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Self-reported and accelerometer-derived physical activity levels and coronary artery calcification progression in older women: results from the Healthy Women Study

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Abstract

Objective: Despite the well-supported biological link between physical activity (PA) and atherosclerosis, most previous studies have reported a null association between PA and coronary artery calcification (CAC). The aim of this study was to examine the relationship between PA and CAC progression in 148 Healthy Women Study (HWS) participants over 28 years of observation.

Methods: The HWS was designed to examine cardiovascular risk factor changes from premenopause to postmenopause. Based on CAC scores collected on two follow-up visits (electron beam tomography [EBT] 1 and EBT4) scheduled 12 years apart, participants were classified into one of three groups: (1) no-detectable CAC group (n = 37; 0 CAC on both visits); (2) incident CAC group (n = 46; 0 CAC on the first visit and >0 CAC on the last visit); or (3) prevalent CAC group (n = 65; >0 CAC on both visits). PA data were collected regularly throughout the study using self-report questionnaires and accelerometers on EBT4.

Results: The percentage of HWS participants with no detectable CAC decreased from 56.1% on EBT1 to 25.0% on EBT4. Times spent per day in accumulated moderate- to vigorous-intensity PA (MVPA) and bouts of MVPA were each significantly higher in the no-detectable CAC group when compared with the prevalent CAC group (both $P \leq 0.01$). After covariate adjustment, these differences remained statistically significant (both $P < 0.05$). Although self-reported summary estimates collected throughout the study were significantly associated with accelerometer data on EBT4, there were no significant differences in self-reported PA levels by CAC group after covariate adjustment.

Conclusions: Study findings suggest that low levels of accelerometer-derived MVPA may be indicative of subclinical disease in older women.

Key Words: Coronary heart disease – Motor activity – Ambulatory monitoring – Coronary calcification – Women.

Cardiovascular disease (CVD), which includes coronary heart disease (CHD), is the leading cause of death among women in the United States.[1] Substantial scientific evidence supports the importance of physical activity (PA) in reducing the lifetime risk of CHD.[1,2] This reduction in risk may be caused by the beneficial effect of PA on several related risk factors, including obesity, hypertension, elevated triglyceride levels, low concentrations of high-density lipoprotein cholesterol (HDL-c), high insulin resistance, and glucose intolerance.[3] It is also possible that the benefits of PA are independent of traditional risk factors and affect plaque morphology and risk of thrombosis[4] or coronary blood flow and myocardial metabolism.[5] Regardless of mechanism, inadequate PA levels are thought to be both a sign of existing disease[6] and a predictor of future disease.[2,7] Yet the specific mechanisms by which PA supports cardiovascular health in women remain unclear.[8]

Clarifying the biological link between PA and CHD is an important public health priority given that a large proportion of related deaths occur in women without clinical symptoms.[9] The amount of calcification in coronary arteries, as measured by electron beam tomography (EBT), provides a noninvasive measure of subclinical atherosclerosis and is strongly independently

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related to the risk of clinical CHD. Coronary artery calcification (CAC) scores via EBT are associated with coronary atherosclerosis detected during pathology[10] and angiographic studies.[11] CAC scores are also directly associated with many cardiovascular risk factors, especially apolipoprotein B, HDL-c, blood pressure, smoking, and diabetes.[12-19] Given the beneficial effect of PA on CHD and related risk factors, it seems intuitive that PA would also be inversely related to CAC.

Although previous studies have explored the association between PA and CAC, most have reported null findings.[4,19-23] Past studies have principally examined the cross-sectional relationship between PA and extent of CAC, which is not reflective of the atherosclerotic process that develops over several decades. Several studies have also used self-report methods to assess PA exposure. Therefore, one possible explanation for previous null findings might relate to the limitations of self-reported PA instruments in producing an estimate that is reflective of CAC. Recent results by Hamer et al[23] also failed to show a significant relationship between accelerometer-derived PA estimates and extent of CAC. However, the associations between accelerometer estimates and CAC were not presented separately by sex.[23] PA levels[24] and CAC scores[25] tend to be higher in men than in women. Therefore, nonstratified analysis, regardless of statistical adjustment, could lead to inappropriate inferences. Therefore, the purpose of this study was to examine the association of self-reported and accelerometer-derived estimates of PA with CAC measured over 12 years in a cohort of women followed up for up to 28 years. This design provides the unique opportunity to explore the relationship of PA (assessed via self-report and accelerometer) to the progression of CAC in a well-characterized study of women and CVD.

METHODS

Study design overview

Detailed descriptions of the Healthy Women Study (HWS) have been published previously.[26,27] Briefly, the HWS, a prospective cohort study, was designed to examine changes in the biological and behavioral risk factors for CVD as women progressed through the menopausal transition. From 1983 to 1984, women aged 42 to 50 years were recruited from driver's license lists within selected zip codes in Allegheny County, PA. Eligible women were invited to a baseline visit. After the baseline assessment, women reported their menstrual status on monthly postcards. Menopause was defined as no menses for 12 consecutive months or initiation of hormone therapy. Postmenopausal women were then scheduled for a follow-up evaluation (first year postmenopausal visit). Subsequent evaluations were repeated at 2, 5, and 8 years postmenopause. After the eighth postmenopausal visit, women were invited to have an EBT scan of their heart and aorta (1997-1998). EBT scans were repeated in 2002-2003 (EBT2), 2004-2007 (EBT3), and 2010-2011 (EBT4). All measures relevant to these analyses were completed on EBT1 and EBT4.

