HHS Public Access

Author manuscript

Atherosclerosis. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Atherosclerosis. 2018 May ; 272: 200–206. doi:10.1016/j.atherosclerosis.2018.03.037.

Fatigability and functional performance among older adults with low-normal ankle-brachial index: Cross-sectional findings from the Baltimore Longitudinal Study of Aging

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Abstract

Background and aims—Peripheral artery disease (PAD) is associated with poor mobility and fatigue, but the relationship between preclinical ankle-brachial index (ABI) and early markers of fatigue and functional decline has not been defined.

Methods—570 adults, 50 and older, from the Baltimore Longitudinal Study of Aging (N = 570), with normal values of ABI (1–1.29), were classified into ABI tertiles. Perceived fatigability was assessed after a 5-min, treadmill walk (1.5 mph) using the Borg rating of perceived exertion (RPE, range 6–20). Functional evaluation included the Health, Aging and Body Composition Physical Performance Battery (HABC PPB), time to complete a 400-m corridor walk (LDCW), and VO_2 peak (ml/kg/min). High RPE and poor walking endurance (PWE) were defined as RPE≥10 and taking >5 min for the LDCW, respectively. Differences between tertiles in fatigability and functional measures were tested adjusting for demographics, behavioral characteristics, self-reported fatigue, and medical history.

Results—Mean LDCW time and RPE were greater for participants in the lowest tertile compared to those in the highest; mean VO_2 peak and HABC PPB scores were lower, suggesting hierarchical associations between fatigue, functional performance, and ABI ($p < 0.05$ for all). Odds of PWE

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Conflict of interest

All other coauthors have nothing to disclose.

Author contributions

Pablo Martinez-Amezcua and Jennifer 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.

were greater for those in the lowest ABI tertile compared to the highest; odds of reporting high RPE were greater for those in the middle tertile.

Conclusions—Lower ABI is associated with poorer physical function and increased fatigability, suggesting that early changes in ABI may infer greater risk of functional decline, even among those who may not progress to PAD.

Keywords

Fatigability; peripheral artery disease; functional performance

Introduction

The capacity to ambulate without limitation is critical for maintaining independent living and good quality of life. With aging, the risk of mobility limitations rises substantially (1,2) with approximately one third of US adults older than 65 reporting limitations in at least one form of ambulation, including walking or climbing stairs, and the trend seems to be increasing (3).

Lower limb peripheral arterial disease (PAD) has been associated with poor physical functioning,(4–6) as well as increased fatigue and reduced quality of life in middle and older aged adults (4,7). Although in 2010 PAD affected approximately 8–10 million adults in the US and over 200 million globally (8–10), the majority of individuals are often asymptomatic and unaware of their disease until the severity is high (11,12). Commonly, early symptoms of PAD, including fatigue, tiredness, and leg cramping, are often mistaken for “normal aging,” as symptoms are generally relieved with periods of rest. Additionally, as a response to fatigue, individuals tend to slow down and reduce activity levels, which also might delay recognition of both fatigue and PAD (13–15). Given this often silent progression, understanding changes in fatigue and physical functioning that occur in the early preclinical stages of PAD may help identify individuals at greater risk of mobility limitations, facilitating earlier diagnoses and more effective treatment of PAD.

Due to its subjective nature, measurement of fatigue is problematic, with perception of fatigue varying greatly among individuals. In this context, similar levels of reported fatigue might arise from substantially different levels and intensities of activity (13,16). Fatigability, a relatively new and emerging concept in the gerontological literature, gauges severity of fatigue in relation to a standardized task (16). In the general aging population, high fatigability has been associated with slower gait speed and lower functional performance over time, independent of reported tiredness and low energy level [8], indicating that fatigability may act as an early and sensitive biomarker of impending functional decline(17). Previous research supports a link between PAD, reduced functional performance, and subjective measures of fatigue and vitality (4,7); however, the associations among those in the lower portion of normal range of ABI and functional performance and fatigability remain undefined. Early recognition of reduced physical functioning and high fatigability may assist in diagnosing atherosclerotic burden and provide earlier opportunities for intervention and prevention of progression.

Accordingly, this study aimed to assess differences in fatigability and physical functioning among community dwelling older adults with low normal ankle-brachial index. We hypothesized that persons with low-normal ABI would have poorer physical functioning and higher fatigability, independent of self-reported fatigue and energy level.

Patients and methods

Study population

The Baltimore Longitudinal Study of Aging (BLSA) is a study of normative human aging conducted by the National Institute on Aging Intramural Research Program. A general description of the sample and enrollment criteria has been previously reported (18). Briefly, the BLSA is a continuously enrolled cohort established in 1958 with some targeted recruitment (women, racial minorities) over its history. All participants are community dwelling volunteers who undergo a comprehensive health and functional screening evaluation and are free of all 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. The sample for this cross-sectional analysis consists of 279 men and 291 women aged 50 to 93 who had an objective measurement of physical activity, received a comprehensive physical examination, health history assessment, and ABI assessment between January 2007 and August 2015. Participants who reported history of PAD were excluded. Trained and certified technicians administered all assessments following standardized protocols. The Internal Review Board of the National Institute for Environmental Health Sciences approved the study protocol and participants provided written informed consent.

