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Original Contribution

The Association Between Physical Activity and Subclinical Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis

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Prior reports regarding the association between physical activity and subclinical cardiovascular disease have not been consistent. The authors assessed physical activity and walking pace via questionnaire among 6,482 US adults aged 45–84 years without prior clinical cardiovascular disease participating in the Multi-Ethnic Study of Atherosclerosis from 2000 to 2002. Ankle-brachial index (ABI), coronary artery calcification, and internal and common carotid intima-media thickness (IMT) were measured. Metabolic equivalent-hours/week of physical activity were calculated. These data were analyzed by using multivariable linear or relative prevalence regression in gender-specific strata. After adjustment for age, race/ethnicity, clinic site, education, income, and smoking (model 1), increasing total, moderate + vigorous, and intentional-exercise physical activity were not associated with IMT or coronary artery calcification in either gender. These factors were associated with increased ABI ($P < 0.05$) in women only. Walking pace was associated favorably with common carotid IMT, ABI, and coronary artery calcification in men and with common carotid IMT and ABI in women (all $P < 0.05$) after adjustment for model 1 variables. These associations were attenuated and, for common carotid IMT, no longer significant when lipids, hypertension, diabetes, and body mass index were added to the model. These data suggest that walking pace is associated with less subclinical atherosclerosis; these associations may be mediated by cardiovascular disease risk factors.

atherosclerosis; carotid arteries; coronary vessels; exercise; motor activity; peripheral vascular diseases

Abbreviations: ABI, ankle-brachial index; CAC, coronary artery calcification; IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent; TWPAS, Typical Week Physical Activity Survey.

The American lifestyle can be characterized as largely sedentary, with many people failing to engage in sufficient moderate- or vigorous-intensity physical activity (1). Observational studies suggest that moderate-intensity + vigorous-intensity physical activity is protective against incident cardiovascular disease (2, 3). Of note, however, is substantially more evidence on the association between physical activity and cardiovascular disease in men than in women (3). It is likely that physical activity reduces cardiovascular disease incidence via beneficial effects on important cardiovascular disease risk factors including lipids, diabetes, hypertension, and obesity (4). It is plausible that moderate + vigorous physical activity would be associated with less atherosclerosis.

However, few studies have examined the effect of physical activity on subclinical atherosclerosis measures such as carotid intima-media thickness (IMT) or coronary artery calcification (CAC). Those that have been conducted provided mixed results. Some have found no association between leisure-time or sports physical activity and carotid IMT (5, 6), while another study reported an inverse association between leisure-time physical activity and IMT in men but not in women (7). One study suggested that long-duration physical activity was associated with less CAC (8), whereas others

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reported no association between physical activity and CAC (9, 10). Differences in physical activity assessment techniques between studies and limitations of self-reported physical activity instruments may contribute to the heterogeneity of results across studies (11). Gender differences may also be seen because of the greater tendency of women versus men to be inactive during leisure time (12). There is also evidence that physical activity types differ by gender (13).

In this paper, we examine the association between physical activity and carotid, coronary, and peripheral subclinical atherosclerosis. Physical activity was assessed by using a self-report questionnaire developed for the Multi-Ethnic Study of Atherosclerosis (MESA), which was based on an instrument developed specifically to assess physical activity among women from several race/ethnicity groups across a wide range of activities (14).

MATERIALS AND METHODS

Study design

MESA is a population-based sample of 6,814 men and women from 4 ethnic groups. Details regarding design, recruitment, and objectives of MESA have been published previously (15). Briefly, eligible MESA participants were defined as persons living within the defined geographic boundaries of each field center who were aged 45–84 years at enumeration via a phone interview; were black, Chinese, white, or Hispanic; and did not meet any of the exclusion criteria. Exclusion criteria included a self-reported medical history of heart attack, angina, cardiovascular procedures, heart failure, cerebrovascular disease, active treatment for cancer, or pregnancy.

Those eligible were invited to a clinic for further examination. During the baseline examination (2000–2002), standardized questionnaires and calibrated devices were utilized to obtain demographic data, tobacco use data, information on medical conditions, current prescription medication usage, weight, and height. Resting, seated blood pressure was measured 3 times by using a Dinamap automated oscillometric sphygmomanometer (model Pro 100; Critikon, Tampa, Florida); the last 2 measurements were averaged for analysis. Hypertension was defined on the basis of use of an antihypertensive medication or systolic/diastolic blood pressure $\geq$140/90 mm Hg. Fasting blood samples were drawn and were sent to a central laboratory for measurement of glucose and lipids (16). Persons were considered to have diabetes if they used hypoglycemic drugs or if their fasting blood glucose was $\geq$7.0 mmol/L (126 mg/dL). Persons were considered to have impaired fasting glucose if they did not have diabetes according to the preceding criteria but their fasting blood glucose level was $>$5.6–$<$7.0 mmol/L ($\geq$100–$<$126 mg/dL) in accordance with the 2004 American Diabetes Association definition (17).

Subclinical disease measures

Chest computed tomography was performed by using either a cardiac-gated electron-beam scanner or a prospectively electrocardiogram-triggered scan acquisition at 50% of the R-R interval with a multidetector system, acquiring a block of 4 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (15). Phantoms of known physical calcium concentration in participants were scanned twice. Scans were read centrally; measurement of CAC was calibrated against the phantom. For each scan, a total phantom-adjusted Agatston score, defined as the sum of calcium measures from the left anterior descending, circumflex, and left and right coronary arteries, was calculated; the mean score was used in these analyses.

