.01 (−0.03, 0.02)	.499
QIII (30.0 to <33.9)	−0.03 (−0.08, 0.03)	.377	QIII (37.1 to <42.3)	−0.02 (−0.04, 0.01)	.207
QIV (33.9 to 55.8)	Ref		QIV (42.3 to 71.7)	Ref	
PFS Physical score/5pts	−0.03 (−0.04, −0.02)	<.001	PFS Physical score/5pts	−0.03 (−0.04, −0.03)	<.001
Model 2	β Coefficient	<i>p</i> Value	Model 2	β Coefficient	<i>p</i> Value
PA Quartiles (MET-hrs/d)			PA Quartiles (MET-hrs/d)		
QI (24.4 to <26.9)	−0.17 (−0.23, −0.10)	<.001	QI (25.0 to <33.0)	−0.04 (−0.06, −0.01)	.008
QII (26.9 to <30.0)	−0.06 (−0.12, 0.00)	.062	QII (33.0 to <37.1)	−0.01 (−0.04, 0.01)	.359
QIII (30.0 to <33.9)	−0.02 (−0.08, 0.04)	.500	QIII (37.1 to <42.3)	−0.02 (−0.04, 0.01)	.208
QIV (33.9 to 55.8)	Ref		QIV (42.3 to 71.7)	Ref	
PFS Physical score/5pts	−0.02 (−0.04, −0.01)	<.001	PFS Physical score/5pts	−0.03 (−0.03, −0.02)	<.001

Notes: MET = metabolic equivalent; PA = physical activity; PFS = Pittsburgh Fatigability Scale. Physical activity was measured with the Framingham Physical Activity Index and rescaled to every 5 MET-hours/d. Perceived physical fatigability was measured with the Pittsburgh Fatigability Scale (PFS, range 0–50) and rescaled to every 5 points. All models accounted for family structure. Model 0 adjusted for field center. Model 1 adjusted for age, sex, and field center. Model 2 adjusted for Model 1 + body mass index, smoking status, heart disease, stroke, hypertension, diabetes mellitus, lung disease, cancer (except for skin cancer), arthritis, and depressive symptoms.

in older adults (15). Meanwhile, lower physical activity increases the risk for several adverse health conditions, including metabolic syndrome, type 2 diabetes, depression, dementia, and osteoarthritis (21,35). Thus, it is plausible that the impact of lower physical activity on greater perceived physical fatigability reflects a higher disease burden. Furthermore, excessive amounts of fat mass and lack of muscle, a result of reduced physical activity, may contribute to low

levels of anabolic hormones, insulin resistance with muscle fat infiltration, increased inflammatory activity with cytokine secretion relating to oxidative stress, and increased apoptotic activity (36), all potentially leading to greater perceived physical fatigability. Like the related concept of muscle fatigue, poor skeletal muscle adaptations and less efficient mitochondrial function due to lack of physical activity may also lead to greater fatigability (37,38). Collectively, lower

Figure 1. Statistical mediation analyses for the associations of lower physical activity, greater perceived physical fatigability on slower gait speed (m/s): The Long Life Family Study. Physical activity was measured with the Framingham Physical Activity Index and rescaled to every 5 metabolic equivalent (MET)-hours/day. Perceived physical fatigability was measured with the Pittsburgh Fatigability Scale (PFS, range 0–50) and rescaled to every 5 points. Model accounted for family structure and adjusted for age, sex, body mass index, smoking status, heart disease, stroke, hypertension, diabetes mellitus, lung disease, cancer (except for skin cancer), arthritis, depressive symptoms, and field center. *Bias-corrected confidence interval.

levels of physical activity working through higher disease burden, disproportional fat/lean mass, and greater muscle fatigue may all generate greater perceived fatigability, which could in turn reduce physical fitness and ultimately impair physical function. Future work should focus on deciphering the biological basis of the relation between physical activity and perceived physical fatigability in the disablement pathway, in order to better understand their directionality.