Study procedure

Participants were admitted to the clinical unit of the Translational Gerontology Branch of the National Institute on Aging for three days of extensive testing. Certified nurse practitioners and specialized technicians administered all assessments following standardized protocols. A nurse practitioner administered a detailed health examination and interview during the physical examination. Information from this interview was used to derive self-reported functional ability, reported tiredness and energy level, and history of chronic conditions.

Measurement of physical function

Long-Distance Corridor Walk (LDCW)

Endurance walking ability was assessed using the long-distance corridor walk (LDCW), a two-phase, self-paced endurance walking test and a validated measure of cardiorespiratory fitness (19,20). The test was performed on a 20-meter course in an uncarpeted corridor, marked by cones at each end. During the first phase, participants were instructed to walk for 2.5 min at their usual pace, until directed to stop. The second phase followed immediately, and participants were asked to complete 10 laps (400 meters) “as quickly as possible, without running, at a pace that can be maintained.” Standard 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. Walking endurance was assessed as the ability and time to

complete the LDCW and was treated as a continuous variable (time to complete) as well as a binary outcome with poor walking endurance defined as either: (i) the inability to complete the 400m walk, or (ii) taking more than 5 min to complete the 400 m portion of the walk (21).

Cardiorespiratory fitness

Peak cardiorespiratory fitness (VO_2 peak ml/kg/min) was measured during the second phase of the LDCW assessed using a Cosmed k4b2 portable metabolic analyzer (Cosmed, Rome, Italy). The Cosmed uses a rubberized facemask and turbine for gas collection. Before testing, the Cosmed system was warmed up for a minimum of 20 min and calibrated using reference gases of known concentrations and a 3.0-liter syringe for flow. Breath-by-breath measurement of oxygen consumption per unit time (ml/kg/min) was collected and averaged into 30-second intervals to reduce variability. To calculate VO_2 peak (ml/kg/min), readings from the first 1.5 min 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 mean volume of oxygen consumed per kilogram of body weight during 400m of peak sustained walking (22,23).

Physical performance battery

The Health, Aging and Body Composition Physical Performance Battery (HABC PPB) was used to assess physical functioning (24). The HABC PPB is a composite measure of ability and time to complete 10 chair stands, 3 progressively harder standing balance poses (side-by-side, semi-tandem, and full-tandem), timed 6-m walk at usual gait speed, and timed-narrow 6-m walk test (walking between 2 parallel lines separated by 20 cm). Ratio scores ranging from 0 to 1 were calculated for each component of the battery, where 1 represents the maximal performance observed for healthy older adults. Participants unable to complete a test were scored 0 for that test. Ratio scores from the four tests were summed to obtain a continuous value ranging from 0 to 4, where participants with higher levels of physical performance receive a higher HABC PPB score.

Fatigue and fatigability assessment

Fatigue

Measures of fatigue were examiner-administered, reference the past month, and covered perceived tiredness and energy level. Measures were dichotomized with cutoffs identified from literature as follows: (1) persons reporting they “felt unusually tired during the day” all, most, or some (vs none) of the time, were classified as “tired”, and (2) those rating their usual energy level at 6 or lower on a 0–10 scale (0 = no energy at all, 10 = the most energy ever had) were considered “low energy”(25).

Perceived fatigability

Perceived fatigability was assessed immediately following a slow-paced 5-minute standardized 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) (range 6–20; 6 = no exertion at all, 9 = very light, 11 = light, 13 = somewhat hard, 20 = maximal exertion).

(16) The speed of 0.67 m/s was selected because it is sufficiently low demand to minimize participant exclusion at older ages and lower functional thresholds. In the current analyses, perceived fatigability was treated as a continuous variable (6–20) as well as a binary outcome with high perceived fatigability defined as an RPE of 10 or greater (16).

Measurement of ankle-brachial index

Systolic blood pressure was taken at both right and left arms and ankles using an automated testing device (Colin VP2000/1000). Systolic pressures in the brachial arteries and posterior tibial arteries were measured with the proper size cuffs at rest in the supine position. ABI was calculated by dividing the ankle systolic pressure by the brachial systolic pressure for each side, the lowest value was selected. Automated devices have been validated against Doppler and shown to be reliable, particularly for values of ABI greater than 1 (26,27). Moreover, this measurement method is not examiner dependent. To facilitate recognition of differences in physical functioning and fatigability among those with clinically normal ABI, our primary analysis focused on participants with ABI (1.0 to 1.39). As a sensitivity analysis, we explored those with ABI <1.0 (n = 39).

Covariates

Demographic characteristics, history of comorbidities including congestive heart failure, coronary heart disease, stroke, hypertension, diabetes, hypercholesterolemia and smoking were obtained during a health interview. Height and weight were measured using standard clinical procedures and body mass index was calculated by dividing weight in kilograms by height in meters squared. Grip strength was measured using a hand-held isometric Jamar dynamometer in both hands, the highest measure in Kg was selected. Physical activity was objectively measured using the Actiheart accelerometer, a combined heart rate and uniaxial activity monitor (Actiheart, CamNtech, Cambridge, United Kingdom). Devices were provided at the end of the examination at the clinical unit and worn at all times, in free-living conditions for 7 days. A minimum of 3 days of wear was required for inclusion in the analyses.