For carotid ultrasonography, images of the right and left common carotid and internal carotid arteries were captured, including images of the near and far walls, using high-resolution B-mode ultrasound (18). Images were digitized and analyzed centrally. We defined the common or internal carotid artery IMT as the mean of all available maximum wall thicknesses across both left and right sides.

To obtain ankle-brachial index (ABI), participants rested supine for 5 minutes, then systolic blood pressure was measured in both arms and legs with the appropriate-sized arm cuff. For each leg, the systolic blood pressure in each posterior tibial and dorsalis pedis artery was measured. All pressures were detected with a continuous-wave Doppler ultrasound probe. The leg-specific ABI was calculated as the higher systolic blood pressure in the posterior tibial or dorsalis pedis divided by the higher of the 2 systolic blood pressures in the arms. For this analysis, the minimum ABI was utilized.

Physical activity survey

The MESA Typical Week Physical Activity Survey (TWPAS), adapted from the Cross-Cultural Activity Participation Study (14), was designed to identify the time spent in and frequency of various physical activities during a typical week in the past month. The rationale for the selected time frame was the intention to capture typical activity patterns in one's daily life. The survey has 28 items in categories of household chores, lawn/yard/garden/farm, care of children/adults, transportation, walking (not at work), dancing and sport activities, conditioning activities, leisure activities, and occupational and volunteer activities. Where appropriate, questions differentiated between light-, moderate-, and heavy-intensity activities. Respondents were asked whether they participated in these categories of activity, if yes, they answered questions regarding the average number of days per week and time per day engaged in these activities. Minutes of activity were summed for each discrete activity type, converted to hours for ease of presentation, and multiplied by metabolic equivalent (MET) level (19). The MESA TWPAS by design had the following summary measures: total hours/week and total MET-hours/week for the 9 physical activity categories, 3 intensity levels (light, moderate, vigorous), and total physical activity (light + moderate + vigorous). The survey also inquired about the typical pace at which participants walked in 5 categories ranging from very slow to brisk. For these analyses, we excluded participants who did not complete the survey ($n = 19$) or who reported an average physical activity per day of 0 or more than 24 hours.

After reviewing the patterns of response regarding physical activity categories (e.g., few reporting vigorous physical

Table 1. Characteristics of 6,482 MESA Participants by Gender, United States, 2000–2002[a,b]

Characteristic	Women (n = 3,393)	Men (n = 3,089)
Age, years	62.4 (10.3)	62.3 (10.2)
Race/ethnicity		
White	38.6	39.6
Chinese	12.1	12.6
Black	27.5	25.3
Hispanic	21.8	22.5
Education		
<High school	20.2	16.4
High school	49.3	41.9
College	15.8	19.2
Graduate school	14.7	22.6
Annual income		
<$50,000	64.4	51.2
$50,000–$99,999	21.9	28.1
≥$100,00	9.8	17.1
Body mass index, kg/m^2	28.6 (6.2)	27.8 (4.5)
Hypertension	46.9	43.1
Impaired fasting glucose	23.3	37.8
Diabetes	13.8	16.0
Smoking		
Former	29.8	45.0
Current	11.3	14.5
Total cholesterol, mg/dL	200 (35)	188 (35)
HDL cholesterol, mg/dL	56 (15)	45 (12)
Triglycerides, mg/dL	129 (83)	136 (96)
Common carotid IMT, mm	0.85 (0.18)	0.89 (0.20)
Internal carotid IMT, mm	1.01 (0.58)	1.14(0.62)
Ankle-brachial index	1.09 (0.11)	1.14 (0.12)
CAC >0	40.4	61.5
Total physical activity		
No. of hours/week	84.7 (31.6)	80.4 (31.5)
MET-hours/week	187.3 (84.9)	185.7 (96.2)
Moderate physical activity (3–6 METs)		
No. of hours/week	19.7 (16.8)	21.5 (17.7)
MET-hours/week	69.3 (57.7)	74.9 (60.4)
Vigorous physical activity (>6 METs)		
Any	20.3	42.6
No. of hours/week	0.9 (3.4)	3.2 (7.5)
MET-hours/week	6.2 (23.5)	21 (51.8)
Intentional exercise		
No. of hours/week	4.9 (6.7)	6.1 (7.6)
MET-hours/week	20.4 (28.7)	26.7 (34.1)
Walking pace (mph[c])		
Slow (<2)	30.5	24.7
Medium (2–3)	50.3	50.1
Fast (>3)	19.2	25.2

Abbreviations: CAC, coronary artery calcification; HDL, high density lipoprotein; IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent; mph, miles per hour.

[a] All values are expressed as mean (standard deviation) or percentage.

[b] For all comparisons, $P < 0.01$ except for systolic blood pressure ($P < 0.05$), HDL cholesterol ($P = 0.1$), age ($P = 0.7$), race/ethnicity ($P = 0.3$), and total hours of physical activity ($P = 0.5$).

[c] One mile = 1.6 km.

activity), we created 3 derived variables. The first was moderate + vigorous physical activity (sum of moderate and vigorous MET-hours/week). To capture activities typically recommended by physical activity guidelines, we also created an intentional exercise variable (sum of walking for exercise, sports/dancing, and conditioning MET-hours/week). Finally, typical walking pace was examined with respect to subclinical atherosclerosis.

Statistical analysis

For each measure of physical activity (activity-specific and summary measures), descriptive statistics were utilized to determine the distribution of physical activity by gender. For exploratory analyses, we considered using exact quartiles of physical activity. However, for several measures, more than 25% of participants reported no activity. We therefore selected cutpoints that approximately divided participants into quartiles. The physical activity categories we created were integers 1–4, with a higher number indicating more physical activity. For walking pace, 93% of responses were in the middle 3 categories; thus, we combined the lowest 2 and highest 2 categories to create a 3-level ordinal variable (1, 2, and 3 corresponding to 0–<2, 2–3, and >3 miles per hour (1 mile = 1.6 km)). All analyses were stratified by gender.

