Title

25-Year Physical Activity Trajectories and Development of Subclinical Coronary Artery Disease as Measured by Coronary Artery Calcium: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Journal

Mayo Clinic Proceedings, 92(11)

ISSN

0025-6196

Authors

Laddu, Deepika R
Rana, Jamal S
Murillo, Rosenda
et al.

Publication Date

2017-11-01

DOI

10.1016/j.mayocp.2017.07.016

Peer reviewed

HHS Public Access

Author manuscript

Mayo Clin Proc. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Mayo Clin Proc. 2017 November ; 92(11): 1660–1670. doi:10.1016/j.mayocp.2017.07.016.

25-year Physical Activity Trajectories and Development of Subclinical Coronary Artery Disease as Measured by Coronary Artery Calcium: The CARDIA Study

Deepika R. Laddu, PhD[a,*], **Jamal S. Rana, MD, PhD**[b,c,d], **Rosenda Murillo, PhD**[e], **Michael E. Sorel, MS**[b], **Charles P. Quesenberry Jr, PhD**[b], **Norrina B. Allen, PhD**[f], **Kelley P. Gabriel, PhD**[g], **Mercedes R. Carnethon, PhD**[f], **Kiang Liu, PhD**[f], **Jared P. Reis, PhD**[h], **Donald Lloyd-Jones, MD, ScM**[f], **J. Jeffrey Carr, MD**[i], and **Stephen Sidney, MD, MPH**[b]

[a]Department of Physical Therapy, University of Illinois at Chicago, Chicago, IL

[b]Division of Research, Kaiser Permanente Northern California, Oakland, CA

[c]Department of Medicine, University of California, San Francisco, San Francisco, CA

[d]Division of Cardiology, Kaiser Permanente Northern California, Oakland, CA

[e]Department of Psychological, Health, and Learning Sciences, University of Houston, Houston, TX

[f]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

[g]Department of Epidemiology, Human Genetics and Environmental Sciences. University of Texas Health Science Center at Houston, School of Public Health – Austin Campus, Austin, TX

[h]Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD

[i]Departments of Radiology and Biomedical Informatics, Vanderbilt University School of Medicine, Nashville, TN

Abstract

OBJECTIVE—To evaluate 25-year physical activity (PA) trajectories from young to middle-age and assess associations with the prevalence of coronary arterial calcification (CAC).

PATIENTS and METHODS—3,175 participants in CARDIA study self-reported PA by questionnaire at 8 follow up exams over 25 years (March 1985- June 1986 to June 2010-May

For Reprints and Correspondence: Jamal S. Rana MD, PhD, 3600 Broadway, Division of Cardiology, Kaiser Permanente Oakland Medical Center, Oakland, CA 94611, Telephone: 510-752-1276, Fax 510-752-7456, jamal.s.rana@kp.org.

*JSR and DRL contributed equally to the paper.

Conflicts of Interest and Financial Disclosures: There are no conflicts of interest, relationships with industry to report, or relationships relevant to the contents of this paper to disclose by any of the authors.

2011). The presence of CAC (CAC>0) at year 25 was measured using computed tomography. Group-based trajectory modeling was used to identify PA trajectories with increasing age.

RESULTS—We identified 3 distinct PA trajectories: Trajectory 1: Below PA guidelines (n= 1813; 57.1%); Trajectory 2: Meeting PA guidelines (n= 1094; 34.5%); and, Trajectory 3: Three times PA guidelines (n= 268; 8.4%). Trajectory 3 participants had higher adjusted odds of CAC>0 (AOR 1.27; 95% CI: 0.95, 1.70) versus those in Trajectory 1. Stratification by race showed that whites engaged in PA three times the guidelines had higher odds of developing CAC>0 with OR 1.80 (95% CI: 1.21, 2.67). Further stratification by gender showed higher odds for white males (OR 1.86; 95% CI: 1.16, 2.98), while similar, but non- significant trends were noted for white females (OR 1.71; 95% CI: 0.79, 3.71). However, no such higher odds of CAC>0 for Trajectory 3 were observed for black participants.

CONCLUSIONS—White individuals who participated in three times the recommended PA guidelines, over 25-years, had higher odds of developing coronary subclinical atherosclerosis by middle-age. These findings warrant further exploration, especially by race, into possible biological mechanisms for CAC risk at very high levels of PA.

Keywords

Coronary Calcification; physical activity; trajectories

INTRODUCTION

Coronary artery calcification (CAC) has emerged as a strong predictor of incident coronary heart disease and provides predictive information beyond standard risk factors [1], allowing for substantially improved risk stratification for future cardiovascular disease (CVD) events. (2) Physical activity (PA) has shown to be associated with a reduction in CVD morbidity and mortality.[2,3] Given the importance of primary prevention of coronary heart disease, there remains a need to better understand risk factors and lifestyle behaviors that can have an impact from an earlier age.

National guidelines, including the 2008 Physical Activity Guidelines for Americans, advocate the benefits of PA, specifically prolonged bouts of moderate to-vigorous intensity PA or exercise.[4] There is agreement from large epidemiological studies suggesting there are relative cardiovascular (CV) benefits and reduced risk of CVD incidence and CV mortality of a physically active lifestyle in study populations of mid- to late-life men and women.[2,5,6] However, in healthy individuals, the “optimum” dose of PA necessary to derive the upper threshold of CV benefit, and potential harms associated with very high levels of activity remains undefined[4] and equally controversial.[5,6] Recent studies of frequency and dose of PA have shown a U-shaped association with vascular disease risk and mortality [6–8], suggesting an attenuation of health benefits at higher PA doses above the recommended PA levels (150 minutes moderate-to-vigorous intensity PA per week). [2,5]

There is paucity of data regarding the association of PA and development of subclinical atherosclerosis. Cross-sectional data have shown that asymptomatic patients with two or more metabolic risk factors and who regularly engage in PA (≥30 min, 1 to 2 times/week)

have a lower prevalence of CAC than do those who are sedentary.[9] On the other hand, no association between PA and presence of CAC has been observed among middle-aged adults.[10–12]. Likewise, evidence in older postmenopausal women showed that higher levels of PA were associated with no detectable CAC [13] or lower CAC. [14] In the Coronary Artery Risk Development in Young Adults Study (CARDIA) population, high levels of cardiorespiratory fitness, evaluated at baseline, were associated with a lower risk of having CAC 15 years later.[15] However, a common limitation among these studies is that the evaluation of PA or fitness was limited to a single baseline assessment. PA can vary greatly over the life-course; [15] therefore, longitudinal data are needed to describe age-related changes in PA and how they may relate to CAC.