Setting and participants

Recruitment and data collection were conducted at the University of Pittsburgh. Women were initially interviewed by telephone to determine study eligibility. Eligibility criteria for study enrollment included the following: menstrual bleeding within the previous 3 months; no surgically induced menopause; diastolic blood pressure lower than 100 mm Hg; and not currently using lipid-lowering, antihypertensive, or psychotropic medications, insulin, thyroid hormone, or estrogens. Of the 2,405 women contacted by telephone, 88.9% (n = 2,138) consented to an eligibility interview, and 42.1% (n = 901) were deemed eligible at that time and during a subsequent home interview. Sixty percent of eligible women (n = 541) enrolled in the study.[27] The average age at baseline examination was 47.6 ± 1.6 years. Each participant provided a written informed consent form, and all protocols were approved by the institutional review board at the University of Pittsburgh.

Participant characteristics

Sociodemographic characteristics and health behavior data were collected repeatedly in the HWS using standardized questionnaires. Use of prescription medication (ie, hormone therapy or lipid-lowering, antihypertensive, and antidiabetes medications) was also collected throughout the 28 years of participant follow-up.

Coronary artery calcification

EBT scans were performed using a GE-Imatron C-150 scanner (Ultrafast CT; Imatron, South San Francisco, CA). For evaluation of the coronary arteries, 30 to 40 contiguous 3-mm-thick transverse images were obtained from the level of the aortic root to the apex of the heart. Images are obtained during maximal breath holding using electrocardiogram triggering, so that each 100-millisecond exposure is obtained at 80% of the R-R interval. CAC scores were calculated by the method of Agatston et al[28] using a densitometric program available on the Imatron C-150 workstation. Calcification was considered present in the coronary arteries when at least three contiguous pixels of 130 Hounsfield units were detected overlying the vessels of interest. HWS participants were classified into one of three groups based on CAC scores collected on the EBT1 and EBT4 visits. The no-detectable CAC group was defined as 0 CAC score on both EBT1 and EBT4; the incident CAC group was defined as a CAC score of 0 on EBT1 and higher than 0 on EBT4; and the prevalent CAC group was defined as a CAC score higher than 0 on both EBT1 and EBT4 visits.

Physical activity

Paffenbarger Physical Activity Questionnaire

The Paffenbarger Physical Activity Questionnaire (PPAQ)[29,30] is a reliable and valid estimate of the previous week's PA. PPAQ was interviewer-administered by trained study staff at the baseline visit and at 1-year postmenopausal, 5-years postmenopausal, and EBT1 (approximately 8-y postmenopausal)

follow-up visits. PA levels were calculated as the sum of participation in walking, stair climbing, and sports and recreational activities. Walking one block was equivalent to 56 kcal/week, and climbing up and down one flight of stairs was equivalent to 14 kcal/week. Energy expended in sports and recreational activities was computed as the product of the duration and frequency of each reported activity (h/wk), weighted by an estimate of the metabolic equivalent (MET) of that activity[31] and summed for all activities performed. Derived estimates were multiplied by the individual's body weight (kg) to estimate PA energy expenditure (kcal/wk).

Modifiable Activity Questionnaire

On EBT4, PPAQ was replaced with the Modifiable Activity Questionnaire (MAQ) to better reflect the types of activities common among older women. MAQ is an interviewer-administered questionnaire that assesses past year leisure-time and occupational PA.[32] Because of the limited reported occupational activity in the HWS population,[33] only the leisure-time estimate is reported. PA levels were calculated as the product of the duration and frequency of 39 common leisure activities (h/wk), weighted by a standardized estimate of the MET of each activity,[31] and then summed for all activities performed. Leisure-time PA was expressed as MET times hours per week. MAQ is a reliable and valid estimate of self-reported PA.[34]

Accelerometer

On the EBT4 follow-up study, an accelerometer ancillary study was added to the study protocol. Accelerometer data were collected using the ActiGraph GT1M accelerometer (Pensacola, FL). The ActiGraph GT1M accelerometer is a small ($3.8 \times 3.7 \times 1.8$ cm^3) uniaxial piezoelectric activity monitor that measures acceleration in the vertical plane. Data output from the accelerometer is expressed in activity counts, which quantify the amplitude and frequency of detected accelerations; activity counts are summed over an investigator-specified time interval (ie, epoch). For the current study, a 60-second epoch was reported. Technical specifications, as well as the reliability and validity of the ActiGraph accelerometer,[35,36] have been described previously.

Participants wore the accelerometer on the dominant hip every day for seven consecutive days. The participants were asked to record the time at which they put on the monitors (or got up, if monitor was worn during sleep) in the morning and the time they took off the monitors (or went to bed, if monitor was worn during sleep) at night in a PA diary provided by the study staff. We asked the participants to wear the monitor for 24 hours each day to allow for future comparisons with objective sleep assessments. At the end of each week, the participants returned the accelerometer and PA diary to the study staff.