An association between physical activity categories and subclinical atherosclerosis was first assessed by analysis of variance (for continuous variables) or Pearson's chi-squared test (for prevalence of CAC). We then utilized linear regression, with common carotid IMT, internal carotid IMT, and ABI as dependent variables and physical activity measures as independent variables. For about half of the MESA participants, the Agatston score is zero (no detectable CAC). Therefore, odds ratios (as a measure of associations with a positive CAC score) estimated via logistic regression tend to be overestimates of the relative risk (20). We utilized relative risk regression for modeling the prevalence of CAC >0 (generalized linear model, specifying a log-link, Gaussian error, and robust standard error estimates). In multivariable analyses, we first adjusted for age, race/ethnicity, pack-years of smoking, clinic site, education, and income

Table 2. Relation Between Physical Activity Categories and Selected Demographic, Behavioral, and Medical Treatment Variables, MESA, United States, 2000–2002[a]

Category	No. of Participants	Age, years	College Graduate	Nonwhite Race/Ethnicity	Current Smoking	Treatment[b]
		Women				
Total physical activity, MET-hours/week						
5–122	775	67.6 (10)	22.2	74.5	8.9	54.5
123–173	883	62.7 (10)	33.7	57.3	12.0	48.4
174–233	883	61.0 (10)	35.5	55.8	11.1	44.2
≥234	852	58.9 (9)	29.5	59.5	13.1	41.1
Moderate + vigorous physical activity, MET-hours/week						
0–34	1,036	64.7 (11)	26.3	69.5	11.9	52.2
35–69	926	63.1 (10)	34.5	57.1	8.5	47.7
70–139	966	60.8 (10)	33.1	57.1	12.2	43.5
≥140	465	59.1 (10)	26.5	60.6	14.0	40.0
Intentional exercise, MET-hours/week						
None	850	63.0 (10)	18.6	71.4	13.9	50.4
1–14	1,123	62.1 (11)	31.5	60.2	10.9	47.1
15–29	649	62.0 (10)	35.8	58.6	10.2	44.2
≥30	771	62.6 (10)	37.6	54.5	10.2	44.7
Walking pace (mph[c])						
Slow (<2)	1,033	64.8 (10)	20.7	70.1	14.2	56.6
Medium (2–3)	1,710	62.1 (10)	32.2	59.8	9.6	45.0
Fast (>3)	650	59.6 (9)	41.5	51.7	11.4	36.2
		Men				
Total physical activity, MET-hours/week						
5–122	845	67.9 (9)	33.9	68.3	11.7	56.1
123–173	737	62.9 (10)	51.8	55.5	14.4	46.3
174–233	739	59.9 (10)	44.3	54.8	14.9	40.3
≥234	768	58.1 (10)	38.3	62.0	17.1	38.2
Moderate + vigorous physical activity, MET-hours/week						
0–34	767	64.2 (10)	40.7	66.9	15.1	51.2
35–69	757	64.4 (10)	49.1	56.4	11.6	49.8
70–139	854	61.8 (10)	45.8	56.2	13.8	43.9
≥140	711	58.7 (10)	30.0	62.9	17.5	36.7
Intentional exercise, MET-hours/week						
None	671	61.7 (10)	26.5	71.8	19.8	42.8
1–14	824	62.0 (10)	40.1	61.5	14.4	48.1
15–29	629	63.5 (11)	46.7	56.0	11.3	45.3
≥30	965	62.3 (10)	50.6	54.5	12.8	45.4
Walking pace (mph)						
Slow (<2)	762	64.3 (11)	29.3	71.5	18.6	52.8
Medium (2–3)	1,549	62.3 (10)	40.9	61.3	14.5	46.0
Fast (>3)	778	60.6 (10)	55.6	47.8	10.3	37.5

Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent; mph, miles per hour.
[a] All values, except numbers of participants, are expressed as mean (standard deviation) or percentage.
[b] Taking medicine for hypertension, diabetes, or dysplipidemia.
[c] One mile = 1.6 km.

Table 3. Subclinical Atherosclerosis Measures by Physical Activity Measures, Stratified by Gender, MESA, 2000–2002[a]