We explored plausible explanations for the differing mediation percentages by generation and contend that the primary driver is the differential strength of associations between physical activity and perceived fatigability/gait speed. Given our findings (Tables 2 and 3), the direct associations between physical activity and gait speed were larger in the probands compared to the offspring, while the direct associations between perceived fatigability and gait speed were similar for both generations. For probands, PFS Physical scores across all physical activity quartiles ranged from 18.1 (QIV) to 31.9 (QI), well over the established cutpoint defining greater perceived physical fatigability (PFS ≥ 15) (2,30). It stands to reason that these participants likely had limited physical capacity, thus their physical activity directly reflected their fatigue level and physical function (ie, gait speed), as indicated by the mediation percentage being 22.5% for both perceived physical fatigability and physical activity (Figure 1). On the other hand, offspring had lower perceived physical fatigability across all physical activity levels; only the lowest physical activity quartile met the definition of greater perceived physical fatigability. This means that the offspring would have more reserve between daily physical activity level and actual energy capacity (17). Furthermore, their self-reported physical activity levels may also reflect both capacity and willingness/motivation to move, which may not fully represent their fatigue level and physical function. Altogether, this may explain why the mediation percentage of perceived physical

fatigability in the offspring was larger at 39.5%, while the mediation percentage of physical activity was attenuated at 6.7% (Figure 1).

A limitation of this work includes its cross-sectional design; thus, a longitudinal study is warranted in order to establish causality. Our findings support the direction of the relation with lower levels of physical activity to greater perceived fatigability. Given the aforementioned theory of the effects of physical activity on muscle fatigue (37) and the importance of physical activity in this vicious cycle (17), perceived physical fatigability is a likely mediator. Second, the LLFS cohort is composed almost entirely of non-Hispanic White families enriched for exceptional longevity and comparatively healthier than most, somewhat limiting generalizability. Third, there might be residual confounding, especially due to a lack of adjustment for inflammation. Inflammatory biomarkers have not yet been assayed for Visit 2 LLFS, but are expected to become available soon, so future work can address this issue. Lastly, other unobserved factors could potentially be contributing to the disablement pathway, thus a more complex conceptual model might be fitted to explore other underlying structures. Strengths of this work include measuring perceived physical fatigability, which limits self-pacing bias (39), thus allowing for a more sensitive and reliable examination with less potential for misclassification (15). Furthermore, the LLFS contains a large sample size of oldest-old and older adults, which allowed us to explore and evaluate the bidirectionality of the disablement pathway across a wide age range.

In conclusion, we found that greater perceived physical fatigability using the PFS explained the association of lower physical activity on slower gait speed considerably more among the offspring compared to the probands, implying that perceived physical fatigability is a potential mediator in the disablement pathway related to slower gait speed. Future work will evaluate this bidirectional

relation with longitudinal data to confirm the causal directionality and to better understand whether increasing physical activity could be an effective intervention to reduce perceived physical fatigability in order to slow the downward spiral leading to worse physical function among older adults across generations.

Supplementary Material

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

Funding

This work was supported by the National Institutes of Health/National Institute on Aging (U01 AG023712, U01 AG023744, U01 AG023746, U01 AG023749, U01 AG023755, and P01 AG08761). Additionally, the Claude D. Pepper Older Americans Independence Center, Research Registry and Developmental Pilot Grant (National Institutes of Health/National Institute on Aging P30 AG024827), and the Intramural Research Program, NIA supported N.W.G. to develop the Pittsburgh Fatigability Scale. The Epidemiology of Aging training grant at the University of Pittsburgh (National Institute on Aging T32 AG000181) supported T.G. Furthermore, a career development award from the Pittsburgh Claude D. Pepper Older Americans Independence Center (P30 AG024827) and National Institutes of Health/National Institute on Aging (K01 AG057726) supported A.J.S. And the National Institutes of Health/National Institute on Aging (K01AG057798) supported S.L.A.

Author Contributions

Y.Q., T.G., N.W.G., and R.M.B. had full access to all of the data for the study and take responsibility for the integrity of the data and accuracy of the data analyses. All authors: interpretation of data and critical revision of the manuscript for important intellectual content. All authors read and approved the submitted manuscript.

Conflict of Interest

None declared.

