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GENDER DIFFERENCES IN DAILY AMBULATORY ACTIVITY PATTERNS IN PATIENTS WITH INTERMITTENT CLAUDICATION

Andrew W. Gardner[a], **Donald E. Parker**[b], **Polly S. Montgomery**[a], **Aman Khurana**[c], **Raphael M. Ritti-Dias**[d], and **Steve M. Blevins**[e]

[a]CMRI Diabetes and Metabolic Research Program, Harold Hamm Oklahoma Diabetes Center, Oklahoma University Health Sciences Center (OUHSC), Oklahoma City, OK

[b]Department of Biostatistics and Epidemiology, OUHSC, Oklahoma City, OK

[c]Cardiovascular Section, Department of Medicine, OUHSC, Oklahoma City, OK

[d]School of Physical Education, Pernambuco University, Pernambuco, Brazil

[e]General Internal Medicine Section, Department of Medicine, OUHSC, Oklahoma City, OK

Abstract

Purposes—To compare the pattern of daily ambulatory activity in men and women with intermittent claudication, and to determine whether calf muscle hemoglobin oxygen saturation (StO_2) is associated with daily ambulatory activity.

Methods—Forty men and 41women with peripheral arterial disease limited by intermittent claudication were assessed on their community-based ambulatory activity patterns for one week with an ankle-mounted step activity monitor, and on calf muscle StO_2 during a treadmill test.

Results—Women had lower adjusted daily maximal cadence (mean ± SE) for five continuous minutes of ambulation (26.2 ± 1.2 strides/min vs. 31.0 ± 1.2 strides/min; p = 0.009), for one minute of ambulation (43.1 ± 0.9 strides/min vs. 47.2 ± 0.9 strides/min; p=0.004), and for intermittent ambulation determined by the peak activity index (26.3 ± 1.2 strides/min vs. 31.0 ± 1.2 strides/min; p = 0.009). Women also had lower adjusted time to minimum calf muscle StO_2 during exercise (p = 0.048), which was positively associated with maximal cadence for five continuous minutes (r = 0.51; p < 0.01), maximal cadence for 1 minute (r = 0.42; p < 0.05), and peak activity index (r = 0.44; p < 0.05). These associations were not significant in men.

Conclusion—Women with intermittent claudication ambulate slower in the community setting than men, particularly for short continuous durations of up to five minutes and during intermittent ambulation at peak cadences. Furthermore, the daily ambulatory cadences of women are correlated with their calf muscle StO_2 during exercise, as women who walk slower in the community setting reach their minimum calf muscle StO_2 sooner than those who walk at faster paces. Women with intermittent claudication should be encouraged to not only walk more on a daily basis, but to do so at a pace that is faster than their preferred speed.

Address correspondence to: Andrew W. Gardner, Ph.D., Hobbs-Recknagel Professor, General Clinical Research Center, University of Oklahoma Health Sciences Center, 1122 N.E. 13th Street, Suite 150, Oklahoma City, OK 73117. Telephone (405) 271-4272 ext. 42743, FAX: 405-271-4273, andrew-gardner@ouhsc.edu.

INTRODUCTION

Intermittent claudication is a symptom of peripheral arterial disease (PAD), and is associated with elevated rates of mortality(1–4) and morbidity.(5) Intermittent claudication afflicts 5% of the US population older than 55 years of age,(6) and occurs during ambulation when the peripheral circulation is inadequate to meet the metabolic requirement of the active leg musculature. Thus, intermittent claudication impairs ambulation(7;8) and reduces daily physical activity.(9)

Daily physical activity is lower in patients limited by intermittent claudication than in age-matched controls,(9;10) and is associated with mortality risk,(11;12) 6-minute walk distance,(13) physical function,(14) and peak walking time (PWT), defined as the time at which ambulation can not continue due to maximal pain during a standardized treadmill test,(13;15) In particular, the ambulatory cadence (i.e., stride rate) of daily activities is more closely related to PWT than the total number of ambulatory strides or the number of minutes spent ambulating each day,(15) suggesting that intensity of daily ambulation is dependent upon severity of intermittent claudication. Therefore, factors that influence intermittent claudication may be key measures in accounting for differences in ambulatory cadence in patients with PAD.