Category	No. of Participants	Common Carotid IMT	Internal Carotid IMT	Ankle-Brachial Index	CAC >0
		Women			
Total physical activity, MET-hours/week					
5–122	775	0.89 (0.20)	1.09 (0.67)	1.07 (0.12)	52.5
123–173	883	0.84 (0.18)	1.03 (0.59)	1.09 (0.10)	40.3
174–233	883	0.84 (0.18)	0.99 (0.54)	1.09 (0.11)	37.3
≥234	852	0.83 (0.17)*	0.96 (0.50)*	1.10 (0.10)*	32.7*
Moderate + vigorous physical activity, MET-hours/week					
0–34	1,036	0.87 (0.20)	1.07 (0.63)	1.07 (0.12)	45.1
35–69	926	0.85 (0.18)	1.00 (0.55)	1.08 (0.11)	42.2
70–139	966	0.84 (0.18)	1.00 (0.58)	1.10 (0.10)	37.5
≥140	465	0.83 (0.17)*	0.95 (0.49)**	1.10 (0.11)*	32.5*
Intentional exercise, MET-hours/week					
None	850	0.87 (0.19)	1.05 (0.61)	1.07 (0.11)	42.9
1–14	1,123	0.84 (0.18)	1.01 (0.60)	1.09 (0.11)	39.4
15–29	649	0.85 (0.19)	1.00 (0.55)	1.09 (0.10)	37.9
≥30	771	0.84 (0.18)***	0.99 (0.53)	1.10 (0.10)*	41.1
Walking pace (mph[b])					
Slow (<2)	1,033	0.89 (0.20)	1.12 (0.66)	1.07 (0.12)	48.3
Medium (2–3)	1,710	0.84 (0.18)	1.00 (0.57)	1.09 (0.10)	39.5
Fast (>3)	650	0.82 (0.16)**	0.90 (0.42)*	1.11 (0.10)*	30.2*
		Men			
Total physical activity, MET-hours/week					
5–122	845	0.94 (0.22)	1.25 (0.70)	1.12 (0.14)	71.0
123–173	737	0.89 (0.19)	1.15 (0.65)	1.14 (0.12)	61.2
174–233	739	0.87 (0.20)	1.08 (0.56)	1.15 (0.12)	58.7
≥234	768	0.86 (0.19)*	1.07 (0.55)*	1.15 (0.12)*	54.0*
Moderate + vigorous physical activity, MET-hours/week					
0–34	767	0.91 (0.21)	1.18 (0.68)	1.13 (0.14)	62.6
35–69	757	0.91 (0.20)	1.18 (0.65)	1.13 (0.12)	65.3
70–139	854	0.89 (0.20)	1.10 (0.59)	1.15 (0.12)	62.4
≥140	711	0.87 (0.20)*	1.10 (0.56)**	1.15 (0.12)**	55.3*
Intentional exercise, MET-hours/week					
None	671	0.90 (0.20)	1.14 (0.65)	1.13 (0.14)	58.6
1–14	824	0.88 (0.20)	1.16 (0.64)	1.14 (0.13)	58.4
15–29	629	0.90 (0.21)	1.15 (0.65)	1.14 (0.12)	65.7
≥30	965	0.89 (0.20)	1.12 (0.58)	1.15 (0.12)**	63.5**
Walking pace (mph)					
Slow (<2)	762	0.93 (0.21)	1.21 (0.68)	1.11 (0.15)	66.9
Medium (2–3)	1,549	0.89 (0.21)	1.13 (0.63)	1.14 (0.12)	62.0
Fast (>3)	778	0.86 (0.18)*	1.09 (0.55)*	1.16 (0.10)*	55.3*

Abbreviations: CAC, coronary artery calcification; IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent; mph, miles per hour.

* $P < 0.001$; ** $P < 0.01$; *** $P < 0.05$ for comparisons across categories.

[a] All values, except numbers of participants, are expressed as mean (standard deviation) or percentage.

[b] One mile = 1.6 km.

(model 1). Model 2 included all variables in model 1 plus the following biologic parameters: body mass index, hypertension, systolic blood pressure, diabetes, and lipids (total cholesterol, high density lipoprotein cholesterol). Tests for linear trends across ordinal physical activity categories were performed by using Wald tests. We assessed for potential effect modification by introducing the interaction term physical activity category × race/ethnicity (race/ethnicity coded as integers) to the models and determining its significance by using a Wald test. For all analyses, we utilized a 2-tailed test of $P < 0.05$ for statistical significance. Analyses were performed by using Stata version 8 software (Stata Corporation, College Station, Texas).

RESULTS

The physical activity survey was completed by 6,795 (99.7%) participants. We excluded 5 who reported no physical activity and 308 who reported an average physical activity per day of more than 24 hours, resulting in a 6,482-participant sample. Their characteristics are presented in Table 1. By design, race/ethnicity and age were balanced across gender categories. Men were more likely to report higher education and income levels, to have diabetes, and to be current or former smokers. Women were more likely to have hypertension. Carotid IMT was higher in men, as was the presence of any CAC. Few had an ABI $\leq$0.9. There were significant differences in summary physical activity measures by gender (Table 1). Women reported fewer hours engaged in intentional exercise, and a greater proportion reported walking at a slower pace.

The relation between physical activity categories or walking pace and age, race/ethnicity, education, current smoking, and current pharmacologic treatment for diabetes, hypertension, or dyslipdemia is presented in Table 2. For most physical activity measures and walking pace, men and women in the highest category tended to be younger, had higher educational levels, and, compared with persons who were less active or walked slower, were less likely to be taking a drug for a cardiovascular disease risk factor.

Carotid atherosclerosis measures (common carotid and internal carotid IMT), ABI, and CAC prevalence data by physical activity measures are presented in Table 3. Among women and men, increasing total physical activity and moderate + vigorous physical activity were significantly associated with more favorable IMT, ABI, and CAC measures. Intentional exercise was associated with thinner common carotid IMT and higher ABI in women but not with internal carotid IMT or CAC. In contrast, among men, intentional exercise was favorably associated with only ABI and was significantly associated with increased CAC. Walking pace was significantly associated with lower common carotid and internal carotid IMT, lower prevalence of CAC, and higher ABI in both men and women.

The results of multivariable analyses examining the association between type of physical activity and subclinical atherosclerosis are presented in Table 4. After adjustment for model 1 variables, we observed no association between total physical activity, moderate + vigorous physical activity, or intentional exercise and any measure except for the association between these measures and ABI in women. In contrast, walking pace remained associated with common carotid IMT after adjustment for model 1 variables in men and women; this association was attenuated and nonsignificant after adjusting for the additional factors in model 2 (Table 5). After full adjustment, walking pace was associated with a lower internal carotid IMT in women. Walking pace remained associated with higher ABI in both men and women. A fast walking pace was marginally associated with a lower prevalence of CAC in women after adjustment for model 1 variables; the point estimate was similar, but significant for men. For men, walking pace remained favorably associated with CAC after full adjustment.