Data from the accelerometer were downloaded and screened for wear time using methods described by Troiano et al.[37] Briefly, device nonwear was defined as 60 consecutive minutes of 0 counts, with an allowance for 1 to 2 minutes of detected counts between 0 and 100. Wear time was determined by subtracting derived nonwear time from 24 hours.[37] Summary estimates were computed if daily accelerometer wear time was at least 10 hours. Total accelerometer count per day was calculated using summed daily counts detected over wear periods. Time spent per day (min/d) at different intensity levels was estimated using the threshold values proposed by Matthews.[35] Resulting activity count ranges from sedentary (0-99 cpm), to light intensity (100-759 cpm), to moderate intensity (760-5,724 cpm), and to vigorous intensity (≥5,725 cpm). Two summary estimates of time spent per day in moderate- to vigorous-intensity PA (MVPA) were computed using thresholds of 760 cpm or higher. The first MVPA estimate included every minute above threshold, whereas the second estimate only included accumulated time spent in modified activity bouts as defined by Troiano et al[37] (10 consecutive minutes above the 760 cpm threshold with an allowance of 1-2 min below the threshold). Moderate- to vigorous-intensity activities are defined as those requiring 3 METs or more (eg, brisk walking).[38,39] Weekly summary estimates were computed by averaging daily estimates across the total number of days worn for participants with 4 days or more, with 10 hours/day or more of wear time.

Cardiovascular risk factors

Height, body weight, waist circumference, and fasting (12-h) blood draw were repeatedly collected in the HWS throughout the 28 years of follow-up. Height and weight were measured with a stadiometer and a calibrated balance beam scale, and body mass index (BMI) was computed as body mass in kilograms divided by height in meters squared. Waist circumference (cm) was measured in standing position at the navel (horizontal plane at the center of the navel) using a fiberglass retractable tape measure. Blood pressure was measured using the Multiple Risk Factor Intervention Trial protocol.[12] Total cholesterol, HDL-c, triglycerides, and glucose were determined by conventional methods. Low-density lipoprotein cholesterol (LDL-c) was estimated by the Friedewald equation, and insulin was measured via radioimmunoassay.

Statistical methods

Summary measures (mean and SD) and frequency distribution (proportion and 95% CI) were computed. The assumption of normality was tested using Shapiro-Wilk tests. The distributions of several PA estimates were positively skewed; therefore, square-root transformation was applied to reach normality. These variables were then backtransformed and are presented as means and SDs. Pearson's correlations (r) were used to examine the associations between (1) self-reported PA estimates collected over 28 years of follow-up and accelerometer data collected on EBT4 and (2) accelerometer data and CVD risk factors collected on EBT4. Then, analysis of variance or χ^2 test was used to compare CVD risk factors, medication use, and PA levels collected on the EBT1 and EBT4 visits by CAC group. Dunnett's post hoc tests were used to examine differences in continuous variables between the no-detectable CAC group (referent group) and the incident and prevalent CAC groups. Generalized linear mixed models

were used to compare PA levels between the no-detectable CAC group (referent group) and the incident and prevalent CAC groups after adjustments for participant age (years) and BMI (kg/m^2) at each relevant visit and use of lipid-lowering or antihypertensive medications on the EBT1 and EBT4 visits. Statistical analyses were generated using SAS/STAT software, version 9.2, of the SAS System for Windows (Cary, NC).

RESULTS

Of the 245 women who attended the EBT4 visit, 166 (67.8%) also completed the accelerometer ancillary study. Of those, 156 (94.0%) women had valid accelerometer data. HWS participants with accelerometer data were significantly less likely to report current cigarette smoking on EBT4 when compared with those who completed the EBT4 visit but did not participate in the accelerometer ancillary study (0% vs 2.8%; $P = 0.001$). Although no other statistically significant differences related to participant characteristics, CVD risk factors, or CAC scores were noted, qualitative differences in CVD risk factors on EBT4 are reported to aid in the interpretation of results. Participants who completed the accelerometer ancillary study were slightly younger (73.3 ± 1.6 vs 73.5 ± 1.7 y), had slightly higher BMI (27.3 ± 5.7 vs 27.2 ± 5.0 kg/m^2) and slightly larger waist circumference (89.7 ± 13.1 vs 89.4 ± 14.7 cm), lower systolic (123.5 ± 20.2 vs 125.2 ± 17.7 mm Hg) and diastolic (65.4 ± 10.8 vs 67.3 ± 9.8 mm Hg) blood pressures, higher total cholesterol (218.5 ± 45.6 vs 216.8 ± 36.6 mg/dL) and LDL-c (126.8 ± 40.5 vs 124.5 ± 32.3 mg/dL) levels, similar HDL-c levels (67.8 ± 14.3 vs 67.9 ± 18.2 mg/dL), and lower triglyceride (118.8 ± 50.2 vs 122.4 ± 56.9 mg/dL) and glucose (103.3 ± 14.0 vs 105.2 ± 14.8 mg/dL) levels when compared with those who did not participate. Of the 156 HWS participants with valid accelerometer data, eight did not have CAC scores on EBT1, which resulted in a final analytical sample of 148 HWS participants.