We have previously shown that women with intermittent claudication have lower daily physical activity than men, even though their ankle/brachial index (ABI) is similar.(16) It is unclear whether the activity level of women is lower in a community based setting because of spending less time in physical activity, because of engaging in less intense physical activity, or a combination of both. Further, women have shorter PWT during standardized treadmill exercise,(16) and greater calf muscle ischemia during treadmill exercise than men, measured by hemoglobin oxygen saturation (StO_2).(17) These findings suggest that the greater ambulatory impairment in women becomes even more pronounced at relatively higher exercise intensities. Calf muscle StO_2 explained differences in PWT between men and women during treadmill exercise,(17) but the association between calf muscle StO_2 and daily ambulatory activity in men and women has not been evaluated.

The purposes of this study are (a) to compare the pattern of daily ambulatory activity in men and women with intermittent claudication by evaluating both the cadence and time spent ambulating throughout the day, and (b) to determine whether calf muscle StO_2 is associated with daily ambulatory cadence and time. The hypotheses are that women have lower daily ambulatory cadences than men, and that calf muscle StO_2 is directly associated with ambulatory cadences obtained during community-based ambulatory monitoring for one week.

METHODS

SUBJECTS

Recruitment—Patients participated in this study at the General Clinical Research Center (GCRC), at the University of Oklahoma Health Sciences Center (HSC). Patients were recruited by referrals from the HSC vascular clinic, as well as by newspaper advertisements. The procedures used in this study were approved by the Institutional Review Board at the University of Oklahoma HSC. Written informed consent was obtained from each patient prior to investigation.

Screening—Patients with intermittent claudication secondary to vascular insufficiency were included in this study if they met the following criteria: (a) a history of any type of exertional leg pain, (b) ambulation during a graded treadmill test limited by leg pain consistent with intermittent claudication,(7) and (c) an ABI ≤ 0.90 at rest(18) or an ABI ≤ 0.73 after exercise because some PAD patients have normal values at rest which only become abnormal following an exercise test.(19) Patients were excluded from this study for the following conditions: (a) absence of PAD (ABI > 0.90 at rest and ABI > 0.73 after exercise), (b) inability to obtain an ABI measure due to non-compressible vessels, (c) asymptomatic PAD determined from the medical history and verified during the graded treadmill test, (d) use of medications indicated for the treatment of intermittent claudication (cilostazol and pentoxifylline) initiated within three months prior to investigation, (e) exercise tolerance limited by factors other than leg pain (e.g., severe coronary artery disease, dyspnea, poorly controlled blood pressure), (f) active cancer, renal disease, or liver disease, (h) calf skin fold > 50 mm because of potential interference with the light path of the near infra-red spectrometer (NIRS) probe from penetrating the subcutaneous tissue, and (i) pulse arterial oxygen saturation of the index finger < 95% because of the potential deleterious effect on calf muscle StO_2 from poor pulmonary gas exchange.

MEASUREMENTS

Medical History, Physical Examination, and Anthropometry—Patients arrived at the GCRC in the morning fasted, but were permitted to take their usual morning medication regimen. Demographic information, height, weight, cardiovascular risk factors, co-morbid conditions, claudication history, blood samples, and a list of current medications were obtained from a medical history and physical examination at the beginning of the study. During the physical examination, arterial oxygen saturation was measured from the index finger using a standard pulse oximeter. Afterwards, subcutaneous fat over the medial gastrocnemius muscle was measured from a skinfold using a Lange skinfold caliper according to standard guidelines,(20) and waist circumference was recorded using a plastic measuring tape.(20)

Walking Impairment Questionnaire (WIQ)—Self-reported ambulatory ability was assessed using a validated questionnaire for PAD patients that assesses ability to walk at various speeds and distances, and to climb stairs.(21)

Gardner Treadmill Test

Claudication Times and Peak Oxygen Uptake: Patients performed a progressive, graded treadmill protocol to determine study eligibility, as well as to obtain outcome measures related to peak exercise performance.(7) The claudication onset time (COT), defined as the walking time at which the patient first experienced pain, and the PWT, defined as the time at which ambulation could not continue due to maximal pain, were both recorded to quantify the severity of claudication. Peak oxygen uptake was measured by oxygen uptake obtained during the peak exercise work load with a Medical Graphics VO2000 metabolic system (Medical Graphics Inc, St. Paul, MN). Using these procedures, the test-retest intraclass reliability coefficient is R = 0.89 for COT,(7) R = 0.93 for PWT,(7) and R = 0.88 for peak oxygen uptake.(22)

ABI and Ischemic Window: As previously described, ABI measures were obtained from the more severely diseased lower extremity before and 1, 3, 5, and 7 minutes after the treadmill test.(7;23) The reduction in ankle systolic blood pressure after treadmill exercise from the resting baseline value was quantified by calculating the area under the curve, referred to as the ischemic window.(24) Because the ischemic window is a function of both PAD severity and the amount of exercise performed, the ischemic window was normalized per meter walked.