We did not find evidence in favor of an interaction between the 4 physical activity measures assessed and race/ethnicity. In a sensitivity analysis, we limited the sample to only those 3,679 participants not taking medications for hypertension, diabetes, or dyslipidemia. We observed patterns similar to those in the full analysis, with the exception that, among women, increasing moderate + vigorous physical activity was marginally associated with internal carotid IMT after full adjustment; the beta-coefficient for the highest category was −0.07 mm (95% confidence interval: −0.14, 0) and the *P* for trend was 0.04. For men, after full adjustment, moderate + vigorous physical activity was associated with ABI; the beta-coefficient for the highest category was 0.03 (95% confidence interval: 0.01, 0.04) and the *P* for trend was <0.01.

DISCUSSION

Our results suggest that, among women and men aged 45–84 years and free of clinical cardiovascular disease, self-reported physical activity as assessed by a TWPAS is not associated with carotid or coronary atherosclerosis after taking into account potentially confounding variables. Various classifications of physical activity, be it total, moderate + vigorous, or intentional exercise-related physical activity, did not appear to be reliably related to the amount of carotid or coronary atherosclerosis. We did observe a modest association of both moderate + vigorous physical activity and intentional exercise with ABI in women. In addition, when we excluded those pharmacologically managing major cardiovascular disease risk factors, there was some evidence of an association between moderate + vigorous physical activity and internal carotid IMT in women and ABI in men. In contrast, typical walking pace was associated with internal carotid and common carotid IMT and ABI in women and with common carotid IMT, ABI, and CAC in men, even after adjustment for sociodemographic factors and smoking. These associations were perhaps mediated by biologic risk factors.

The difficulty of capturing physical activity exposure via questionnaire has been extensively reviewed. Potential limitations include inaccurate participant recall, duration of the assessment period, arbitrary cutpoints for categorization, and potentially differential activities by gender or age (11). Some also suggest that combining duration of physical activity with MET levels to produce composite scores may

Table 4. Association Between Physical Activity Measures and Subclinical Atherosclerosis, Stratified by Gender, MESA, United States, 2000–2002[a]

	Women, MET-Hours/Week						Men, MET-Hours/Week					
	123–173		174–233		≥234		123–173		174–233		≥234	
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
						Total physical activity[b]						
Common carotid IMT												
Model 1[c]	−0.01	−0.03, 0.01	0.01	−0.01, 0.02	0.01	−0.01, 0.03	0.00	−0.02, 0.02	0.00	−0.02, 0.02	−0.01	−0.03, 0.01
Model 2[d]	0.00	−0.02, 0.02	0.01	−0.01, 0.03	0.01	−0.01, 0.03	0.00	−0.02, 0.02	0.00	−0.02, 0.02	0.00	−0.02, 0.02
Internal carotid IMT												
Model 1	0.00	−0.05, 0.05	−0.01	−0.07, 0.04	−0.02	−0.08, 0.04	0.02	−0.04, 0.08	−0.02	−0.08, 0.04	−0.01	−0.07, 0.05
Model 2	0.02	−0.04, 0.07	0.00	−0.05, 0.06	−0.01	−0.06, 0.05	0.03	−0.03, 0.09	−0.02	−0.08, 0.04	0.00	−0.06, 0.06
Ankle-brachial index												
Model 1	0.01	−0.002, 0.02	0.01	−0.001, 0.02	0.02	0.01, 0.03*	0.00	−0.01, 0.02	0.00	−0.01, 0.02	0.01	−0.01, 0.02
Model 2	0.01	−0.003, 0.02	0.01	−0.003, 0.02	0.02	0.01, 0.03*	0.00	−0.01, 0.01	0.00	−0.01, 0.01	0.01	−0.01, 0.02
CAC >0												
Model 1	0.96	0.88, 1.05	0.97	0.88, 1.07	0.95	0.85, 1.05	0.97	0.02, 1.03	1.01	0.95, 1.08	1.00	0.93, 1.07
Model 2	0.98	0.90, 1.06	0.97	0.88, 1.06	0.96	0.87, 1.06	0.98	0.93, 1.05	1.01	0.95, 1.07	1.00	0.93, 1.07
	35–69		70–139		≥140		35–69		70–139		≥140	
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
						Moderate + vigorous physical activity[e]						
Common carotid IMT												
Model 1	−0.01	−0.02, 0.01	0.00	−0.01, 0.02	0.00	−0.02, 0.02	0.00	−0.02, 0.02	0.00	−0.02, 0.02	0.00	−0.02, 0.02
Model 2	−0.01	−0.02, 0.01	0.00	−0.02, 0.01	0.00	−0.02, 0.02	0.00	−0.01, 0.02	0.00	−0.02, 0.02	0.01	−0.01, 0.03
Internal carotid IMT												
Model 1	−0.03	−0.08, 0.02	0.00	−0.05, 0.05	−0.04	−0.10, 0.02	0.01	−0.05, 0.07	−0.05	−0.10, 0.01	−0.02	−0.08, 0.04
Model 2	−0.02	−0.06, 0.03	0.02	−0.03, 0.06	−0.03	−0.09, 0.06	0.01	−0.05, 0.07	−0.04	−0.10, 0.02	−0.01	−0.07, 0.05
Ankle-brachial index												
Model 1	0.00	−0.01, 0.01	0.01	0.00, 0.02	0.02	0.01, 0.03*	0.00	−0.01, 0.02	0.01	0.001, 0.02	0.01	0.00, 0.02
Model 2	0.01	0.00, 0.02	0.01	0.00, 0.02	0.02	0.01, 0.03*	0.01	−0.01, 0.02	0.01	0.001, 0.02	0.01	0.00, 0.02
CAC >0												
Model 1	1.03	0.94, 1.11	1.03	0.94, 1.13	0.96	0.85, 1.09	1.01	0.95, 1.08	1.04	0.98, 1.11	1.03	0.96, 1.10
Model 2	1.03	0.96, 1.13	1.04	0.95, 1.14	0.97	0.87, 1.10	1.01	0.95, 1.08	1.05	0.99, 1.11	1.03	0.96, 1.11
	1–14		15–29		≥30		1–14		15–29		≥30	
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
						Intentional exercise[f]						
Common carotid IMT												
Model 1	−0.01	−0.03, 0.00	0.00	−0.02, 0.01	−0.01	−0.03, 0.00	−0.02	−0.03, 0.00	−0.01	−0.03, 0.01	−0.01	−0.03, 0.01
Model 2	−0.01	−0.02, 0.01	0.00	−0.01, 0.02	−0.01	−0.02, 0.01	−0.02	−0.04, 0.00	−0.01	−0.03, 0.01	0.00	−0.02, 0.02

