Association Between Cardiovascular Risk and Perceived Fatigability in Mid-to-Late Life

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Background—Cardiovascular disease (CVD) and fatigue commonly co-occur in older adults, yet the subjective nature of fatigue and its situational dependence leave the true magnitude of this association undefined.

Methods and Results—Six-hundred and twenty-five participants with no history of CVD (aged 68.1+12.0 years), from the Baltimore Longitudinal Study of Aging who underwent ≥2 clinic visits between 2007 and 2015 were classified according to sex-specific predicted 10-year CVD risk scores using the Framingham CVD risk score (Framingham) and the Pooled Cohort Equation at baseline. Perceived fatigability was assessed using the Borg rating of perceived exertion scale after a 5-minute treadmill walk (0.67 m/s, 0% grade). Linear models were used to assess the association between baseline CVD risk and perceived fatigability an average of 4.5 years later, adjusted for demographics, behaviors, and medical history. In final models, a 5% higher baseline Pooled Cohort Equation score was associated with greater perceived fatigability at follow-up (β=0.13 rating of perceived exertion, *P*=0.008). Stratified analyses suggested this association was stronger among those aged ≤70 years and those with obesity. Of the individual CVD risk score components, older age was most strongly associated with perceived fatigability (β=0.48, *P*<0.001), followed by women (β=0.11, *P*=0.002), and treated hypertension (β=0.11, *P*=0.003). There was no association with the Framingham risk score.

Conclusions—Perceived fatigability was higher among participants with greater CVD risk measured using the Pooled Cohort Equation risk score. The strong associations with hypertension and obesity suggest prevention and promotion of cardiovascular health may also lower perceived fatigability, particularly among those aged ≤70 years or living with obesity. (*J Am Heart Assoc*. 2019;8:e013049. DOI: 10.1161/JAHA.119.013049.)

Key Words: cardiovascular disease risk factors • cardiovascular risk • fatigability • older adults

Cardiovascular disease (CVD) is the leading cause of the death worldwide with the number of CVD deaths expected to increase from an estimated 17.9 million in 2016 to >23.6 million by 2030.[1,2] In 2015, the American Heart Association estimated that 85.6 million Americans had >1 type of CVD, and of these, 43.7 million (51.1%) were ≥60 years old.[3] The onset and progression of elevated CVD risk is detrimental to quality of life and future health outcomes, particularly among older adults, often inducing activity limitations[4] and fatigue,[5] which further exacerbate the progression of CVD events. Efforts to prevent CVD and its associated health outcomes are thus paramount to preserving health and functional status in a rapidly aging population.

Fatigue is a common complaint among older adults and a prominent symptom among those with chronic cardiovascular conditions.[6] Because of its subjective nature, the severity of fatigue is often difficult to quantify and define, as it is confounded by reductions in the amount and/or intensity of physical activity as older adults adjust their exertion levels to attenuate or avoid fatigue. In this context, people reporting a similar level of fatigue could differ dramatically in terms of physical capacity,[7] thus potentially under-or-over-stating the true magnitude and intensity of the association between fatigue and cardiovascular conditions.

Fatigability is a relatively recent construct developed and validated in the gerontological literature to better understand the development and progression of fatigue, and associated changes with mobility and functional capacity with aging.[8]

Clinical Perspective

What Is New?

- Introduce the construct of fatigability, or fatigue in relationship to a standardized task, to scientists and clinicians working in cardiovascular disease research.
- Perceived fatigability was higher among those with greater cardiovascular disease risk at baseline.
- Strong associations were observed among those aged ≤70 years or living with obesity.

What Are the Clinical Implications?

- Perceived fatigability may provide an early, sensitive measure of functional status.
- Findings from our work to date reveal differential associations across indicators of health and disease.
- Future interventions to attenuate fatigability in older adults may focus on reducing cardiovascular disease burden.

