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The Association Between Physical Activity and Both Incident Coronary Artery Calcification and Ankle Brachial Index Progression: The Multi-Ethnic Study of Atherosclerosis

Joseph A C Delaney, PhD^{2,*}, Nicole E. Jensky, PhD, MPH^{1,*}, Michael H. Criqui, MD, MPH¹, Melicia C. Whitt-Glover, PhD³, João A. C. Lima, MD⁴, and Matthew A. Allison, MD, MPH¹

¹Department of Epidemiology, University of Washington, Seattle, WA

²Division of Preventive Medicine, Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA

³Gramercy Research Group, Winston Salem, NC

⁴Division of Cardiology, Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD

Abstract

Objective—Both coronary artery calcification (CAC) and the ankle brachial index (ABI) are measures of subclinical atherosclerotic disease. The influence of physical activity on the longitudinal change in these measures remains unclear. To assess this we examined the association between these measures and self-reported physical activity in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods—At baseline, the MESA participants were free of clinically evident cardiovascular disease. We included all participants with an ABI between 0.90 and 1.40 (n=5656). Predictor variables were based on self-reported measures with physical activity being assessed using the Typical Week Physical Activity Survey from which metabolic equivalent-minutes/week of activity were calculated. We focused on physical activity intensity, intentional exercise, sedentary behavior, and conditioning. Incident peripheral artery disease (PAD) was defined as the progression of ABI to values below 0.90 (given the baseline range of 0.90 to 1.40). Incident CAC was defined as a CAC score >0 Agatston units upon follow up with a baseline score of 0 Agatston units.

Results—Mean age was 61 years, 53% were female, and mean body mass index was 28 kg/m². After adjusting for traditional cardiovascular risk factors and socioeconomic factors, intentional

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Corresponding Author: Matthew Allison, University of California San Diego, Dept. Family and Preventive Medicine, 8950 Villa La Jolla Drive suite A206, La Jolla, CA 92037, mallison@ucsd.edu, p. (858) 822-7671, f. (858) 822-7662.

*These authors contributed equally and are co-first authors

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exercise was protective for incident peripheral artery disease (Relative Risk (RR)= 0.85, 95% Confidence Interval (CI): 0.74 to 0.98). After adjusting for traditional cardiovascular risk factors and socioeconomic factors, there was a significant association between vigorous PA and incident CAC (RR=0.97, 95% CI: 0.94 to 1.00). There was also a significant association between sedentary behavior and increased amount of CAC among participants with CAC at baseline ($\log(\text{Agatston Units} + 25) = 0.027$, 95% CI 0.002, 0.052).

Conclusions—These data suggest that there is an association between physical activity/sedentary behavior and the progression of two different measures of subclinical atherosclerotic disease.

Keywords

Ankle Brachial Index; Coronary Artery Calcification; Physical Activity; Epidemiology; Prospective Cohort Study

INTRODUCTION

Both coronary artery calcium (CAC) and the ankle brachial index (ABI) are measures of subclinical cardiovascular disease (CVD).^{1, 2} From a prevention perspective, it is important to monitor these subclinical CVD measures and determine which risk factors may contribute to their changes. In this regard, the direct effects of physical activity (PA) on the development or progression of subclinical atherosclerosis are not well established.^{3, 4}

The ABI is used to detect peripheral artery disease (PAD), with a value < 0.90 being indicative of significant flow limiting atherosclerotic disease in the lower extremity,⁵ which can lead to mobility loss⁶ and mortality.^{7, 8} In patients with intermittent claudication, a decline to a lower ABI has been linked to decreased participation in moderate and vigorous PA.⁹ However, it is unknown whether a population free of baseline CVD would show a similar association.

CAC is a measure of atherosclerotic plaque evolution and provides an excellent marker of coronary artery disease. However, there are inconsistencies in the literature related to the association between PA and CAC. Prior research suggests that chronic exercise attenuates the presence and extent of CAC,¹⁰ while slower walking time is associated with more CAC^{2, 11} and higher levels of cardio-respiratory fitness at a particular age or age range[?] are associated with a lower risk of having CAC 15 years later.¹² Conversely, other studies have indicated that high intensity PA¹³ and/or intentional exercise are unrelated to CAC.² To our knowledge, no studies have evaluated different types of PA and changes in CAC over follow-up.

It is important to determine what type and how much activity is most effective at reducing or preventing subclinical CVD. Additionally, since sedentary behaviors are significant CVD mortality predictors¹⁴ and are associated with higher odds of metabolic syndrome and individual CVD risk factors,¹⁵ determining how sedentary behaviors influence both prevalent and incident subclinical CVD is also relevant to prevention. As such, the aim of

this study was to determine the associations between different types of PA and the incidence and progression of both CAC and the ABI in the Multi-Ethnic Study of Atherosclerosis.