StO_2 of the Calf Musculature—Calf muscle StO_2 was measured before, during, and after exercise using a continuous-wave, NIRS spectrometer (InSpectra model 325; Hutchinson Technology, Inc, Hutchinson, MN), an optical cable attached to a 25-mm probe, InSpectra software (version 2.0), and a dedicated laptop computer as previously described.(25) The probe was attached to the skin over the medial gastrocnemius muscle of the more severely affected leg using a double-sided adhesive light-excluding patch.(26) A baseline measure of calf muscle

StO_2 was obtained at rest as patients stood on the treadmill for two minutes to allow for equilibration. From the start of treadmill exercise, the minimum StO_2 value and the time taken to reach the minimum value were obtained.

6-Minute Walk Test—Patients performed an over ground, 6-minute walk test supervised by trained exercise technicians.(27) The pain-free and total distance walked during the test were recorded. The test-retest intraclass reliability coefficient is R = 0.75 for distance to onset of claudication pain, and R = 0.94 for total 6-minute walking distance.(27)

Ambulatory Activity Monitoring

Instrumentation and Procedures: Daily ambulatory activity was assessed using a step activity monitor (Step Watch 3, Cyma Inc., Mountlake Terrace, WA) as previously described. (10) Ambulatory activity was measured during seven consecutive days in which patients were instructed to wear the monitor during waking hours and to remove it before retiring to bed. The step activity monitor was attached to the right ankle above the lateral malleolus using elastic Velcro straps, and continuously recorded the number of steps taken on a minute-to-minute basis. The accuracy of the step activity monitor exceeds 99 ± 1% in patients with intermittent claudication.(10)

Variables Obtained from the Step Activity Monitor: The step activity monitor records the number of ambulatory strides taken per minute for each minute throughout a 24-hour period. After data from the step activity monitor is downloaded to a computer, the software program displays the number of strides taken each day and the number of minutes spent ambulating each day. The daily ambulatory strides and time are further analyzed by the software program, and are quantified into the following variables: maximum cadence for 60, 30, 20, and 5 continuous minutes of ambulation each day, maximum cadence for 1 minute of ambulation each day (i.e., the minute having the single highest cadence value each day), and peak activity index obtained by ranking all minutes of the day according to cadence, and then taking the highest 30 values. These outcome measures are recorded and averaged for each day, and then the daily averages are averaged over the seven-day monitoring period. In subjects with intermittent claudication, the test-retest intraclass reliability coefficient for the measurement of total daily strides and total daily minutes of activity over the 7-day period are R = 0.87 and R = 0.85, respectively.(10) The intraclass reliability coefficients for the remaining variables pertaining to daily ambulatory cadences range from R = 0.83 to R = 0.94.(10)

STATISTICAL ANALYSES

As an initial examination of clinical characteristics of men and women, differences in means of measurement variables in men and women were examined using the Independent Samples t-test and group differences for dichotomous variables were examined with Chi Square procedures. Since this examination yielded a significant difference in means for abdominal obesity, the comparisons between gender of means for ambulatory activity and exercise performance variables were done using ANCOVA with abdominal obesity as a covariate. To minimize the possible distorting effect of extreme values, both Pearson and Spearman partial correlation coefficients were computed within each gender for each pair of variables of interest, with Spearman reported only if the two estimates differed by more than 0.1. All analyses were performed using the NCSS statistical package. Statistical significance was set at $p < 0.05$. Measurements are presented as means ± standard deviations.