Previous research has shown that those with preclinical peripheral artery disease, as indicated by low ankle brachial index, experience greater fatigability and lower walking endurance than those with normal ankle brachial index,[9] suggesting that high fatigability may act as an early indicator of peripheral artery disease. Further, cardiovascular risk factors like arterial stiffness and diabetes mellitus have been positively associated with higher fatigue,[10,11] yet the contribution of these risk factors to the development of fatigability has not been defined. Given that most CVD risk factors are modifiable, efforts to prevent the onset and progression of fatigability with aging may benefit from evaluation and management of cardiovascular health earlier in life. Moreover, high fatigability may also act as a symptom of preclinical CVD, assisting with earlier clinical diagnoses.

Accordingly, this study assesses the association between CVD risk and fatigability measured, on average, 4.5 years later in a population of well-functioning middle-aged and older adults with no history of CVD. In addition, we explored the independent associations between fatigability and factors most commonly associated with CVD risk (eg, hypertension, hypercholesterolemia, diabetes mellitus, etc). We hypothesized that people with higher CVD risk would have higher fatigability and that this would be primarily driven by hypertension, given its high prevalence among older adults.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Intramural Research Program of the National Institute on Aging at https://blsa.nih.gov.

Study Population

The Baltimore Longitudinal Study of Aging (BLSA) is a study of normative human aging, established in 1958 and conducted by the National Institute on Aging Intramural Research Program. A general description of the sample and enrollment criteria has been previously reported.[12] Briefly, the BLSA is a continuously enrolled cohort with some targeted recruitment (women, racial minorities) over its history. All participants are community-dwelling volunteers who pass a comprehensive health and functional screening evaluation, and are free of major chronic conditions and cognitive and functional impairments at the time of enrollment. Once enrolled, participants are followed for life, regardless of disease development, and undergo extensive testing every 1 to 4 years depending on age. The eligible sample for the current study consists of 742 participants who underwent perceived fatigability and health history assessments at least twice between 2007 and 2015. Participants with missing data on baseline information including total cholesterol, high-density lipoprotein cholesterol, or smoking status (n=49) were excluded. Participants were also excluded if they had previously been diagnosed with CVD (n=68), resulting in a final sample of 625 participants. BLSA study protocol was approved by the National Institute for Environmental Health Sciences Internal Review Board and all participants provided written informed consent.

Predicted 10-Year CVD Risk

The exposure variable was sex-specific predicted 10-year CVD risk calculated using both the Framingham CVD risk score (Framingham)[13] and Pooled Cohort Equation (PCE)[14] when perceived fatigability was first measured, which serves as the baseline for this study. The adjudicated end points for these 2 risk scores are slightly different. For estimated absolute end points, the Framingham score indicates a broader composite of CVD events containing coronary heart disease, cerebrovascular events, peripheral artery disease, and heart failure, while the PCE score mainly covers hard cardiovascular events including coronary heart disease death, myocardial infarction, and fatal and non-fatal stroke. The risk scores indicate a probability of first developing any of the listed end points over a 10-year period. Both risk scores include variables for age, sex, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertension medication use, diabetes mellitus status, and current smoking status. Furthermore, self-identified black or non-black race is included only in the PCE score, which helps to differentiate the

elevated CVD risk among those of black race. Given these differences, we chose to examine the association between fatigability and both risk scores to more fully discern whether these differences play a role in the relationship between CVD risk and fatigability.

Perceived Fatigability

Perceived fatigability was assessed immediately following a slow-paced 5-minute treadmill walk (1.5 mph; 0.67 m/s; 0% grade) by asking participants to rate their perceived exertion using the Borg rating of perceived exertion (RPE) scale (range 6–20; 6=no exertion at all, 9=very light, 11=light, 13=somewhat hard, 20=maximal exertion). The Borg RPE has previously been validated for the assessment of perceived fatigability within the BLSA[7] and has been found to have excellent test-retest reliability across a variety of testing conditions and populations.[15]