Statistical methods

To facilitate interpretation of results, participants were grouped into tertiles based on ABI (first (1–1.13); second (1.13–1.19); third (1.19–1.39)), and baseline characteristics were evaluated using ANOVA and chi-squared tests. *Post hoc* Tukey comparison tests were performed to detect mean differences among groups (Table 1).

Univariate linear regressions were used to estimate and compare means of RPE, HABC PPB, and time to complete the LDCW by tertiles. Subsequently, 2 sets of covariates were identified as potential confounders and incorporated to multivariate linear regression models (Table 2). The first set, Model 1, was adjusted for age, sex, BMI and race. The second set, Model 2, was adjusted for the same variables in Model 1+ history of coronary heart disease, heart failure, stroke, hypertension, hypercholesterolemia, smoking, the log of total daily

physical activity counts, and height (only for time to complete LDCW). Complete data for ABI were available and missing values were not imputed for any of the covariates.

Logistic regression models were used to assess the odds of high perceived fatigability and poor walking endurance by ABI tertiles, using the third (highest) tertile as the reference group (Table 2). To assess if fatigability measures were independent of self-reported fatigue, we additionally adjusted for tiredness and low energy (Model 3).

To assess if the effect of low ABI, on physical function, was greater in the presence of fatigability, we performed a stratified analysis; two-by-two contingency matrices were built where those in the 1st ABI tertile were labeled as normal low ABI and participants in the 2nd and 3rd tertiles were labeled as normal high ABI, and participants were classified in low and high fatigability based on their RPE scores where low fatigability represents RPE<10 and high fatigability is RPE ≥10. The group with high ABI and low RPE was selected as the reference (Table 3). In this analysis, we adjusted for all variables included in Model 2. Finally, we also tested whether within the lowest ABI tertile (1st), the presence of high fatigability had an effect on physical function (Table 3).

Sensitivity analyses, were performed to explore differences and odds of binary outcomes for participants with low and borderline values of ABI according to clinical guidelines (ABI <1.0) compared to those in the third ABI tertile. All analyses we performed using STATA version 13 (Statacorp, College Station, TX), and two-sided *p*-values smaller than 0.05 were considered statistically significant.

Results

A total of 570 participants were included in the analysis: 196 in the first ABI tertile, 185 in the second, and 189 in the third (Table 1). The mean age was 69.98 ± 9.50 and did not differ across tertiles, 49% of the study population was female and 68% were of white race. There were no significant differences between tertiles by BMI, height, physical activity, history of chronic conditions, reported difficulty walking ¼ mile, or reported tiredness or low energy. Those with lower ABI were more likely to have poorer physical functioning (e.g., gait speed, 400m time, VO_2 peak and HABC PPB score) compared to those with higher ABI ($p<0.05$ for all). Moreover, there was a trend towards higher RPE and reported low energy levels among those with higher ABI ($p=0.06$ and $p= 0.12$, respectively).

Physical performance

Time to complete the 400-meter walk averaged 266.4 ±50 seconds (4:26 min). In unadjusted models, the first tertile was the slowest group with a mean of 273.14 seconds (4:33 min) followed by the second with 267.24 (4:27 min) and third with 258.69 (4:19 min). The 14.4-second difference between the third and first tertiles was significant ($p<0.01$). In fully adjusted models, this difference was attenuated from 15 to 10 seconds, but remained significant ($p=0.015$) (Table 2, Model 2).

Overall, 130 (22.8%) participants demonstrated poor walking endurance. The proportion was significantly higher among people in first tertile (31.1%) compared to third (17.5%)

(p=0.003). Odds of poor walking endurance were significantly increased for people in the first tertile compared to those in the third (OR: 2.14, p=0.002). These findings were slightly attenuated, but remained significant after adjusting for potential confounders, as well as reported tiredness and low energy (Table 2, Models 1–3).

VO_2 peak averaged 18.04 ± 4.5 ml/kg/min overall, and was lowest in the first ABI tertile compared to the third (βVO_2 peak= −1.50 ml/kg, p= 0.003). Although this difference was lessened after adjusting for potential confounders, significance persisted in fully adjusted models (Table 2, Models 1 & 2).

The mean overall HABC PPB score was 2.91±0.50, out of a possible 4.0 score (Table 1). Participants in the lowest ABI tertile tended to score lower compared to those in the highest (−0.14 units, p<0.01 for both). This association remained unattenuated after adjusting for age, sex, BMI, physical activity and history of chronic conditions (Table 2, Models 1 & 2).

