Physical Activity and Subclinical Measures of Atherosclerosis: Study Replication and Sensitivity Analysis

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Abstract

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Background: Atherosclerosis contributes greatly to morbidity and mortality in the United States. Prevention of incidence, and progression of atherosclerosis through lifestyle modification represents an opportunity to reduce the burden of this disease. Ankle brachial index (ABI) and coronary artery calcification (CAC) are subclinical measures of atherosclerosis. The effects of physical activity on such subclinical measures in unselected populations is not comprehensively described.

Objective: To conduct a replication of the 2013 study by *Delaney et al.* and sensitivity analysis to examine whether higher physical activity has a protective effect on cardiovascular disease risk.

Methods: The replication analyses were based on the methods of *Delaney et al.* Physical activity measures were used as predictive variables for incident coronary artery calcification and peripheral artery disease in Multi-Ethnic Study of Atherosclerosis (MESA) participants clinically free of cardiovascular disease. Physical activity predictors (intentional, sedentary, vigorous, moderate & vigorous, and conditioning)

were as continuous variables and measured in Metabolic Equivalents of Task (MET) minutes per week. Additionally, progression of coronary artery calcification and peripheral artery function were determined.

Results: The mean age of participants was 61.8 years, with mean body mass index of 28.2 kg/m^2 and 48% of participants were male. Following adjustment for traditional risk factors for cardiovascular disease and socioeconomic factors, increased intentional activity (OR = 0.64, 95% CI 0.48,0.85) was found to be protective against progression to an ankle brachial index (ABI) of <0.90. Increased sedentary behavior was also observed to lower the odds (OR = 0.52, 95% CI 0.35,0.78) of low ABI progression. Additionally, increased sedentary behavior was associated with an increase in coronary artery calcification (CAC) progression (Coefficient = +0.062, 95% CI 0.014, 0.111). In sensitivity analyses, the associations between increased intentional activity and sedentary behaviors persisted. No significant relationships were consistently observed between other physical activity variables and subclinical measures of atherosclerosis.

Conclusion: The key finding of *Delaney et al.* that intentional physical activity may be protective against progression to low ABI was consistent throughout the present replication and sensitivity analysis. A positive association between sedentary behavior and CAC progression was also found to be consistent. Exercise may be a low risk intervention to reduce mortality and morbidity due to progression of subclinical peripheral arterial disease to clinical disease.

1. Introduction

Cardiovascular disease (CVD) contributes profoundly to the overall disease burden in the United States. It is estimated that more than 1 in 3 American adults are living with at least one form of CVD, with projections predicting that the prevalence will increase significantly by 2030.[1] Although the mortality rate attributed to CVD has decreased in recent years, CVD was listed as the cause underlying more than 800,000 deaths in 2014 alone. Furthermore, CVD is the most costly group of medical conditions in the United States, accounting for approximately $316 billion in total costs between 2012 and 2013 alone.[1]

Given the immense burden of CVD, its prevention has become a public health priority in the united states. Physical activity (PA) is one of the key behaviors that promotes cardiovascular health, reducing risk of developing CVD and adverse CVD outcomes.[2–4] Conversely, physical inactivity or sedentary behaviors contribute to increased CVD risks in adults.[2–4] Despite the known benefits of increased PA and reduced sedentary behaviors, the influence of these measures on the incidence and progression of atherosclerotic processes which underlie CVD is still unclear.

Ankle Brachial Index (ABI) is a non-invasive measure of CVD, which can be used to assess subclinical atherosclerosis.[5] This measure is used in various settings to screen for peripheral artery disease (PAD).[5] Lower ABI values indicate that blood flow may be obstructed in the lower extremities, suggesting the presence of atherosclerotic plaques or even PAD with values <0.90.[6] Although PA has been shown to promote normal ABI values in certain populations, the generalizability of these findings to more diverse populations is still unclear.

Coronary Artery Calcification (CAC) is another non-invasive measure used in screening for subclinical CVD, specifically coronary artery disease (CAD). Presence of calcification in the coronary artery suggest progression of atherosclerosis.[7] Current national recommendations related to CAD prevention

encourage PA and discourage inactivity.[2–4] However, it is uncertain whether physical activities offer additional benefit beyond that of other therapeutic modalities.

Describing the influences of different intensities and forms of PA on measures of subclinical atherosclerosis is imperative in informing recommendations and approaches to optimize CVD prevention efforts. Furthermore, determining how the lack of PA effects subclinical atherosclerosis offers additional evidence to promote PA. A 2013 investigation by Delaney *et al.* attempted to address these points; they found that intentional PA reduced the risk of developing low ABI and increased sedentary behaviors contributed to CAC progression.[8] Study replication and sensitivity analyses are methods by which these finding and underlying assumptions can be reevaluated for reliability and further contextualization. The aims of this project were to conduct a replication of the 2013 study by *Delaney et al.* and sensitivity analysis to examine whether higher physical activity has a protective effect on cardiovascular disease risk.

2. Methods

2.1 Study Design

The Multi-Ethnic Study of Atherosclerosis (MESA) is a large cohort of persons from four different ethnic groups followed prospectively between 2000 – 2012 for the occurrence of morbidity and mortality, particularly as they related atherosclerotic diseases. Individuals were eligible to participate in MESA if they were living in one of the six study areas (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan; NY, and St. Paul, MN) and were between the ages of 45 – 85 years at the time of recruitment. Eligible participants were also clinically free of atherosclerosis. The presence of clinically prevalent atherosclerosis was determined by self-reported history of angina, cardiovascular disease, cerebrovascular disease, or previous cardiovascular procedures. Potential participants were excluded if they had previous amputations, were pregnant or actively undergoing cancer treatment. The

initial sample consisted of 6,814 eligible participants. A thorough description of MESA objectives and design have previously been published.[9]

2.2 Data Collection

MESA data collection methods are comprehensively described by Bild et al.[9] In brief, MESA participants completed baseline clinical assessments, laboratory measures, and standardized questionnaires (2000-2002). Subsequent examinations were completed between 2004-2005 (exam 3) and/or 2006-2007 (exam 4). Questionnaires were used to collect demographic, anthropometric, tobacco use, medical history, and prescription medication use data. Clinical assessments and laboratory measures were used to evaluate blood pressure, diabetes status, blood lipid profiles, as well as a set of measures of sub-clinical atherosclerosis including coronary artery calcification (CAC), and Ankle Brachial Index (ABI).

The MESA Typical Week Physical Activity Survey (TWPAS) was used to estimate the amount and frequency of physical activity (PA) for study participants. This survey was adapted from a previous study activity survey.[10] PA patterns were broken down by the TWPAS into 28 items, divided into 10 categories: household chores, lawn/yard/garden/farm, care of children/adults, transportation, walking (not at work), dancing, sport activities, conditioning activities, leisure activities, and occupational and volunteer activities. Participants were asked if they engaged in any of the activity categories. If they did participate in the activity category, they were asked how often during the week they engaged in that activity, for how long and at what intensity (light, moderate or vigorous).

2.3 Variable Definitions

Covariates

Covariates used in the replication analysis were defined according to the methods used and described by Delaney *et al.*[8] Hypertension was defined as the use of antihypertensive medications, an averaged systolic blood pressure of >140 mmHg, or an averaged diastolic blood pressure > 80 mmHg at baseline exam. Individuals were considered to have diabetes if they reported antihyperglycemic agent use or had a fasting blood glucose >126 mg/dL. If a participant did not meet these diabetes criteria, but had a fasting blood glucose between 100-125 mg/dL, they were considered to have impaired glucose tolerance. Participants with a total cholesterol to high density lipoprotein cholesterol ratio >5 or who reported cholesterol lowering medications were classified as having dyslipidemia.