Covariates

Covariates including age, sex, race, alcohol intake, and smoking status were self-reported via an interviewer-administered questionnaire at baseline and follow-up. Current alcohol consumption was defined as >1 drink/day. Smoking status was classified as current smokers versus past or never smokers. During the interview, participants were also asked to report whether they were ever told by a doctor or other health professional that they had any of the following conditions: diagnosed CVD including angina, myocardial infarction, congestive heart failure, peripheral artery disease, and vascular-related procedures (including coronary artery bypass grafting or angioplasty); hypertension or high blood pressure; diabetes mellitus; pulmonary disease, kidney disease, peripheral neuropathy, cancer, or lower extremity arthritis pain. Participants having diagnosed CVD at baseline were excluded. Except for hypertension and diabetes mellitus which were included in the CVD risk score calculations, the rest of the responses were summed and categorized into several chronic conditions (range 0–4). Current medication use was assessed as part of the in-person visit.

Height and weight were assessed in light clothing using a stadiometer and calibrated scale, respectively, and body mass index (BMI) was calculated as mass in kilograms divided by height in meters squared (kg/m^2). Systolic blood pressure was measured 3 times in each arm using an automated testing device (Colin VP2000/1000), following standardized procedures.[9] The average of these 3 trials on both arms (total 6 trials)

Table 1. Baseline Characteristics According to Fatigability Category among 625 Participants

Characteristics	Overall	RPE 6 to 7	RPE 8 to 9	RPE 10 to 11	RPE ≥12	P Trend (unadjusted)	P Trend (adjusted for age and sex)
	N=625	n=290	n=152	n=112	n=71		
Age (y), mean±SD	68.08±12.04	62.85±11.58	70.32±10.47	73.12±10.50	76.72±9.23	<0.001	<0.001
Female, %	56.64	53.10	59.21	58.93	61.97	0.116	0.008
Black race, %	27.64	29.31	28.29	32.14	21.13	0.463	0.386
Current smoker, %	1.28	1.38	1.97	0.89	0	0.389	0.696
Current alcohol drinker*, %	83.84	87.59	81.58	81.25	77.46	0.018	0.079
Total cholesterol (mg/dL), mean±SD	192.5±34.5	192.5±35.1	192.0±34.4	191.6±34.6	194.8±32.7	0.786	0.853
HDL-C (mg/dL), mean±SD	60.8±16.7	59.8±16.6	61.8±17.1	62.6±14.9	60.3±18.2	0.316	0.297
SBP (mm Hg), mean±SD	114.7±13.4	112.9±13.0	116.8±13.8	115.0±12.9	117.4±14.5	0.007	0.234
DBP (mm Hg), mean±SD	64.8±8.5	65.5±8.4	65.1±8.3	64.7±8.2	61.5±8.9	0.002	0.997
BMI (kg/m^2), mean±SD	26.7±4.5	26.2±4.2	26.9±4.8	27.0±4.6	27.8±4.9	0.005	<0.001
Hypertension†, %	35.84	25.86	42.11	43.75	50.70	<0.001	0.002
Diabetes‡, %	5.12	4.48	5.26	3.57	9.86	0.236	0.160
Have chronic disease§, %	44.00	34.48	52.63	49.11	56.34	<0.001	0.060
Framingham score	12.65±10.10	10.41±9.03	13.79±9.86	13.70±9.44	17.67±13.05	<0.001	0.014
PCE score	15.47±14.48	10.12±10.94	17.15±14.15	20.28±15.52	26.14±16.84	<0.001	0.004

BMI indicates body mass index; DBP, diastolic blood pressure; Framingham, Framingham CVD risk score; HDL-C, high-density lipoprotein cholesterol; PCE, Pooled Cohort Equation; RPE, Rating of Perceived Exertion after a slow-paced 5 min treadmill walk; SBP, systolic blood pressure; SD, standard deviation.
*Current alcohol drinker is defined by >1 drink/day.
†Hypertension is defined by SBP ≥140 mm Hg or DBP ≥ 90 mm Hg or treatment with antihypertensive drugs.
‡Diabetes is defined by fasting blood glucose ≥126 mg/dL or treatment with hypoglycemic drugs.
§Chronic diseases include history of: pulmonary disease, kidney disease, neuropathy, cancer, lower extremity arthritis pain.