Participant characteristics are shown in Table 1. The majority were white (92.6%), reflecting the racial composition of the HWS population at baseline. Given that the prevalence of medication use known to influence cardiovascular risk factors changed drastically during the 12-year interval between visits, statistical differences between the visits were not computed. More specifically, the proportion of HWS participants reporting current lipid-lowering or antihypertensive therapy was substantially higher on the EBT4 follow-up (6.1%-46.0% and 10.1%-48.7%, respectively). This change in medication use status probably contributed to the more

TABLE 1. *Participant characteristics of the analytic sample on the first (EBT1) and last (EBT4) visits in the Healthy Women Study (n = 148)*

	EBT1 follow-up visit	EBT4 follow-up visit
Cardiovascular risk factors		
Age, y[a]	61.9 ± 1.7	73.2 ± 1.7
Body mass index, kg/m^2[a]	27.2 ± 5.2	27.3 ± 5.1
Waist circumference, cm[a]	83.1 ± 12.9	89.7 ± 13.2
Systolic blood pressure, mm Hg[a]	121.7 ± 18.3	123.8 ± 20.4
Diastolic blood pressure, mm Hg[a]	71.3 ± 8.9	65.4 ± 10.9
Total cholesterol, mg/dL[a]	215.2 ± 34.8	218.4 ± 45.9
Low-density lipoprotein cholesterol, mg/dL[a]	129.0 ± 34.2	126.7 ± 40.6
High-density lipoprotein cholesterol, mg/dL[a]	61.6 ± 17.1	67.7 ± 14.4
Triglycerides, mg/dL[a]	126.0 ± 74.6	119.3 ± 50.4
Glucose, mg/dL[a]	91.0 ± 14.1	103.4 ± 14.2
Insulin, mU/dL[a]	–	13.1 ± 5.1
Current cigarette smoker[b]	8.2 (3.7-12.6)	0.0 (0.0-0.0)
No detectable coronary artery calcification[b]	56.1 (48.1-64.1)	25.0 (18.0-32.0)
Medication use		
Current use of hormone therapy[b]	55.8 (47.4-63.8)	4.7 (1.3-8.2)
Duration of hormone therapy use, y[c]	4.5 (2.0-7.0)	22.4 (3.2-24.8)
Current use of lipid-lowering medication[b]	6.1 (2.2-9.9)	46.0 (37.9-54.0)
Current use of antihypertensive medication[b]	10.1 (5.2-15.0)	48.7 (40.6-56.7)
Current use of antidiabetes medication[b]	–	6.1 (2.2-9.9)
PA[d]		
Self-reported leisure-time PA, kcal/wk[c,e]	1,848.7 ± 309.8	–
Self-reported leisure-time PA, MET h/wk[c,e]	–	18.0 ± 4.3
Accelerometer-derived estimates		
Wear time, min/d[a]	–	1,042.2 ± 114.5
Total accelerometer count, ct/d[c,e]	–	172,873.0 ± 7,834.0
Sedentary, min/d[a]	–	745.3 ± 108.7
Light-intensity PA, min/d[c,e]	–	227.7 ± 2.9
Moderate- to vigorous-intensity PA, min/d[c,e]	–	61.8 ± 4.8
Moderate- to vigorous-intensity PA bouts, min/d[c,e]	–	14.3 ± 6.6

EBT, electron beam tomography; PA, physical activity; MET, metabolic equivalent; ct/d, counts per day.
[a]Mean ± SD.
[b]Percent (95% CI).
[c]Median (interquartile range).
[d]Self-reported leisure-time PA was assessed on the EBT1 visit using the Paffenbarger Physical Activity Questionnaire and on the EBT4 visit using the Modifiable Activity Questionnaire.
[e]Square-root transformation was applied. Data are backtransformed and presented as mean ± SD.

TABLE 2. *R values between self-reported PA estimates collected over 28 years of follow-up and accelerometer-derived PA on the EBT4 follow-up visit in the Healthy Women Study (n = 148)*

	Self-reported PA				
	Baseline, kcal/wk (n = 148)[a]	1-y postmenopausal visit, kcal/wk (n = 139)[a]	5-y postmenopausal visit, kcal/wk (n = 138)[a]	EBT1, kcal/wk (n = 147)[a]	EBT4, MET h/wk (n = 146)[a]
Total accelerometer count, ct/d[a]	0.13	0.22[b]	0.17[c]	0.24[b]	0.39[d]
Sedentary, min/d	−0.14[c]	−0.10	−0.27[b]	−0.20[e]	−0.24[b]
Light-intensity PA, min/d[a]	0.03	0.01	−0.11	0.02	0.07
Moderate- to vigorous-intensity PA, min/d[a]	0.12	0.22[e]	0.17[e]	0.24[b]	0.38[d]
Moderate- to vigorous-intensity PA bouts, min/d[a]	0.08	0.22[b]	0.21[e]	0.22[b]	0.42[d]

Self-reported leisure-time PA was assessed at baseline, 1-year postmenopausal visit, 5-year postmenopausal visit, and EBT1 visit using the Paffenbarger Physical Activity Questionnaire. On the EBT4 visit, self-reported leisure-time PA was assessed using the Modifiable Activity Questionnaire.
PA, physical activity; EBT, electron beam tomography; MET, metabolic equivalent; ct/d, counts per day.
[a]Square-root transformation was applied.
[b]$P < 0.01$.
[c]$P < 0.10$.
[d]$P < 0.001$.
[e]$P < 0.05$.

favorable levels of many cardiovascular risk factors on the EBT4 (ie, diastolic blood pressure, LDL-c, HDL-c, and triglycerides) when compared with the EBT1 follow-up visit. However, the proportion of no detectable CAC decreased from the first EBT visit across all successive follow-up visits (EBT1, 56.1%; EBT2, 45.0%; EBT3, 35.6%; and EBT4, 25.0%).