Dependent Variables

Definition of the dependent variables CAC and ABI used in both replication and sensitivity analyses followed those previously published by Delaney *et al.*[8] Computed tomography was used to measure CAC as mean phantom-adjusted Agatston score for each participant. Phantom adjustment was used to ensure that scans were comparable between sites in this multi-site study. CAC progression was defined as the difference in CAC between exam 3 and baseline. In incident CAC analysis, only individuals with CAC of 0 at baseline were included. We defined incident CAC as a binary variable where participants were free of CAC at baseline, but had CAC of >0 at follow up.

ABI was determined by using a continuous-wave doppler ultrasound probe to measure blood pressure in both arms and legs. The higher systolic pressure measured in the arms was divided by the higher systolic pressure measured in each of the posterior tibial and dorsalis pedis arteries to calculate ABI used for analysis. Continuous progression of ABI was defined as the difference between exam 3 and

baseline ABI. Incident progression to low ABI was a binary variable, defined as those with normal baseline ABI (0.90 – 1.40) who had ABI <0.90 at follow up.

Independent variables

In the replication analysis, PA measures were again defined according to Delaney *et al*.[8] The total time (in minutes) reported for each activity measured by the TWPAS was converted into metabolic equivalents-minutes per week (MET-min/wk) based on previously assigned conversion factors based on intensity level.[10] Intentional activities were defined as the sum of activities that are typically done purposely for exercise, such as sports activities, dancing, conditioning activities, and walking. Conditioning activities were moderate or vigorous activities that could be completed in a gym (biking, boxing, exercise machines, aerobics, etc.) but did not include team sports or walking. The amounts of reading and television watching reported were summed to create a sedentary behavior measure. Time spent participating in other sedentary activities, such as working or recreating on a computer, were not considered in the sedentary behavior variable. Summary measures were on activity intensity (low/no, moderate, vigorous), activity type (conditioning, sedentary, intentional), and proportion of participants reporting specified activities (conditioning, vigorous, intentional).

In addition to these PA variables, additional PA variables were defined for use in sensitivity analysis. Minutes of PA measures were defined as the sum of minutes of the corresponding PA category (Intentional activity, sedentary behavior, the sum of moderate and vigorous activities, vigorous and condition activity). Each of the predictor PA measures used were also converted to binary variables based on whether the participants performed more than the median reported MET-min/wk. The meeting vigorous PA recommendations variable were defined as a binary variable based on if a participant met vigorous activity recommendations of >75 minutes. Similarly, the meeting combined PA

recommendations was defined as >150 minutes of moderate activity or a combination of moderate and vigorous activity >150 where a vigorous activity minute is equivalent to moderate activity minutes.

2.4 Statistical analysis

Replication Analysis

We used analytical approaches which were adapted from the original analysis by Delaney *et al.*[8] MESA participants who completed a follow up assessment at either exam 3 or exam 4 and had normal baseline ABI (0.90 – 1.40) were included in statistical analyses. Additional exclusions were made if participants were missing data for any of the covariates listed in Table 1 and Table 2. Upon discussion with investigators from Delaney *et al*[8], it was determined individuals for whom only income data were not available should not be excluded from further analysis, as income is a sensitive survey question in the United States and tends to have a high rate of missingness. Individuals with baseline CAC >0 were excluded from incident CAC analysis as they already had experienced the outcome of interest prior to study enrollment.

Both continuous and categorical variables were used to describe study sample characteristics. Mean and standard deviation were used to summarize continuous variables, while absolute number and percentage were used to summarize categorical variables. To reduce skew, we performed a log transformation for all covariates that were found to be a skewed distribution. All PA measures and sedentary behavior measures were log transformed to attenuate the effect of outliers on regression models.

We used intentional activity, sedentary behavior, the sum of moderate and vigorous activities, and conditioning activities as the independent variables, each as MET-min/wk, for replication analysis. Our four outcome variables (ABI progression, CAC progression, incident CAC, or incident low ABI) were

each analyzed using these independent variables. ABI and CAC progression models used continuous outcomes, whereas incident low ABI and CAC models used binary outcomes. We used four different levels of adjustment to analyze each of our outcomes of interest. Model 1 was not adjusted for other covariates. Model 2 was adjusted for sex, ethnicity and age. Model 3 was adjusted for the suspected confounders (age, ethnicity, sex, body mass index, pack years of tobacco use, family history of myocardial infarction, hypertension, dyslipidemia and diabetes). Model 4 was adjusted for socioeconomic variables (education, alcohol use, smoking status, income, and lack of health insurance), in addition to the candidate confounders adjusted for in model 3.

We used logistic regression models to estimate the probability of developing incident CAC and incident low ABI. Although the rare disease assumption (<10% incidence) was violated for the incidence of CAC making the estimates difficult to directly interpret on the risk scale, the relative risks reported by Delaney *et al*[8] were used to guide interpretation of logistic regression analysis and the underlying estimates remain statistically valid. The rare disease assumption held for ABI analyses. We used linear regression to model the continuous progression of ABI. The approach used by Kronmal *et al*[11] was used as a model for our analysis of continuous CAC progression.

Sensitivity Analysis

We used similar statistical approaches for sensitivity analysis to further investigate the possible interactions between PA and sedentary behavior and incident low ABI. Total reported minutes for each of the five previously identified predictor measures were used as independent variables in a logistic regression analysis of incident low ABI as a binary outcome. Binary exposure variables, using median cut offs previously described, were also analyzed using logistic regression analysis of incident low ABI. We also used the binary predictor variable of meeting PA recommendations for vigorous or moderate and vigorous activity minutes in a logistic regression model estimating the probability of developing low ABI.

Each of the sensitivity analysis used the same adjustment scheme as replication analysis. We used a 2-tailed test with an α level of 0.05 for all tests of statistical significant. Stata 13.0 was used to perform analyses.

3. Results

3.1 Study Sample Selection

Figure 1 depicts the process by which the samples used for this study were derived from the greater MESA cohort. Participants that did not return for follow-up assessment (n=1,056) during the study period and those missing outcome, exposure, or covariate data (n=213) were not included in the analysis. Following discussion with the original authors, those with Chronic Kidney Disease (CKD) at baseline (n=12), as defined by an eGFR < 30, were also excluded. An additional 41 participants were not included in the ABI replication and sensitivity analysis due to progression to a high ABI (>1.40) during the study period and the undetermined presence of stiff arteries, as the high ABI has been observed in individuals with advanced atherosclerotic place.[12]