References

- Fielding RA, Guralnik JM, King AC, et al.; LIFE Study Group. Dose of physical activity, physical functioning and disability risk in mobility-limited older adults: results from the LIFE study randomized trial. *PLoS One*. 2017;12:e0182155. doi:10.1371/journal.pone.0182155
- Simonsick EM, Schrack JA, Santanasto AJ, Studenski SA, Ferrucci L, Glynn NW. Pittsburgh Fatigability Scale: one-page predictor of mobility decline in mobility-intact older adults. *J Am Geriatr Soc*. 2018;66:2092–2096. doi:10.1111/jgs.15531
- Perera S, Patel KV, Rosano C, et al. Gait speed predicts incident disability: a pooled analysis. *J Gerontol A Biomed Sci Med Sci*. 2015;71(1):63–71. doi:10.1093/gerona/glv126
- Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011;305:50–58. doi:10.1001/jama.2010.1923
- Stroud NM, Minahan CL. The impact of regular physical activity on fatigue, depression and quality of life in persons with multiple sclerosis. *Health Qual Life Outcomes*. 2009;7:68. doi:10.1186/1477-7525-7-68
- Rogers LQ, Markwell SJ, Courneya KS, McAuley E, Verhulst S. Physical activity type and intensity among rural breast cancer survivors: patterns and associations with fatigue and depressive symptoms. *J Cancer Surviv*. 2011;5(1):54–61. doi:10.1007/s11764-010-0160-8
- Webel AR, Perazzo J, Decker M, Horvat-Davey C, Sattar A, Voss J. Physical activity is associated with reduced fatigue in adults living with HIV/AIDS. *J Adv Nurs*. 2016;72(12):3104–3112. doi:10.1111/jan.13084
- Engberg I, Segerstedt J, Waller G, Wennberg P, Eliasson M. Fatigue in the general population—associations to age, sex, socioeconomic status, physical activity, sitting time and self-rated health: the northern Sweden MONICA study 2014. *BMC Public Health*. 2017;17(1):654. doi:10.1186/s12889-017-4623-y
- Shepherd AI, Pulsford R, Poltawski L, et al. Physical activity, sleep, and fatigue in community dwelling stroke survivors. *Sci Rep*. 2018;8:7900. doi:10.1038/s41598-018-26279-7
- Matias M, Baciarello G, Neji M, et al. Fatigue and physical activity in cancer survivors: a cross-sectional population-based study. *Cancer Med*. 2019;8(5):2535–2544. doi:10.1002/cam4.2060
- Moreh E, Jacobs JM, Stessman J. Fatigue, function, and mortality in older adults. *J Gerontol A Biomed Sci Med Sci*. 2010;65(8):887–895. doi:10.1093/gerona/glq064
- Egerton T, Chastin SF, Stensvold D, Helbostad JL. Fatigue may contribute to reduced physical activity among older people: an observational study. *J Gerontol A Biol Sci Med Sci*. 2016;71(5):670–676. doi:10.1093/gerona/glv150
- Hacker ED, Kim I, Park C, Peters T. Real-time fatigue and free-living physical activity in hematopoietic stem cell transplantation cancer survivors and healthy controls: a preliminary examination of the temporal, dynamic relationship. *Cancer Nurs*. 2017;40(4):259–268. doi:10.1097/ncc.0000000000000459
- Egerton T, Helbostad JL, Stensvold D, Chastin SF. Fatigue alters the pattern of physical activity behavior in older adults: observational analysis of data from the generation 100 study. *J Aging Phys Act*. 2016;24(4):633–641. doi:10.1123/japa.2015-0237
- Schrack JA, Simonsick EM, Glynn NW. Fatigability: a prognostic indicator of phenotypic aging. *J Gerontol A Biol Sci Med Sci*. 2020;75(9):e63–e66. doi:10.1093/gerona/glaa185
- 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
- Newman AB, Glynn NW, Taylor CA, et al. Health and function of participants in the long life family study: a comparison with other cohorts. *Aging (Albany, NY)*. 2011;3:63–76. doi:10.18632/aging.100242
- Sebastiani P, Hadley EC, Province M, et al. A family longevity selection score: ranking sibships by their longevity, size, and availability for study. *Am J Epidemiol*. 2009;170:1555–1562. doi:10.1093/aje/kwp309
- Glynn NW, Santanasto AJ, Simonsick EM, et al. The Pittsburgh Fatigability Scale for Older Adults: development and validation. *J Am Geriatr Soc*. 2015;63(1):130–135. doi:10.1111/jgs.13191
- Kannel WB, Sorlie P. Some health benefits of physical activity: the Framingham Study. *Arch Intern Med*. 1979;139(8):857–861. doi:10.1001/archinte.1979.03630450011006
- Kannel WB, Belanger A, D'Agostino R, Israel I. Physical activity and physical demand on the job and risk of cardiovascular disease and death: the Framingham Study. *Am Heart J*. 1986;112:820–825. doi:10.1016/0002-8703(86)90480-1
- 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 (Lond)*. 2019;43(4):832–841. doi:10.1038/s41366-018-0087-0
- Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49:M85–M94. doi:10.1093/geronj/49.2.m85
- Sayers SP, Guralnik JM, Newman AB, Brach JS, Fielding RA. Concordance and discordance between two measures of lower extremity function: 400 meter self-paced walk and SPPB. *Aging Clin Exp Res*. 2006;18:100–106. doi:10.1007/BF03327424
- Elo IT, Mykyla L, Sebastiani P, Christensen K, Glynn NW, Perls T. Age validation in the long life family study through a linkage to early-life census