MATERIALS AND METHODS

Study design

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based sample of 6,814 men and women from 4 ethnic groups. Details regarding design, recruitment, and objectives of MESA have been published previously.¹⁶ Briefly, eligible MESA participants were defined as persons living within the defined geographic boundaries of each of the six field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN) who were aged 45–84 years at enumeration via a phone interview. Participants did not meet any of the exclusion criteria including a self-reported medical history of heart attack, angina, cardiovascular procedures, heart failure, cerebrovascular disease, active treatment for cancer, pregnancy or amputation at follow up exam.

Data Collection

Eligible participants were invited to a clinic for further examination. During the baseline examination (2000–2002) and follow up examinations (exam 3, 2004–2005 and exam 4, 2005–2007), standardized questionnaires and calibrated devices were utilized to obtain demographic data, tobacco use data, information on medical conditions, current prescription medication usage, weight, and height. Resting, seated blood pressure was measured 3 times using a Dinamap automated oscillometric sphygmomanometer (model Pro 100; Critikon, Tampa, Florida); the last 2 measurements were averaged for analysis. Hypertension was defined as use of an antihypertensive medication, systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mm Hg.

Laboratory Measures

Fasting blood samples were drawn and were sent to a central laboratory for measurement of glucose and lipids.¹⁷ Participants were considered to have diabetes if they used hypoglycemic drugs or if their fasting blood glucose was ≥ 7.0 mmol/L (126 mg/dL). Participants were considered to have impaired fasting glucose if they did not have diabetes according to the preceding criteria but their fasting blood glucose level was $100 < 126$ mg/dL in accordance with the 2004 American Diabetes Association definition.¹⁸ Individuals with total:high-density lipoprotein cholesterol ratio >5 or those who reported the use of a medication to treat high cholesterol were classified as dyslipidemic.

Electron Beam Computed Tomography

Chest computed tomography was performed by using either a cardiac-gated electron-beam scanner or a prospectively electrocardiogram-triggered scan acquisition at 50% of the R-R interval with a multi-detector system, acquiring a block of 4 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode. Phantoms of known physical calcium concentration in participants were scanned twice. Scans were read at a central reading center. The measurement of CAC was calibrated against the phantom. For each scan, a total phantom-

adjusted Agatston score, defined as the sum of calcium measures from the left main, left anterior descending, circumflex, and right coronary arteries, was calculated. The mean score was used in these analyses. We defined CAC progression as a continuous change in CAC from baseline to exam 3. For incident CAC analysis, we excluded participants with CAC>0 at baseline. Incident CAC was a binary variable, defined as those without CAC at baseline but had a CAC score greater than zero at follow up.

Ankle Brachial Index

To obtain the ABI, participants rested supine for 5 minutes, and then systolic blood pressures were measured in both arms and legs with the appropriate-sized cuffs. For each leg, the systolic blood pressure in each posterior tibial and dorsalis pedis artery was measured. All pressures were detected with a continuous-wave Doppler ultrasound probe. The leg-specific ABI was calculated as the higher systolic blood pressure in the posterior tibial or dorsalis pedis divided by the higher of the 2 systolic blood pressures in the arms. For this analysis, the lower of the two leg specific ABIs was utilized. We defined ABI progression as a change in ABI from baseline to exam 3, measured as a continuous variable. We defined incident PAD as a binary variable where the ABI was between 0.90 and 1.40 (a normal ABI)¹⁹ at baseline and decreased to < 0.90 at follow up (exam 3).⁵

Physical activity survey

The MESA Typical Week Physical Activity Survey (TWPAS), adapted from the Cross Cultural Activity Participation Study,²⁰ was designed to identify time spent in and frequency of various PA during a typical week in the past month. The rationale for the selected time frame was the intention to capture the typical activity patterns in a participant's daily life. The survey includes 28 items in categories of household chores, lawn/yard/garden/farm, care of children/adults, transportation, walking (not at work), dancing and sport activities, conditioning activities, leisure activities, and occupational and volunteer activities. Participants were first asked if they participated in these categories of activity (yes/no), and if yes, they answered the questions regarding the average number of days per week and time per day engaged in these activities. If appropriate, questions also differentiated the intensity of activities as light, moderate and vigorous.

The sum of minutes spent in all activity types was multiplied by the metabolic equivalent (MET) level assigned to each activity.²¹ Summary measures include total minutes/day and total MET-min/day for nine physical activity categories and three intensity levels (light, moderate and vigorous). After reviewing the patterns of response regarding PA intensity, we grouped no and low PA into one intensity level. Moderate and vigorous PA were combined as another variable since approximately 64% of the participants reported no vigorous PA. To capture activities typically recommended by PA guidelines, we created an intentional exercise variable that was the sum of activities that were consciously done for exercising such as sports/dancing, conditioning activities and walking regardless of the intensity level.² Also, we looked at sedentary behaviors in MET-min that included the sum of reading and watching television. Lastly, we evaluated an additional category that considered conditioning alone in MET-min, which included biking, rowing, exercise machines, aerobics, running, kickboxing etc. at moderate or vigorous intensity. Conditioning did not

include walking or team sports, but rather moderate or vigorous activities that are generally performed in a gym.