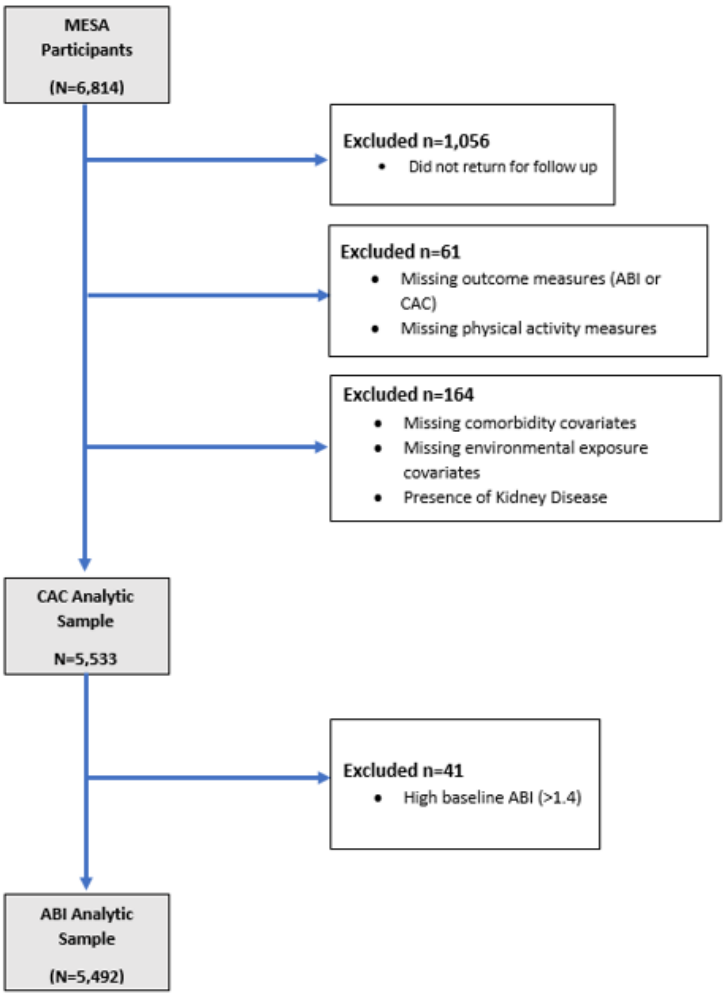

Figure 1. Selection criteria

4.1 Replication Results

ABI Sample Characteristics

Of the 6,814 persons from the MESA cohort, 5,492 participants were included in the ABI analysis. Table 1 displays the descriptive characteristics of this sample. The mean age was 61.8 years, with an average BMI of 28.2 kg/m^2. Nearly half (48%) of participants identified as male. The racial and ethnic composition of the sample was 39.4% non-Hispanic White, 26.8% African American, 21.5% Hispanic and 12.3% Asian. Upon initial assessment, 43.4% had hypertension, 11.7% had diabetes, 34.2% had dyslipidemia, and 33.1% had a family history of MI. Baseline participation in intentional exercise activities was reported by 77.9% of participants, while 35.2% reported participation in conditioning activities and 32.7% reported participation in vigorous activities.

Physical Activity and ABI

Less than 2% (n=109) of participants included in the analysis progressed to an ABI of <0.90 between baseline and reassessment. At baseline, those who would progress to a low ABI had a lower mean ABI (1.031), were older (mean age of 67.6 years), reported a greater number of pack years as smokers, had higher proportions of selected comorbidities and reported less physical activity than those who did not. Additionally, the group that progressed to a low ABI had a greater proportion of African Americans (44%) and higher mean CAC at baseline (309 Agatston units).

Table 3 demonstrates the odds ratios of progression to low ABI as a binary variable and continuous ABI progression for each physical activity measure. Following adjustment for traditional CVD risk factors and socioeconomic variables, intentional physical activity was found to be protective against progression to low ABI (OR = 0.64, CI 95% 0.48, 0.85). An increase in sedentary behavior was found to reduce the odds ratio of progressing to low ABI in adjusted models (OR =0.52, CI 95% 0.35,0.78). Conditioning activity was

found to be protective against progression to low ABI, but the association was only significant when unadjusted by socioeconomic variables. No significant associations were found between continuous ABI progression and any physical activity measures.

CAC Sample Characteristics

Characteristics of the study sample used for CAC analysis are presented in Table 2. Data were available for 5,533 of the MESA participants. The characteristics of this sample closely mirror the subset used for ABI analysis. Those with baseline CAC (n=2,678) had a mean Agatston score of 280 Agatston units and were older, majority male, had a greater mean number of pack years as a smoker, and experienced higher proportions of reported comorbidities than those without baseline CAC, those with incident CAC and those without a change in CAC. In addition, this group performed more vigorous, sedentary, intentional, and conditioning activities than any other group.

There were 2,441 participants free of CAC at baseline, 459 of which developed CAC during the study period. Compared to those with no change in CAC, those with incident CAC were older, had higher BMI, had a greater number of pack years smoked, and had a greater proportion with comorbidities. The incident CAC group performed much less vigorous, moderate and low/no intensity physical activities than those who did not develop CAC.

Physical Activity and CAC

Odds ratios for incident CAC as a binary variable and continuous CAC progression (Δlog (Agatston Units + 25)) for each physical activity measure are presented in Table 4. Adjusting for socioeconomic and traditional CVD risk factors, increased participating in conditioning activities was associated with an increased odds of incident CAC (OR=1.87, CI 95% 1.17,2.96). No other measures of activity were associated with a change in incident CAC odds. In the fully adjusted linear regression analysis of CAC progression,

sedentary behavior was found to be positively associated with CAC progression (beta = 0.062 CI 95% 0.014, 0.111). The level of physical activity was not found to be statistically significantly associated with CAC progression.

3.2 Sensitivity Analysis

In a sensitivity analysis of the interaction between activity measures and ABI, physical activity was further considered as a binary variable and as an absolute measure of time performing each activity. Table 5 shows both the odds ratios for progression to low ABI, as well as continuous ABI progression, for each activity measured in minutes per week. After adjusting for traditional CVD and socioeconomic factors, intentional activity (OR = 0.64, CI 95% 0.47, 0.86) was protective against progression to low ABI. A similar effect was also observed with increased sedentary behavior (OR = 0.53 CI 95% 0.35, 0.80) and reduced odds of low ABI progression. Additionally, there was a positive association found between intentional activity and ABI progression when no adjustment was made for socioeconomic predictors.

Results from ABI analysis using the binary activities variables of median cut-offs or meeting identified physical activity recommendations are presented in Table 6 and Table 7, respectively. Again, increasing intentional activity (OR = 0.51, CI 95% 0.27, 0.99) or sedentary behavior (OR 0.26, CI 95% 0.13, 0.53) were found to be protective against development of low ABI. No significant associations between meeting physical activity recommendations through vigorous or a combination of moderate and vigorous activity and progression to low ABI were found.

4. Discussion

The results of our study replication are broadly consistent with those of Delaney *et al*.[8] Our findings also suggest that performing intensive physical activities is protective against incident low ABI and sedentary behavior contributes to the progression of CAC. Sensitivity analysis further supported a

protective influence of intentional PA against incidence of low ABI. These data suggest higher amounts of intentional PA may be protective against low ABI, even without adjusting for intensity. We also observed a paradoxical lowering of the odds ratio for progression to low ABI for individuals who participated in more sedentary behaviors.

The combined results of our study replication and sensitivity analysis support a reduction in sedentary behaviors and increase intentional activity as lifestyle modifications to support cardiovascular health.

Although our results were generally consistent with previously published findings, there are several limitations and assumptions to consider in interpreting this study. We were unable to identically replicate the sample used in Delaney *et al.* based solely on their original report, which required multiple assumptions when crafting our selection criteria. The statistical methods for study replication differed from those used in the original study and have important shortcomings and benefits to consider when comparing findings. Despite the potential value of sensitivity analyses in providing additional supporting evidence, the chosen analyses may not have addressed important features of predictors or outcomes that may influence results meaningfully. Beyond these various limitations and potential concerns, there are also several features of MESA itself that add uncertainty to the studies that use these data and contribute to misleading conclusions.

4.1 Sampling

Criteria used to select the study sample for this analysis were based on those outlined by Delaney *et al*.[8] and later refined following discussions with one of the original investigators. A direct comparison of the samples and subgroups are presented in the appendix. We determined that it was not viable to exclude all MESA cohort members for all covariate data that was available except for income level.

Exclusion based on missing income data reduced the sample to nearly 200 hundred participants lower than that used in the original analysis. Upon discussion with an investigator from the original study, we determined that individuals missing income data were recoded to reflect their unknown income status and still included in the analysis. A comparable approach was used in the present analysis.