Internal carotid IMT												
Model 1	−0.02	−0.07, 0.03	−0.02	−0.07, 0.04	−0.03	−0.09, 0.02	0.02	−0.04, 0.08	0.02	−0.05, 0.08	−0.01	−0.07, 0.05
Model 2	−0.01	−0.06, 0.04	−0.01	−0.06, 0.05	−0.01	−0.07, 0.04	0.02	−0.04, 0.08	0.02	−0.04, 0.09	0.00	−0.06, 0.06
Ankle-brachial index												
Model 1	0.01	0.004, 0.02	0.02	0.004, 0.03	0.02	0.01, 0.04**	0.002	−0.01, 0.01	0.00	−0.01, 0.01	0.01	0.00, 0.02
Model 2	0.01	0.01, 0.02	0.02	0.01, 0.03	0.03	0.02, 0.04**	0.01	−0.01, 0.02	0.00	−0.01, 0.02	0.01	0.00, 0.03
CAC >0												
Model 1	0.95	0.87, 1.03	0.95	0.87, 1.05	0.98	0.89, 1.08	0.98	0.91, 1.05	1.04	0.96, 1.12	1.05	0.98, 1.12
Model 2	0.98	0.90, 1.06	0.99	0.90, 1.09	1.02	0.93, 1.12	0.99	0.93, 1.06	1.06	0.99, 1.13	1.05	0.98, 1.12

Abbreviations: CAC, coronary artery calcification; CI, confidence interval; IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent.

* P for trend < 0.05; ** P for trend < 0.001.

[a] Values shown are difference (mm) in IMT, ankle-brachial index, and relative risk for CAC.

[b] Reference category: 5–122 MET-hours/week.

[c] Model 1 was adjusted for age, race/ethnicity, clinic site, education, income, and pack-years of smoking.

[d] Model 2 was adjusted for model 1 variables plus body mass index, hypertension, systolic blood pressure, diabetes, lipids (total cholesterol, high density lipoprotein cholesterol).

[e] Reference category: 0–34 MET-hours/week.

[f] Reference category: none.

not accurately reflect threshold effects (21). For example, walking at a moderate intensity (2 METs) for a longer duration (60 minutes) may not be equivalent to walking at a more vigorous intensity (4 METs) for a shorter duration (30 minutes), yet both would yield the same score using our approach. Physical activity self-report surveys are subject to recall and social desirability bias (22). Another consideration is potential confounding by indication because persons with diabetes, hypertension, and dyslipidemia may have been counseled to increase their physical activity, which may lead to either more physical activity or at least reporting more physical activity. The effect of these potential biases is likely misclassification and thus a diminished ability to detect significant associations between physical activity and subclinical disease. A further limitation is that temporality cannot be ascertained. In particular, it is plausible that advanced subclinical atherosclerosis leads to diminished ability to perform moderate + vigorous physical activity, rather than the converse.

There is evidence that cardiorespiratory fitness is an important predictor of cardiovascular disease burden and mortality and that fitness may be a better indicator of risk than amount of physical activity performed (23). We hypothesize that typical walking pace may be a proxy for fitness in this survey, which may explain more consistent relations observed between walking pace and the atherosclerosis measures we investigated. Walking pace was associated with reduced coronary heart disease incidence independent of age, cardiovascular disease risk factors, and number of walking hours for men in the Health Professionals Follow-up Study (24). A similar result was found for women in the Nurses' Health Study (25). We are not aware of studies relating walking pace to IMT, ABI, or CAC in population-based samples. It has been reported that, among those with peripheral arterial disease, a lower walking speed is associated with incident cardiovascular disease events (26).