The association between self-reported PA collected over 28 years and accelerometer data collected on EBT4 is shown in Table 2. Total accelerometer counts were significantly correlated with self-reported PA estimates collected at the 1-year postmenopausal, EBT1, and EBT4 visits (r = 0.22-0.39; all $P < 0.01$). Sedentary time (min/d) was significantly related to self-reported PA estimates collected at the 5-year postmenopausal, EBT1, and EBT4 visits ($r = -0.20$ to -0.27; all $P < 0.05$). MVPA times, both accumulated (r = 0.17-0.38; all $P < 0.05$) and within activity bouts (r = 0.21-0.42; all $P < 0.05$), were significantly related to self-reported PA estimates collected at all visits, except at baseline.

The relations between CVD risk factors and accelerometer-derived PA data are presented in Table 3. Total accelerometer counts were inversely related to BMI, waist circumference, systolic blood pressure, triglycerides, and insulin ($r = -0.17$ to -0.30; all $P < 0.05$) and were directly related to HDL-c ($r = 0.21$; $P < 0.05$). Sedentary time was directly related to BMI, waist circumference, systolic blood pressure, and insulin (r = 0.17-0.24; all $P < 0.05$). Accumulated time spent in MVPA was inversely related to BMI, waist circumference, systolic blood pressure, triglycerides, insulin, and glucose ($r = -0.16$ to 0.30; all $P < 0.05$), and was directly related to HDL-c ($r = 0.19$; $P < 0.05$). Similar associations were shown between MVPA bouts and CVD risk factors; however, the relationship with systolic blood pressure was not statistically

TABLE 3. *R values between traditional cardiovascular risk factors and accelerometer-derived PA estimates collected on EBT4 visit in the Healthy Women Study (n = 148)*

	Total accelerometer count, ct/d[a]	Sedentary, min/d[a]	Light-intensity PA, min/d[a]	Moderate- to vigorous-intensity PA, min/d[a]	Moderate- to vigorous-intensity PA bouts, min/d[a]
Age, y	−0.16[b]	−0.06	−0.05	−0.16[c]	−0.09
Body mass index, kg/m^2	−0.25[d]	0.18[c]	−0.002	−0.26[d]	−0.34[e]
Waist circumference, cm	−0.31[e]	0.21[d]	0.03	−0.30[e]	−0.37[e]
Systolic blood pressure, mm Hg[a]	−0.17[c]	0.17[c]	−0.12	−0.19[c]	−0.11
Diastolic blood pressure, mm Hg[a]	−0.02	0.11	−0.07	−0.01	0.04
Total cholesterol, mg/dL[a]	0.07	0.02	0.01	0.10	0.08
Low-density lipoprotein cholesterol, mg/dL[a]	0.05	0.05	0.02	0.08	0.06
High-density lipoprotein cholesterol, mg/dL[a]	0.21[c]	−0.15[b]	−0.002	0.19[c]	0.23[d]
Triglycerides, mg/dL[a]	−0.21[c]	0.13	−0.07	−0.17[c]	−0.23[d]
Glucose, mg/dL[a]	−0.16[b]	0.06	−0.05	−0.19[c]	−0.18[c]
Insulin, mU/dL[a]	−0.30[e]	0.24[d]	−0.12	−0.29[e]	−0.35[e]

PA, physical activity; EBT, electron beam tomography; ct/d, counts per day.
[a]Square-root transformation was applied to normalize variable distribution.
[b]$P < 0.10$.
[c]$P < 0.05$.
[d]$P < 0.01$.
[e]$P < 0.001$.

TABLE 4. *Unadjusted cardiovascular disease risk factors, medication use, and PA levels on the EBT1 and EBT4 follow-up visits by CAC group in the Healthy Women Study (n = 148)*