Although the overall samples used were similar, there are differences worth noting between the incident ABI subgroups used in the previous and the present analyses. We identified 109 participants who developed low ABI between baseline and follow up. The original analysis identified 161 participants who developed incident low ABI. The nearly 33% difference in number of participants who developed low ABI is likely due to discrepancies in participant exclusions based on covariate data. Although Delaney *et al* described covariates in some detail, it was difficult to determine which specific MESA variables were used for several of the covariates.

Following data exploration, we attempted to select variables that most closely aligned with the descriptions and sample used in Delaney *et al.* One specific area of ambiguity was in determining which tobacco variables were used. MESA datasets include variables on cigarette, pipe, and cigar smoking status.[13] It was not clear which variable(s) were used in the original analysis for smoking status. Like many studies, Delaney *et al.* described covariates in a general sense (current smoking) despite the presence of quite detailed smoking phenotype data in the MESA cohort. We determined to use only cigarette smoking status due to concern for excessive participant exclusion and a preference not to use missing data techniques other than complete case analysis. Similar challenges were faced when attempting to determine what MESA variables were used to assess participants' current alcohol use or cholesterol lowering medication. The assumption that the variables selected during study replication and sensitivity analysis were correct is potentially a source of observed sample and subgroup discrepancies.

In comparing the original and replication incident low ABI subgroups, the subgroup used in this analysis had a greater number of pack years smoked, a higher proportion of ex-smokers, a greater proportion with dyslipidemia, and were less active, on average, at baseline. Smoking history, hypercholesterolemia, and physical inactivity are each associated with an increased risk of developing PAD.[5] Despite the increase in these risk factors compared to the original incident subgroup, the present subgroup had an average baseline BMI of nearly 1 kg/m^2 lower. High BMI has also been associated with an increased risk of developing PAD.[5] Given the stronger associations previously observed between smoking and PAD compared to most other risk factors, in addition to other risk factors, it is likely that this incident ABI group had a greater odds of developing PAD than the group used in the original analysis. The greater baseline risk may have contributed to both the greater affect size and overall number of associations observed in both replication and sensitivity analyses of PA and PAD or ABI progression.

4.2 Replication and Sensitivity Analysis

Analytical Approaches

In replicating the analysis of Delaney *et al.* we attempted to maintain selection criteria, variable definitions, and structure of analysis. We decided to utilize logistic regression for statistical analysis of incident progression to low ABI and incident CAC for each of the defined PA exposure variables. This approach was less analytically onerous, while still providing results that are readily interpretable and applicable in clinical settings. It is important to note that the odds ratios provides an exaggerated approximation of relative risk, which becomes more accurate as the true incidence of outcome approaches 0.[14] The odds ratio is generally accepted as an adequate approximation of the risk ratio when the rare disease assumption, that is an incidence of less than 10%, is met. The incidence of new CAC was >10% in this study sample, thus violating the rare disease assumption and resulting in odds ratios which greatly exaggerates the relative risk. However, the lack of statistical significance between any predictors

variables and CAC incidence in Delaney *et al*. and in this replication analysis suggest that there is no influence between PA and incident CAC. For continuous ABI and CAC progression analysis, the same approaches were used as outlined in Delaney *et al.*

ABI and Intentional Activity

The results from the present analysis support the previous findings and suggest that participation in intentional exercise activities is protective against progression to low ABI as defined by low ABI. Delaney et al. found that in those who participated in more intentional activities, the relative risk of progression to low ABI was RR = 0.85 (95% CI 0.74, 0.96). The greater magnitude of effect observed in the present study is likely the result of the difference in sample and statistical methods already described.

Results from the sensitivity analyses of incident progression to low ABI and activity measures were consistent with the results of our replication analysis. The protective effect of intentional activity against incident ABI <0.90 was maintained even when minutes of activity or binary classification of activity exposure were used as predictor variables. The consistency of these results with the key results of Delaney *et al.* indicate that these findings are robust to analytical approaches and variations in the definitions of covariates.

Our findings of a protective effect of intentional exercise activities against progression to low ABI are consistent with previous studies. The Sugar, Hypertension And Physical Exercise (SHAPE2) study observed the effects of participants with either Type 2 diabetes or hypertension who were randomized to a 6-month exercise program, which included both strength and aerobic training, or a control which did not include exercise. Analysis of this intervention found that exercise had a significant increased ABI at 6 months, whereas controls experienced a drop in ABI.[15] Furthermore, this analysis found that intentional

exercise increased the percentage of participants with normal ABI, while there was also a decrease in the percentage of individuals with borderline ABI.

In addition to the consistency of the finding that intentional exercise activities are protective against progression to low ABI in this and previous studies, these results also align with current national recommendations for the prevention and management PAD. A 2013 evidence summary prepared for the U.S. Preventive Services Task Force (USPSTF) noted the risk of developing PAD was lower in those who were more active compared with those who engaged in less activity.[5] In 2016, the American Heart Association (AHA) and the American College of Cardiology (ACC) provided joint clinical guidelines for the management of PAD.[16] These guidelines include strong recommendation for patients with symptomatic PAD to engage in intentional exercise activities that are supervised to improve functional status through improved vascular adaptation, quality of life, and reduce symptoms. Furthermore, it is considered a front-line treatment option for PAD. These recommendations are based on extensive reviews and meta-analyses of randomized controlled trials.[17,18]

We did not observe a significant protective effect when current American College of Sports Medicine (ACSM)/AHA PA recommendations for cardiovascular health in adults of 150 minutes of moderate PA or equivalent moderate and vigorous activity as a predictor of incident progression to low ABI.[4] These recommendations are primarily based on evidence from adults up to the age of 65 years. The current ACSM/AHA recommendations for older adults place less emphasis on a high level of activity, have lower thresholds for activity intensity, and focus on incorporation of therapeutic or preventative activities.[3] Given that a sizeable portion of the MESA population and the sample used for these analyses are between the ages of 65 – 85 years, it is problematic to directly apply either of these recommendations to this mixed sample. Regardless, both recommendations acknowledge the benefits of a greater level of intentional activities as tolerable for a given population and align with our findings overall.

CAC and Sedentary Behavior

CAC analysis replication results also align with the findings of Delaney *et al.* Of those with baseline CAC, participants who reported more sedentary behavior had more CAC progression. The magnitude of this interaction was slightly larger than that observed in the original study. Differences observed between the magnitude of this effect may be attributable to covariate definitions for the exclusion criteria which result in prevalent and incident CAC groups that reported less activity and more sedentary behavior than corresponding groups in Delaney et al. Similar associations between sedentary behaviors and CAC have been reported in the time since Delaney et al. reported their findings.[19]

The finding of this positive correlation between sedentary behavior and CAC progression provides additional support to current activity recommendations for adults and older adults. A substantial amount of evidence exists supporting the deleterious effect of increased sedentary behavior on health status, particularly for individuals with existing health conditions.[3,4] These body of evidence is the basis of current PA recommendations to limit the amount of sedentary behavior, especially for older adults, to support cardiovascular and overall health.[2]

Both Delaney *et al.* and our analysis found no significant associations between increased sedentary behavior and increased risk of incident CAC. This is potentially attributable to the relatively low amount and similarity of which CAC analysis subgroups reported sedentary behavior. Participants in the incident CAC group had a mean sedentary behavior of 1689 MET-minutes per week, whereas the No CAC group had a mean of 1615 MET-minutes per week. Delaney *et al.* had a similar pattern of sedentary behavior reporting in CAC analysis subgroups. Previous sedentary behavior pattern estimates for American adults using accelerometer data suggest that adults and older adults participate in sedentary behavior for more than 7.7 hours (greater than 50% of wakeful hours) each day.[20] This level of sedentary behavior would correspond to nearly twice the amount of weekly sedentary behavior reported by the

sample in this analysis. If participants underreported their activity to this extent, it is possible that the differences in sedentary behavior and the effects on incident CAC could not be detected due measurement error in this variable, especially if the measurement error was differential based on participant characteristics.