To place the small differences in IMT into perspective, a meta-analysis of observational studies suggests that a 0.10-mm common carotid artery IMT difference is associated with an increased risk of myocardial infarction (hazard ratio = 1.14) and stroke (hazard ratio = 1.17) (27). For comparison, the observed differences in common carotid IMT between the highest and lowest category of physical activity or walking pace ranged from 0.04 mm to 0.08 mm. The differences in ABI and CAC found in the present study were also modest. However, differences that may be small, particularly from a clinical perspective (which is focused on individual patients), may be meaningful at a population level (28). It is also possible that the effect sizes for IMT and ABI reflect shorter-term influences of physical activity on subclinical activity because the questionnaires assessed recent physical activity exposure. The associations initially observed were attenuated by adjustment for age, socioeconomic factors, tobacco use, and clinic site. A strong relation between socioeconomic status and leisure-time physical activity has been demonstrated (12, 29), as has the relation between the local environment and physical activity (30). The associations were further attenuated, and in most cases no longer significant, after further adjustment for traditional cardiovascular disease risk factors. Although these data are

Table 5. Association Between Walking Pace[a] and Subclinical Atherosclerosis, Stratified by Gender, MESA, United States, 2000–2002[b]

	Women, Walking Pace (mph)				Men, Walking Pace (mph)			
	Medium (2–3)		Fast (>3)		Medium (2–3)		Fast (>3)	
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
Common carotid IMT								
Model 1[c]	−0.01	−0.03, −0.002	−0.02	−0.04, 0.00*	−0.01	−0.02, 0.01	−0.03	−0.04, −0.01*
Model 2[d]	−0.003	−0.02, 0.01	0.00	−0.02, 0.02	−0.002	−0.02, 0.01	−0.01	−0.03, 0.01
Internal carotid IMT								
Model 1	−0.03	−0.08, 0.01	−0.10	−0.15, −0.04*	−0.02	−0.07, 0.04	−0.03	−0.09, 0.03
Model 2	−0.01	−0.06, 0.03	−0.07	−0.12, −0.01*	−0.01	−0.06, 0.05	−0.01	−0.07, 0.05
Ankle-brachial index								
Model 1	0.01	0.00, 0.02	0.01	0.00, 0.03*	0.01	0.0, 0.02	0.02	0.01, 0.04**
Model 2	0.01	0.00, 0.02	0.02	0.01, 0.03**	0.01	0.0, 0.02	0.03	0.02, 0.04**
CAC >0								
Model 1	0.94	0.88, 1.01	0.89	0.80, 1.00	0.96	0.91, 1.01	0.90	0.84, 0.96*
Model 2	0.99	0.02, 1.06	0.95	0.85, 1.06	0.97	0.92, 1.02	0.92	0.86, 0.98*

Abbreviations: CAC, coronary artery calcification; CI, confidence interval; IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis; mph, miles per hour.

* P for trend < 0.05; ** P for trend < 0.01.

[a] Reference category for walking pace is slow (<2 miles per hour (1 mile = 1.6 km)).

[b] Values shown are difference (mm) in IMT, ankle-brachial index, and relative risk for CAC.

[c] Model 1 was adjusted for age, race/ethnicity, clinic site, education, income, and pack-years of smoking.

[d] Model 2 was adjusted for model 1 variables plus body mass index, hypertension, systolic blood pressure, diabetes, lipids (total cholesterol, high density lipoprotein cholesterol).

cross-sectional and thus do not provide evidence for mediation, it is plausible that the mechanism by which walking pace impacts atherosclerosis is via salutatory influences on factors such as glucose and lipid metabolism or blood pressure.

In the Cardiovascular Health Study of adults aged >65 years, greater intensity and duration of leisure-time physical activity over the prior 2 weeks was associated with a lower prevalence of low ABI among the cohort free of cardiovascular disease at baseline; however, these investigators did not find an association between either intensity or duration and carotid IMT (31). Leisure-time physical activity was not related to carotid IMT in the NHLBI Family Heart Study, despite expected associations with risk factors such as body mass index and glucose (32). In the Atherosclerosis Risk in Communities study (subjects aged 45–64 at baseline), no association was found between leisure-time or sports physical activity and carotid IMT; however, lack of occupational physical activity was associated with a higher carotid IMT (5). Follow-up of this cohort reported a lower risk of incident coronary heart disease for both men and women with increases in both sports and leisure physical activity but no association between occupational physical activity and coronary heart disease (33).

In a volunteer sample of asymptomatic adults with at least 2 risk factors for metabolic syndrome, those who regularly engaged in long-duration physical activity had a lower prevalence of CAC than did those who were sedentary or participated in moderate-duration physical activity (8). However, at least 2 other studies have reported no association between physical activity and CAC (9, 10).

In addition to the limitations of physical activity assessment via survey discussed above, there are additional limitations to our analyses. The MESA TWPAS survey was adapted from a study that included only women; it is possible that this instrument is less valid for men. We did not explore race/ethnicity differences in the associations between physical activity and subclinical atherosclerosis because of smaller sample sizes for stratified analyses and therefore lower power. However, we did not find evidence of significant interactions between the physical activity measures and race/ethnicity.

These results suggest that walking pace is associated with subclinical atherosclerosis, which may account for the association between walking pace and incident cardiovascular disease. We do not interpret our findings as suggesting that intensity or duration of physical activity is not important. However, the associations we found were modest, and other mechanisms may also be contributing factors to cardiovascular benefit beyond atherosclerosis, such as the effect of physical activity on myocardial function, coronary artery size and vasodilatory capacity, vascular tone, and vulnerability to arrhythmias (4). There is also evidence that increased leisure-time physical activity is associated with reduced levels of several inflammatory markers including C-reactive protein and fibrinogen (34). A recent joint American College of Sports Medicine/American Heart Association guideline suggests that "all healthy adults aged 18–65 yr need moderate-intensity aerobic physical activity for a minimum of 30 min on five days each week or vigorous-intensity aerobic activity for a minimum of 20 min on three days each

week. Combinations of moderate- and vigorous intensity activity can be performed to meet this recommendation'' (35, p. 1423). These results of our study support encouraging sedentary adult men and women to increase their physical activity and to walk at a brisker pace, and they suggest such activity may have beneficial effects on atherosclerosis.