In the current study, we examined the effects of long-term PA patterns and their association with subclinical atherosclerosis during a 25-year transition from young-adulthood to middle-age in the CARDIA study. We hypothesized that higher PA levels from young adulthood to midlife will be associated with lower year- 25 CAC prevalence.

METHODS

Study population

The CARDIA study is a multicenter, community-based, longitudinal cohort study designed to investigate the development of coronary heart disease risk factors in young adults. The baseline cohort consisted of 5115 African-American and White men and women, aged 18–30 years (baseline), who were recruited between March 1985–June 1986 from 4 cities in the United States (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California) with population-based samples approximately balanced within center by sex, age (18–24 years and 25–30 years), race (white or black), and education (≤high school graduate or >high school graduate). Participant data have been collected across 8 examination cycles including baseline and at years 2, 5, 7, 10, 15, 20, and 25 with retention of the cohort of 91%, 86%, 81%, 79%, 74%, 72%, and 72% respectively. Details about the study design, sampling strategy, eligibility criteria and baseline demographic characteristics have been previously published.[16]

For this analysis, we excluded 1616 (32%) participants who did not have CAC assessment at the Year 25 exam (June 2010–May 2011), and further, if they did not have at least 3 measures of PA during the 25 years of follow up (exams 1–8) (n= 324). The remaining 3,175 participants were included in the analytic sample, representing 62.1% of the initial CARDIA cohort at baseline. The study was approved by the institutional review board at each center and written informed consent was obtained from all participants.

Physical Activity Measurement

At each of the 8 examinations, self-reported leisure-time PA was ascertained by the interviewer-administered CARDIA Physical Activity History questionnaire.[17] Participants were asked about the frequency of participation in 13 specific categories (8 vigorous-intensity; 5 moderate-intensity) of recreational sports, exercise, home maintenance, and occupational activities during the previous 12 months. Intensity for each activity was

expressed as metabolic equivalents (METs), in which one MET is defined as the energy expended at rest, which is approximately equivalent to an oxygen consumption of 3.5 mL per kg of body weight per minute.[18] Vigorous activities (≥6 METs) included running or jogging; racquet sports; biking; swimming; exercise or dance class; job lifting, carrying, or digging; shoveling or lifting during leisure; and strenuous sports. Moderate-intensity activities (3–5 METs) included non-strenuous sports, walking and hiking, golfing and bowling, home exercises or calisthenics, and home maintenance or gardening.[19] Each activity was scored according to whether it was performed for ≥1 hour during any 1 month during the past year, the number of months it was performed at that level, and the number of months the activity was performed frequently. Each activity were then assigned an intensity score, ranging from 3–8 METs, and a duration threshold (ranging from 2–5 hours/week), above which participation was considered to be frequent.[20]

A total PA score was computed using a computer-based algorithm, by multiplying the frequency (number of months) by the intensity score of the activity with a weighting factor to represent duration of participation.[20] The total activity score was the sum of scores for all activities expressed in exercise units (EU), and a threshold of 300 EU was used as the criterion to create distinct PA trajectory groups. For reference, a total activity score of 300 EU approximates Health and Human Services recommendations of approximately 150 minutes of moderate intensity activity per week. [21] Previously in CARDIA, the 300 EU threshold has shown to provide a more conservative estimate of meeting PA guidelines (sensitivity and specificity of 64.5% and 97.1%, respectively). [22,23] The CARDIA PA questionnaire shows test-retest reliability in the range of 0.77 to 0.84 [20] which is comparable to that of other activity questionnaires.[17]

Computed Tomography

Subclinical coronary atherosclerosis was assessed as presence of any CAC at year 25 (2010–2011) using computed tomography (CT) of the chest. At all centers, calcified coronary artery plaque measurement was done with an electrocardiographically gated multi-detector computed tomography (CT) scanner, using a standardized protocol [24] with published accuracy and reproducibility.[25] Images were transmitted electronically to the CARDIA Reading Center, and image analysts blinded to participant characteristics calculated a total CAC score using a modified Agatston method,[26] with select over-reading by a physician expert in cardiovascular imaging. Briefly, total calcium scores were obtained by summing all lesions within a given artery and across all arteries (left main, left anterior descending, left circumflex, and right coronary artery). Similar to a prior CARDIA analysis, the outcome of this study was the presence of CAC defined as a total calcification score > 0 Agatston units measured at year 25. [27] A minimal CAC score >0 has been identified as a significant predictor of incident CHD [28] and marker of mortality risk in young and middle-aged adults. [29] Additionally, CAC>20 and CAC>100 were examined in sensitivity analyses.[27,30]

Other Measurements

Standardized protocols for data collection were used across study centers and examinations. Before each examination, participants were asked to fast for at least 12 hours and avoid smoking or engaging in heavy PA for at least 2 hours. At each examination, height, weight,

and waist circumference were measured as described previously (15). Blood pressure was measured at every exam as described previously.[27] Plasma concentrations of total cholesterol, and triglycerides were measured at all examinations using enzymatic methods.[16] high density lipoprotein cholesterol (HDL-C) was measured after dextran-magnesium precipitation,[31] and serum low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation.[32] Hyperlipidemia was defined as a total cholesterol level of ≥240mg/dl.[33] Glucose was collected fasting according to standardized CARDIA procedures and diabetes mellitus was defined as self-reported physician diagnosis of diabetes, a fasting glucose level ≥126 mg/dL or use of hypoglycemic agents.[31,32]

Information regarding age, race/ethnicity, cigarette use, medications, and medical history was reported through questionnaire. The use of antihypertensive and lipid-lowering medications was assessed by self-report at each examination.