RESULTS

The clinical characteristics of the men and women with intermittent claudication are shown in Table I. The groups were similar on all variables ($p > 0.05$), except that women had a higher prevalence of abdominal obesity ($p = 0.003$). Exercise performance measures of the men and women adjusted for abdominal obesity are shown in Table II. Women had lower values for maximal walking time ($p = 0.025$), peak oxygen uptake ($p < 0.001$), calf muscle StO_2 at rest ($p = 0.010$), time to minimum StO_2 during exercise ($p = 0.048$), 6-minute walk pain-free ($p = 0.040$) and total walking distance ($p < 0.001$), WIQ speed score ($p = 0.002$) and WIQ stair climbing score ($p < 0.001$).

Ambulatory activity measures of the men and women recorded during a 7-day monitoring period and adjusted for abdominal obesity are shown in Table III. Men and women had similar daily values for total strides ($p > 0.05$) and total activity time ($p > 0.05$). However, women had a lower daily average cadence ($p = 0.022$), a lower peak activity index ($p = 0.009$), and lower maximal cadences for five continuous minutes of ambulation ($p = 0.009$) and for one minute of ambulation ($p = 0.004$).

The partial correlation coefficients between the time to minimum calf muscle StO_2 during treadmill exercise and the ambulatory activity measures of the men and women are shown in Table IV. In women, after adjusting for covariates, the time to minimum calf muscle StO_2 was positively associated with peak activity index ($p < 0.05$), and with daily maximal cadences for continuous durations of 20 minutes ($p < 0.05$), five minutes ($p < 0.01$), and one minute ($p < 0.05$). In contrast, the time to minimum calf muscle StO_2 was not significantly correlated with any of the ambulatory activity measures in men.

DISCUSSION

This investigation extends our previous finding that daily physical activity levels of women with intermittent claudication are lower than men(16) by demonstrating that this is primarily due to lower ambulatory cadences rather than spending less time in physical activity. Another new finding of this study was that daily ambulatory cadences were directly correlated with calf muscle StO_2 measurements in women but not in men.

Differences in Daily Ambulatory Cadence between Men and. Women

One novel aspect to this investigation was to compare the pattern of daily ambulatory activity between men and women in a community based setting, rather than to simply examine the total activity level. We found that women ambulate at slower cadences than men for relatively short durations of one and five minutes, and that their average daily cadence is 13% slower as well. In addition to ambulating more slowly during continuous ambulatory periods of up to five minutes, women also ambulate 15% slower on an intermittent basis. The slower intermittent ambulation is reflected by the peak activity index, which is the average cadence of the 30 minutes having the highest cadence values throughout the day. In contrast to ambulatory cadence, which represents the intensity of daily ambulation, the women spent a similar amount of time in daily ambulation as men, and the total number of daily strides was similar as well. Thus, the primary gender-related difference in daily ambulatory patterns of patients with intermittent claudication is that women ambulate at slower cadences.

The current study may explain why we previously found an 18% lower total daily activity level in women than in men as measured by an accelerometer.(16) An accelerometer worn at the waist measures vertical accelerations during both ambulatory and non-ambulatory movements. Our current finding that women are similar to men on both daily strides and daily ambulatory time, suggests that the lower total daily energy expenditure of women found in our previous study may be due to lower accelerations generated during slower ambulation. Furthermore, although the total number of strides taken each day was similar between men and women, the women ambulated at a slower cadence for continuous durations of up to five minutes, and for intermittent walking. Our previous finding of objectively measured lower total daily activity

(16) and our current finding of slower ambulation in women supports earlier work that women with PAD self-report leaving their house and neighborhood less frequently, walking fewer blocks, and sweating less often than women without PAD.(28)

Differences in Calf Muscle StO_2 During Exercise in Men and Women

The most important characteristic of calf muscle StO_2 during exercise in patients with intermittent claudication is the observed time to reach the minimum StO_2 value, as this measure is positively associated with COT and PWT, and negatively associated with ischemic window in patients with intermittent claudication.(17;25) The current study supports our previous findings that women have shorter time to minimum calf muscle StO_2 and PWT during treadmill exercise.(17) The shorter time to reach minimum calf muscle StO_2 in women suggests that they have greater impairment in the increase in capillary blood volume during exercise.(29) This notion of greater microcirculatory impairment in women with intermittent claudication is supported from recent work in our laboratory showing that small artery elasticity index is 18% lower in women.(30)

The novel aspect to this finding is that the time to minimum calf muscle StO_2 was significantly correlated with daily ambulatory cadence in women, but not in men. The more rapid oxygen desaturation in the calf muscle of women during exercise suggests that more ambulatory activity in the community setting is performed while experiencing calf ischemia than compared to men walking at any given intensity. Women may decrease their ambulatory cadence because they experience painful ambulation more frequently or, alternatively, they may select slower ambulatory paces while walking in the community setting as a strategy to avoid experiencing the onset of claudication. Walking slowly due to the onset of claudication is more likely to occur with longer activity durations, as measured by the maximum 5-minute cadence, whereas the strategy of ambulating slowly to avoid experiencing claudication is more likely to be evident for short activity duration, as measured by the maximum 1-minute cadence, or for intermittent ambulation, as measured by the peak activity index.