was used for analysis. Total cholesterol, high-density lipoprotein cholesterol, and fasting glucose were measured using blood samples collected between 7 and 8 AM after an overnight fast (from the prior night starting at 10 PM). Participants were not permitted to smoke, engage in physical activity, or take medications before the blood sample collection. The concentration of total cholesterol was measured by an enzymatic method (Abbott Laboratories ABA-200 ATC Biochromatic Analyzer, Irving, TX). The concentration of high-density lipoprotein cholesterol was evaluated by a dextran sulfate-magnesium precipitation procedure.[16] The fasting plasma glucose concentration was determined by the glucose oxidase method (Beckman Instruments, Inc., Fullerton, CA).[17]

Statistical Analysis

To characterize the population (N=625), participants were classified into 4 groups based on their RPE at their most recent visit, and baseline characteristics were reported as mean±SD or frequencies (proportions). Tests for linear trend were conducted to detect mean differences among groups (Table 1) using *t* test.

In preliminary analyses, univariate linear regression models were conducted to estimate the continuous crude regression coefficients (β) and 95% CIs for the associations between baseline 10-year predicted CVD risk and most recent measure of perceived fatigability. Subsequently, multivariable models were conducted to account for established and potential confounders using progressive covariate adjustment (Table 2). Model 1 was adjusted for age, sex, and time since baseline. Model 2 was additionally adjusted for BMI, and Model 3 further adjusted for several chronic diseases, and alcohol intake. Because of strict application of the CVD risk scores and potential confounding by medication use, sensitivity analyses were performed to assess the robustness of our results by: (1) excluding participants with subsequent CVD events (n=29), (2) excluding participants using statins (n=21), (3) stratifying by use of beta-blockers, and (4) stratifying by use of anti-hypertension medications among hypertensive participants (n=308).

To assess whether the burden of 10-year predicted CVD risk on perceived fatigability was differential by age or BMI, stratified analyses were also performed. Participants were dichotomized at age 70 and an interaction term between the dichotomous age variable and continuous RPE was added to the Model 3 (Figure). In a separate model, participants were also dichotomized at BMI ≥30 kg/m² and an interaction term between dichotomous BMI and continuous RPE was explored. Finally, to explore the burden of the individual contributions of the components of the 10-year predicted CVD risk scores on fatigability, each component was modeled independently and standardized βs were estimated from linear regression models adjusted for age, sex, time since baseline, and self-identified race (Table 3). All analyses were performed using STATA version 14 (Statacorp, College Station, TX), and 2-sided *P*-values <0.05 were considered significant.

Results

Baseline Characteristics of Population

Of the 625 participants aged 32 to 95 years at baseline (mean±SD: 68.1±12.0) included in the analysis, 354 (56.6%) were women, and 179 (27.6%) were of black race. The mean follow-up time was 4.5±1.8 years. The predicted Framingham score among all participants was 12.7±10.1, and the PCE score was 15.5±14.5. The mean perceived fatigability (RPE) for the population was 8.6±2.4. Those with higher RPE were more likely to be older, have a higher BMI, and to have hypertension, and other non-cardiovascular chronic conditions, and they were less likely to consume alcohol on a regular basis. Moreover, there was a trend towards higher Framingham and PCE scores among those in the higher RPE categories (unadjusted *P*-trend<0.001) (Table 1).

Association Between Predicted 10-Year CVD Risk and Perceived Fatigability

On a continuous scale, perceived fatigability was higher among participants with higher predicted 10-year CVD risk as

Table 2. Continuous Association Between CVD Risk Score and Perceived Fatigability (Borg RPE) (N=625)

Predictor	5% Higher Framingham Score		5% Higher PCE Score	
	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value
Crude model	0.27 (0.18, 0.36)	<0.001	0.33 (0.27, 0.39)	<0.001
Model 1	0.15 (0.03, 0.28)	0.018	0.15 (0.06, 0.25)	0.002
Model 2	0.07 (−0.06, 0.20)	0.283	0.14 (0.04, 0.24)	0.006
Model 3	0.05 (−0.08, 0.19)	0.408	0.13 (0.04, 0.23)	0.008