- records. *J Gerontol B Psychol Sci Soc Sci*. 2013;68:580–585. doi:[10.1093/geronb/gbt033](https://doi.org/10.1093/geronb/gbt033)
27. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248. doi:[10.1016/j.jacc.2017.11.006](https://doi.org/10.1016/j.jacc.2017.11.006)
 28. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(Suppl. 1):S13–S27. doi:[10.2337/dc18-S002](https://doi.org/10.2337/dc18-S002)
 29. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385–401. doi:[10.1177/014662167700100306](https://doi.org/10.1177/014662167700100306)
 30. LaSorda KR, Gmelin T, Kuipers AL, et al. Epidemiology of perceived physical fatigability in older adults: the long life family study. *J Gerontol A Biol Sci Med Sci*. 2020;75(9):e81–e88. doi:[10.1093/gerona/glz288](https://doi.org/10.1093/gerona/glz288)
 31. Krull JL, MacKinnon DP. Multilevel modeling of individual and group level mediated effects. *Multivariate Behav Res*. 2001;36(2):249–277. doi:[10.1207/s15327906mbr3602_06](https://doi.org/10.1207/s15327906mbr3602_06)
 32. 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(5):630–635. doi:[10.1093/gerona/glx181](https://doi.org/10.1093/gerona/glx181)
 33. Urbanek JK, Zipunnikov V, Harris T, Crainiceanu C, Harezlak J, Glynn NW. Validation of gait characteristics extracted from raw accelerometry during walking against measures of physical function, mobility, fatigability, and fitness. *J Gerontol A Biol Sci Med Sci*. 2018;73:676–681. doi:[10.1093/gerona/glx174](https://doi.org/10.1093/gerona/glx174)
 34. Schrack JA, Wanigatunga AA, Zipunnikov V, Kuo PL, Simonsick EM, Ferrucci L. Longitudinal association between energy regulation and fatigability in mid-to-late life. *J Gerontol A Biol Sci Med Sci*. 2020;75(9):e74–e80. doi:[10.1093/gerona/glaa011](https://doi.org/10.1093/gerona/glaa011)
 35. Haseler C, Crooke R, Haseler T. Promoting physical activity to patients. *BMJ*. 2019;366:l5230. doi:[10.1136/bmj.l5230](https://doi.org/10.1136/bmj.l5230)
 36. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity-definition, etiology and consequences. *Curr Opin Clin Nutr Metab Care*. 2008;11(6):693. doi:[10.1097/MCO.0b013e328312c37d](https://doi.org/10.1097/MCO.0b013e328312c37d)
 37. Bogdanis GC. Effects of physical activity and inactivity on muscle fatigue. *Front Physiol*. 2012;3:142. doi:[10.3389/fphys.2012.00142](https://doi.org/10.3389/fphys.2012.00142)
 38. Santanasto AJ, Glynn NW, Jubrias SA, et al. Skeletal muscle mitochondrial function and fatigability in older adults. *J Gerontol A Biol Sci Med Sci*. 2015;70(11):1379–1385. doi:[10.1093/gerona/glu134](https://doi.org/10.1093/gerona/glu134)
 39. Egerton T. Self-reported aging-related fatigue: a concept description and its relevance to physical therapist practice. *Phys Ther*. 2013;93:1403–1413. doi:[10.2522/ptj.20130011](https://doi.org/10.2522/ptj.20130011)