Although the calf muscle StO2 is a significant factor influencing daily ambulatory cadences in women, factors other than calf muscle StO_2 may be associated with daily ambulatory cadences in men. These may include factors that correlate with PWT during a standardized treadmill test, such as cardiopulmonary function,(31) walking economy,(32) muscle mass,(33) muscle strength,(34) obesity,(35) metabolic syndrome,(36) and current smoking.(37) The reasons for why calf muscle StO_2 is more strongly associated with daily ambulatory cadences in women requires further investigation beyond the scope of this study.

Study Limitations

There are limitations to this study that are associated with the measurement of calf muscle StO_2 as previously described.(25) Briefly, myoglobin may partially contribute to the calf muscle StO_2 measurement, capillary and venular blood have different oxygen saturations and may mix in the local tissue, and the subcutaneous fat thickness directly under the probe may interfere with the measure of calf muscle StO_2. However, we believe these limitations have minimal influence on calf muscle StO_2 as discussed earlier.(25) Another limitation is related to the comparison of calf muscle StO_2 between men and women. On average, men are taller than women and have longer stride lengths. Thus, walking at a given speed during the treadmill test requires shorter subjects to take more strides, which may partially explain the shorter time to minimum calf muscle StO_2 in the women. However, we did not believe that adjusting for height was appropriate because this would essentially control for gender and would over-adjust the model.

There are limitations associated with the step activity monitor such as the possibility that patients did not wear the step activity monitor during portions of their waking hours, thereby resulting in an underestimate of daily ambulation.(15) We believe this possibility is unlikely because long durations in which no active minutes were recorded during daytime hours were rarely evident from the software graphs depicting the number of strides taken on a minute-to-minute basis. Even during several hours of being sedentary, a few minutes in which some strides occur were typically evident, indicating that the step activity monitor had not been removed. Another limitation is that the type of sedentary activity which takes place during non-active minutes cannot be determined by the step activity monitor. Consequently, it is not possible to quantify the time spent in various sedentary activities such as watching television, reading, taking naps, and sitting while eating. Furthermore, the step activity monitor does not quantify non-ambulatory physical activity, and therefore it underestimates the total amount of daily physical activity to some extent. Additionally, the types of ambulatory activities cannot be determined. Thus, it is possible that men were engaged in activities requiring higher ambulatory cadences, which may be unrelated to the vascular status of the calf musculature. However, this is unlikely because claudication typically limits the cadence that can be sustained, especially during prolonged ambulatory bouts. Thus, most PAD patients are not capable of performing activities requiring high ambulatory cadences.

Finally, there are limitations associated with the design of the study. The correlations calculated between daily ambulatory activity and calf muscle StO_2 from this cross-sectional design do not allow causality to be established, as it is possible that daily ambulation influences calf muscle StO_2 or vice versa. Furthermore, the results of this study are only applicable to PAD patients who are limited by intermittent claudication, and may not be generalized to patients with less severe or more severe PAD. Another potential weakness to the design of this study was not having ambulatory activity data of men and women controls to compare with the PAD patients. We did not include controls because we have already found that PAD patients have lower values on nearly all ambulatory measures,(16) and we believed it to be duplication of effort to include controls in the current investigation.

Conclusion and Clinical Implication

Women with intermittent claudication ambulate slower in the community setting than men, particularly for short continuous durations of up to five minutes and during intermittent ambulation at peak cadences. Furthermore, the daily ambulatory cadences of women are correlated with their calf muscle StO_2 during exercise, as women who walk slower in the community setting reach their minimum calf muscle StO_2 sooner than those who walk at faster paces. The clinical significance is that women with intermittent claudication should be encouraged to not only walk more on a daily basis, but to do so at a pace that is faster than their preferred speed.