	EBT1 follow-up visit				EBT4 follow-up visit			
	No detectable CAC (n = 37)	Incident CAC (n = 46)	Prevalent CAC (n = 65)	P^a	No detectable CAC (n = 37)	Incident CAC (n = 46)	Prevalent CAC (n = 65)	P^a
Cardiovascular risk factors								
Age, y[b]	61.9 ± 1.7	61.8 ± 1.6	62.0 ± 1.9	0.79	73.3 ± 1.5	73.4 ± 1.6	73.1 ± 1.8	0.70
Body mass index, kg/m^2[b]	25.3 ± 3.0	26.4 ± 4.5	28.8 ± 6.1	0.002[c]	25.7 ± 3.7	27.1 ± 5.1	28.4 ± 5.5	0.03[c]
Waist circumference, cm[b]	79.8 ± 8.3	79.9 ± 9.9	87.2 ± 15.6	0.002[c]	86.7 ± 9.8	88.0 ± 11.8	92.5 ± 15.3	0.06
Systolic blood pressure, mm Hg[b]	117.2 ± 18.1	120.8 ± 17.5	124.9 ± 18.6	0.11	123.3 ± 15.5	121.6 ± 17.7	125.6 ± 24.3	0.58
Diastolic blood pressure, mm Hg[b]	70.8 ± 8.2	71.5 ± 9.6	71.5 ± 9.0	0.92	68.0 ± 7.4	65.6 ± 10.5	63.8 ± 12.6	0.16
Total cholesterol, mg/dL[b]	218.3 ± 34.1	213.8 ± 29.4	214.9 ± 38.8	0.82	232.3 ± 44.9	224.8 ± 42.4	205.7 ± 46.3	0.01[c]
Low-density lipoprotein cholesterol, mg/dL[b]	133.8 ± 33.6	124.1 ± 27.4	129.8 ± 38.5	0.44	139.3 ± 38.5	131.4 ± 37.7	116.1 ± 41.8	0.01[c]
High-density lipoprotein cholesterol, mg/dL[b]	62.6 ± 18.1	65.5 ± 17.2	58.2 ± 16.1	0.08	71.3 ± 14.0	70.2 ± 14.6	63.8 ± 13.8	0.02[c]
Triglycerides, mg/dL[b]	109.5 ± 50.0	121.7 ± 73.5	138.2 ± 84.8	0.16	109.1 ± 40.9	114.2 ± 46.2	128.8 ± 56.9	0.12
Glucose, mg/dL[b]	86.0 ± 6.0	89.9 ± 9.5	94.5 ± 18.5	0.01[c]	98.8 ± 6.6	104.0 ± 14.1	105.5 ± 16.7	0.07[c]
Insulin, mU/dL[b]	–	–	–	–	12.2 ± 4.1	12.6 ± 5.1	14.0 ± 5.6	0.17
Medication use								
Current use of lipid-lowering medication[d]	2.7 (0.0-7.9)	2.0 (0.0-6.4)	10.8 (3.2-18.3)	0.02	27.0 (12.7-41.3)	37.0 (23.0-50.9)	63.1 (51.3-74.8)	0.001
Current use of antihypertensive medication[d]	5.4 (0.0-12.7)	6.5 (0.0-13.7)	15.4 (6.6-24.2)	0.01	40.5 (24.7-56.4)	39.1 (25.0-53.2)	60.0 (48.1-71.9)	0.05
Current use of antidiabetes medication[d]	–	–	–	–	0.0 (0.0-0.0)	4.4 (0.0-10.2)	10.8 (3.2-18.3)	0.09
PA								
Self-reported PA, kcal/wk[e]	1,772.2 ± 206.1	2,000.0 ± 307.9	1,787.0 ± 374.0	0.72	–	–	–	–
Self-reported PA, MET h/wk[e]	–	–	–	–	24.0 ± 4.4	17.2 ± 4.3	15.4 ± 4.0	0.07[c]
Accelerometer-derived estimates								
Wear time, min/d[b]	–	–	–	–	1,031.8 ± 95.1	1,035.9 ± 112.2	1,052.7 ± 126.5	0.61
Total count, ct/d[e]	–	–	–	–	195,958.6 ± 5,442.4	171,724.8 ± 5,282.6	161,122.8 ± 10,586.1	0.08[c]
Sedentary, min/d[b]	–	–	–	–	719.6 ± 88.0	736.7 ± 100.9	776.3 ± 121.4	0.09
Light-intensity PA, min/d[e]	–	–	–	–	233.5 ± 2.7	228.5 ± 2.6	223.6 ± 3.3	0.64
Moderate- to vigorous-intensity PA, min/d[e]	–	–	–	–	73.7 ± 3.0	64.6 ± 3.6	53.5 ± 6.1	0.01[c]
Moderate- to vigorous-intensity PA bouts, min/d[e]	–	–	–	–	23.4 ± 4.7	14.5 ± 5.9	9.9 ± 7.3	0.006[c]

No detectable CAC indicates a CAC score of 0 on EBT1 and EBT4. Incident CAC indicates a CAC score of 0 on EBT1 and higher than 0 on EBT4. Prevalent CAC indicates a CAC score higher than 0 on EBT1 and EBT4.

PA, physical activity; EBT, electron beam tomography; CAC, coronary artery calcification; MET, metabolic equivalent.

[a]Analysis of variance was used to test for differences in cardiovascular disease risk factors and accelerometer-derived PA levels between CAC categories for normally distributed variables. χ^2 test or Freeman-Halton test was used to determine differences in medication use between CAC categories.

[b]Mean ± SD.

[c]Dunnett's post hoc tests were used to examine differences in accelerometer-derived PA levels between the no-detectable CAC group (referent) and the incident and prevalent CAC groups; the no-detectible CAC group was significantly different from the prevalent CAC group ($P \leq 0.05$).

[d]Percent (95% CI).

[e]Square-root transformation was applied. Data are backtransformed and presented as mean ± SD.

significant. Time spent in light-intensity PA was not significantly related to any CVD risk factor.

Thirty-seven (25%) participants were classified into the no-detectable CAC group, 46 (31.1%) were classified into the incident CAC group, and the remaining 65 (43.9%) were classified into the prevalent CAC group. CVD risk factors and medication use on the EBT1 and EBT4 visits are shown in Table 4, stratified by CAC group. On EBT1, BMI, waist circumference, and glucose were significantly higher in the prevalent CAC group when compared with the no-detectable CAC group. The proportion of the use of lipid-lowering and antihypertensive medications also significantly varied by CAC group. On EBT4, BMI and glucose were significantly higher in the prevalent CAC group when compared with the no-detectable CAC group. Total cholesterol, LDL-c, and HDL-c levels were significantly lower in the prevalent CAC group when compared with the no-detectable CAC group. The lower total cholesterol and LDL-c found in the prevalent CAC group are probably caused by the increased proportion of current use of lipid-lowering therapy shown in this group (63.1% vs 27.0% and 37.0% in the no-detectable and incident CAC groups, respectively; $P = 0.001$). Given this, the lower HDL-c levels in the prevalent CAC group are worth noting. Use of antihypertensive or antidiabetes medications did not significantly vary by CAC group. There were no significant differences in self-reported PA levels at baseline, 1 year, 5 years, and 8 years postmenopause by CAC group (data not shown). Furthermore, PA levels on EBT1 were not significantly different between groups; however, self-reported PA on EBT4 was significantly higher in the no-detectible CAC group than in the prevalent CAC group. Total accelerometer counts and time spent in MVPA, including sustained bouts of MVPA, were significantly lower in the prevalent CAC group when compared with the no-detectable CAC group. PA levels were not significantly different between the incident CAC group and the no-detectable CAC group.