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REFERENCES

1. Adams PF, Schoenborn CA. Health behaviors of adults: United States, 2002–04. *Vital Health Stat 10*. 2006;(230): 1–140.
2. Wannamethee SG, Shaper AG. Physical activity in the prevention of cardiovascular disease: an epidemiological perspective. *Sports Med.* 2001;31(2):101–114.
3. Batty GD. Physical activity and coronary heart disease in older adults. A systematic review of epidemiological studies. *Eur J Public Health*. 2002;12(3):171–176.
4. Thompson PD, Buchner D, Pina IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation*. 2003;107(24): 3109–3116.
5. Folsom AR, Eckfeldt JH, Weitzman S, et al. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Stroke*. 1994;25(1):66–73.
6. Ebrahim S, Papacosta O, Whincup P, et al. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. *Stroke*. 1999;30(4):841–850.
7. Stensland-Bugge E, Bønaa KH, Joakimsen O, et al. Sex differences in the relationship of risk factors to subclinical carotid atherosclerosis measured 15 years later: the Tromsø study. *Stroke*. 2000;31(3):574–581.
8. Desai MY, Nasir K, Rumberger JA, et al. Relation of degree of physical activity to coronary artery calcium score in asymptomatic individuals with multiple metabolic risk factors. *Am J Cardiol.* 2004;94(6):729–732.
9. Folsom AR, Evans GW, Carr JJ, et al. Association of traditional and nontraditional cardiovascular risk factors with coronary artery calcification. *Angiology.* 2004;55(6):613–623.
10. Taylor AJ, Watkins T, Bell D, et al. Physical activity and the presence and extent of calcified coronary atherosclerosis. *Med Sci Sports Exerc.* 2002;34(2):228–233.
11. LaMonte MJ, Ainsworth BE. Quantifying energy expenditure and physical activity in the context of dose response. *Med Sci Sports Exerc.* 2001;33(suppl 6):S370–S378.
12. Crespo CJ, Smit E, Andersen RE, et al. Race/ethnicity, social class and their relation to physical inactivity during leisure time: results from the Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Prev Med.* 2000;18(1):46–53.
13. Lee YS. Gender differences in physical activity and walking among older adults. *J Women Aging*. 2005;17(1–2):55–70.
14. Ainsworth BE, Irwin ML, Addy CL, et al. Moderate physical activity patterns of minority women: the Cross-Cultural Activity Participation Study. *J Womens Health Gend Based Med.* 1999;8(6):805–813.
15. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol.* 2002; 156(9):871–881.
16. Cushman M, Cornell ES, Howard PR, et al. Laboratory methods and quality assurance in the Cardiovascular Health Study. *Clin Chem.* 1995;41(2):264–270.
17. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2004;27(suppl 1):S5–S10.
18. O'Leary DH, Polak JF, Wolfson SK Jr, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. CHS Collaborative Research Group. *Stroke*. 1991;22(9):1155–1163.
19. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* 2000;32(suppl 9):S498–S504.
20. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*. 1998;280(19):1690–1691.
21. Winett RA, Carpinelli RN. Examining the validity of exercise guidelines for the prevention of morbidity and all-cause mortality. *Ann Behav Med.* 2000;22(3):237–245.
22. Adams SA, Matthews CE, Ebbeling CB, et al. The effect of social desirability and social approval on self-reports of physical activity. *Am J Epidemiol.* 2005;161(4):389–398.
23. LaMonte MJ, Blair SN. Physical activity, cardiorespiratory fitness, and adiposity: contributions to disease risk. *Curr Opin Clin Nutr Metab Care*. 2006;9(5):540–546.
24. Tanasescu M, Leitzmann MF, Rimm EB, et al. Exercise type and intensity in relation to coronary heart disease in men. *JAMA*. 2002;288(16):1994–2000.
25. Manson JE, Hu FB, Rich-Edwards JW, et al. A prospective study of walking as compared with vigorous exercise in the

prevention of coronary heart disease in women. *N Engl J Med.* 1999;341(9):650–658.
26. Schiano V, Brevetti G, Sirico G, et al. Functional status measured by walking impairment questionnaire and cardiovascular risk prediction in peripheral arterial disease: results of the Peripheral Arteriopathy and Cardiovascular Events (PACE) study. *Vasc Med.* 2006;11(3):147–154.
27. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007; 115(4):459–467.
28. Rose G. Strategy of prevention: lessons from cardiovascular disease. *BMJ (Clin Res Ed)*. 1981;282(6279):1847–1851.
29. Hawkins SA, Cockburn MG, Hamilton AS, et al. An estimate of physical activity prevalence in a large population-based cohort. *Med Sci Sports Exerc*. 2004;36(2):253–260.
30. Diez Roux AV, Evenson KR, McGinn AP, et al. Availability of recreational resources and physical activity in adults. *Am J Public Health*. 2007;97(3):493–499.
31. Siscovick DS, Fried L, Mittelmark M, et al. Exercise intensity and subclinical cardiovascular disease in the elderly. The Cardiovascular Health Study. *Am J Epidemiol.* 1997; 145(11):977–986.
32. Kronenberg F, Pereira MA, Schmitz MK, et al. Influence of leisure time physical activity and television watching on atherosclerosis risk factors in the NHLBI Family Heart Study. *Atherosclerosis*. 2000;153(2):433–443.
33. Folsom AR, Arnett DK, Hutchinson RG, et al. Physical activity and incidence of coronary heart disease in middle-aged women and men. *Med Sci Sports Exerc.* 1997;29(7):901–909.
34. Geffken DF, Cushman M, Burke GL, et al. Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol.* 2001;153(3): 242–250.
35. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* 2007;39(8):1423–1434.