Statistical analyses

Group-based trajectory class modeling was used to identify and categorize CARDIA participants based on patterns of longitudinal change in PA during the 25 years of follow-up. (27, 28) These models were fit using SAS Proc Traj. [34] Group-based trajectory analysis, an application of finite mixture modeling, is designed to identify clusters of individuals with similar patterns of change over time. Relative to standard growth trajectory analyses focusing on population mean trajectories (with individual level random effects for time-associated regression coefficients), this approach allowed us to identify groups of individuals who experience similar levels and patterns of change from young adulthood to midlife. Model fit was assessed using the Bayesian Information Criterion (BIC). In our final model, we had 3 classes with cubic order terms, from which we calculated the posterior predicted class membership probability for each individual. As in other studies, mean posterior probabilities were calculated to account for uncertainty in the PA trajectory group assignment and to ensure internal reliability of the model. In all models, participants were assigned to the trajectory group for which they had the greatest posterior predictive probability (i.e., has a high probability of belonging to the assigned trajectory group, and a low probability of belonging to another group) over the 25-year follow up. Trajectory groups were qualitatively examined and named to describe the visual pattern of change. Similar group-based trajectory methodology in CARDIA has been previously described. [27]

Distributions of covariates at baseline and at Year 25 were described for each PA trajectory group using means, medians, and proportions as appropriate. Differences and trends were tested using linear regression models and χ^2 analyses for continuous and categorical characteristics, respectively.

Multivariable logistic regression models were used to estimate the association of each 25-year PA trajectory class with Year 25 CAC>0. Regression analyses were sequentially adjusted for age (Model 1), with further adjustment for race and gender and additionally for covariates reported at the year 25 follow-up (Y25) examination): education, and CVD risk factors and behaviors (e.g., smoking status, diabetes, hyperlipidemia, BMI and hypertension status (Model 2). Potential effect modification by gender and race was explored by testing

the statistical significance of appropriate cross-product terms and by comparing risk estimates in the gender × race -stratified analyses.

Two sensitivity analyses were performed, using alternative thresholds to define prevalence-CAC. First, we defined the prevalence of CAC as >20 Agatston units. Second, prevalence CAC was defined as CAC>100 Agatston units. Multivariable logistic regression models were used to estimate the association of each 25-year PA trajectory class with CAC>20 and CAC>100, respectively.

Tests of statistical significance were 2-tailed, with an α level of .05. SAS version 9.3 (SAS Institute Inc.) was used to perform all statistical analyses.

RESULTS

3175 men and women who participated in CARDIA from 1985–2011 who had CAC data available at year 25 were included in the analyses. Of the 3,175 eligible participants, 47.4% were black and 56.6% were women (Table 1).

Three distinct PA trajectories were identified, (Figure 1) and the mean posterior probability for individuals in each group, presented as the mean ± SD; Trajectory 1: Below PA guidelines (N=1813; 57.1%; 0.95 ± 0.11); Trajectory 2: Meeting PA guidelines (N=1094; 34.5%; 0.91 ± 0.13); and, Trajectory 3: Three times PA guidelines (n=268; 8.4%; 0.93 ± 0.12). In general, all three PA trajectories showed a general age-related decline from young adulthood to midlife (Fig. 1). PA levels declined more during early adulthood than during midlife. A consistent rate of decline in PA levels was observed among participants engaged in three times the PA guidelines (Trajectory 3), whereas PA engagement plateaued with increasing age in Trajectories 1 and 2.

Baseline characteristics (mean ± SD) of the CARDIA subsample (n = 3175) across the three PA trajectory groups are presented in Table 1. In the total analytic sample, the mean age of participants was 25.4 yrs. (± 0.5yrs), and the cohort consisted of 18.9% black men, 24.6% white men, 28.6% black women, and 28% white women. At baseline, individuals in Trajectory Class 3 (i.e., three times PA Guidelines) were more likely to be male ($P<.001$), whereas individuals in Trajectory 1, which was below PA guidelines, were more likely to be women (69.3%) and black (54.9%) (*all* $P<.001$). CV risk factors also differed across the three PA groups at baseline and at Year 25. Whereas there was no difference at baseline, at Year 25, hypertension ($P<.001$) and, type 2 diabetes ($P=.001$), were the highest among participants who engaged below the PA guidelines. Current smoking status, though lower among participants who engaged in three times the PA guidelines at Year 25, did not significant differ across the three PA groups. Although, HDL-cholesterol levels did not significantly differ across overall PA groups at baseline or year 25 (both $P<.05$), further analyses revealed white males consistently had the lowest HDL levels across nearly all three PA groups, and compared to black males and black and white females (data not shown). Finally, at Year 25, the prevalence of CAC>0 (41.8%; $P<.001$) and, similarly, CAC>20 (25.0%; $P<.001$) was highest among participants who engaged in three times the PA guidelines.

The adjusted OR for presence of CAC>0 according to PA trajectories at the Year 25 follow-up are shown in Table 2, with Trajectory 1 (below PA guidelines) as the reference group. Minimal adjustment for age (Model 1) demonstrated a significantly higher odds of CAC prevalence among participants who were meeting PA guidelines (OR 1.22; 95% CI: 1.04, 1.43) and engaged in three times the PA guidelines (OR 1.76; 95% CI 1.35, 2.29), compared to participants with activity levels below PA guidelines. In the fully adjusted model (Model 2), findings of a higher odds of CAC>0 were attenuated and no longer significant (AOR=1.00, 95% CI: 0.80, 1.15) for meeting PA guidelines; and, AOR 1.27; 95% CI: 0.95, 1.70 for three times the PA guidelines.

Interactions between PA trajectory class and CAC>0 across race (P=.11) and race-sex categories (P=.48) were tested but were not statistically significant. However, to evaluate the clinical significance of findings reported in table 2, we further assessed potential gender and race differences in the association between PA trajectory group and CAC (Table 2). Fully adjusted models, stratified by race revealed white but not black participants who were exceeding PA guidelines had a significant increased odds of CAC (AOR 1.80 95% CI: 1.21, 2.67); further stratification by gender/race groups (e.g., white men, black men, white women, and black women) showed that white men who exceeded PA guidelines had significantly higher odds of CAC, (AOR 1.86; 95% CI: 1.16, 2.98). However, the AOR estimating the association between the PA trajectory classes and CAC prevalence were not statistically significant for black men, black women, or white women likely due to the low number of participants with detected CAC>0 in these respective groups.

