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Walking and calcified atherosclerotic plaque in the coronary arteries: the NHLBI Family Heart Study

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Abstract

Objective—Studies have reported mixed findings on the association between physical activity and subclinical atherosclerosis. We sought to examine whether walking is associated with prevalent coronary artery calcification (CAC) and aortic calcification (AC).

Approach and Results—In a cross-sectional design, we studied 2,971 participants of the NHLBI Family Heart Study without a history of myocardial infarction, coronary artery bypass grafting or percutaneous transluminal angioplasty. A standardized questionnaire was used to ascertain the number of blocks walked daily to compute walking metabolic equivalent hours. CAC was measured by cardiac CT. We defined prevalent CAC and AC using an Agatston score of at least 100 and used generalized estimating equations to calculate adjusted prevalence ratios.

Mean age was 55 years and 60% of participants were women. Compared to the ≤ 3.75 met-hrs/wk group, prevalence ratios for CAC after adjusting for age, sex, race, smoking, alcohol use, total physical activity (excluding walking) and familial clustering were 0.53 95% CI: 0.35–0.79 for >3.75–7.5 met-hrs/wk, 0.72, 95% CI: 0.52–0.99 for >7.5–15 met-hrs/wk, and 0.54, 95% CI: 0.36–0.81 for >15–22.5 met-hrs/wk, (p trend 0.01). The walking-CAC relation remained significant for those with BMI ≥ 25 (p trend 0.02) and persisted with CAC cutoffs of 300, 200, 150, 50, but not 0. When examined as a continuous variable, a J-shaped association between walking and CAC was found. The walking-AC association was not significant.

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Disclosure

None

Conclusion—Our findings suggest that walking is associated with lower prevalent coronary artery calcification (but not aortic calcification) in adults without known heart disease.

Keywords

subclinical atherosclerosis; physical activity; coronary artery calcification; aortic calcification

INTRODUCTION

Atherosclerosis is a major cause of cardiovascular disease (CVD) in the world. Imaging biomarkers of subclinical atherosclerosis, such as coronary artery calcification (CAC) and aortic calcification (AC), are established predictors of coronary heart disease and cardiovascular events.[1] It is well known that physical activity is integral to the primary prevention of cardiovascular diseases. Physical activity is strongly associated with reduction in blood pressure, improvement in lipid profiles, reduction of cardiac ischemia, improvement in endothelial function and decrease in all-cause and CVD mortality.[2–5]

However, studies have reported mixed findings on the association between physical activity and markers of subclinical atherosclerosis. Though many have suggested an inverse relationship between physical activity and CAC,[6,7] others have found no such association.[8,9] Aortic calcification is also an emerging predictor of cardiac morbidity and mortality and thus may be utilized as another imaging biomarker of atherosclerosis.[10,11] However, no prior studies have evaluated the association between physical activity and AC in a cohort of adult men and women.

Few studies have examined walking as the primary exposure of physical activity in relation to CAC.[12] Walking is a basic measure of physical activity that may be more sustainable than forms of vigorous exercise.[13] Moderate walking has been demonstrated to have similar risk reductions in cardiovascular risk factors and possibly CVD as compared to more strenuous activities.[13] Walking is a primary activity that is in line with the American Heart Association's recommendations for physical activity in adults, and endorsed by the American College of Cardiology Foundation.[4] A better understanding of the relationship between physical activity and subclinical atherosclerosis could lead to implementation of targeted public health interventions for the primary prevention of cardiovascular disease. Therefore, we sought to address whether physical activity, as determined by a walking metabolic index, is associated with prevalent CAC and AC in adult men and women from the NHLBI Family Heart Study.

METHODS

Materials and Methods are available in the online-only Data Supplement.

Briefly, we studied 2,971 participants of the NHLBI Family Heart Study without a history of myocardial infarction, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty in a cross-sectional design. A standardized questionnaire was used to ascertain the number of blocks that each participant walked daily to compute the walking metabolic equivalent hours per week. CAC was measured by cardiac computed tomography

(CT) scans. We defined prevalent CAC and AC using an Agatston score of at least 100 and used generalized estimating equations to calculate adjusted prevalence ratios.