Fatigability

On a continuous scale, perceived fatigability was higher among participants in the second tertile compared to those in the third (β=0.57 RPE, p=0.019). These differences were modestly attenuated after adjusting for reported tiredness and low energy, but remained significant (Table 2, Models 1 & 2). In categorical analyses, the odds of reporting high fatigability (RPE≥10) were 1.71 times higher for participants in first tertile (Table 2, Unadjusted model, p=0.014). After adjusting for potential confounders (Table 2, Models 1 & 2) the odds remained higher for this group (OR: 1.59, p<0.05 for both models), but after adjusting for reported tiredness and low energy, the odds ratio was no longer significant.

Stratified analysis

The group with high RPE and low ABI had a lower HABC PPB score, slower 400-meter time, lower VO_2 peak, and was more likely to have poor walking endurance compared with both the reference group (low RPE, higher ABI) and those with similar ABI but with low RPE (Table 3 (p<0.05 for all)). Moreover, the combined effects of high RPE and low ABI were higher than expected (supra-additive), with the β coefficients and odds ratio exceeding the sum of high RPE and low ABI independently.

Sensitivity analysis

There were 39 participants with clinically low ABI (<1.0). Compared to participants in the highest tertile of ABI, they were, on average, 31.2 seconds slower during the 400m walk, had greater odds of showing poor walking endurance (OR: 4.05, p<0.001), had lower VO_2 peak (2.03 mL/kg/min) and had greater odds of a high fatigability (OR: 2.85, p=0.004). Nevertheless, none of these results remained significant after adjusting for the covariates in model 1 (age, sex, BMI and race). The mean scores of the HABC PPB and RPE were significantly different for this group compared with the highest ABI tertile, and these associations persisted in fully adjusted models (Table 4).

Discussion

Among community-dwelling adults aged 50 and over free from PAD with clinically normal ABI values, we found that lower values of ABI are associated with poorer physical function and greater fatigability. Importantly, there were no differences in demographic characteristics and burden of chronic diseases by ABI tertile, indicating that the differences in physical function and fatigability may be directly attributable to reduced ABI values, even within the clinically normal range. These findings support the hypothesis that low ABI values are consistent with poorer physical functioning and higher fatigability and suggest that early changes in ABI may infer greater risk of functional decline and eventual disability, even among those who may not progress to PAD.

Although there were no differences in the self-reported fatigue variables by ABI group, the associations with fatigability persisted, even in fully adjusted models. These results suggest that participants who report similar levels of fatigue differ in terms of fatigability during a standardized task by ABI status. Moreover, the effect of low ABI on physical function was significantly increased in the presence of fatigability, suggesting that fatigability might be an important predictor of lower extremity function for those with low normal values of ABI. In the Atherosclerosis Risk in Communities (ARIC) cohort, significant differences in self-reported fatigue, as measured with the 12-item short form survey, were found, where people with PAD or borderline PAD reported less vitality, but among participants with normal ABI there were no differences (4). Combined with the current findings, these results advocate for the value of fatigability in detecting earlier differences in fatigue burden and progression to decreased functional ability.

The primary purpose of this study was to investigate the association of ABI with function and fatigability among those at risk of PAD, because this group is more likely to benefit from primary prevention efforts/interventions. Additionally, we performed sensitivity analyses to examine potential differences in the association between ABI and physical functioning/fatigability among participants with low/borderline levels of ABI. However, given our study population was comprised of mainly healthy volunteers, the prevalence of low/borderline ABI was very low in our sample (n = 39 (6.4%)), reducing the statistical power to detect the effect of lower ABI values on fatigability and function. Although this limited our analyses, we ascertained a dose-response effect of ABI on the study outcomes in univariate models, with a sustained, significant differences in RPE and HABC PPB in fully adjusted models. Future studies in clinical populations should validate and advance the understanding of these findings among PAD patients. Another limitation of our study is that, given the cross-sectional design, we cannot ascertain causality. Reverse causality is always a concern in cross-sectional examinations. However, the previous evidence on the association between ABI and fatigue and physical function supports our hypothesis of ABI leading to fatigability. Future longitudinal studies, to establish the directionality of our findings, are warranted

It has been previously reported that participants with low normal values of ABI (1–1.10), have increased rates of all-cause mortality, cardiovascular mortality, subclinical cardiovascular disease (28) and functional decline (29,30). Specifically, findings from the

LIFE study indicated that participants with low normal ABI values took longer to walk a "normal paced" 400-meter walk (31). The current study adds to these findings by illuminating differences by ABI status during a fast-paced 400-meter walk, poor walking endurance, the HABC PPB, and perceived fatigability. Comparing beta coefficients for tertiles and age from the fully adjusted regression models, the differences between first and third tertiles are equivalent to a 2.2-year increase in age for time to walk 400 meters, a 6.3-year increase for HABC PPB score, and an 8-year increase for RPE.

There are multiple plausible mechanisms that can explain the association between ABI and fatigability that we found such as lower limb ischemia, deconditioning resulting from decreased levels of physical activity (32) and reduced muscular strength. People with lower values of ABI have been found to have increased fat tissue and reduced calf muscle area (33). Among the consequences of chronic ischemia to the lower limb musculature, many are relevant to fatigability, including decreased muscle metabolism, impaired mitochondrial respiration, reduced mitochondrial enzyme expression and impaired oxidative energy production; leading to impaired muscle functioning. These mechanisms warrant further investigation in future studies.