In sensitivity analyses, findings of higher odds of CAC prevalence among white participants exceeding PA guidelines were similar but attenuated in models using the alternative threshold of CAC>20 as the outcome; however, associations between 25-year PA trajectories and presence of CAC>100 were not significant among all CARDIA participants (Supplemental Table 1 and 2). Finally, all analyses were repeated with additional adjustment for year 25 HDL levels; however, the results remained similar to those reported in Table 2.

DISCUSSION

In this prospective, observational study we identified three distinct PA trajectories over 25-years from young adulthood to middle-age: participants who engaged in PA below national guidelines (trajectory 1); who met PA guidelines (trajectory 2); and, who exceeded PA guidelines (trajectory 3). We found 27% higher odds of CAC>0 among participants who exceeded PA guidelines versus those below PA guidelines. Further stratification by gender and race showed that white men who reported PA that exceeded guidelines had greater odds of CAC prevalence by middle-age; similar non-significant trends were noted for white women. Few data are available regarding the association of PA patterns from young adulthood to middle-age on subclinical coronary atherosclerosis.

The present findings align with other large epidemiological studies that focused on the cumulative doses of exercise, and reported a U or reverse J-shaped relationship between high doses of leisure time PA and CV and all-cause mortality.[6–8] Specifically, the Million Women Study showed that women who engaged in any form of exercise at least once a week had a

lower incidence of coronary heart disease (CHD) compared to inactive women, but engagement in PA beyond once a week was associated with smaller benefits up to a certain point beyond which there were no additional risk reduction. [7] Similarly, in the Copenhagen City Heart Study, when compared to light joggers, moderate and strenuous joggers, had significantly higher mortality risk (HR: 3.06 [95% CI: 1.11 to 8.45] and 9.08 [95% CI: 1.87 to 44.01], respectively).[8]

Other studies have reported potentially adverse cardiovascular effects of long-term vigorous, extreme endurance exercise. For instance, some athletes demonstrate exercise induced elevations in cardiac troponin levels,[35] increased incidence of atrial fibrillation,[36] myocardial late gadolinium enhancement, which is predictive of subclinical myocardial damage,[37] and even evidence of myocardial fibrosis [38] and biventricular systolic and diastolic dysfunction. [39,40] Finally, Möhlenkamp et al. showed that compared to age-matched Framingham risk score controls, healthy male marathon runners (50–72yrs) had higher CAC scores; and those with CAC≥100 were also noted to have myocardial late gadolinium enhancement, a predictor of subclinical myocardial damage. [37] It was suggested that that the higher CAC scores in the marathoners can either be explained by higher values of unmeasured risk factors [37]; alternatively, the sheer stress of faster heart rate and systolic blood pressure during exercise training could have accelerated the atherosclerotic process in the runners.[5]

The results from the present study showing relationship between higher doses of PA (i.e., exceeding PA guidelines) and CAC development, suggest yet another possible mechanistic explanation for the existence of an upper limit for cardiovascular benefit. However, we cannot exclude the possibility of a chance finding, given the low prevalence of metabolic risk factors among the highest activity trajectory group. Nonetheless, further evidence examining the cardiac benefits versus risk of prodigious amounts of exercise to the level of “excessive” is warranted. However, it may also be possible that higher PA engagement confers atherosclerotic benefit, by promoting plaque stabilization and preventing its rupture leading to thrombosis. Along these lines, recent studies in healthy middle-age highly-active adults have reported that higher doses of exercise were associated with higher levels of CAC and that the atherosclerotic plaques were in fact likely to be more calcified plaques, suggesting that the stable nature of coronary plaques in highly active individuals may mitigate plaque rupture.[41,42] Additional research investigating whether higher PA levels, including type and duration of PA, are associated with increased plaque calcium density for a given CAC volume, indicative of plaque stability to evaluate CV risk, is needed.[43]

On the contrary, others have challenged the “extreme exercise” hypothesis, viewing evidence as being relatively weak and not clinically important, given the known benefits of exercise on both cardiac and vascular structure and function.[44–49] For example, in a population-based cohort of nearly 75,000 non-elite level Swedish skiers who participated in long-distance skiing race, those who finished more races (and presumably older and trained for more years) had lower mortality.[48] Earlier evidence has suggested that, physiologically, elite ultra-endurance athletes have increased diameter and dilation of the coronaries [45,50] partly due to adaptations of the vascular structure, and possibly an increase in the caliber and/or number of resistance arterioles.[50] So although there can be presence of increased atherosclerosis in

endurance athletes compared with sedentary males with similar risk profile,[51] it may not necessarily translate into adverse clinical outcomes due to presence of enlarged coronary artery size and dilatory capacity.[52,53] Similarly, it is argued that risk of brady-arrhythmias and atrial fibrillation[54] is modest, give the coronaries of endurance athletes presumably have superior vasomotor reserve and reduced risk of plaque rupture leading to thrombosis.[45,49]