RESULTS

Of the 2,971 participants analyzed, 60.3% were women, and the mean age was 55 ±12.7 years. Table 1 presents lifestyle and clinical characteristics of participant across walking activity categories. The median adjusted walking activity level was 9.33 met-hours/week, (IQR 14.93 met-hours/week). The median CAC score was 0.5 (IQR 61.5), and the median AC score was 93, (IQR 1364). CAC was present in 54%, while AC was present in 65% of participants. CAC and AC were moderately correlated (*Spearman's rho: 0.69, p<0.0001*).

Using prevalence ratios, we found evidence of an inverse association between physical activity and CAC. The >15–22.5 met-hrs/wk group had a 46% lower prevalence of CAC as compared to the reference group (≤ 3.75 met-hrs/wk) in the full model after adjusting for age, sex, race, smoking, alcohol use, total exercise metabolic activity index (excluding walking) and familial clustering. The prevalence ratios for CAC with 95% confidence intervals for each walking activity category are shown in Table 2, *p trend = 0.01* in the fully adjusted model (Table 2). The relationship between walking and AC was significant in the crude model (*p trend = 0.01*), but not in the fully adjusted model (*p trend = 0.75*) (Table 3). However, when we examined walking as a continuous variable (walking metabolic activity), a spline model suggested that there may be a J-shaped association between walking and CAC (suppl Figure 1). Test for linearity using the likelihood ratio test yielded a p-value of 0.01.

In a secondary analysis stratified by body mass index (BMI) (<25 and ≥25 kg/m^2), the walking-CAC association remained statistically significant for those with BMI ≥ 25, *p trend* = 0.02 (Table 4). We did not have adequate number of participants with a BMI < 25 for separate analysis (n=721). In sensitivity analysis, we found similar results across various CAC thresholds. This association between walking and CAC persisted when we repeated the main analyses using CAC cutoffs of 300, 200, 150, 50, but not 0 (suppl Table I). The walking-AC relation was not significant across other thresholds (suppl Table I).

DISCUSSION

Our study suggests that walking is associated with prevalent CAC (J-shaped association) but not AC in adult men and women who are free of clinically evident cardiovascular disease. This association persists even for those who are overweight and obese (body mass index ≥ 25 kg/m^2) and even after adjusting for other leisure time physical activities. Our study is one of the few studies that evaluated walking as a primary measure of physical activity in relation to CAC.[12] Also, this is the first study to examine the association between physical activity and prevalent AC in a large cohort of adult men and women.

Our results are complementary to and extend the findings from prior reports. In a group of asymptomatic young adults in the Coronary Artery Risk Development in Young Adults (CARDIA) study, odds ratios of having CAC 15 years later were significantly lower for moderately and highly fit participants.[7] In the Multi-Ethnic Study of Atherosclerosis

(MESA) cohort, an inverse association between physical activity and CAC progression and ankle brachial index was noted.[6] Our findings are also in the same direction as those of trials such as the Lifestyle Heart Trial, in which participants who had exercise training with other lifestyle modifications, had a slower rate of atherosclerosis progression, and the Heidelberg Regression Study.[14–17] These studies demonstrated that even patients who already had known coronary artery disease had decreased rate of atherosclerosis progression after physical activity interventions.

However, other studies have found no association between physical activity and CAC.[8,9,18] In the Whitehall II cohort, physical activity was measured using accelerometers, but no association was seen between physical activity and CAC. However the participants were followed for only about seven days, which may not be long enough to evaluate the association.[18] Also, awareness of being recorded may alter participant activity levels and thus introduce bias. In a cross-sectional study of the MESA cohort, no relation between physical activity and CAC was observed.[19] In that study, moderate and vigorous physical activity were combined into one variable, and intentional exercise was evaluated separately. However, the main exposure in our study was a weekly walking metabolic index (walking activity), which mainly consists of low to moderate physical activity. Also, the MESA study differs from that of our study in that it consisted of individuals from at least four different ethnic groups. Thus, the heterogeneity across studies could be due to study design, study population, assessment of physical activity and unaccounted genetic and environmental factors.