Model 1 adjusted for age, sex, and time since baseline. Model 2 adjusted for Model 1+ BMI (kg/m²). Model 3 adjusted for Model 2 + number of chronic diseases (ranging from 0 to 4), and alcohol intake (current drinkers, abstainers). BMI indicates body mass index; Framingham score, Framingham CVD risk score; PCE, Pooled Cohort Equation; RPE, Rating of Perceived Exertion after a slow-paced 5 min treadmill walk.
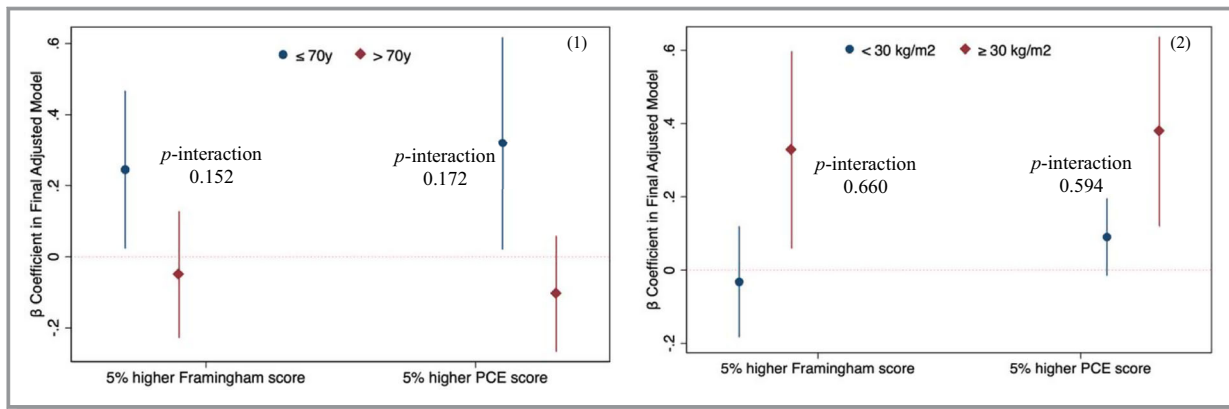
Figure. Continuous association between cardiovascular disease risk score and perceived fatigability (Borg RPE) Stratified by: (1) Age and (2) body mass index categories*. Framingham score indicates Framingham CVD risk score; PCE, Pooled Cohort Equation; RPE, rating of perceived exertion after a slow-paced 5-minute treadmill walk. *Model adjusted for age, sex, body mass index (kg/m^2), several chronic diseases (ranging from 0 to 4), alcohol intake (current drinkers, abstainers), and time since baseline.

measured using the Framingham and the PCE scores. Each 5% higher Framingham risk score corresponded to a 0.27 higher perceived fatigability as measured by RPE ($P<0.001$), and each 5% higher in the PCE score corresponded to a 0.33 higher in RPE ($P<0.001$). These associations were attenuated after adjusting for age, sex, and time since baseline, (Table 2, Model 1) but remained significant. After further adjusting for BMI, only the association with the PCE score remained ($\beta=0.14$ RPE, $P=0.006$, Table 2, Model 2). In the final model which also included several chronic diseases and reported alcohol intake, the association with the PCE score remained essentially unchanged ($\beta=0.13$ RPE, $P=0.008$) (Table 2, Model 3).

Table 3. Associations Between Each CVD Risk Score Components and Perceived Fatigability

	Standardize β Coefficient*	P Value	Fully Adjusted Standardized β Coefficient†	P Value
Age, y	0.461	<0.001	0.481	<0.001
Female	0.118	0.001	0.112	0.002
Black	0.075	0.038	0.063	0.082
Total cholesterol, mg/dL	0.033	0.355	0.003	0.292
HDL-C, mg/dL	0.009	0.808	−0.040	0.227
SBP, mm Hg	0.028	0.442	0.039	0.289
Anti-hypertension medication	0.116	0.002	0.109	0.003
Diabetes	0.035	0.333	0.037	0.296

HDL-C indicates high-density lipoprotein cholesterol; SBP, systolic blood pressure.
*Adjusted for age and time since baseline.
†Adjusted for age, sex, back/non-black and time since baseline.