In conclusion, lower ABI values, even in clinically normal ranges, are associated with poorer physical function and fatigability independent of self-reported fatigue. As fatigability is a validated early marker of impending mobility loss, identifying its onset and progression, and the factors –like ABI- contributing to it, may help identify targets for early interventions to curb the development of ABI and prevent the onset of decreased mobility and eventual disability.

Acknowledgments

Kunihiro Matsushita has received research funding and honoraria from Fukuda Denshi.

Financial support

This work was supported in part by the Intramural Research Program of the National Institute on Aging. Extramural funding provided by NIH/NCI R21AG053198 and NIH/NIA P30AG021334.

References

1. Satariano WA, Guralnik JM, Jackson RJ, Marottoli RA, Phelan EA, Prohaska TR. Mobility and aging: New directions for public health action. Am J Public Health. 2012; 102(8):1508–15. [PubMed: 22698013]
2. Centers for Disease Control and Prevention. Prevalence and most common causes of disability among adults-United States, 2005. MMWR Morb Mortal Wkly Rep. 2009; 58(16):421–6. [PubMed: 19407734]
3. Fuller-Thomson E, Yu B, Nuru-Jeter A, Guralnik JM, Minkler M. Basic ADL disability and functional limitation rates among older americans from 2000–2005: The end of the decline? Journals Gerontol - Ser A Biol Sci Med Sci. 2009; 64(12):1333–6.
4. Wu A, Coresh J, Selvin E, Tanaka H, Heiss G, Hirsch AT, et al. Lower Extremity Peripheral Artery Disease and Quality of Life Among Older Individuals in the Community. J Am Heart Assoc [Internet]. 2017; 6(1):e004519. Available from: http://jaha.ahajournals.org/lookup/doi/10.1161/JAHA.116.004519.
5. McDermott P, Liu K, Guralnik JM, Celic L, Criqui MH, Chan C, Martin GJ, Schneider J, Pearce WH, Taylor LM, Clark EMMG. The ankle brachial index is associated with leg function and

physical activity. Ann Intern Med [Internet]. 2002; 136:873–83. ST–The ankle brachial index is associate. Available from: http://dx.doi.org/.

6. Matsushita, K., Ballew, SH., Sang, Y., Kalbaugh, C., Loehr, LR., Hirsch, AT., et al. Ankle-brachial index and physical function in older individuals: The Atherosclerosis Risk in Communities (ARIC) study; Atherosclerosis [Internet]. 2016. p. 1-8.Available from: http://linkinghub.elsevier.com/retrieve/pii/S0021915016314915%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/28012644
7. Wassel CL, Allison MA, Ix JH, Rifkin DE, Forbang NI, Denenberg JO, et al. Ankle-brachial index predicts change over time in functional status in the San Diego Population Study. J Vasc Surg [Internet]. 2016; 64(3):656–662.e1. Available from: http://dx.doi.org/10.1016/j.jvs.2016.02.066.
8. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, et al. Ethnic-Specific Prevalence of Peripheral Arterial Disease in the United States. Am J Prev Med. 2007; 32(4):328–33. [PubMed: 17383564]
9. Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. Lancet [Internet]. 2013; 382(9901):1329–40. Available from: http://dx.doi.org/10.1016/S0140-6736(13)61249-0.
10. Varu VN, Hogg ME, Kibbe MR. Critical limb ischemia. J Vasc Surg [Internet]. 2010; 51(1):230–41. Available from: http://dx.doi.org/10.1016/j.jvs.2009.08.073.
11. Widener JM. Peripheral arterial disease and disability from NHANES 2001–2004 data. J Vasc Nurs [Internet]. 2011; 29(3):104–12. Available from: http://dx.doi.org/10.1016/j.jvn.2011.06.002.
12. Ouriel K. Peripheral arterial disease. Lancet. 2001; 358(9289):1257–64. [PubMed: 11675083]
13. Eldadah BA. Fatigue and Fatigability in Older Adults. PM R [Internet]. 2010; 2(5):406–13. Available from: http://dx.doi.org/10.1016/j.pmrj.2010.03.022.
14. McDermott M, Greenland P, Guralnik J, Criqui M, Dolan NC, Chan C, et al. Leg Symptoms in Peripheral Arterial Disease Associated Clinical Characteristics and Functional Impairment. 2001; 286(13):1599–606.
15. McDermott MM, Mehta S, Greenland P. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. Arch Intern Med. 1999; 159:387–92. [PubMed: 10030313]
16. Simonsick EM, Schrack JA, Glynn NW, Ferrucci L. Assessing fatigability in mobility-intact older adults. J Am Geriatr Soc. 2014; 62(2):347–51. [PubMed: 24417536]
17. 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(6):1287–92. [PubMed: 27253228]
18. Stone JL, Norris AH. Activities and attitudes of participants in the Baltimore Longitudinal Study. J Gerontol [Internet]. 1966; 21(4):575–80. Available from: http://geronj.oxfordjournals.org/cgi/doi/10.1093/geronj/21.4.575.
19. 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(1):127–32. [PubMed: 16420209]
20. 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(11):1544–8. [PubMed: 11890597]
21. Simonsick EM, Newman AB, Visser M, Goodpaster B, Kritchevsky SB, Rubin S, et al. Mobility limitation in self-described well-functioning older adults: importance of endurance walk testing. J Gerontol A Biol Sci Med Sci. 2008; 63(8):841–7. [PubMed: 18772472]
22. 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):329–36.
23. Schrager, Ma, Schrack, Ja, Simonsick, EM., Ferrucci, L. Association Between Energy Availability and Physical Activity in Older Adults. Am J Phys Med Rehabil [Internet]. 2014; 93(10):876–83. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002060-201410000-00005.
24. Simonsick EM, Newman AB, Nevitt MC, Kritchevsky SB, Ferrucci L, Guralnik JM, et al. Measuring higher level physical function in well-functioning older adults: expanding familiar