When we examined walking as a continuous variable, a nonparametric model suggested a J-shaped association between walking and CAC. Prior studies have described the association between physical activity and CVD outcomes as curvilinear.[20,21] Although less reduction in CVD events was observed at high levels of moderate to vigorous activity, the protective effect for CVD mortality was still present as compared to those who were sedentary.[21] Another plausible explanation for why we might find a J-shaped association lies in the method of measurement of the outcome (CAC). Although the Agatston method is the standard for scoring coronary calcification, some have suggested that other methods of determining coronary calcification should be considered. The Agatston method is upweighted with greater calcium density of the plaque.[22] However, some studies suggest that greater plaque density may actually be associated with stable disease or even decreased risk of coronary heart disease.[22,23]

Although AC has been found to be an independent predictor of cardiovascular events and correlated with CVD risk factors,[10,11,24,25] studies evaluating the association between physical activity and AC are sparse. One prior study that included 276 obese elderly women with peripheral fat distribution found that high intensity physical activity was associated with increased androgens, low interleukin 6 and less AC.[26] Although we hypothesized that physical activity would be inversely associated with both CAC and AC, the relation between physical activity and AC was not significant in our data except at much higher thresholds. There are some considerations regarding why these results may differ. First, current CT imaging techniques do not allow for quantifying medial and intimal calcification separately. Prior studies have demonstrated that medial calcification, which is associated with

conditions of metabolic imbalance such as diabetes and kidney disease, may be commonly present in the abdominal aorta, but is not found in the coronary arteries.[27,28] We adjusted for diabetes, and even after excluding participants with diabetes (6.7% of our population), the effect estimates were not significantly different. Additionally, investigators from the Framingham Heart Study noted that genetic factors play a prominent role in the presence and extent of AC. They found that 49% of the variation in AC in their study population was due to heritable factors.[29] Although we adjusted for familial clustering in our analysis, it is possible that there are genetic and environmental factors that remain unaccounted for and that separate factors may influence calcification at each site.[29] Also, AC is more prevalent than, and may predate the development of CAC.[30] Given our study design, we could not evaluate a temporal relationship. Lastly, since aortic calcification is more prevalent, it is possible that a higher measurement threshold may be more clinically pertinent.

Physical activity improves blood lipids.[5,31,32] Other potential mechanisms by which physical activity might decrease atherosclerotic disease risk include improvement in blood viscosity, vascular function, platelet activity, blood pressure, triglycerides, and anti-thrombotic effects.[5,32–34] Physical activity has also been found to increase the production of nitric oxide and prostacyclins, which enhances vasodilation, thereby improving endothelial function.[35] It decreases platelet aggregation and adhesion,[36] and enhances fibrinolysis and improves fibrinogen levels.[33] All these effects can slow the progression of atherosclerotic cardiovascular disease.

Our study has limitations. Physical activity was self-reported via standardized questionnaires and interviews, thus the social desirability bias may have impacted reported levels. It has been suggested that combining the duration of walking time with MET levels to produce a met-activity index may not accurately reflect activity level in all situations.[19] For instance, if one walks at a moderate intensity for a long period of time, that may not be equivalent to walking at a more vigorous intensity. Although we adjusted for cardiovascular risk factors based on a priori knowledge, due to the observational nature of the study, unknown confounders may be present and residual confounding cannot be entirely excluded. The cross-sectional design does not allow us to examine changes in physical activity over time. Also, physical activity may be related to other healthy behaviors, and thus may be part of a group of behaviors inversely associated with CAC.

Despite these limitations, our study has several strengths. First, it includes a large sample size, which allows for greater power. Second, our study population included Caucasians and African Americans, men and women, thus increasing generalizability. Third, we incorporated extensive data on lifestyle factors, cardiovascular risk factors and anthropometric measurements into our analysis. Fourth, we used a standardized approach to CAC measurement that has been previously validated.[37] Lastly, our study is one of the few to evaluate walking activity, an essential and sustainable form of physical activity, in relation to CAC and the first to examine the association between walking and aortic calcification in adult and men.