We noted differential effect of higher levels of PA on odds of CAC. Our findings demonstrating a greater odds of CAC>0 in white males engaged in three-times PA guidelines, with similar trends observed in white females; however, interactions between race or across race-sex categories in the association between trajectory class and CAC>0 were not statistically significant. We therefore cannot completely explain why the associations between higher PA levels three times above guidelines and higher CAC prevalence was present in white men only. In this regard, another study by Erquo et al (2015) showed that, after adjustment for CVD risk factors, black race was significantly associated with greater carotid intima media thickness (CIMT) but less CAC (CAC>100) than white race. [55] The authors further note that the higher concentration of various inflammatory mediators observed in the black participants, suggests that the increased risk of CVD in Blacks may be related to higher plaque vulnerability of less calcified coronary lesions. [55] Similar to results of Erquo and colleagues, white males in our analyses had the lowest HDL levels across all four race-gender groups. Given that HDL is positively associated with PA and has a plays an essential role in protecting against CVD, it is possible that higher levels of HDL provide more protection against the development of CAC in black men; whereas lower HDL levels may not be sufficient to elicit similar protection against the development of CAC in white men. However, in the present analyses, additional adjustment for HDL revealed no difference in the reported associations between 25-year PA trajectories and CAC prevalence among white and black male and females; thus, additional data are needed to understand the role of HDL in CAC development. Further, the lack of association of trajectory class with CAC among blacks may have been due to small sample sizes, as very few blacks were in the exceeded PA guidelines trajectory group. There are some data that suggests plaque is less calcified in blacks than whites, which may be explained by differences in vitamin D and calcium metabolism, or bone regulatory factors, inflammatory markers, hemostasis, and fibrinolysis. [56] Previously, most studies assessing impact of high levels of PA on cardiac outcomes did not include blacks and further exploration on environmental, biochemical and genetic factors are needed to asses any differences by race.

PA engagement is a continuously evolving process throughout life. However, there are no studies that have examined the changes in PA with subclinical CAC development, a measure of atherosclerosis. Earlier studies that have shown that a high level of leisure time PA has been shown to delay coronary atherosclerosis progression have been restricted to older populations ranging from 52–80 years;[11,12,14] and many have been of cross-sectional design,[9,10,12] and therefore without data about changes in PA patterns, and the interrelationships of aging and time as predictors of PA over the life span, (41) Other prospective studies that have analyzed PA changes over time are limited in their methods to categorize individuals, for example by averaging repeated assessments of PA, or through modeling change in PA relative to some baseline value;[11,12,14]

The strengths and limitations of this study are noteworthy. This study employed innovative trajectory modeling methods which incorporates both the time and sequence of assessments to identify subgroups in the population which share similar trajectories of PA during young adulthood and middle-age. Trajectories of PA levels were obtained based on measures from up to 8 follow-up exams, with a minimum of 3 PA measures, thus reflects long-term PA patterns. However, self-reported questionnaires were used to capture changes in PA, which are subject to participant recall and social desirability bias.[12] Additionally, self-reported PA does not provide information regarding activity intensity, and rather, provides a more conservative estimate of minutes of PA engagement per week. Substantial evidence indicates that cardiorespiratory fitness (CRF) is one of the strongest predictors of atherosclerotic CVDs and mortality.[46] Presumably, higher PA contributes to higher cardio-respiratory fitness (CRF), which may obviate risk associated with higher CAC scores, and provide CV protection.[57]

However, the extent to which these findings are explained by baseline CRF, family history of coronary artery disease (CAD), psychosocial or socioeconomic characteristics or related lifestyle factors, or genetics is yet to be assessed, and may introduce additional confounding to our PA and CAC investigation. Likewise, we acknowledge the potential for misclassification bias regarding the self-reported use of cardio-protective medications, as we are unable to confirm if CARDIA participants were correctly reporting their medication use on questionnaires. Another limitation is that although trajectory modeling accounts for group variations, it does not capture individual variations in PA levels, which may exist within trajectory groups, and thus, may explain the non-significant associations between 25-year PA trajectories and CAC prevalence development particularly among participants meeting PA guidelines (trajectory 2). Further, the trajectory groups identified in this younger population may not be generalizable to other populations. Lastly, Trajectory 3 participants (three times PA guidelines) included relatively few black females, as PA levels were generally lower among this group, and therefore we were underpowered to detect an association within this subgroup.

Conclusions

In summary, our results showed that white individuals who participated in three times the recommended guidelines for physical activity, over 25-years had higher odds of developing coronary subclinical atherosclerosis by middle-age. Collectively, these data suggest that the biological mechanisms associated with increased CAC and high levels of PA deserve further evaluation. Likewise the impact of modestly higher levels of CAC in aging, highly active individuals on cardiovascular outcomes also deserves further attention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge the investigators, staff, and CARDIA study participants and for their valuable contributions.

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the NHLBI; the National Institutes of Health; or the U.S. Department of Health and Human Services.

Sources of Funding: The Coronary Artery Risk Development in Young Adults Study (CARDIA) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201300025C & HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and Johns Hopkins University School of Medicine (HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging (NIA) and an intra-agency agreement between NIA and NHLBI (AG0005), and R01 for the year 25 CAC measures R01 HL 098445.

ABREVIATIONS AND ACRONYMS

CARDIA	The Coronary Artery Risk Development in Young Adults Study
CAC	Coronary artery calcification
CAD	Coronary artery disease
CRF	cardiorespiratory fitness
CT	Computed Tomography
CVD	Cardiovascular Disease
CV	Cardiovascular
PA	physical activity
EU	exercise units
AOR	adjusted odd's ratio

References

1. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008; 358(13):1336–1345. [PubMed: 18367736]
2. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med. 2015; 175(6):959–967. [PubMed: 25844730]
3. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012; 380(9838):219–229. [PubMed: 22818936]
4. Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Report. Department of Health and Human Services; Washington, DC: US: 2008. p. 683
5. Eijsvogels TM, Thompson PD. Exercise Is Medicine: At Any Dose? JAMA. 2015; 314(18):1915–1916. [PubMed: 26547459]
6. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. J Am Coll Cardiol. 2014; 64(5):472–481. [PubMed: 25082581]
7. Armstrong ME, Green J, Reeves GK, Beral V, Cairns BJ. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. Circulation. 2015; 131(8):721–729. [PubMed: 25688148]
8. Schnohr P, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of jogging and long-term mortality: the Copenhagen City Heart Study. J Am Coll Cardiol. 2015; 65(5):411–419. [PubMed: 25660917]