ABI and Sedentary Behaviors

In addition to these key findings, we also observed other interactions worthy of note. There was evidence throughout the replication and sensitivity analyses which paradoxically suggested that sedentary behavior was found to lower the odds ratio of progression to low ABI. A similar trend was shown by Delaney *et al*, although no significance was observed. It is possible that these findings were disproportionally influenced by activity patterns of a few participants due to relatively small size of incident progression to low ABI subgroup. However, there are other possible explanations for these findings.

Perhaps sedentary behavior contributed to peripheral artery calcification and arterial stiffness, which resulted in falsely normal ABI. Participants who otherwise could have been classified as having incident PAD, would not be captured in the incident progression to low ABI group. We did observe both subgroups in ABI analysis had non-negligible mean CAC at baseline. Additionally, there is some evidence in certain populations which may support the feasibility of this mechanism, such as those with impaired kidney function.[12]

4.3 Limitations

There are potential limitations to this analysis on multiple levels, from the underlying design of MESA, to the choice between two similar variables. Many of these are directly related to assumptions made in service of pursing the aims of this study. Although assumptions such as these exist in ostensibly

all research, it is important to continuously consider the potential influence they have on the resulting conclusions.

Subjective Activity Measures

One of the main assumptions that likely effect the findings of this analysis was the way activity patterns were measured and how those measures were used. Given the scale of MESA, it is understandable why subjective measures of physical activity and sedentary behaviors were used. An underlying assumption of these measures are that when compared across a large sample they provide a relative distribution of activity patterns for individuals and that these patterns are representative of the typical habits of participants.

The validity and accuracy of a given subjective activity measure can vary greatly between different study populations or study methods.[21,22] The TWPAS used in MESA was based on a previous study of activity patterns in African American and Native Americans. This study included only women who had a mean age of nearly 10 years younger than the mean age of MESA participants.[10] Furthermore, even when subjective measurement tools are validated, they have been shown to offer only moderate reliability.[23] It is difficult to predict what cumulative impact the misclassification in physical activity levels as measured by the subjective activity measures had on the findings of this analysis, but given previous evidence it likely resulted in an overestimation of PA, underestimation of sedentary behavior, and an overall dilution of potential interactions.[21] This would be especially problematic if specific sub-populations over or under reported physical activity to a different degree (*e.g.,* if high BMI participants over-reported intensity of activity compared to moderate BMI participants). Previous investigation into the differential reporting of PA between sub-populations have found significant associations between key characteristics, such as BMI and racial or ethnic groups, and the degree of reporting error.[24]

Study Replication

Another important limitation for this replication and sensitivity analysis, which can be inherent to any replication analysis, is the assumption that the original report provides the requisite information to appropriately recreate the analysis. During study development, analysis, and interpretation, there are numerous occasions where assumptions or deciding between two approaches must be made. Given the limitations many scientific journals place on the length of published works, it is impossible to compressively convey every decision, let alone rationales or underlaying assumptions that led to those decisions, when reporting findings. This requires authors to selectively report information deemed to be the most relevant to the study. Delaney *et al.* was not exempt from these constraints.

In attempting to replicate the original analysis described by Delaney *et al,* there were numerous instances where decisions relevant to the analysis had to be made based on information or assumption not described in the published report. Communication with original investigators provided some clarification, particularly with respects to application of inclusion criteria for missing income data or kidney function, as previously discussed, but was not able to elucidate all analysis considerations. Assumptions made on analysis features that remained ambiguous, such as selection of variables used to assess potential confounders like smoking status, alcohol use, and health status potentially limit the comparability between the analyses, and thus the value of this replication. Given the overall similarities in study samples and key findings, it is unclear to what extent these assumptions effected this analysis. However, a key piece of this work was to verify that these results were robust to reasonable differences in study sample definition and covariate selection, so this is an expected part of this family of replication activities.

Clinical and Public Health Applications

A fundamental purpose for this type of investigation is to develop recommendations to promote public health and to inform clinical practice. It is difficult to craft an analysis that can equally serve these ends. On one end, research that results in findings that are readily generalizable to large, diverse populations is ideal for developing or evaluating public health recommendations. Conversely, specific clinical guidelines to address a specific condition, such as atherosclerosis, may require evidence from a specific and homogenous population. An outcome of this dichotomy is that findings of a given analysis may be used in one setting readily, but will be more limited in the other.

In terms of the present analysis and original analysis by Delaney *et al,* these findings provide evidence for a diverse population of adults in the United States. These findings can almost directly be applied to, or used to evaluate, current PA recommendations for cardiovascular health as described previously. Even with this population level evidence, these findings were difficult to apply to national recommendations for different age groups of adults. In a clinical setting, these findings can broadly be used to guide lifestyle goals to promote cardiovascular health; they offer little benefit in terms of understanding what strategies or interventions can be used to shift activity patterns to align with those our findings suggest are protective.

4.4 Future Directions

Future investigations should take into consideration these findings and the limitations identified. Large cohort studies investigating PA and indicators of cardiovascular health should include objective activity measures to ensure validity of any subjective measures used and reliability of PA exposure. Future replication studies should include rigorous consideration of assumptions and limitations of the original analysis and those potentially inherent to the replication analysis itself. Finally, measures of why

participants have the activity pattern they do and more detail descriptions of participants for more stratified analysis, should be included to add value to the findings in both clinical and public health settings.

5. Conclusions

The findings of this study replication and sensitivity analysis confirm the original results from Delaney *et al.* and continue to support the encouragement of intentional physical activities to protect against PAD. Furthermore, the intentionality of PA may be an important consideration when making activity recommendations, rather than a numerical target of 150 minutes per week. These results also provide evidence that sedentary behavior contributes to CAC progression, suggesting that any activity to reduce sedentary behavior would protect against CAC progression and CVD. Furthermore, these results provide additional support to current national physical activity recommendations to support health. [2–4]

6. Tables

Table 1.

Baseline cohort characteristics for ABI analysis.