approaches in the Health ABC study. J Gerontol A Biol Sci Med Sci. 2001; 56(10):M644–9. [PubMed: 11584038]

25. Ware, J., Kosinski, M., Keller, SD. A 12-Item Short-Form Health Survey : Construction of Scales and Preliminary Tests of Reliability and Validity Author (s): John E. Ware, Jr., Mark Kosinski and Susan D. Keller. Vol. 34. Lippincott Williams & Wilkins; 1996. p. 220-33.Stable URL : http://www.jstor. Med Care
26. Takahashi I, Furukawa K, Ohishi W, Takahashi T, Matsumoto M, Fujiwara S. Comparison between oscillometric- and Doppler-ABI in elderly individuals. Vasc Health Risk Manag. 2013; 9(1):89–94. [PubMed: 23493262]
27. Verberk WJ, Kollias A, Stergiou GS. Automated oscillometric determination of the ankle-brachial index: A systematic review and meta-analysis. Hypertens Res [Internet]. 2012; 35(9):883–91. Available from: http://dx.doi.org/10.1038/hr.2012.83.
28. McDermott MMG, Liu K, Criqui MH, Ruth K, Goff D, Saad MF, et al. Ankle-brachial index and subclinical cardiac and carotid disease: The Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol. 2005; 162(1):33–41. [PubMed: 15961584]
29. Ankle Brachial Index Collaboration. Ankle Brachial Index Combined With Framingham Risk Score to Predict. Jama [Internet]. 2008; 300(2):197–208. Available from: http://jama.jamanetwork.com/.
30. McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, et al. Associations of Borderline and Low Normal Ankle-Brachial Index Values With Functional Decline at 5-Year Follow-Up. The WALCS (Walking and Leg Circulation Study). J Am Coll Cardiol [Internet]. 2009; 53(12):1056–62. Available from: http://dx.doi.org/10.1016/j.jacc.2008.09.063.
31. McDermott MM, Applegate WB, Bonds DE, Buford TW, Church T, Espeland MA, et al. Ankle Brachial Index Values, Leg Symptoms, and Functional Performance Among Community-Dwelling Older Men and Women in the Lifestyle Interventions and Independence for Elders Study. J Am Heart Assoc [Internet]. 2013; 2(6):e000257–e000257. Available from: http://jaha.ahajournals.org/cgi/doi/10.1161/JAHA.113.000257.
32. Parsons TJ, Sartini C, Ellins EA, Halcox JPJ, Smith KE, Ash S, et al. Objectively measured physical activity and sedentary behaviour and ankle brachial index: Cross-sectional and longitudinal associations in older men. Atherosclerosis [Internet]. 2016; 247:28–34. Available from: http://dx.doi.org/10.1016/j.atherosclerosis.2016.01.038.
33. McDermott MM, Hoff F, Ferrucci L, Pearce WH, Guralnik JM, Tian L, et al. Lower extremity ischemia, calf skeletal muscle characteristics, and functional impairment in peripheral arterial disease. J Am Geriatr Soc. 2007; 55(3):400–6. [PubMed: 17341243]

Highlights

- Lower ABI even within the normal ranges has a deleterious effect on function
- Lower ABI within normal range is associated with higher fatigability
- High fatigability increases the effect of lower ABI on physical function

Table 1

Demographic characteristics, chronic conditions and functional measures by ABI tertiles