The multivariate adjusted PA levels by CAC group are shown in Table 5. There were no statistically significant differences in self-reported PA estimates, collected at any time point, between CAC groups. The difference in accumulated times spent in MVPA was significantly lower in the prevalent CAC group than in the no-detectable CAC group ($P < 0.05$). Furthermore, time in sustained bouts of MVPA was significantly lower in the prevalent CAC group than in the no-detectable CAC group ($P < 0.04$).

DISCUSSION

The current investigation adds to the limited number of studies that have examined the relationship between PA and CAC. This study adds to previous work through serial CAC measures that characterize CAC progression (ie, no detectible CAC, incident CAC, and prevalent CAC). Results of our study showed that accelerometer-derived estimates of time spent in MVPA were lowest among women in the prevalent CAC group and highest among women in the no-detectable CAC group. These results support the theory that healthier individuals tend to participate in higher-intensity PA. Interestingly, in the current study, light-intensity PA was not significantly associated with any CVD risk factors. Furthermore, time spent being sedentary or in light-intensity PA was not significantly different among the CAC groups. Together, these findings suggest that the ability to perform lower-intensity activities may not be limited by underlying diseases.

One mechanism proposed to support the protective role of PA in atherosclerosis is the modification of related risk factors.[3,4] The atherosclerotic process is initiated when the

TABLE 5. *Adjusted mean ± SE of accelerometer-derived PA levels collected on the EBT4 visit by CAC group in the Healthy Women Study (n = 148)*

PA	No detectable CAC (n = 37)	Incident CAC (n = 46)	Prevalent CAC (n = 65)	*P*	
				No detectable CAC vs incident CAC	No detectable CAC vs prevalent CAC
Self-reported estimates					
Baseline, kcal/wk[a]	1,226.8 ± 2.0	1,215.8 ± 5.8	1,350.5 ± 5.2	0.71	0.35
1-y postmenopausal visit, kcal/wk[a]	1,430.6 ± 1.9	1,562.8 ± 5.8	1,546.1 ± 5.1	0.53	0.62
5-y postmenopausal visit, kcal/wk[a]	1,665.8 ± 1.7	1,668.2 ± 5.0	1,635.0 ± 4.5	0.84	0.58
EBT1, kcal/wk[a]	1,859.3 ± 3.7	2,013.0 ± 10.0	1,872.2 ± 9.3	0.52	0.87
EBT4, MET h/wk[a]	18.3 ± 0.04	16.3 ± 0.10	16.9 ± 0.09	0.48	0.73
Accelerometer-derived estimates					
Total count, ct/d[a]	179,623.4 ± 86.4	160,961.4 ± 240.1	157,101.3 ± 216.4	0.29	0.11
Sedentary, min/d	737.3 ± 11.9	757.0 ± 19.8	767.9 ± 18.8	0.55	0.14
Light-intensity PA, min/d[a]	231.4 ± 0.03	224.7 ± 0.10	219.8 ± 0.09	0.71	0.22
Moderate- to vigorous-intensity PA, min/d[a]	65.1 ± 0.05	57.4 ± 0.14	53.2 ± 0.13	0.45	0.046
Moderate- to vigorous-intensity PA bouts, min/d[a]	16.5 ± 0.07	10.4 ± 0.19	9.2 ± 0.17	0.17	0.035

Generalized linear mixed models were used to compare PA levels between the no-detectable CAC group (referent group) and the incident and prevalent CAC groups after adjustment for age (years) and body mass index (kg/m^2) at relevant visit and reported use of lipid-lowering or antihypertensive medications on EBT1 and EBT4.

No detectable CAC indicates a CAC score of 0 on EBT1 and EBT4. Incident CAC indicates a CAC score of 0 on EBT1 and higher than 0 on EBT4. Prevalent CAC indicates a CAC score higher than 0 on EBT1 and EBT4.

PA, physical activity; EBT, electron beam tomography; CAC, coronary artery calcification; MET, metabolic equivalent; ct/d, counts per day.

[a]Square-root transformation was applied. Data are backtransformed and presented as adjusted mean ± standard error.

intimal layer of arteries is damaged.[40] This damage is brought on by several factors, including elevated cholesterol and triglyceride levels and resultant abnormal lipoprotein concentrations, hypertension, and cigarette smoking. PA helps prevent or manage elevated triglyceride levels and hypertension and, with concomitant weight loss, improves LDL-c concentrations.[3] However, the magnitude of this effect is influenced by individual-level differences and characteristics of PA (ie, activity type, intensity, frequency, and duration).[3] Over time, lipid accumulation and connective tissue matrix production by smooth cells increase the volume of one or more key atherosclerotic plaques, which can become calcified with time. These plaques can encroach on the lumen and disrupt blood flow. If the plaque becomes unstable and ruptures, the resultant thrombus can occlude the lumen of the same or distal vessels.[40] Given the dramatic differences in medication use between CAC groups, it is difficult to discern whether the observed association between higher-intensity PA and CAC was mediated through improvements in cardiovascular risk factors. However, significant associations were found between accelerometer estimates of higher-intensity PA and obesity, HDL-c, triglycerides, glucose, and insulin, lending support to this proposed mechanism.