9. 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. [PubMed: 15374775]
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. [PubMed: 11828230]
11. Folsom AR, Evans GW, Carr JJ, Stillman AE. Association of traditional and nontraditional cardiovascular risk factors with coronary artery calcification. Angiology. 2004; 55(6):613–623. [PubMed: 15547647]
12. Bertoni AG, Whitt-Glover MC, Chung H, et al. The association between physical activity and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol. 2009; 169(4):444–454. [PubMed: 19075250]
13. Gabriel KP, Matthews KA, Perez A, et al. Self-reported and accelerometer-derived physical activity levels and coronary artery calcification progression in older women: results from the Healthy Women Study. Menopause. 2013; 20(2):152–161. [PubMed: 22914209]
14. Storti KL, Pettee Gabriel KK, Underwood DA, Kuller LH, Kriska AM. Physical activity and coronary artery calcification in two cohorts of women representing early and late postmenopause. Menopause. 2010; 17(6):1146–1151. [PubMed: 20651620]
15. Lee CD, Jacobs DR Jr, Hankinson A, Iribarren C, Sidney S. Cardiorespiratory fitness and coronary artery calcification in young adults: The CARDIA Study. Atherosclerosis. 2009; 203(1):263–268. [PubMed: 18653190]
16. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988; 41(11):1105–1116. [PubMed: 3204420]
17. Pereira MA, FitzerGerald SJ, Gregg EW, et al. A collection of Physical Activity Questionnaires for health-related research. Med Sci Sports Exerc. 1997; 29(6 Suppl):S1–205. [PubMed: 9243481]
18. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 6th. Baltimore, Md: Lippincott Williams & Wilkins; 2000.
19. Sidney S, Jacobs DR Jr, Haskell WL, et al. Comparison of two methods of assessing physical activity in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Epidemiol. 1991; 133(12):1231–1245. [PubMed: 2063831]
20. Jacobs DR, Hahn LP, Haskell WL, Pirie P, Sidney S. Validity and reliability of short physical activity history: CARDIA and the Minnesota Heart Health Program. J Cardiopulmonary Rehab. 1989; 9:448–459.
21. Hankinson AL, Daviglus ML, Bouchard C, et al. Maintaining a high physical activity level over 20 years and weight gain. Jama. 2010; 304(23):2603–2610. [PubMed: 21156948]
22. Gabriel KP, Sidney S, Jacobs DR Jr, et al. Convergent validity of a brief self-reported physical activity questionnaire. Med Sci Sports Exerc. 2014; 46(8):1570–1577. [PubMed: 24496119]
23. Parker ED, Schmitz KH, Jacobs DR Jr, Dengel DR, Schreiner PJ. Physical activity in young adults and incident hypertension over 15 years of follow-up: the CARDIA study. Am J Public Health. 2007; 97(4):703–709. [PubMed: 17329668]
24. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology. 2005; 234(1):35–43. [PubMed: 15618373]
25. Detrano RC, Anderson M, Nelson J, et al. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility–MESA study. Radiology. 2005; 236(2):477–484. [PubMed: 15972340]
26. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990; 15(4): 827–832. [PubMed: 2407762]
27. Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. Jama. 2014; 311(5):490–497. [PubMed: 24496536]

28. Budoff MJ, McClelland RL, Nasir K, et al. Cardiovascular events with absent or minimal coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J. 2009; 158(4):554–561. [PubMed: 19781414]
29. Nakanishi R, Li D, Blaha MJ, et al. All-cause mortality by age and gender based on coronary artery calcium scores. Eur Heart J Cardiovasc Imaging. 2015
30. Reis JP, Loria CM, Lewis CE, et al. Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age. Jama. 2013; 310(3): 280–288. [PubMed: 23860986]
31. Warnick GR, Benderson J, Albers JJ. Dextran sulfate-Mg2+ precipitation procedure for quantitation of high-density-lipoprotein cholesterol. Clin Chem. 1982; 28(6):1379–1388. [PubMed: 7074948]
32. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18(6):499–502. [PubMed: 4337382]
33. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014; 129(25 Suppl 2):S1–45. [PubMed: 24222016]
34. Jones BL, Nagin D, K R. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. Sociological Methods & Research. 2001; 29:374–393.
35. Shave R, Baggish A, George K, et al. Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications. J Am Coll Cardiol. 2010; 56(3):169–176. [PubMed: 20620736]
36. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. Europace. 2009; 11(9):1156–1159. [PubMed: 19633305]
37. Mohlenkamp S, Lehmann N, Breuckmann F, et al. Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. Eur Heart J. 2008; 29(15):1903–1910. [PubMed: 18426850]
38. Breuckmann F, Mohlenkamp S, Nassenstein K, et al. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. Radiology. 2009; 251(1):50–57. [PubMed: 19332846]
39. Oxborough D, Birch K, Shave R, George K. “Exercise-induced cardiac fatigue”–a review of the echocardiographic literature. Echocardiography. 2010; 27(9):1130–1140. [PubMed: 20678128]
40. Scott JM, Esch BT, Haykowsky MJ, et al. Effects of high intensity exercise on biventricular function assessed by cardiac magnetic resonance imaging in endurance trained and normally active individuals. Am J Cardiol. 2010; 106(2):278–283. [PubMed: 20599016]
41. Merghani A, Maestrini V, Rosmini S, et al. Prevalence of Subclinical Coronary Artery Disease in Masters Endurance Athletes With a Low Atherosclerotic Risk Profile. Circulation. 2017; 136(2): 126–137. [PubMed: 28465287]
42. Aengevaeren VL, Mosterd A, Braber TL, et al. Relationship Between Lifelong Exercise Volume and Coronary Atherosclerosis in Athletes. Circulation. 2017; 136(2):138–148. [PubMed: 28450347]
43. Baggish AL, Levine BD. Coronary Artery Calcification Among Endurance Athletes: “Hearts of Stone”. Circulation. 2017; 136(2):149–151. [PubMed: 28696264]
44. Bhella PS, Hastings JL, Fujimoto N, et al. Impact of lifelong exercise “dose” on left ventricular compliance and distensibility. J Am Coll Cardiol. 2014; 64(12):1257–1266. [PubMed: 25236519]
45. Levine BD. Can intensive exercise harm the heart? The benefits of competitive endurance training for cardiovascular structure and function. Circulation. 2014; 130(12):987–991. [PubMed: 25223769]
46. Lavie CJ, O’Keefe JH, Sallis RE. Exercise and the heart–the harm of too little and too much. Curr Sports Med Rep. 2015; 14(2):104–109. [PubMed: 25757005]
47. Lew WY. Exercise: commitment to a young heart. J Am Coll Cardiol. 2014; 64(12):1267–1269. [PubMed: 25236520]