Statistical Analysis

We included all participants with an ABI between 0.90 and 1.40 at baseline. These participants were used for both the ABI and CAC analysis to ensure that the two endpoints were on comparable populations. Participants were excluded from the analysis if they were missing one or more of the covariates (as defined in Table 1) or if they did not return for a follow-up measurement (5758 of the 6814 MESA participants returned for a follow-up CAC scan during the period of this study). For incident CAC analysis, we also excluded participants with CAC>0 at baseline (n=2661).

Characteristics of the population were described using mean and standard deviation for continuous variables, while categorical variables were summarized as a count and percentage of the study population. We assessed normality in our covariates and highly skewed variables were log transformed to achieve normality. Minutes of PA and sedentary behavior were converted to hours to make the beta in the regression equations more interpretable. Both sedentary and PA hours were log transformed to account for outliers that could otherwise have been overly influential in the regression models. The differences in the distributions of the baseline characteristics were determined by t-tests or chi-square tests, as appropriate.

We had 5 independent exposure variables (moderate/vigorous PA, vigorous PA, intentional exercise, sedentary behavior, and conditioning). We analyzed 4 models for the following outcome variables: incident CAC, incident PAD, CAC progression and ABI progression. Incident models were binary outcomes; whereas, progression models were continuous outcomes. Model 1 was the unadjusted model. Model 2 was adjusted for age, sex and ethnicity. Model 3 was adjusted for candidate confounders including age, sex, ethnicity, body mass index, pack years of smoking, family history of myocardial infarction, hypertension, dyslipidemia, and diabetes. Finally, we looked at an additional model (model 4) that included the covariates in model 3 as well as the socio-economic predictors education, alcohol use, current smoking status, education, income, and health insurance status.

Relative risk regression²² was used to model the probability of incident-detectable CAC among those free of CAC at Exam 1. That is, the probability of incident CAC was modeled as a function of covariates using a generalized linear model with log link and binomial error distribution. We used relative risk regression rather than logistic regression because the incidence of new calcification (16.1%) violated the rare disease assumption (<10%) for estimating relative risks. Additionally, we also analyzed increases in the level of CAC among participants with CAC at baseline. For this analysis we used linear regression and followed the approach of Kronmal et al.²³

For incident PAD we used relative risk regression for this analysis and the same levels of statistical adjustment as used for our CAC models. We analyzed continuous progression to a lower ABI using linear regression. For both incident PAD and continuous change in ABI,

we adjusted for baseline ABI to control for regression to the mean. Further, additional analyses excluded participants with baseline leg pain to explore whether leg pain influenced the association between PA and PAD.

For all analyses we stratified by gender and race/ethnicity to test for effect modification. We used multiple imputation as a sensitivity analysis to verify that the complete case approach to missing data used in this analysis was appropriate (data not shown). We utilized a 2-tailed test of $P < 0.05$ for statistical significance. Analyses were performed using SAS 9.2.

RESULTS

General characteristics of the study population are presented in Table 1. Data were available for 5656 participants. Since their PAD status was uncertain due to the presence of stiff arteries, 50 participants who progressed to a higher ABI were not included in Table 1. The mean age was approximately 61 years and 47% were male while 41% Non-Hispanic White, 12% Asian, 26% African American, and 21% Hispanic. The average BMI was 28 kg/m². At baseline, approximately 33% had dyslipidemia, 11% had diabetes, and 42% had hypertension. Just over 78% of the participants reported intentional exercise and 35% reported engaging in conditioning activity. Of the participants with incident PAD (n=161), 64% had hypertension, 21% had diabetes, and 43% were African American. Compared to the participants without an ABI change, those with incident PAD were older (67 years of age), performed less vigorous and moderate activity (MET-min), were more sedentary and performed less intentional exercise. Of those participants with incident CAC (n=580), 45% had hypertension, 13.3% had diabetes, and 30.3% were African American. Compared to those participants that did not have CAC or who had CAC scores that did not progress over time, those who developed incident CAC performed less vigorous and moderate PA, and reported more sedentary behavior and less intentional exercise.

Table 2 demonstrates the incidence of PAD for each measure of PA as a binary variable as well as continuous ABI progression. After adjusting for CVD risk factors and socioeconomic variables, greater intentional exercise reduced the risk of incident PAD (RR=0.85, 95% CI 0.74, 0.98). Among those who developed incident PAD, 60% were in the bottom quartile (<1.066) at baseline. We also looked at conditioning hours and determined that a log increase in conditioning was not significantly associated with incident PAD. Last, we looked at the continuous ABI progression and results were not statistically significant.