In conclusion, the NHLBI Family Heart Study data show a J-shaped association of walking with coronary artery calcification but not aortic calcification in adult men and women who

are free of cardiovascular disease. This study highlights the need for further studies and trials with a long-term follow-up to more clearly elucidate the association between physical activity and calcified atherosclerotic plaque evolution in the aorta and coronary arteries in individuals without known cardiovascular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CAC	coronary artery calcification
AC	aortic calcification
PA	physical activity
BMI	body mass index
CVD	cardiovascular disease
CARDIA	Coronary Artery Risk Development in Young Adults
MESA	Multi-ethnic Study of Atherosclerosis

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Highlights

- The NHLBI's Family Heart Study data demonstrate that walking is associated with coronary artery calcification (J-shaped association), but not aortic calcification, in adult men and women without known coronary heart disease. This association persists even among those who are overweight or obese.
- This is one of the few studies to evaluate walking activity, an essential and sustainable form of physical activity, in relation to subclinical atherosclerosis and the first to examine the association between walking and aortic calcification in adult and men.
- This study highlights the importance of moderate activity as a key component in the primary prevention of cardiovascular disease.
- Further studies with a long-term follow-up are needed to more clearly elucidate the association between physical activity and calcified atherosclerotic plaque evolution in the aorta and coronary arteries over time.

Table 1

Participant characteristics in categories of walking metabolic activity (n=2,971)

Variable	≤ 3.75 met-hr/wk (n=829)	>3.75–7.5 met-hrs/wk (n=423)	>7.5–15 met-hrs/wk (n=873)	>15–22.5 met-hrs/wk (n=450)	>22.5 met-hrs/wk (n=392)
Age, years	56.8±12.8	55.2±13.5	54.2±12.5	53.6±12.5	54.2±11.8
Women (n, %)	550 (66.3%)	257 (60.8%)	492 (56.4%)	243 (54.0%)	243 (62.0%)
Race (n, %)					
White	576 (69.7%)	362 (86.0%)	725 (83.9%)	390 (86.9%)	340 (87.2%)
Black	250 (30.3%)	59 (14.0%)	139 (16.1%)	59 (13.1%)	50 (12.8%)
Marital status					
Never married	77 (9.3%)	28 (6.6%)	47 (5.4%)	29 (6.4%)	23 (5.9%)
Married	553 (66.7%)	296 (70.0%)	671 (76.9%)	361 (80.2%)	308 (78.6%)
Separated/divorced/widowed	199 (24.0%)	99 (23.4%)	155 (17.8%)	60 (13.3%)	61 (15.6%)
Total family Income					
<$25,000	226 (27.8%)	85 (20.6%)	126 (14.8%)	54 (12.3%)	47 (12.2%)
≥$25,000 – <$75,000	409 (50.4%)	215 (52.1%)	456 (53.5%)	233 (53.2%)	204 (53.0%)
≥$75,000	177 (21.8%)	113 (27.4%)	271 (31.8%)	151 (34.5%)	134 (34.8%)
BMI, kg/m^2	31.2±7.0	29.6±6.1	28.9±5.8	28.7±5.8	27.9±5.5
Hypertension (n, %)	473 (57.1%)	170 (40.2%)	334 (38.2%)	150 (33.3%)	129 (32.9%)
SBP (mmHg)	126.6±23.5	122.4±19.0	120.9±20.7	119.0±17.8	118.9±19.8
DBP (mmHg)	72.1±11.0	70.7±10.1	70.9±10.1	71.0±10.1	70.1±10.9
Diabetes Mellitus (n, %)	138 (16.7%)	38 (9.0%)	97 (11.1%)	35 (7.8%)	35 (8.9%)
Current Smokers (n, %)	111 (13.4%)	49 (11.6%)	110 (12.6%)	46 (10.2%)	46 (11.7%)
Pack years smoked	9.1±19.6	8.4±18.1	9.0±17.7	9.0±18.2	8.3±15.8
Triglycerides (mg/dL)	141.5±90.9	142.8±94.4	133.4±83.9	132.9±88.4	124.8±94.2

Variable	≤ 3.75 met-hr/wk (n=829)	>3.75–7.5 met-hrs/wk (n=423)	>7.5–15 met-hrs/wk (n=873)	>15–22.5 met-hrs/wk (n=450)	>22.5 met-hrs/wk (n=392)
LDL Cholesterol (mg/dL)	112.6±33.8	114.7±34.1	114.0±35.2	116.0±32.6	111.9±32.0
Average hours of TV/computer per day	3.3±2.5	2.7±2.0	2.6±1.7	2.4±1.7	2.2±1.4
Alcoholic drinks per week, #	2.6±6.6	3.7±7.7	3.8±6.8	4.0±8.3	5.3±13.2

BMI = body mass index, LDL = low density lipoprotein

Characteristics are shown as follows: mean ± standard deviation for continuous variables and frequencies (percentages) for categorical variables.