Sensitivity analyses revealed these results to be robust. To minimize the influence of CVD events on perceived fatigability, participants with a subsequent CVD diagnosis (n=29) were excluded from the final model. The results remained essentially unchanged: each 5% higher Framingham score corresponded to 0.10 higher RPE ($P=0.151$) and each 5% higher PCE score corresponded to a 0.14 higher RPE ($P=0.005$) (Table S1). To assess the potential effects of medication use, participants using statins (n=21) were excluded since the derivation cohort for PCE risk score was free of statin use; the results remained essentially unchanged (Table S2). Further analyses to assess the effects of beta-blockers and anti-hypertensive medications, on RPE did not reveal any significant findings (Tables S3 and S4).

Stratified Analysis

In age-stratified analyses, the positive association between predicted CVD risk and RPE tended to be higher among participants ≤70 years across both risk scores but PCE score did not reach significance ($\beta=0.25$ RPE ($P_{interaction}=0.152$) for Framingham score; $\beta=0.32$ RPE ($P_{interaction}=0.172$) for PCE score), with null effects among those aged >70. In BMI-stratified analyses, the combined effects of predicted CVD risk and obesity trended toward being larger among obese participants (BMI ≥30 kg/m^2) than non-obese participants for both risk scores ($\beta=0.33$ RPE ($P_{interaction}=0.660$) for Framingham score; $\beta=0.38$ RPE ($P_{interaction}=0.594$) for PCE score) (Figure).

Association Between Each Component and Perceived Fatigability

To better understand the association between individual components of CVD risk and perceived fatigability, each

component of the risk score was evaluated independently, accounting for age, sex and race (Table 3). Older age was most strongly associated with higher perceived fatigability (standardized β=0.48, *P*<0.001), followed by women (standardized β=0.11, *P*=0.002). Of the remaining CVD risk factors, the presence of hypertension was most strongly association with higher perceived fatigability (standardized β=0.11, *P*=0.003), followed by black race (standardized β=0.06, *P*=0.082) (Table 3).

Discussion

Our results show that higher baseline CVD risk is associated with higher perceived fatigability an average of 4.5 years later, and that among modifiable CVD risk factors, treated hypertension was most strongly associated with higher perceived fatigability. Given the temporality, these findings illustrate the evolution of the association between CVD risk and perceived fatigability in a cohort of well-functioning older adults who are free of CVD events, and suggest that CVD risk, particularly hypertension, may be an important factor in the development and progression of fatigability in older adults. Previous studies exploring the burden of fatigue among those with CVD have consistently found a positive association between high fatigue and history of CVD events,[5] particularly stroke,[18] but the true burden of fatigue is difficult to discern because of its subjectivity. The current work expands on this research by anchoring fatigue to a standardized physical task and demonstrating a direct link between CVD risk and fatigability among CVD-free older adults.

In the current study, the PCE score demonstrated greater discriminatory power to detect the association between CVD risk and fatigability than the Framingham score. This may be because non-black participants demonstrated poorer CVD risk profiles in our population, which was not detected by the Framingham score since it did not include race. Further, our finding that the association between CVD risk and fatigability is stronger among those aged ≤70 years compared with those >70 years may indicate that elevated cardiovascular risk in early-to-mid-life is more deleterious in the development of fatigability compared with later-stage risk. To this end, corresponding interventions to promote cardiovascular health may be most beneficial when implemented in middle-, or even younger-age. Stronger associations between CVD risk and fatigability were also seen among those who are obese. This is consistent with recent findings, suggesting that higher BMI and central adiposity are strongly associated with physical fatigability in older adults.[19,20] Although there is currently no clinical threshold for using RPE scores to assess fatigability, to put these results in some context we compared the RPE score for CVD burden with the beta coefficients for age from the same regression models. The difference in RPE score corresponding to a 5% higher PCE risk score (0.14 RPE score) was equivalent to nearly 2 years of age, suggesting that relatively small increments in RPE are equivalent to substantial differences in age.