Table 3 shows the incidence of CAC and we determined that after adjusting for traditional cardiovascular risk factors and socioeconomic status, vigorous PA was associated with a reduction in the risk of incident CAC (RR=0.97, 95% CI 0.94, 1.00, p=0.048). We also computed linear regression analysis for CAC progression for different PA exposures. In general, PA was not significantly associated with CAC progression, but an increase in sedentary behavior was significantly associated with greater CAC progression (log(Agatston Units +25)=0.027, 95% CI 0.002, 0.052).

In a *post-hoc* sensitivity analysis, we considered interactions between race and exercise for all of the associations with a statistically significant main effect (intentional exercise and

ABI, vigorous activity and CAC, being sedentary and CAC progression). We found two interactions among the nine tests; vigorous activity was more protective for African Americans ($p=0.0363$) against incident CAC and being sedentary was even worse for Hispanic-Americans ($p=0.0344$) for CAC progression.

DISCUSSION

To our knowledge, the associations between PA and progression of either CAC or the ABI have not been previously investigated. Our results suggest that when one is participating in intentional exercise, it protects against incident PAD. Sensitivity analysis revealed that results were similar even after excluding patients with baseline exercise calf pain. These data suggest that any activity reduction secondary to leg pain did not bias the relationship between intentional exercise and incident PAD. In individuals with pre-existing CAC, those who engage in increased sedentary behavior are more likely to have greater CAC progression suggesting that engaging in a less sedentary lifestyle may slow disease progression. Finally, there was some indication that vigorous activity may protect against incident CAC, although the finding was marginal in significance.

Our study results are similar to previous cross-sectional studies that examined the association between PA and ABI. The Cardiovascular Health Study (CHS) of adults aged >65 years reported that greater intensity and duration of leisure-time PA over the prior 2 weeks was associated with a lower prevalence of low ABI among the cohort free of cardiovascular disease at baseline.²⁴ In this regard, moderate-to-vigorous and intentional exercise were associated with a more favorable ABI value in the CHS cohort,² while in a cohort of Japanese women sedentary behavior was associated with a lower ABI.²⁵ Findings from the current study suggest that intentional exercise is protective against incident PAD though the potential mechanisms are unclear. As a reduction in ABI is associated with a significantly higher risk for incident CVD events²⁶ future PA interventions are necessary to determine what specific types of exercises reduce the likelihood of decreased ABI over time and to uncover basic mechanisms that will perhaps lead to intervention.

Our report also suggests that vigorous PA is protective against incident CAC. These findings are complementary with previous reports that indicated that long-duration PA was associated with less prevalent CAC compared to sedentary individuals or those who participated in moderate duration PA among participants with higher metabolic risk scores.²⁷ Similarly, the Harvard Alumni Study determined that vigorous activities are associated with a reduced risk of CHD, whereas moderate or light activities have no clear association with the risk of CHD.²⁸ Potentially, vigorous PA is beneficial because it alters body composition, lipid profile, and fasting insulin, hypertension,^{29, 30} all of which are atherosclerotic risk factors and may also be a reason for less incident PAD.

Conversely, previous studies suggest that there is no association between the extent of CAC and PA (using a sports, leisure and work PA index).¹³ The lack of an association between PA and the extent of CAC suggests the risk reduction associated with PA is mediated by other factors.¹³ Interestingly, even after accounting for socio-economic variables, another analyses indicated that there were no significant associations between low levels of

subclinical vascular disease and PA (exercise intensity and intentional exercise) in MESA;^{2, 31} however, this report was cross-sectional. The disparities among studies may be due to differences in the study design, study population, and/or quantification of PA.

Our results suggest that sedentary behavior can increase the progression of CAC once it is present. Other studies have demonstrated that prolonged sitting also predicted an increased risk of CVD, even after accounting for time spent in recreational activity.³² Furthermore, the Nurses' Health Study compared women who remained sedentary with women who increased PA expenditure. The women who engaged in the most PA, were less likely to have a coronary event.³³ Given the high prevalence of sedentary behavior within the United States, an effort to help individuals achieve even modest increases in PA will likely lead to favorable changes in CVD risk factors such as CAC and PAD.³²

The differences between the detected associations between PA and different measures of sub-clinical disease (CAC and ABI) may be related to different mechanisms being at work. PA improves the lipid profile^{29, 30} which may be more directly relevant to changes in CAC. Low ABI is often treated with walking and there is good evidence from randomized controls that walking improves outcomes for peripheral artery disease³³ so we may be seeing the equivalent of early intervention of exercise in participants who remain active. Since these two sites respond to different levels and intensity of PA, it is not surprising to see different associations between these measures and PA. However, none of this changes the clear indication that increased PA is conferring benefits on lower levels of sub-clinical cardiovascular disease in this cohort.