In a 2008 case-control study by Möhlenkamp et al,[41] 108 male marathon runners aged 50 to 72 years were matched to controls, by age and Framingham Risk Score (FRS), selected from the Heinz Nixdorf Recall Study.[42] Although marathon runners (cases) had significantly higher PA levels when compared with both control groups, correlations with CAC were not statistically significant among marathon runners or age-matched controls. Furthermore, CAC distributions (CAC score ≥100) between marathon runners and age-matched controls were similar (36.1% vs 36.6%, respectively). However, the proportion of CAC scores 100 or higher was significantly higher in marathon runners when compared with FRS-matched controls (36.1% vs 21.8%, respectively). The authors suggested that the divergence between FRS and extent of CAC among cases might reflect the initiation of marathon training during middle age, which is not necessarily indicative of lifelong PA levels. Also, although PA results in positive CVD risk factor changes, it may not result in the regression of atherosclerotic plaque once present. Therefore, PA might confer benefit by slowing or controlling the atherosclerotic process, rather than by reversing the process. Unfortunately, clarifying the specific mechanisms by which PA prevents or modifies coronary atherosclerosis is challenging, given that change values from serial measures of the extent of calcification are often not clinically meaningful. Additional work related to estimating changes in the atherosclerotic process using CAC scores is needed.

Of the limited previous investigations examining the association between PA and CAC, only two have reported a statistically significant association between PA and CAC,[43,44] whereas the remaining investigations found no significant relationship.[4,19-23,41] These previous studies of PA and CAC as surrogate markers for atherosclerosis are often plagued by three basic problems. First, most studies used self-report methods to ascertain PA exposure. However, self-reported estimates can be influenced by recall issues or incomplete assessment of PA across multiple domains and intensity levels.[45,46] Second, the development of atherosclerosis and/or calcification reflects a long incubation period.[40] Therefore, measurement of current PA versus current CAC does not take into account the evolution of the atherosclerotic process and assumes that PA levels are stable over the life course. In the current study, estimates reflecting past PA levels were obtained via self-report methods, which weaken our ability to examine the predictive role of PA in atherosclerotic progression. Third, examining associations between PA and CAC in men and women combined, regardless of whether sex was included as a covariate in the model, may be inappropriate. In the study performed by Hamer et al,[23] the average accelerometer count per minute and the proportion of participants accumulating at least 30 minutes of MVPA per day were significantly higher in men when compared with women. Furthermore, although not reported in the study of Hamer et al,[23] CAC scores tend to be much higher in men when compared with women.[25] Sex differences in both PA levels and extent of CAC do not support the presentation of related associations with men and women combined.

Limitations should be considered when interpreting the results of the current investigation. First, the women included in the current investigation were specifically recruited for being in good health (ie, no existing long-term disease at baseline), and most were white. Therefore, HWS participants may not be representative of the general population. Second, CAC measures do not provide information about changes in atherosclerotic plaque that eventually progress to clinical disease.[12] This, coupled with the fact that accelerometer data were collected on the EBT4 visit, limits our ability to establish causality between PA and CAC, including the ways in which PA may modify risk for future cardiac events. It is possible that women with detectable CAC on EBT1 might have reduced their PA by EBT4, which is supported by the PA levels of the incident CAC group. It is also possible that the higher MVPA levels shown in the no-detectable CAC group are indicative of life-long participation in PA, which would make them less vulnerable to calcification of plaques. Measures of inflammation, which some studies suggest could be indicative of a greater atherosclerotic burden or a high-risk atherosclerotic phenotype,[47] were not available on the most recent HWS follow-up visits. Third, because of limited sample size, we were unable to further categorize the incident CAC group to determine whether PA levels differed between those who developed CAC on EBT2, EBT3, or EBT4. This smaller sample size may have also influenced the ability to detect statistically significant associations between self-reported PA and categories of CAC progression. The current study consisted of secondary data analysis to explore a research question not considered in the original design of the HWS. Finally, waist-worn uniaxial accelerometers provide an accurate measure of predominantly ambulatory activities and, therefore, do not capture all activities that may contribute to improved health.[37] Walking is one of the most common activities reported

by older women[48]; therefore, we are confident that the accelerometer detected most PAs among this group of older women.

CONCLUSIONS

The current study adds to previous research by exploring the longitudinal relationship between PA and atherosclerotic progression over 28 years of follow-up in a well-characterized population-based cohort of women. Furthermore, we report both self-reported and device-based estimates of PA in relation to the level of CAC progression. In both unadjusted and adjusted analyses, accelerometer-derived MVPA levels are higher in the no-detectable CAC group than in the prevalent CAC group. These findings suggest that low levels of higher-intensity PA, as measured by an accelerometer, may be indicative of underlying subclinical disease. Additional work, using larger population-based studies with longer follow-up, is needed to clarify whether PA is predictive of atherosclerotic progression or regression.

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