Previous research has established an association between chronic fatigue and hypotension,[21] but the association with hypertension has been less studied. Recently, studies focusing on patients with stroke and transient ischemic attack, reported that hypertensive subjects showed higher odds of being fatigued compared with their normotensive counterparts[22]; however, the cause of the association between hypertension and fatigue remains unclear. Although the potential fatiguing effects of many antihypertension medications, including beta-blockers, has been postulated,[23] our sensitivity analysis did not support this mechanism. Similarly, fatigue is also a persistent symptom among patients with diabetes mellitus, which is believed to be alleviated through improved glycemic control.[24] Our study also indicated that the burden of fatigability is greater among women and those of black race, which are consistent with findings from previous studies on fatigue and health inequities.[25–27]

The mechanisms contributing to higher fatigability among those with higher CVD risk remain to be explored. CVD risk places extra burden on multiple physiologic systems, including the coronary, pulmonary and vascular systems, which may contribute to increased perception of exertion or fatigue after a physical task because of hypoxemia and intermittent claudication.[9] Other possible explanations include high inflammatory burden, immunity dysfunction and sleep disruptions that occur with CVD progression. Previous studies have demonstrated higher inflammatory burden among those with CVD, which may be a direct contributor to higher fatigability.[28–31] Similarly, immunity cells such as B-cells, T Lymphocytes, and unconventional T cells, are more active among those with CVD, and produce more inflammatory factors under hypertensive conditions.[31] Finally, sleep duration and quality are often impaired among those with hypertension and sleep apnea.[32] Together, these mechanisms may contribute to long-term physiological stress, manifesting as high fatigability and eventual poor physical performance.[33]

There are some limitations in the current study that should be considered. First, the BLSA participants are relatively healthy compared with the general older adult population, thus the magnitude of the results is likely understated compared with clinical populations. However, the strength of these results suggests that interventions to reduce CVD risk even in early-to-mid-life among well-functioning populations may be an effective strategy for reducing fatigability with aging. Future studies in sicker, more clinical populations are warranted. Second, there are missing data because of loss to

follow-up. Exploratory analyses indicated that the RPE scores are comparable between participants with and without missing data, thus it is unlikely that loss to follow-up altered the results. Some strengths should also be acknowledged. Objective measurement of perceived fatigability attenuates variability in subjective reporting, increasing the sensitivity and thus reducing the potential for misclassification. Further, the extensive data available on CVD risk enabled us to examine the independent and combine effects of CVD burden in the development of fatigability.

Conclusion

In conclusion, higher baseline CVD risk is associated with higher levels of perceived fatigability an average of 4.5 years later among well-functioning older adults free of CVD. Our findings provide researchers and clinicians new insights into the prevention and management of fatigability, enhancing understanding of the etiology of fatigability with aging and its association with CVD risk factors. Further studies are needed to confirm this association in clinical populations and to evaluate potential interventions to alleviate fatigability through effective evaluation and management of cardiovascular health.

Author Contributions

Qiao and Schrack contributed to the literature search, study design, data interpretation, statistical analyses, and writing and editing of the manuscript. All other co-authors contributed to the study design, data interpretation, and editing of the manuscript.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Sensitivity Analyses of Association between CVD Risk Score and Perceived Fatigability (Borg RPE), Excluding Those with Subsequent Diagnosed CVD (N=596).