Potential limitations of the current study include self-reported PA using a questionnaire that may lead to inaccurate participant recall or social desirability bias in quantifying PA levels. Future studies may be necessary to investigate these associations using an objective measure to define PA rather than a questionnaire, due to these limitations in self-reported PA.^{35, 36} Additionally, improvements in the accuracy of self-report PA measures are needed because objective measures may not be feasible for all study designs (e.g. longitudinal studies in large cohorts). Furthermore, we made composite PA variables that may not capture important threshold effects. However, these measurement errors are likely to be non-differential in a prospective cohort study so the net effect would likely be to bias results towards the null (a conservative bias) and to increase variance; so, if anything, this study likely understates the potential benefits of PA on incident ABI and CAC. Although this was a prospective study design, the study is limited by a relatively short follow-up period (approximately 3 years). Also, few subjects had incident PAD, limiting our power to detect small associations. Even in the statistically significant models, the effect size for PA was small. Another possible limitation is that the TWPAS measures acute PA and measure of PA over a longer time frame might have more influence on CAC and ABI than an acute measure. Finally, there is always a possibility that intentional exercise is correlated with other "health seeking behaviors" and protective effects may apply to a cluster of behaviors of which intentional exercise is one part.

The strengths of this study include a large sample size that includes ample representation of men and women, as well as multiple ethnic groups. Furthermore, all subjects underwent

standardized examination procedures and used validated questionnaires over the multiple study visits. While we tested four outcomes and five measures of activity, we would have expected to find approximately one association by chance alone and we found five which makes it improbable that these findings can be the result of multiple testing.

The results of our study support the encouragement of intentional exercise to protect against incident PAD. In addition, vigorous PA may be protective against incident CAC by undefined mechanisms. Conversely, increasing sedentary behavior leads to greater CAC progression, suggesting that any type of activity is better than sedentary behavior for participants with early coronary artery disease and, therefore, people with CVD should implement activity such as walking into their daily lives.³⁷ From a public health perspective, increasing PA may reduce CAC progression (which is associated with cardiovascular events³⁸) as well as ABI (also associated with events³⁹), but also activity has other social, physical and psychological benefits⁴⁰ and light PA has minimal side effects. These results reinforce that sedentary individuals who become physically active even at an older age may still obtain cardiovascular benefits.³² Further work is necessary to confirm these findings using a stronger measure of PA and to address the underlying mechanisms that lead to the association between increased PA and reduced subclinical atherosclerosis

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References

1. Ingelsson E, Sullivan LM, Murabito JM, Fox CS, Benjamin EJ, Polak JF, Meigs JB, Keyes MJ, O'Donnell CJ, Wang TJ, D'Agostino RB Sr, Wolf PA, Vasan RS. Prevalence and prognostic impact of subclinical cardiovascular disease in individuals with the metabolic syndrome and diabetes. *Diabetes*. 2007; 56:1718–1726. [PubMed: 17369522]
2. Bertoni AG, Whitt-Glover MC, Chung H, Le KY, Barr RG, Mahesh M, Jenny NS, Burke GL, Jacobs DR. The association between physical activity and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2009; 169:444–454. [PubMed: 19075250]
3. Cronenwett JL, Warner KG, Zelenock GB, Whitehouse WM Jr, Graham LM, Lindenauer M, Stanley JC. Intermittent claudication. Current results of nonoperative management. *Arch Surg*. 1984; 119:430–436. [PubMed: 6703900]
4. Bird CE, Criqui MH, Fronck A, Denenberg JO, Klauber MR, Langer RD. Quantitative and qualitative progression of peripheral arterial disease by non-invasive testing. *Vasc Med*. 1999; 4:15–21. [PubMed: 10355865]
5. Allison MA, Criqui MH, McClelland RL, Scott JM, McDermott MM, Liu K, Folsom AR, Bertoni AG, Sharrett AR, Homma S, Kori S. The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol*. 2006; 48:1190–1197. [PubMed: 16979004]
6. McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, Sharma L, Criqui MH. Associations of borderline and low normal ankle-brachial index values with functional decline at 5-