Variable	Overall N=570	1st tertile 1.0–1.13 n=196	2nd tertile 1.13–1.19 n=185	3rd tertile 1.19–1.39 n=189	*p* value
Age, years	69.98 ± 9.50	69.42 ± 9.92	70.09 ± 9.73	70.46 ± 8.81	0.558
Female	291 (48.95)	108 (55.10)	97 (52.43)	86 (45.50)	0.15
Race:					0.40
White	387 (67.89)	124 (63.27)	127 (68.65)	136 (71.96)	
African-American	145 (25.44)	58 (29.59)	44 (23.78)	43 (22.75)	
Other	38 (6.67)	14 (7.14)	14 (7.57)	10 (5.29)	
BMI, kg/m^2	27.17 ± 4.58	27.54 ± 4.90	27.35 ± 4.83	26.61 ± 3.92	0.112
Height	168.93 ± 9.26	168.14 ± 9.60	168.48 ± 9.05	170.20 ± 9.02	0.067
Chronic conditions:					
Congestive heart failure	5 (0.88)	1 (0.51)	1 (0.54)	3 (1.59)	0.44
Coronary heart disease	25 (4.39)	7 (3.57)	7 (3.78)	11 (5.82)	0.49
Stroke	15 (2.63)	4 (2.04)	5 (2.70)	6 (3.17)	0.78
Hypertension	267 (46.84)	88 (44.90)	84 (45.41)	95 (50.26)	0.51
Diabetes	95 (16.67)	33 (16.84)	29 (15.68)	33 (17.46)	0.89
Hypercholesterolemia	343 (60.18)	115 (58.67)	107 (57.84)	121 (64.02)	0.41
Smoking	19 (3.35)	11 (5.64)	2 (1.09)	6 (3.17)	**0.05**
No difficulty walking 1/4 mile	547 (96.13)	187 (95.41)	179 (96.76)	181 (96.28)	0.82
TLAC	1.28 ± 0.32	1.27 ± 0.31	1.31 ± 0.33	1.28 ± 0.33	0.429
Time to complete LDCW, sec	266.40 ± 49.96	273.14 ± 52.55	267.24 ± 51.67	258.69 ± 44.44	**0.021**
Poor walking endurance	130 (22.81)	61 (31.12)	36 (19.46)	33 (17.46)	**0.003**
VO_2 peak, mL/Kg/min	18.04 ± 4.55	17.12 ± 4.16	18.42 ± 4.61	18.62 ± 4.76	0.007
HABC PPB, score	2.91 ± 0.50	2.82 ± 0.55	2.94 ± 0.49	2.96 ± 0.46	**0.011**
RPE, score	8.53 ± 2.23	8.61 ± 2.09	8.78 ± 2.35	8.20 ± 2.21	0.06
Usual gait speed, m/s	1.16 ± 0.23	1.13 ± 0.21	1.19 ± 0.25	1.18 ± 0.22	**0.021**
Grip strength	32.92 ± 10.82	32.01 ± 10.38	32.53 ± 11.50	34.24 ± 10.50	0.113

Variable	Overall N=570	1st tertile 1.0–1.13 n=196	2nd tertile 1.13–1.19 n=185	3rd tertile 1.19–1.39 n=189	*p* value
Tiredness	203 (35.73)	75 (38.46)	69 (37.30)	59 (31.38)	0.30
Low energy	93 (16.37)	39 (19.9)	31 (16.76)	23 (12.30)	0.13

Bold font indicates a statistically significant difference from ANOVA and Chi squared tests (*p*-value <0.05)
Values are means ± standard deviations or frequencies (proportions).
Chronic conditions were self-reported in the interview: “has a doctor (or other health professional) ever said you had.”

TLAC: Aaverage of total logged activity counts per day; RPE: Borg rating of perceived exertion (6–20); HABC PPB: health ABC physical performance battery score (0–4); VO_2 peak: peak rate of oxygen consumption in the 400-meter walk per kilogram of body weight (ml/kg/min); tiredness: answered “felt unusually tired during the day” all, most or some of the days during the past month (*vs.* none); low energy: rated usual energy level ≤6 in a scale of 0–10.

Table 2

Linear and logistic regressions of ABI tertiles on physical performance and fatigability

Outcomes		1st tertile (ABI: 1.0–1.13)	2nd Tertile (ABI: 1.13–1.19)
Performance	**Time to complete LDCW, seconds**	β coefficient [95% CI]	β coefficient [95% CI]
	Unadjusted	**14.44 [4.235, 24.649]**	8.55 [−1.744, 18.839]
	Model 1	**10.28 [1.826, 18.736]**	3.88 [−4.622, 12.376]
	Model 2	**10.51 [2.048, 18.966]**	5.42 [−3.089, 13.934]
	Poor walking endurance	OR [95% CI]	OR [95% CI]
	Unadjusted	**2.14 [1.32, 3.46]**	1.14 [0.68, 1.93]
	Model 1	**2.08 [1.08, 3.66]**	0.89 [0.49, 1.63]
	Model 2	**2.20 [1.23, 3.95]**	0.95 [0.51, 1.77]
	Model 3	**2.05 [1.14, 3.69]**	0.89 [0.48, 1.68]
	VO_2 peak, mL/Kg/min	β coefficient [95% CI]	β coefficient [95% CI]
	Unadjusted	**−1.50 [−2.524, −0.479]**	−0.20 [−1.234, 0.829]
	Model 1	**−1.21 [−2.074, −0.350]**	0.06 [−0.813, 0.925]
	Model 2	**−1.29 [−2.148, −0.440]**	−0.18 [−1.055, 0.692]
	HABC PPB, score	β coefficient [95% CI]	β coefficient [95% CI]
	Unadjusted	**−0.14 [−0.243, −0.040]**	−0.01 [−0.117, 0.088]
	Model 1	**−0.14 [−0.233, −0.057]**	−0.001 [−0.093, 0.084]
	Model 2	**−0.16 [−0.246, −0.075]**	−0.03 [−0.116, 0.057]
Fatigability	**High perceived fatigability**	OR [95% CI]	OR [95% CI]
	Unadjusted	**1.71 [1.11, 2.64]**	1.54 [0.99, 2.38]
	Model 1	**1.59 [1.02, 2.51]**	1.42 [0.89, 2.25]
	Model 2	**1.59 [1.01, 2.54]**	1.47 [0.92, 2.35]
	Model 3	1.55 [0.97, 2.47]	1.45 [0.90, 2.33]
	RPE, score	β coefficient [95% CI]	β coefficient [95% CI]
	Unadjusted	0.40 [−0.076, 0.884]	**0.57 [0.093, 1.051]**
	Model 1	0.34 [−0.109, 0.785]	**0.46 [0.015, 0.905]**
	Model 2	0.44 [0.000, 0.889]	**0.55 [0.106, 0.989]**
	Model 3	0.40 [−0.043, 0.838]	**0.51 [0.068, 0.941]**