Variable	Total	Progress to low ABI[a]	No ABI change
	n = 5492	n = 109	n = 5383
Age, years (SD)	61.8 (10.1)	67.6 (9.8)	61.6 (10.1)
BMI, kg/m^2 (SD)	28.2 (5.4)	28.9 (5.9)	28.2 (5.4)
Alcohol, drink/wk (SD)	4 (8.4)	3.6 (6.1)	4 (8.4)
Pack years smoker (SD)	11 (20.7)	19.1 (31.7)	10.9 (20.4)
Ex-smoker (%)	36.5	39.5	36.5
Current smoker (%)	12.3	20.1	12.1
Male (%)	47.6	40.4	47.8
Hypertension (%)	43.4	63.3	43.0
Diabetes (%)	11.7	21.1	11.5
Dyslipidemia (%)	34.2	39.4	34.1
Family history of MI (%)	33.1	36.7	33.1
Socio-economic (%)			
No health insurance	8.4	8.3	8.5
Income <$25 K	31.8	39.5	31.6
Income $50 - $100 K	26.2	20.2	26.3
Income >$100 K	14.1	6.4	14.3
Less than high school education	16.5	28.5	16.3
College education	18.3	14.7	18.4
Graduate school	19	15.6	19.0
Race/ethnicity (%)			
Non-Hispanic White	39.4	32.1	39.6
Asian	12.3	4.6	12.4
African American	26.8	44	26.5
Hispanic	21.5	19.3	21.5
Activity proportions (%)			
Conditioning reported	35.2	29.4	35.2
Vigorous activity reported	32.6	23.9	32.6
Intentional exercise reported	78	66.1	78.0
Activity			
Vigorous, MET-min/wk (SD)	934 (2753)	683 (2813)	933 (2753)
Moderate, MET-min/wk (SD)	4856 (4452)	3901 (3551)	4856 (4452)
Now/low, MET-min/wk (SD)	6433 (3213)	6207 (3032)	6438 (3217)
Sedentary behavior, MET-min/wk (SD)	1698 (1142)	1690 (1005)	1698 (1145)
Intentional activities, MET-min/wk (SD)	2474 (2933)	1688 (1931)	2490 (2948)
Conditioning activity, MET-min/wk (SD)	490 (1236)	243 (502)	484 (1246)
Outcomes			
Ankle-brachial index	1.114 (0.111)	1.031 (0.081)	1.116 (0.111)
Coronary Artery Calcium at baseline (Agatston) units)	133 (376)	309 (790)	129 (362)

[a] Low ABI defined as >0.90

Table 2.

Baseline cohort characteristics for CAC analysis.

Variable	Total	Prevalent CAC[a]	Incident CAC[b]	No CAC/No
	n = 5533	n = 2678	n = 459	n = 2396
Age, years (SD)	61.8 (10.1)	65.9 (9.5)	60.7 (9.1)	57.3 (9)
BMI, kg/m^2 (SD)	28.2 (5.4)	28.3 (5.2)	29.4 (5.9)	28.0 (5.5)
Alcohol, drink/wk (SD)	4 (8.4)	4.6 (8.5)	3.8 (8.9)	3.4 (8.2)
Pack years smoker (SD)	11 (20.7)	14.5 (24)	10.1 (21.3)	7.4 (15.3)
Ex-smoker (%)	36.6	42.8	37	29.5
Current smoker (%)	12.2	12.1	12.4	12.4
Male (%)	47.9	59.1	47.5	35.5
Hypertension (%)	43.3	52.8	47.1	32.1
Diabetes (%)	11.8	14.8	13.3	8.1
Dyslipidemia (%)	34.3	42.9	35.9	24.2
Family history of MI (%)	33.2	36.5	34	29.4
Socio-economic (%)				
No health insurance	8.4	6.5	7.6	10.7
Income <$25 K	31.7	34.6	31.8	28.4
Income $50 - $100 K	26.2	24.6	26.4	28
Income >$100 K	14.1	13.3	11.5	15.5
Less than high school education	16.5	16.8	19	15.7
College education	18.2	17.6	15	19.6
Graduate school	19	18.9	19.2	19.2
Race/ethnicity (%)				
Non-Hispanic White	39.5	45.2	35.1	34
Asian	12.2	12.2	8.1	12.9
African American	26.7	22.6	31.4	30.5
Hispanic	21.5	19.9	25.5	22.6
Activity proportions (%)				
Conditioning reported	35.2	35.4	34	35.3
Vigorous activity reported	32.7	32.9	28.1	33.2
Intentional exercise reported	77.9	78.8	74.7	77.5
Activity				
Vigorous, MET-min/wk (SD)	937 (2754)	965 (2843)	823 (2497)	927 (2700)
Moderate, MET-min/wk (SD)	4862 (4463)	4645 (4414)	4919 (4438)	5094 (4511)
Now/low, MET-min/wk (SD)	6429 (3210)	5943 (3086)	6590 (3221)	6941 (3263)
Sedentary behavior, MET-min/wk (SD)	1699 (1142)	1775 (1124)	1689 (1153)	1615 (1155)
Intentional activities, MET-min/wk	2482 (2945)	2573 (3070)	2392 (2891)	2399 (2809)
Conditioning activity, MET-min/wk	490 (1237)	511 (1295)	454 (1231)	473 (1170)
Outcomes				
Ankle-brachial index	1.117 (0.117)	1.107 (0.134)	1.131 (0.095)	1.126 (0.097)
Coronary Artery calcium at baseline (Agatston units)	135 (384)	280 (514)	0(0)	0 (0)

[a] Prevalent CAC defined as CAC >0 at baseline

[b] Incident CAC defined as CAC >0 at follow up for those with CAC =0 at baseline

Table 3.

Association between self-reported measures of physical activity and ankle brachial index (ABI) progression

	Activity	Continuous ABI Progression Coefficient[a] (95%CI)	Progression to low ABI OR[b] (95% CI)
Model 1	Intentional activity	0.003 (-0.002, 0.008)	0.74 (0.63, 0.88)*
Model 2		0.003 (-0.002, 0.007)	0.72 (0.61, 0.86)*
Model 3		0.002 (-0.004, 0.009)	0.68 (0.54, 0.85)*
Model 4		0.002 (-0.006, 0.009)	0.64 (0.48, 0.85)*
Model 1	Sedentary	-0.004 (-0.008, -0.001)*	1.01 (0.79, 1.29)
Model 2		0.000 (-0.004, 0.003)	0.86 (0.67, 1.11)
Model 3		0.000 (-0.006, 0.005)	0.65 (0.47, 0.89)*
Model 4		0.005 (-0.002, 0.012)	0.52 (0.35, 0.78)*
Model 1	Moderate & Vigorous[c]	0.002 (-0.001, 0.005)	0.79 (0.67, 0.93)*
Model 2		0.000 (-0.003, 0.003)	0.87 (0.73, 1.05)
Model 3		-0.002 (-0.006, 0.002)	0.84 (0.67, 1.05)
Model 4		0.002 (-0.007, 0.003)	0.74 (0.55, 0.99)*
Model 1	Vigorous[c]	0.001 (-0.003, 0.004)	0.89 (0.62, 1.30)
Model 2		-0.002 (-0.005, 0.002)	0.92 (0.61, 1.37)
Model 3		0.001 (-0.004, 0.006)	0.77 (0.49, 1.20)
Model 4		0.000 (-0.006, 0.006)	0.99 (0.61, 1.61)
Model 1	Conditioning	0.003 (-0.002, 0.008)	0.77 (0.60, 0.99)*
Model 2		0.002 (-0.002, 0.007)	0.75 (0.58, 0.98)*
Model 3		0.002 (-0.004, 0.009)	0.72 (0.54, 0.96)*
Model 4		0.002 (-0.006, 0.009)	0.73 (0.49, 1.09)

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.
*$p < 0.05$.

[a] Linear relationship between activity measures and continuous ABI change

[b] Odds ratio of progressing to ABI <0.90 for a given activity measure

[c] No/low activity is the reference category. (adjusted for low/no activity)

Table 4.

Association between self-reported measures of physical activity and coronary artery calcification (CAC).