- year follow-up: the WALCS (Walking and Leg Circulation Study). *J Am Coll Cardiol.* 2009; 53:1056–1062. [PubMed: 19298919]
7. Sikkink CJ, van Asten WN, van 't Hof MA, van Langen H, van der Vliet JA. Decreased ankle/brachial indices in relation to morbidity and mortality in patients with peripheral arterial disease. *Vasc Med.* 1997; 2:169–173. [PubMed: 9546965]
 8. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, Wautrecht JC, Kornitzer M, Newman AB, Cushman M, Sutton-Tyrrell K, Lee AJ, Price JF, d'Agostino RB, Murabito JM, Norman PE, Jamrozik K, Curb JD, Masaki KH, Rodriguez BL, Dekker JM, Bouter LM, Heine RJ, Nijpels G, Stehouwer CD, Ferrucci L, McDermott MM, Stoffers HE, Hooi JD, Knottnerus JA, Ogren M, Hedblad B, Witteman JC, Breteler MM, Hunink MG, Hofman A, Criqui MH, Langer RD, Fronek A, Hiatt WR, Hamman R, Resnick HE, Guralnik J. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA.* 2008; 300:197–208. [PubMed: 18612117]
 9. Gardner AW, Clancy RJ. The relationship between ankle-brachial index and leisure-time physical activity in patients with intermittent claudication. *Angiology.* 2006; 57:539–545. [PubMed: 17067975]
 10. Wilund KR, Tomayko EJ, Evans EM, Kim K, Ishaque MR, Fernhall B. Physical activity, coronary artery calcium, and bone mineral density in elderly men and women: a preliminary investigation. *Metabolism.* 2008; 57:584–591. [PubMed: 18328364]
 11. Pettee KK, Larouere BM, Kriska AM, Johnson BD, Orchard TJ, Goodpaster BH, Conroy MB, Mackey RH, Underwood DA, Kuller LH. Associations among walking performance, physical activity, and subclinical cardiovascular disease. *Prev Cardiol.* 2007; 10:134–140. [PubMed: 17617776]
 12. 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; 203:263–268. [PubMed: 18653190]
 13. Taylor AJ, Watkins T, Bell D, Carrow J, Bindeman J, Scherr D, Feuerstein I, Wong H, Bhattacharai S, Vaitkus M, O'Malley PG. Physical activity and the presence and extent of calcified coronary atherosclerosis. *Med Sci Sports Exerc.* 2002; 34:228–233. [PubMed: 11828230]
 14. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. *Med Sci Sports Exerc.* 42:879–885. [PubMed: 19996993]
 15. Sisson SB, Camhi SM, Church TS, Martin CK, Tudor-Locke C, Bouchard C, Earnest CP, Smith SR, Newton RL Jr, Rankinen T, Katzmarzyk PT. Leisure time sedentary behavior, occupational/domestic physical activity, and metabolic syndrome in U.S. men and women. *Metab Syndr Relat Disord.* 2009; 7:529–536. [PubMed: 19900152]
 16. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol.* 2002; 156:871–881. [PubMed: 12397006]
 17. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. *Clin Chem.* 1995; 41:264–270. [PubMed: 7874780]
 18. Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2004; 27:S5–S10. [PubMed: 14693921]
 19. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, Howard BV. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation.* 2004; 109:733–739. [PubMed: 14970108]
 20. Ainsworth BE, Irwin ML, Addy CL, Whitt MC, Stolarczyk LM. Moderate physical activity patterns of minority women: the Cross-Cultural Activity Participation Study. *J Womens Health Gen Based Med.* 1999; 8:805–813. [PubMed: 10495261]
 21. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* 2000; 32:S498–504. [PubMed: 10993420]

22. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*. 1998; 280:1690–1691. [PubMed: 9832001]
23. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, Bild DE, Burke GL. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2007; 115:2722–2730. [PubMed: 17502571]
24. Siscovick DS, Fried L, Mittelmark M, Rutan G, Bild D, O'Leary DH. Exercise intensity and subclinical cardiovascular disease in the elderly. The Cardiovascular Health Study. *Am J Epidemiol*. 1997; 145:977–986. [PubMed: 9169906]
25. Furukawa Y, Toji C, Fukui M, Kazumi T, Date C. The impact of sedentary lifestyle on risk factors for cardiovascular disease among Japanese young women. *Nippon Koshu Eisei Zasshi*. 2009; 56:839–848. [PubMed: 20169986]
26. Criqui MH, Ninomiya JK, Wingard DL, Ji M, Fronck A. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. *J Am Coll Cardiol*. 2008; 52:1736–1742. [PubMed: 19007695]
27. Desai MY, Nasir K, Rumberger JA, Braunstein JB, Post WS, Budoff MJ, Blumenthal RS. Relation of degree of physical activity to coronary artery calcium score in asymptomatic individuals with multiple metabolic risk factors. *Am J Cardiol*. 2004; 94:729–732. [PubMed: 15374775]
28. Sesso HD, Paffenbarger RS Jr, Lee IM. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. *Circulation*. 2000; 102:975–980. [PubMed: 10961960]
29. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007; 116:1081–1093. [PubMed: 17671237]
30. Leitzmann MF, Park Y, Blair A, Ballard-Barbash R, Mouw T, Hollenbeck AR, Schatzkin A. Physical activity recommendations and decreased risk of mortality. *Arch Intern Med*. 2007; 167:2453–2460. [PubMed: 18071167]
31. Michos ED, Rice KM, Szklo M, Burke GL, Siscovick DS, Tracy RP, Graham Barr R, Nettleton JA, Greenland P, Jacobs DR Jr, Post W. Factors associated with low levels of subclinical vascular disease in older adults: multi-ethnic study of atherosclerosis. *Prev Cardiol*. 2009; 12:72–79. [PubMed: 19476580]
32. Bassuk SS, Manson JE. Physical activity and cardiovascular disease prevention in women: A review of the epidemiologic evidence. *Nutr Metab Cardiovasc Dis*.
33. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA*. 2002; 288:1994–2000. [PubMed: 12387651]
34. Hamburg NM, Balady GJ. Exercise rehabilitation in peripheral artery disease: functional impact and mechanisms of benefits. *Circulation*. 2011; 123(1):87–97. [PubMed: 21200015]
35. Ekelund U, Sepp H, Brage S, Becker W, Jakes R, Hennings M, Wareham NJ. Criterion-related validity of the last 7-day, short form of the International Physical Activity Questionnaire in Swedish adults. *Public Health Nutr*. 2006; 9:258–265. [PubMed: 16571181]
36. Rosenberg DE, Bull FC, Marshall AL, Sallis JF, Bauman AE. Assessment of sedentary behavior with the International Physical Activity Questionnaire. *J Phys Act Health*. 2008; 5 (Suppl 1):S30–44. [PubMed: 18364524]
37. Smith TC, Wingard DL, Smith B, Kritz-Silverstein D, Barrett-Connor E. Walking decreased risk of cardiovascular disease mortality in older adults with diabetes. *J Clin Epidemiol*. 2007; 60:309–317. [PubMed: 17292026]
38. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, Detrano RC, Bild DE, Guerci AD, Liu K, Shea S, Szklo M, Post W, Lima J, Bertoni A, Wong ND. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2013; 61(12):1231–9. [PubMed: 23500326]
39. Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, Aboyans V, Ix JH, Burke GL, Liu K, Shea S. The ankle-brachial index and incident cardiovascular events in the

- MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol.* 2010; 56(18):1506–12.
[PubMed: 20951328]
40. Morgan AL, Tobar DA, Snyder L. Walking toward a new me: the impact of prescribed walking 10,000 steps/day on physical and psychological well-being. *J Phys Act Health.* 7:299–307.
[PubMed: 20551485]

Highlights

1. Exercise is likely misclassified, so associations may be underestimated
2. There is a significant association between sedentary behavior and CAC progression
3. Intentional exercise was protective against incident peripheral artery disease

Table 1

Baseline cohort characteristics

Variable	Total n=5656	Progress to Low ABI n=161	No ABI Change n=5445	Prevalent CAC n=2661	Incident CAC n=580	No CAC/No change n=2415
Age, years (SD)	61.3 (9.9)	67.6 (9.8)	61.2 (9.9)	65.4 (9.4)	60.4 (8.9)	57.1 (8.9)
BMI, kg/m ² (SD)	28.3 (5.4)	29.7 (6.6)	28.2 (5.3)	28.3 (5.1)	29.3 (5.9)	28.0 (5.5)
Alcohol, drink/wk (SD)	4 (8.2)	3.1 (5.6)	3.9 (8.3)	4.5 (8.3)	4.0 (9.8)	3.3 (7.6)
Pack years Smoker (SD)	10.5 (21.5)	16.2 (28.2)	10.4 (21.3)	13.5 (23.1)	9.8 (19.9)	7.4 (19.5)
Ex-Smoker (%)	36.5	35.4	36.5	42.8	37.2	29.4
Current smoker (%)	12.2	19.3	12	11.6	13.3	12.5
Male (%)	47.4	40.4	47.5	59.5	45.2	34.7
Hypertension (%)	42.4	64	41.9	51.6	45.5	31.4
Diabetes (%)	11	21.1	10.7	13.6	13.3	7.6
Dyslipidemia (%)	33.1	36.6	32.9	33	35.9	19.1
Family History of MI (%)	#33.3	36.6	33.2	36.9	32.3	29.6
Socio-Economic (%)						
No Health Insurance	8.5	8.1	*8.5	6.4	7.6	10.9
Income <25K	30.8	39.1	30.8	33.6	31	28
Income 50k-100K	26.4	21.7	26.4	24.7	26.7	28.2
Income >100K	14.3	5.6	14.3	13.5	12.4	15.3
Less than High School Education	16.4	24.8	16.2	16.5	17.9	15.9
College Education	18.3	15.5	18.4	17.7	16.4	19.4
Graduate School	19.1	16.1	19	19.3	19.1	18.9
Race/Ethnicity (%)						
Non-Hispanic White	41	36	40	33.9	37.8	33.9
Asian	12	3.7	12.4	12.3	8.1	12.8
African American	26.4	43.5	26	21.9	30.3	30.5
Hispanic	21.5	16.8	21.6	19.7	23.8	22.9
Activity Proportions (%)						