Third tertile is the reference group for all the models: β coefficients are differences compared to third tertile; OR are relative to the odds of binary outcomes for the third tertile.

Bold font indicates a statistically significant difference or odds compared to third tertile (*p*-value <0.05.)

Model 1: adjusted for age sex race BMI.

Model 2: adjusted for Model 1+ history of congestive heart failure, coronary heart disease, hypertension, diabetes, hypercholesterolemia, smoking, TLAC and height (only time to complete LDCW and poor walking endurance).

Model 3: adjusted for Model 2+ tiredness, low energy.

TLAC, average of minute logged activity counts per day; RPE: Borg rating of perceived exertion (6–20); VO_2 peak: peak rete of oxygen consumption in the 400-meter walk; HABC PPB: health ABC physical performance battery score (0–4); poor walking endurance: taking more than 300 seconds to complete the 400-meter walk of the long-distance corridor walk, or being unable to do so; high perceived fatigability: RPE≤10.

Table 3

Linear and logistic regressions of ABI tertiles on physical performance stratified by fatigability status

		β coefficients [95% CI]	
Outcomes		**ABI**	
		Normal Low: 1st tertile (ABI: 1.0–1.13)	**Normal High: 2nd and 3rd tertiles (ABI: 1.13–1.39)**
HABC PPB	**RPE <10**	**−0.14 [−0.24, −0.04]**	Ref
	RPE ≥10	**−0.27 [−0.40, −0.15]**[a]	**−0.10 [−0.18, −0.05]**
Time to complete LDCW	**RPE <10**	9.33 [−0.81, 19.47]	Ref
	RPE ≥10	**23.19 [11.13, 35.24]**[a]	**10.59 [1.79, 19.38]**
VO_2 peak	**RPE <10**	−1.01 [−2.06, 0.04]	Ref
	RPE ≥10	**−2.08 [−3.31, −0.85]**	−0.37 [−1.29, 0.54]
		Odds Ratio [95% CI]	
Outcomes		**ABI**	
		Normal Low: 1st tertile (ABI: 1.0–1.13)	**Normal High: 2nd and 3rd tertiles (ABI: 1.13–1.39)**
Poor walking endurance	**RPE <10**	1.82 [0.73, 4.54]	Ref
	RPE ≥10	**7.0 [2.81, 17.45]**[a]	1.91 [0.85, 4.26]

Bold font indicates significant difference from the group with low RPE and ABI in the Normal High ABI group (2nd or 3rd tertile.)

[a]Significantly different from the group with low RPE and Normal Low ABI (1st tertile.)

Adjusted for age, sex, race, BMI, history of congestive heart failure, coronary heart disease, hypertension, diabetes, hypercholesterolemia, smoking, TLAC and height (only for time to complete LDCW).

Table 4

Linear regressions of low ABI (<1.0) on physical performance and fatigability

Outcomes	Low ABI (<1.0) n=39		
HABC PPB, score	β	95% CI	*p* value
Unadjusted	**−0.47**	**[−0.65, −0.29]**	**<0.001**
Model 1	**−0.27**	**[−0.43, −0.11]**	**0.001**
Model 2	**−0.26**	**[−0.42, −0.10]**	**0.001**
RPE, score	β	95% CI	*p* value
Unadjusted	**1.68**	**[0.83, 2.52]**	**<0.001**
Model 1	**1.10**	**[0.31, 1.90]**	**0.006**
Model 2	**1.08**	**[0.28, 1.88]**	**0.008**
Model 3	**0.95**	**[0.16, 1.74]**	**0.019**

Third tertile is the reference group for all the models: β coefficients are differences compared to third tertile.
Bold font indicates a statistically significant difference compared to third tertile (*p*-value <0.05).
Model 1: adjusted for age sex race BMI.
Model 2: adjusted for Model 1+ history of congestive heart failure, coronary heart disease, hypertension, diabetes, hypercholesterolemia, smoking, TLAC and height (only time to complete LDCW and poor walking endurance)
Model 3: adjusted for Model 2+ tiredness, low energy.

RPE, Borg rating of perceived exertion (6–20); HABC PPB: health ABC physical performance battery score (0–4).