	Activity	Incident CAC OR[a] (95% CI)	Continuous CAC progression[b] [Δlog (Agatston Units + 25)]
Model 1	Intentional activity	0.97 (0.89, 1.07)	-0.006 (-0.026, 0.132)
Model 2		0.96 (0.88, 1.06)	-0.005 (-0.025, 0.015)
Model 3		1.09 (0.95, 1.25)	-0.012 (-0.039, 0.016)
Model 4		1.10 (0.91, 1.33)	-0.004 (-0.031, 0.023)
Model 1	Sedentary	1.09 (0.95, 1.25)	0.044 (0.016, 0.072)*
Model 2		1.01 (0.88, 1.17)	0.044 (0.016, 0.073)*
Model 3		0.89 (0.72, 1.12)	0.044 (0.004, 0.083)*
Model 4		1.05 (0.77, 1.43)	0.062 (0.014, 0.111)*
Model 1	Moderate + Vigorous[c]	0.97 (0.88, 1.07)	-0.010 (-0.032, 0.011)
Model 2		0.97 (0.88, 1.08)	-0.011 (-0.033, 0.010)
Model 3		1.08 (0.92, 1.26)	-0.008 (-0.037, 0.021)
Model 4		1.04 (0.85, 1.28)	0.013 (-0.019, 0.046)
Model 1	Vigorous[c]	1.05 (0.91, 1.22)	0.000 (-0.033, 0.033)
Model 2		1.05 (0.90, 1.24)	-0.010 (-0.042, 0.022)
Model 3		0.90 (0.70, 1.16)	0.001 (-0.044, 0.046)
Model 4		0.93 (0.65, 1.34)	0.004 (-0.054, 0.062)
Model 1	Conditioning	1.00 (0.84, 1.18)	-0.003 (-0.040, 0.034)
Model 2		1.00 (0.84, 1.19)	-0.007 (-0.043, 0.030)
Model 3		1.37 (1.04, 1.80)*	-0.006 (-0.045, 0.033)
Model 4		1.87 (1.17, 2.96)*	0.014 (-0.033, 0.061)

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.

*$p < 0.05$.

[a] Odds ratio of CAC >0 at follow up for those without previous CAC for given activity measure.

[b] Linear relationship between activity measures and continuous adjusted CAC change

[c] No/low activity is the reference category (adjusted for low/no activity)

Table 5.

Association between self-reported minutes of physical activity and ankle brachial index (ABI) progression.

	Activity	Continuous ABI Progression Coefficient[a] (95%CI)	Progression to low ABI OR[b] (95% CI)
Model 1	Intentional activity	0.004 (0.001, 0.007)*	0.74 (0.62, 0.88)*
Model 2		0.004 (0.001, 0.007)*	0.72 (0.60, 0.86)*
Model 3		0.004 (0.000, 0.008)*	0.67 (0.52, 0.86)*
Model 4		0.002 (-0.003, 0.007)	0.64 (0.47, 0.86)*
Model 1	Sedentary	-0.005 (-0.008, -0.001)*	1.06 (0.81, 1.37)
Model 2		-0.001 (-0.005, 0.003)	0.89 (0.68, 1.16)
Model 3		-0.001 (0.006, 0.004)	0.66 (0.47, 0.92)*
Model 4		0.004 (-0.002, 0.011)	0.53 (0.35, 0.80)*
Model 1	Moderate & Vigorous[c]	0.002 (-0.000, 0.005)	0.84 (0.70, 0.99)*
Model 2		0.000 (-0.003, 0.003)	0.85 (0.71, 1.02)
Model 3		-0.002 (-0.006, 0.002)	0.84 (0.66, 1.06)
Model 4		-0.001 (-0.007, 0.004)	0.73 (0.54, 0.98)*
Model 1	Vigorous[c]	0.000 (-0.003, 0.004)	0.90 (0.61, 1.31)
Model 2		-0.002 (-0.006, 0.002)	0.92 (0.61, 1.38)
Model 3		0.001 (-0.004, 0.006)	0.77 (0.49, 1.21)
Model 4		0.000 (-0.006, 0.006)	1.00 (0.62, 1.62)
Model 1	Conditioning	0.003 (-0.002, 0.008)	0.79 (0.61, 1.02)
Model 2		0.002 (-0.002, 0.007)	0.77 (0.59, 0.99)*
Model 3		0.002 (-0.004, 0.009)	0.72 (0.54, 0.95)*
Model 4		0.002 (-0.006, 0.009)	0.73 (0.50, 1.08)

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.

*$p < 0.05$.

[a] Linear relationship between activity measures and continuous ABI change

[b] Odds ratio of progressing to ABI <0.90 for a given activity measure

[c] No/low activity is the reference category. (adjusted for low/no activity)

Table 6.

Association between level of self-reported physical activity minutes per week and ankle brachial index (ABI) progression using median cut off.

	Activity	Progression to low ABI OR[a] (95% CI)
Model 1	Moderate & Vigorous[c]	0.74 (0.49, 1.10)
Model 2		0.78 (0.52, 1.16)
Model 3		0.81 (0.49, 1.36)
Model 4		0.63 (0.32, 1.28)
Model 1	Vigorous[c]	0.74 (0.47, 1.17)
Model 2		0.88 (0.54, 1.41)
Model 3		0.88 (0.49, 1.58)
Model 4		0.88 (0.42, 1.84)

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.

*$p < 0.05$.

[a] Odds ratio of progressing to ABI <0.90 for when activity recommendations are met

[b] No/low activity is the reference category. (adjusted for low/no activity)

Table 7.

Association between self-reported level of physical activity and ankle brachial index (ABI) progression using median cut off.

	Activity	Progression to low ABI OR[a] (95% CI)
Model 1	Intentional activity	0.56 (0.38, 0.84)*
Model 2		0.54 (0.36, 0.81)*
Model 3		0.62 (0.37, 1.04)
Model 4		0.51 (0.27, 0.99)*
Model 1	Sedentary	0.97 (0.66, 1.43)
Model 2		0.78 (0.52, 1.17)
Model 3		0.44 (0.25, 0.77)*
Model 4		0.26 (0.13, 0.53)*
Model 1	Moderate & Vigorous[b]	0.80 (0.54, 1.17)
Model 2		0.84 (0.57, 1.25)
Model 3		0.89 (0.54, 1.48)
Model 4		0.72 (0.37, 1.41)
Model 1	Vigorous[b]	0.74 (0.47, 1.16)
Model 2		0.87 (0.54, 1.41)
Model 3		0.85 (0.47, 1.55)
Model 4		0.86 (0.40, 1.81)
Model 1	Conditioning	0.82 (0.53, 1.25)
Model 2		0.85 (0.56, 1.30)
Model 3		0.89 (0.52, 1.52)
Model 4		0.78 (0.39, 1.58)

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.

*$p < 0.05$.

[a] Odds ratio of progressing to ABI <0.90 for a given activity measure

[b] No/low activity is the reference category (adjusted for low/no in all models). Median value for these activity measures is 0.

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8. Appendix – Sample Comparison Tables

Baseline cohort characteristics comparisons from ABI analyses.