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Table I

Clinical characteristics of men and women with intermittent claudication. Values are means (standard deviation) or percentage of subjects in each category.

Variables	Men (n = 40)	Women (n = 41)	P Value
Age (years)	66.3 (10.0)	64.1 (10.9)	0.350
Weight (kg)	87.7 (20.3)	79.9 (19.4)	0.085
Body Mass Index (kg/m^2)	28.3 (6.1)	30.3 (6.8)	0.183
Ankle/Brachial Index	0.75 (0.23)	0.68 (0.27)	0.241
Race (% Caucasian)	58	37	0.059
Current Smoking (% yes)	35	51	0.175
Diabetes (% yes)	43	51	0.432
Hypertension (% yes)	88	83	0.562
Dyslipidemia (% yes)	88	95	0.222
Abdominal Obesity (% yes)	35	68	0.003
Metabolic Syndrome (% yes)	78	80	0.741
Obesity (% yes)	35	51	0.141

Table II

Exercise measures of men and women with intermittent claudication. Values are means (SE) adjusted for abdominal obesity.

Variables	Men (n = 40)	Women (n = 41)	P Value
Claudication Onset Time (sec)	236 (27)	182 (26)	0.181
Maximal Walking Time (sec)	509 (44)	360 (43)	0.025
Peak Oxygen Uptake ($ml \cdot kg^{-1} \cdot min^{-1}$)	14.4 (0.5)	10.9 (0.5)	< 0.001
Ischemic Window (mmHg × min/m)	0.55 (0.11)	0.64 (0.11)	0.569
StO_2 at rest (% saturation)	59 (3)	48 (3)	0.010
Minimum StO_2 (% saturation)	19 (3)	15 (3)	0.429
Time to minimum StO_2 (sec)	305 (40)	187 (39)	0.048
6-Minute Walk Pain-Free Distance (meters)	202 (18)	147 (17)	0.040
6-Minute Walk Distance (meters)	379 (14)	297 (13)	< 0.001
WIQ Distance Score (%)	44 (5)	32 (5)	0.104
WIQ Speed Score (%)	41 (3)	26 (3)	0.002
WIQ Stair Climbing Score (%)	53 (4)	30 (4)	< 0.001

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Table III

Ambulatory activity of men and women with intermittent claudication recorded during a 7-day monitoring period. Values are means (SE) adjusted for abdominal obesity.

Variables	Men (n = 40)	Women (n = 41)	P Value
Total Strides (strides/day)	3144 (265)	3372 (268)	0.571
Total Activity Time (min/day)	252 (16)	290 (16)	0.114
Maximum 1-minute cadence (strides/min)	47.2 (0.9)	43.1 (0.9)	0.004
Maximum 5-minute cadence (strides/min)	31.0 (1.2)	26.2 (1.2)	0.009
Maximum 20-minute cadence (strides/min)	18.9 (1.2)	15.7 (1.2)	0.068
Maximum 30-minute cadence (strides/min)	15.9 (1.0)	13.2 (1.0)	0.086
Maximum 60-minute cadence (strides/min)	11.5 (0.8)	9.9 (0.8)	0.175
Peak Activity Index (strides/min)	31.0 (1.2)	26.3 (1.2)	0.009
Average Cadence (strides/min)	12.5 (0.5)	10.9 (0.5)	0.022

Table IV

Ambulatory activity measures recorded during a 7-day monitoring period and their associations with the time to minimum calf muscle hemoglobin saturation (StO_2) during treadmill exercise.

Variables	Time to Minimum StO_2 in 40 Men (r)	Time to Minimum StO_2 in 41 Women (r)
Maximum 1-minute cadence	−0.10	0.42 *
Maximum 5-minute cadence	0.08	0.51 **
Maximum 20-minute cadence	*0.01*	0.38 *
Maximum 30-minute cadence	*−0.01*	0.36
Maximum 60-minute cadence	0.02	0.28
Peak Activity Index	−0.03	0.44 *
Average Cadence	0.03	*0.30*
Total Strides	−0.23	0.18
Total Activity Time	*−0.20*	0.15

r = Pearson partial correlation coefficients or Spearman partial correlation coefficients (indicated in italicized print), adjusting for age, obesity, ankle/brachial index, current smoking, abdominal obesity, dyslipidemia, diabetes, hypertension, and metabolic syndrome.

* $p < 0.05$,

** $p < 0.01$