	5% higher Framingham score		5% higher PCE score	
	β coefficient (95% CI)	*p*-value	**β coefficient (95% CI)**	*p*-value
Crude Model	0.28 (0.19, 0.38)	<0.001	0.33 (0.27, 0.39)	<0.001
Model 1	0.19 (0.06, 0.33)	0.003	0.17 (0.07, 0.27)	0.001
Model 2	0.11 (-0.02, 0.25)	0.097	0.15 (0.05, 0.25)	0.003
Model 3	0.10 (-0.04, 0.23)	0.151	0.14 (0.04, 0.24)	0.005

RPE = Rating of Perceived Exertion after a slow-paced 5 minutes treadmill walk; CVD = cardiovascular disease; Framingham risk score = Framingham CVD risk score; PCE = Pooled Cohort Equation; BMI = body mass index.

Model 1 adjusted for age, sex and time since baseline.

Model 2 adjusted for Model 1+ BMI (kg/m^2).

Model 3 adjusted for Model 2 + number of chronic diseases (ranging from 0-4), and alcohol intake (current drinkers, abstainers).

Table S2. Sensitivity Analyses for Association Between CVD Risk Score and Perceived Fatigability (Borg RPE), excluding Participants Using Statins (N=604).

Predictor	5% higher Framingham score		5% higher PCE score	
	β coefficient (95% CI)	***p*-value**	**β coefficient (95% CI)**	***p*-value**
Crude Model	0.27 (0.17, 0.36)	<0.001	0.33 (0.27,0.38)	<0.001
Model 1	0.16 (0.03, 0.29)	0.019	0.15 (0.05, 0.25)	0.003
Model 2	0.07 (-0.06, 0.20)	0.308	0.13 (0.04, 0.23)	0.008
Model 3	0.05 (-0.08, 0.18)	0.459	0.13 (0.03, 0.23)	0.011

RPE = Rating of Perceived Exertion after a slow-paced 5 minutes treadmill walk; Framingham risk score = Framingham CVD risk score; PCE = Pooled Cohort Equation; BMI = body mass index.

Model 1 adjusted for age, sex, and time since baseline.

Model 2 adjusted for Model 1+ BMI (kg/m^2).

Model 3 adjusted for Model 2 + number of chronic diseases (ranging from 0-4), and alcohol intake (current drinkers, abstainers).

Table S3. Stratified Analyses of Association between CVD Risk Score and Perceived Fatigability (Borg RPE) among Beta-blocker Users (N=625).

	5% higher Framingham score		5% higher PCE score	
	β coefficient (95% CI)	*p*-value	β coefficient (95% CI)	*p*-value
		0.554		0.641
Beta-blocker use (N=85)	0.14 (-0.20, 0.47)	0.423	-0.07 (-0.35,0.20)	0.586
No beta-blocker use (N=540)	0.04 (-0.11,0.18)	0.610	0.18 (0.07,0.29)	0.002

RPE = Rating of Perceived Exertion after a slow-paced 5 minutes treadmill walk; CVD = cardiovascular disease; Framingham risk score = Framingham CVD risk score; PCE = Pooled Cohort Equation; BMI = body mass index.

Model adjusted for age, sex, BMI (kg/m^2), time since baseline, number of chronic disease (ranging from 0-4), and alcohol intake (current drinkers, non-current drinkers).

Table S4. Stratified Analyses of Association between CVD Risk Score and Perceived Fatigability (Borg RPE) among Hypertensive Participants (N=308).

	5% higher Framingham score		5% higher PCE score	
	β coefficient (95% CI)	*p*-value	β coefficient (95% CI)	*p*-value
		0.733		0.460
Anti-hypertension medication (N=224)	-0.03 (-0.22, 0.16)	0.775	0.03 (-0.14,0.20)	0.764
No anti-hypertension medication (N=84)	0.14 (-0.32,0.60)	0.551	0.02 (-0.25,0.29)	0.882

RPE = Rating of Perceived Exertion after a slow-paced 5 minutes treadmill walk; CVD = cardiovascular disease; Framingham risk score = Framingham CVD risk score; PCE = Pooled Cohort Equation; BMI = body mass index.

Model adjusted for age, sex, BMI (kg/m^2), time since baseline, number of chronic disease (ranging from 0-4), and alcohol intake (current drinkers, non-current drinkers).