48. Farahmand BY, Ahlbom A, Ekblom O, et al. Mortality amongst participants in Vasaloppet: a classical long-distance ski race in Sweden. J Intern Med. 2003; 253(3):276–283. [PubMed: 12603494]

49. Joyner, MJ. Is It Possible to Exercise Too Much?. Medscape. http://wwwmedscapecom/viewarticle/835012

50. Haskell WL, Sims C, Myll J, Bortz WM, St Goar FG, Alderman EL. Coronary artery size and dilating capacity in ultradistance runners. Circulation. 1993; 87(4):1076–1082. [PubMed: 8462135]

51. Merghani A, Maestrini V, Rosmini S, et al. Prevalence of Subclinical Coronary Artery Disease in Masters Endurance Athletes with a Low Atherosclerotic Risk Profile. Circulation. 2017

52. Currens JH, White PD. Half a century of running. Clinical, physiologic and autopsy findings in the case of Clarence DeMar ("Mr. Marathon"). N Engl J Med. 1961; 265:988–993. [PubMed: 13882716]

53. Mann GV, Spoerry A, Gray M, Jarashow D. Atherosclerosis in the Masai. Am J Epidemiol. 1972; 95(1):26–37. [PubMed: 5007361]

54. Andersen K, Farahmand B, Ahlbom A, et al. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. Eur Heart J. 2013; 34(47):3624–3631. [PubMed: 23756332]

55. Erqou S, Kip KE, Mulukutla SR, Aiyer AN, Reis SE. Racial differences in the burden of coronary artery calcium and carotid intima media thickness between Blacks and Whites. Neth Heart J. 2015; 23(1):44–51. [PubMed: 25342280]

56. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2005; 111(10):1313–1320. [PubMed: 15769774]

57. LaMonte MJ, Fitzgerald SJ, Levine BD, et al. Coronary artery calcium, exercise tolerance, and CHD events in asymptomatic men. Atherosclerosis. 2006; 189(1):157–162. [PubMed: 16438976]

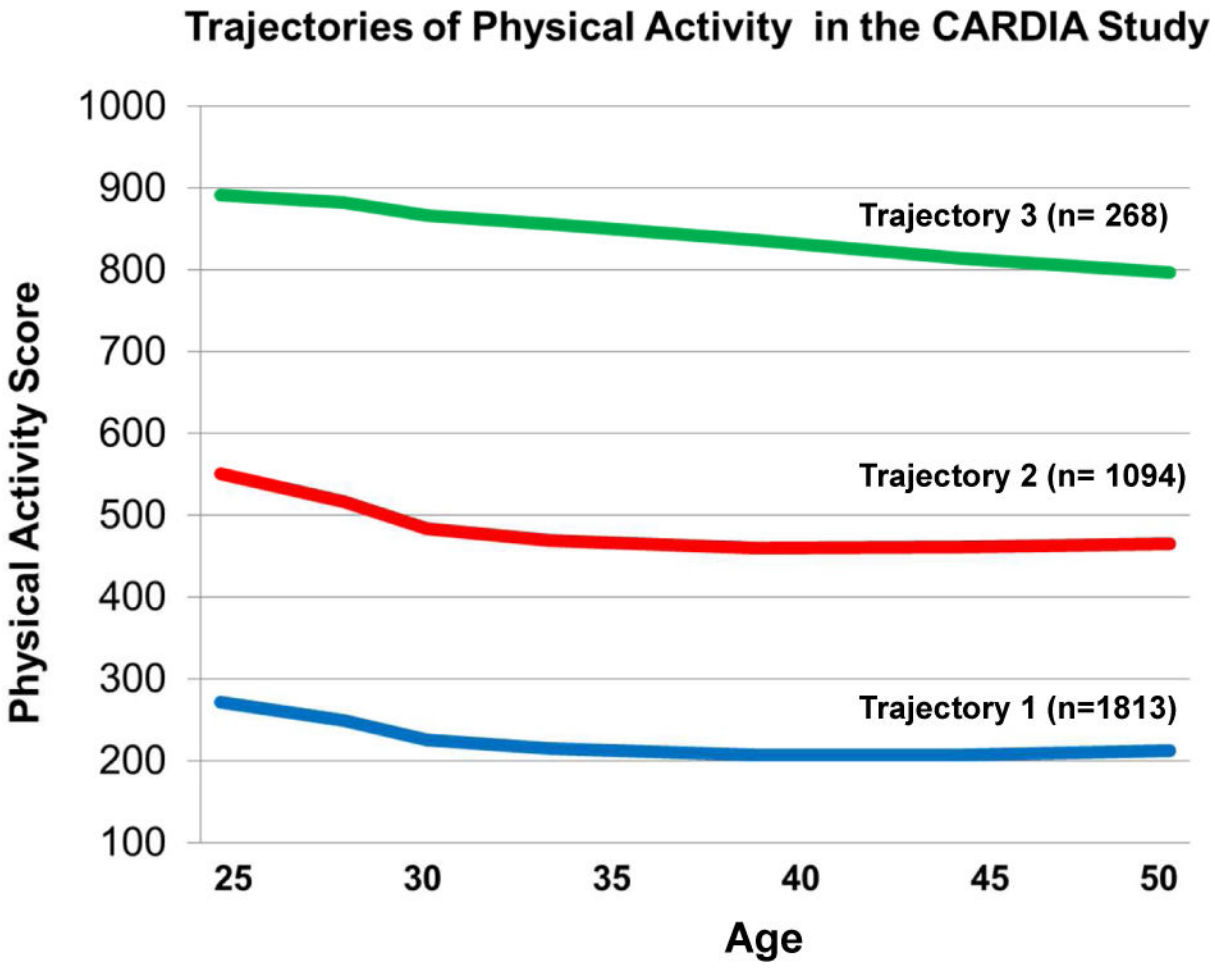

Figure 1. Trajectories of Physical Activity in the CARDIA Study

Plotted lines represent the trajectory class identified for the estimated pattern of physical activity scores by age and number of CARDIA participants in each class. Trajectory 1: Below PA guidelines (n= 1813; 57.1%); Trajectory 2: Meeting PA guidelines (n= 1094; 34.5%); Trajectory 3: Three times PA guidelines (n= 268; 8.4%)