Variable	Total		Progress to low ABI[a]		No ABI change	
Study	Present	Delaney et al.	Present	Delaney et al.	Present	Delaney et al.
	n = 5492	n = 5656	n = 109	n = 161	n = 5383	n = 5445
Age, years (SD)	61.8 (10.1)	61.3 (9.9)	67.6 (9.8)	67.6 (9.8)	61.6 (10.1)	61.2 (9.9)
BMI, kg/m^2 (SD)	28.2 (5.4)	28.3 (5.4)	28.9 (5.9)	29.7 (6.6)	28.2 (5.4)	28.2 (5.3)
Alcohol, drink/wk (SD)	4 (8.4)	4 (8.2)	3.6 (6.1)	3.1 (5.6)	4 (8.4)	3.9 (8.3)
Pack years smoker (SD)	11 (20.7)	105.5 (21.5)	19.1 (31.7)	16.2 (28.2)	10.9 (20.4)	10.4 (21.3)
Ex-smoker (%)	36.5	36.5	39.5	35.4	36.5	36.5
Current smoker (%)	12.3	12.2	20.1	19.3	12.1	12
Male (%)	47.6	47.4	40.4	40.4	47.8	47.5
Hypertension (%)	43.4	42.2	63.3	64	43.0	41.9
Diabetes (%)	11.7	11	21.1	21.1	11.5	10.8
Dyslipidemia (%)	34.2	33.1	39.4	36.6	34.1	32.9
Family history of MI (%)	33.1	33.3	36.7	36.6	33.1	33.2
Socio-economic (%)						
No health insurance	8.4	8.5	8.3	8.1	8.5	8.5
Income <$25 K	31.8	30.8	39.5	39.1	31.6	30.8
Income $50 - $100 K	26.2	26.4	20.2	21.7	26.3	26.4
Income >$100 K	14.1	14.3	6.4	5.6	14.3	14.3
Less than high school	16.5	16.4	28.5	24.8	16.3	16.2
College education	18.3	18.3	14.7	15.5	18.4	184
Graduate school	19	19.1	15.6	16.1	19.0	19
Race/ethnicity (%)						
Non-Hispanic White	39.4	41	32.1	36	39.6	40
Asian	12.3	21	4.6	3.7	12.4	12.4
African American	26.8	26.4	44	43.5	26.5	26
Hispanic	21.5	21.5	19.3	16.8	21.5	21.6
Activity proportions (%)						

Conditioning reported	35.2	35.4	29.4	33.5	35.2	35.2
Vigorous activity reported	32.6	33.1	23.9	22.4	32.6	33.3
Intentional exercise	78	78.1	66.1	69.6	78.0	78.3
Activity						
Vigorous, MET-min/wk (SD)	934 (2753)	975 (2845)	683 (2813)	626 (2495)	933 (2753)	982 (2855)
Moderate, MET-min/wk (SD)	4856 (4452)	4917 (4493)	3901 (3551)	4120 (3800)	4856 (4452)	4938 (4517)
Now/low, MET-min/wk (SD)	6433 (3213)	6091 (2931)	6207 (3032)	5471 (2717)	6438 (3217)	6096 (2931)
Sedentary behavior, MET-	1698 (1142)	1682 (1130)	1690 (1005)	1820 (1140)	1698 (1145)	1678 (1130)
Intentional activities, MET-	2474 (2933)	2504 (2990)	1688 (1931)	2044 (2532)	2490 (2948)	2512 (3011)
Conditioning activity, MET-	490 (1236)	506 (1309)	243 (502)	429 (1275)	484 (1246)	503 (1303)
Outcomes						
Ankle-brachial index	1.114 (0.111)	1.128 (0.090)	1.031 (0.081)	1.045 (0.097)	1.116 (0.111)	1.130 (0.088)
Coronary Artery Calcium at baseline	133 (376)	124 (359)	309 (790)	369 (805)	129 (362)	116 (355)

[a] Low ABI defined as >0.90

Baseline cohort characteristics comparisons from CAC analyses.

Variable	Total		Prevalent CAC[a]		Incident CAC[b]		No CAC/No change	
Study	Present	Delaney et al.	Present	Delaney et al.	Present	Delaney et	Present	Delaney et al.
	n = 5533	n = 5656	n = 2678	n = 2661	n = 459	n = 580	n = 2396	n = 2415
Age, years (SD)	61.8 (10.1)	61.3 (9.9)	65.9 (9.5)	65.4 (9.4)	60.7 (9.1)	60.4 (8.9)	57.3 (9)	57.1 (8.9)
BMI, kg/m^2 (SD)	28.2 (5.4)	28.3 (5.4)	28.3 (5.2)	28.3 (5.1)	29.4 (5.9)	29.3 (5.9)	28.0 (5.5)	28.0 (5.5)
Alcohol, drink/wk (SD)	4 (8.4)	4 (8.2)	4.6 (8.5)	4.5 (8.3)	3.8 (8.9)	4.0 (9.8)	3.4 (8.2)	3.3 (7.6)
Pack years smoker (SD)	11 (20.7)	105.5 (21.5)	14.5 (24)	13.5 (23.1)	10.1 (21.3)	9.8 (19.9)	7.4 (15.3)	7.4 (19.5)
Ex-smoker (%)	36.6	36.5	42.8	42.8	37	37.2	29.5	29.4
Current smoker (%)	12.2	12.2	12.1	11.6	12.4	13.3	12.4	12.5
Male (%)	47.9	47.4	59.1	59.5	47.5	45.2	35.5	34.7
Hypertension (%)	43.3	42.2	52.8	51.6	47.1	45.5	32.1	31.4
Diabetes (%)	11.8	11	14.8	13.6	13.3	13.3	8.1	7.6
Dyslipidemia (%)	34.3	33.1	42.9	33	35.9	35.9	24.2	19.1
Family history of MI (%)	33.2	33.3	36.5	36.9	34	32.3	29.4	29.6
Socio-economic (%)								
No health insurance	8.4	8.5	6.5	6.4	7.6	7.6	10.7	10.9
Income <$25 K	31.7	30.8	34.6	33.6	31.8	31	28.4	28
Income $50 - $100 K	26.2	26.4	24.6	24.7	26.4	26.7	28	28.2
Income >$100 K	14.1	14.3	13.3	13.5	11.5	12.4	15.5	15.3
Less than high school	16.5	16.4	16.8	16.5	19	17.9	15.7	19.9
College education	18.2	18.3	17.6	17.7	15	16.4	19.6	19.4
Graduate school	19	19.1	18.9	19.3	19.2	19.1	19.2	18.9
Race/ethnicity (%)								
Non-Hispanic White	39.5	41	45.2	33.9	35.1	37.8	34	33.9
Asian	12.2	21	12.2	12.3	8.1	8.1	12.9	12.8
African American	26.7	26.4	22.6	21.9	31.4	30.3	30.5	30.5
Hispanic	21.5	21.5	19.9	19.7	25.5	23.8	22.6	22.9
Activity proportions (%)								
Conditioning reported	35.2	35.4	35.4	36.2	34	32.9	35.3	35.1

Vigorous activity	32.7	33.1	32.9	33.8	28.1	27.8	33.2	33.5
Intentional exercise	77.9	78.1	78.8	79.2	74.7	75	77.5	77.6
Activity								
Vigorous, MET-min/wk	937 (2754)	975 (2845)	965 (2843)	1019 (2947)	823 (2497)	798 (2335)	927 (2700)	969 (2840)
Moderate, MET-min/wk	4862 (4463)	4917 (4493)	4645 (4414)	4718 (4430)	4919 (4438)	4759 (4252)	5094 (4511)	5175 (1132)
Now/low, MET-min/wk	6429 (3210)	6091 (2931)	5943 (3086)	5665 (2821)	6590 (3221)	6232 (2896)	6941 (3263)	6526 (2990)
Sedentary behavior,	1699 (1142)	1682 (1130)	1775 (1124)	1749 (1106)	1689 (1153)	1700 (1206)	1615 (1155)	1605 (1132)
Intentional activities,	2482 (2945)	2504 (2990)	2573 (3070)	2595 (3089)	2392 (2891)	2296 (2717)	2399 (2809)	2453 (2958)
Conditioning activity,	490 (1237)	506 (1309)	511 (1295)	534 (1346)	454 (1231)	446 (1186)	473 (1170)	489 (1296)
Outcomes								
Ankle-brachial index	1.117 (0.117)	1.128 (0.090)	1.107 (0.134)	1.125 (0.0087)	1.131 (0.095)	1.135 (0.087)	1.126 (0.097)	1.129 (0.093)
Coronary Artery Calcium at baseline (Agatston) units)	135 (384)	124 (359)	280 (514)	260 (486)	0(0)	0 (0)	0 (0)	0 (0)