Table 2

Prevalence ratios and 95% confidence intervals of CAC based on walking metabolic activity in 2,971 participants from the NHLBI Family Heart Study

	Cases/n	*Crude	Age and sex adjusted	Full model
≤ 3.75 met-hrs/wk	206/829	1.0	1.0	1.0
>3.75–7.5 met-hrs/wk	82/423	0.73 (0.55–0.97)	0.70 (0.50–0.98)	0.53 (0.35–0.79)
>7.5–15 met-hrs/wk	176/873	0.76 (0.60–0.97)	0.81 (0.62–1.06)	0.72 (0.52–0.99)
>15–22.5 met-hrs/wk	83/450	0.68 (0.52–0.91)	0.72 (0.51–1.01)	0.54 (0.36–0.81)
>22.5 met-hrs/wk	79/392	0.76 (0.57–1.02)	0.92 (0.64–1.31)	0.76 (0.50–1.15)
p for trend		0.02	0.32	0.01

*The crude model adjusted for familial clustering. The second model adjusted for age, sex and familial clustering. The full model adjusted for age, sex, race, smoking, alcohol use, total exercise metabolic activity index (excluding walking), and familial clustering.

CAC = coronary artery calcification, defined as CAC>100

Table 3

Prevalence ratios and 95% confidence intervals of AC based on walking metabolic activity in 2,976 participants from the NHLBI Family Heart Study

	Cases/n	*Crude	Age and sex adjusted	Full model
≤ 3.75 met-hrs/wk	443/830	1.0	1.0	1.0
>3.75–7.5 met-hrs/wk	215/424	0.91 (0.72, 1.14)	1.04 (0.76, 1.45)	1.11 (0.75–1.64)
>7.5–15 met-hrs/wk	415/876	0.79 (0.64, 0.96)	0.92 (0.72, 1.19)	0.89 (0.66–1.20)
>15–22.5 met-hrs/wk	216/450	0.81 (0.63, 1.03)	1.02 (0.74, 1.40)	1.11 (0.75–1.64)
>22.5 met-hrs/wk	183/392	0.77 (0.60, 0.98)	0.92 (0.67, 1.27)	0.97 (0.66–1.44)
P trend		0.01	0.63	0.75

*The crude model adjusted for familial clustering. The second model adjusted for age, sex and familial clustering. The full model adjusted for age, sex, race, smoking, alcohol use, total exercise metabolic activity (excluding walking), and familial clustering.

AC = aortic calcification, defined as AC>100

Table 4

Subgroup analysis by BMI ≥ 25 kg/m^2 across categories of walking activity for CAC in 2,251 participants

	Cases/n	*Crude	Age and sex adjusted	Full model
≤ 3.75 met-hrs/wk	171/688	1	1	1
>3.75–7.5 met-hrs/wk	66/329	0.76 (0.56–1.04)	0.72 (0.49–1.04)	0.52 (0.34–0.82)
>7.5–15 met-hrs/wk	130/643	0.77 (0.59–1.00)	0.76 (0.56–1.03)	0.64 (0.45–0.92)
>15–22.5 met-hrs/wk	61/326	0.70 (0.51–0.96)	0.68 (0.46–1.01)	0.53 (0.34–0.82)
>22.5 met-hrs/wk	57/260	0.85 (0.60–1.20)	0.95 (0.63–1.45)	0.73 (0.45–1.19)
P trend		0.09	0.30	0.02

*The crude model adjusted for familial clustering. The second model adjusted for age, sex and familial clustering. The full model adjusted for age, sex, race, smoking, alcohol use, total exercise metabolic activity (excluding walking), and familial clustering.