Variable	Total n=5656	Progress to Low ABI n=161	No ABI Change n=5445	Prevalent CAC n=2661	Incident CAC n=580	No CAC/No change n=2415
Conditioning Reported	35.4	33.5	35.2	36.2	32.9	35.1
Vigorous Activity Reported	33.1	22.4	33.3	33.8	27.8	33.5
Intentional Exercise Reported	78.1	69.6	78.3	79.2	75	77.6
Activity						
Vigorous, MET-min/wk (SD)	975 (2845)	626 (2495)	982 (2855)	1019 (2947)	798 (2335)	969 (2840)
Moderate, MET-min/wk (SD)	4917 (4493)	4120 (3800)	4938 (4517)	4718 (4430)	4759 (4252)	5175 (1132)
Now/low, MET-min/wk (SD)	6091 (2931)	5471 (2717)	6096 (2931)	5665 (2821)	6232 (2896)	6526 (2990)
Sedentary Behavior, MET-min/wk (SD)	1682 (1130)	1820 (1140)	1678 (1130)	1749 (1106)	1700 (1206)	1605 (1132)
Intentional Activities, MET-min/wk (SD)	2504 (2990)	2044 (2532)	2512 (3011)	2595 (3089)	2296 (2717)	2453 (2958)
Conditioning Activity, MET-min/wk (SD)	506 (1309)	429 (1275)	503(1303)	534 (1346)	446 (1186)	489 (1296)
Outcomes						
Ankle-Brachial Index	1.128 (0.090)	1.045 (0.097)	1.130 (0.088)	1.125 (0.087)	1.135 (0.087)	1.129 (0.093)
Coronary Artery Calcium (Agatston units)	124 (359)	369 (805)	116 (335)	260 (486)	0(0)	0 (0)

Table 2

Association Between Activity and ABI Progression

	Activity	Progression to Low ABI
		RR (95% CI)
Model 1	Intentional Activity	0.82 (0.71, 0.94)*
Model 2		0.80 (0.70, 0.92)*
Model 3		0.83 (0.72, 0.96)*
Model 4		0.85 (0.74, 0.98)*
Model 1	Sedentary	1.20 (0.94, 1.52)
Model 2		0.93 (0.74, 1.16)
Model 3		0.90 (0.73, 1.12)
Model 4		0.90 (0.72, 1.12)
Model 1	Moderate+Vigorous ^I	0.92 (0.84, 1.00)
Model 2		0.94 (0.86, 1.02)
Model 3		0.94 (0.86, 1.04)
Model 4		0.94 (0.86, 1.04)
Model 1	Vigorous ^I	0.93 (0.88, 0.98)
Model 2		0.97 (0.92, 1.02)
Model 3		0.98 (0.93, 1.03)
Model 4		0.98 (0.86, 1.04)
Model 1	Conditioning	0.96 (0.86, 1.06)
Model 2		0.99 (0.89, 1.10)
Model 3		1.02 (0.91, 1.13)
Model 4		1.05 (0.94, 1.17)

Model 1= Unadjusted

Model 2= Age, gender, ethnicity

Model 3= Traditional CVD Risk Factors

Model 4= Model 2 + alcohol use, current smoking status, education, income, and health insurance status

^INo/Low activity is the reference category

Table 3

Association Between Activity and CAC

	Activity	Incident CAC RR (95% CI)	Continuous CAC Progression log(Agatston Units +25)
Model 1	Intentional Activity	0.96 (0.90, 1.03)	-0.003 (-0.018, 0.012)
Model 2		0.92 (0.86, 0.99)	-0.004(-0.019, 0.011)
Model 3		0.98 (0.92, 1.04)	0.002 (-0.013, 0.017)
Model 4		0.99 (0.93, 1.05)	0.002 (-0.014, 0.017)
Model 1	Sedentary	1.07 (0.97, 1.18)	0.028 (0.004, 0.052)*
Model 2		0.97 (0.87, 1.08)	0.031 (0.006, 0.055)*
Model 3		0.96 (0.82, 1.06)	0.028 (0.003, 0.052)*
Model 4		0.95 (0.86, 1.05)	0.027 (0.002, 0.052)*
Model 1	Moderate+Vigorous¹	0.97 (0.92, 1.03)	-0.002 (0.015, 0.011)
Model 2		0.99(0.93, 1.04)	-0.002 (-0.015, 0.0011)
Model 3		1.01 (0.96, 1.07)	0.000 (-0.013, 0.012)
Model 4		1.02 (0.94, 1.10)	-0.001 (-0.014, 0.012)
Model 1	Vigorous¹	0.97 (0.95, 0.99)*	-0.002 (-0.007, 0.003)
Model 2		0.96 (0.94, 0.99)	-0.002 (-0.007, 0.003)
Model 3		0.98 (0.95, 1.00)	-0.001 (-0.006, 0.004)
Model 4		0.97 (0.94, 1.00)*	-0.001 (-0.006, 0.004)
Model 1	Conditioning	0.97 (0.92, 1.03)	-0.001 (-0.012, 0.010)
Model 2		0.96 (0.91, 1.01)	-0.001 (-0.013, 0.010)
Model 3		0.99 (0.94, 1.05)	0.003 (-0.009, 0.014)
Model 4		1.00 (0.94, 1.05)	0.003 (-0.008, 0.015)

Model 1= Unadjusted

Model 2= Age, gender, ethnicity

Model 3= Traditional CVD Risk Factors

¹ No/Low activity is the reference category

* p<0.05