Table 1

Participants Characteristics by PA Trajectory Group at Baseline and Exam Year 25[a]

	Below PA guidelines	Meeting PA guidelines	Three times PA guidelines	P-value[b]
n= 3175[c]	1813	1094	268	
Age, baseline, mean (SD)	25.4 (0.5)	25.4 (0.5)	25.4 (0.5)	0.75
Male, (%)	557 (30.7)	614 (56.1)	207 (77.2)	<.001
Gender-Race, (%)				<.001
Black male; n=597 (%)	251 (13.8)	247 (22.6)	99 (36.9)	
White male; n= 781 (%)	306 (16.9)	367 (33.6)	108 (40.3)	
Black female; n= 908 (%)	744 (41.0)	150 (13.7)	14 (5.2)	
White female; n= 889 (%)	512 (28.2)	330 (30.2)	47 (17.6)	
Education ≥ 16 yrs. (%)	484 (26.7)	408 (37.3)	88 (32.8)	<.001
Smoking				0.01
Current (%)	502 (27.8)	284 (26.2)	65 (24.3)	
Past (%)	216 (12.0)	177 (16.3)	34 (12.7)	
BMI (kg/m^2), mean (SD)	24.9 (5.4)	24.0 (4.1)	23.7 (3.2)	<.001
HDL, mean (SD)	49.8 (12.9)	50.2 (12.8)	49.9 (11.1)	0.89
Hyperlipidemia (%)	88 (4.9)	41 (3.8)	10 (3.7)	0.32
Hypertension (%)	70 (3.9)	35 (3.2)	4 (1.5)	0.12
Diabetes (%)	21 (1.2)	6 (0.6)	3 (1.1)	0.24
Year 25				
Education ≥ 16 yrs. (%)	798 (44.0)	601 (54.9)	134 (50.0)	<.001
Smoking				0.08
Current (%)	316 (17.8)	177 (16.4)	41 (15.4)	
Past (%)	371 (20.9)	265(24.5)	50 (18.8)	
BMI (kg/m^2) mean (SD)	31.4 (7.7)	29.0 (6.3)	28.0 (5.1)	<.001
HDL, mean (SD)	54.1 (17.9)	52.9 (16.7)	53.9 (17.0)	0.70
Hyperlipidemia (%)	180 (9.9)	110 (10.1)	27 (10.1)	0.99
Hypertension (%)	704 (38.8)	318 (29.1)	67 (25.0)	<.001
Diabetes (%)	282 (15.6)	120 (11.0)	30 (11.2)	0.001
CAC>0 (%)	525 (29.0)	363 (33.2)	112 (41.8)	<.001
CAC>20 (%)	301 (16.6)	234 (21.4)	67 (25.0)	<.001
CAC>100 (%)	156 (8.6)	115 (10.5)	32 (11.9)	0.09

BMI, body mass index; CAC, coronary artery calcification;

[a] Values are reported as mean (SD) unless otherwise indicated; percentages (%) reflected for each variable are with respect to PA trajectory group.

[b] Values are significantly different among PA trajectories (P<.05).

[c] total sample size, number of observations =3175 except for the following variables at baseline: smoking, n=3155; BMI, n=3164; diabetes, n=3118; at Year 25: smoking, n=3126; BMI, n=3169; diabetes, n=3166

Table 2

Odds ratios for CAC > 0 at 25 years associated with PA Trajectory groups, overall and stratified by race and gender

Total n=3175 (%CAC>0)[a]	**Below PA guidelines (95% CI) 29.0%**	**Meeting PA guidelines (95% CI) 33.2%**	**Three times PA guidelines (95% CI) 41.8%**
Model 1 (adjusted for age)	Reference	1.22 (1.04, 1.43)	1.76 (1.35, 2.29)
Model 2 (fully adjusted)[b,c]	Reference	1.00 (0.80, 1.15)	1.27 (0.95, 1.70)
Model 2[b] stratified by race (includes model 2 covariates except race)			
All Black participants	Reference 28.3%	0.83 (0.62, 1.12) 31.2%	0.89 (0.56, 1.41) 34.5%
All White participants	Reference 29.7%	1.11 (0.87, 1.42) 34.3%	1.80 (1.21, 2.67) 47.1%
Model 2[b] stratified by race and gender (includes model 2 covariates except race and gender)[1,2]			
Black male	Reference 42.2%	0.87 (0.60, 1.26) 38.5%	0.94 (0.57, 1.54) 38.4%
Black female	Reference 23.7%	0.79 (0.50, 1.26) 19.3%	0.46 (0.06, 3.67) 7.1%
White male	Reference 49.0%	1.10 (0.79, 1.51) 48.5%	1.86 (1.16, 2.98) 58.3%
White female	Reference 18.2%	1.17 (0.79, 1.73) 18.5%	1.71 (0.79, 3.71) 21.3%

[1] Black males: Traj 1: n=106; Traj 2: n=95; Traj 3: n=38

Black females: Traj 1: n=176; Traj 2: n= 29; Traj 3: n=1

[2] White males: Traj 1: n=150; Traj 2: n=178; Traj 3: n=63

White females: Traj 1: n=93; Traj 2: n=61; Traj 3: n=10

[a] %CAC>0 = percentage of participants with CAC prevalent (CAC>0) at Yr 25 exam with respect to PA trajectory group.

[b] Model 2 covariates: age, race, gender + Y25 hypertension, diabetes, smoking status, BMI, education, hyperlipidemia.

Interaction between PA trajectory class and race, P=.11

Interaction between PA trajectory class and race-sex categories, P=.48

[c] 63 observations were excluded from all multivariate analyses due to missing values for the response or explanatory variable.