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METABOLIC SYNDROME AND INCIDENT PERIPHERAL ARTERY DISEASE- THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

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Abstract

OBJECTIVE—We evaluated whether metabolic syndrome (MetS) is associated with an increased incidence of lower extremity peripheral artery disease (PAD) in community dwelling people free of clinical cardiovascular disease at baseline. We assessed whether higher levels of inflammatory biomarkers may mediate the association of MetS with incident PAD.

METHODS—MetS was defined at baseline as the presence of three or more of the following components: elevated waist circumference, triglycerides >/=150mg/dL, reduced high-density lipoprotein (HDL) cholesterol, blood pressure >/=130/85mmHg or taking blood pressure medication, and fasting glucose >/=100mg/dL and <126mg/dL. People with diabetes were

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excluded. Incident PAD was defined as a decline in the ankle-brachial index (ABI) from normal (ABI 0.90 –<1.40) at baseline to one of the following outcomes at 3 year follow-up: ABI decline to <0.90 combined with a decline ≥0.15 or medical record confirmed PAD outcome. Multivariable Poisson regression was used to estimate the association between MetS and incident PAD.

RESULTS—Among 4,817 participants without PAD at baseline, 1,382 (29%) had MetS. Adjusting for age, sex, race, smoking, physical activity, low-density lipoprotein cholesterol, baseline ABI, and other confounders, 23/1,382 (1.7%) people with MetS developed PAD vs. 30/3,435 (0.87%) people without MetS (risk ratio=1.78 [95% Confidence Interval (CI), 1.04 to 2.82], P=0.031). Adjusting for C-reactive protein, fibrinogen, or interleukin-6 did not attenuate this association.

CONCLUSION—People free of clinical cardiovascular disease with MetS are at increased risk for PAD. Our findings suggest that this association is not mediated by inflammation.

Keywords

Metabolic syndrome; peripheral artery disease; cardiovascular disease

INTRODUCTION

Lower extremity peripheral artery disease (PAD) affects 8 million men and women in the U.S. aged 40 years or older.[1,2] Metabolic syndrome (MetS) affects 35% of men and women in the U.S. aged 20 years or older and is associated with an increased risk of cardiovascular events and death.[3,4] However, few prospective studies have assessed associations between MetS and the incidence of PAD.

Previous research shows that people with MetS have elevated levels of inflammatory and hemostatic biomarkers.[5,6] Higher levels of C-reactive protein (CRP), fibrinogen, and soluble intercellular adhesion molecule-1 (sICAM-1) have been associated with incident PAD.[7–10] Associations of MetS with elevated levels of inflammatory and hemostatic biomarkers may mediate the association of MetS with incident PAD, but few prior studies have evaluated this.

We used the Multi-Ethnic Study of Atherosclerosis (MESA) cohort to test the hypothesis that MetS is associated with an increased risk of developing PAD among community dwelling men and women who are free of clinical cardiovascular disease at baseline. We further hypothesized that the association of MetS with an increased incidence of PAD would be explained in part by higher levels of CRP, fibrinogen, and interleukin-6 (IL-6) among participants with MetS at baseline.

METHODS

Details of recruitment, enrollment, and data collection in MESA have been published.[11] Between July 2000 and August 2002, 6,814 African-American, Chinese, Hispanic, and non-Hispanic men and women, aged 45 to 84 years, and free of clinically evident cardiovascular disease at enrollment, were recruited from six U.S. communities. Institutional review board

approval was obtained at each participating center. Informed consent was obtained from all subjects.

Exclusion Criteria

Only MESA participants with an eligible baseline ankle brachial index value were included. Of the 6735 MESA participants with a baseline ABI measure, those with diabetes (n=755), a baseline ABI < 0.90 (n=244), or ABI >= 1.40 or "non-compressible" ABI at either baseline or the exam three visit (n=161) were excluded (Figure 1). In addition, those lost to follow-up before exam 3 (n=661) and those missing data for covariates included in our analyses (n=97) were excluded, resulting in a cohort of 4817 participants (Figure 1).

Data Collection

At the baseline examination, standardized questionnaires were administered to obtain demographic information, self-reported smoking history (measured as current, former, or never), number of pack-years smoked, highest level of education achieved, and blocks walked in the last week. Participants were asked to bring their medication bottles to MESA appointments and medication names were recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured. Systolic and diastolic resting blood pressures were measured three times in seated participants using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida). The average of the last two measurements was used in analyses.

Cholesterol Levels, Glucose, Inflammatory Biomarkers, Urinary Creatinine Ratio and intensity of physical activity

At baseline, total, LDL, and HDL cholesterol, triglycerides, glucose, high-sensitivity plasma CRP, IL-6. and fibrinogen levels were measured from blood obtained after a 12 hour fast. Total plasma cholesterol and triglycerides were measured using a cholesterol oxidase method and Triglyceride GB reagent respectively (Roche Diagnostics, Indianapolis, IN 46250). High density lipoprotein cholesterol (HDL-C) was measured using the cholesterol oxidase method (Roche Diagnostics). LDL cholesterol was calculated with the Friedewald equation. CRP and fibrinogen antigen were measured using the BNII nephelometer (N High Sensitivity CRP and N Antiserum to Human Fibrinogen, respectively; Dade Behring Inc., Deerfield, IL). Interleukin-6 (IL-6) was measured using an ultrasensitive ELISA (Quantikine HS Human IL-6 Immunoassay R & D Systems, Minneapolis, MN). The urinary creatinine albumin ratio was measured using spot urine tests as previously described.[11,12] Intensity of physical activity and intentional exercise were measured by self-report as previously described.[13]

ABI Measurement

The ABI was measured at baseline and at three-year follow-up. Systolic blood pressure measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position using a hand-held Doppler instrument with a 5-mHz probe (Nicolet Vascular, Golden, Colorado) after a five minute rest.[15] Brachial artery pressures were averaged to obtain the ABI denominator. To avoid potential bias from subclavian

stenosis, when the two brachial artery pressures differed by 10 mmHg or more, the highest brachial artery pressure was used as the denominator. For each lower extremity, the ABI numerator was the highest pressure (dorsalis pedis or posterior tibial) from that leg.[15]

MetS Definition

MetS was defined at baseline as the presence of three or more of the following components: increased waist circumference (>/=102cm in men and >/=88cm in women), triglycerides >/=150mg/dL, reduced HDL-C (<40mg/dL in men and <50mg/dL in women), blood pressure >/=130/85 mm Hg or taking blood pressure medication, and fasting glucose >/=100 mg/dL and <126 mg/dL.[3,5] In a sensitivity analysis, the criteria for increased waist circumference was modified to an ethnic-specific criterion[3] and analyses were repeated.

Definition of New Onset PAD

The difference between the ABI at baseline and the ABI at three year follow-up in the same leg was calculated for each participant. Incident PAD was defined as a decline in the ABI from a normal range (ABI 0.90 –<1.40) at baseline to the presence of one of the following conditions at three year follow-up: a) an ABI <0.90 in conjunction with an ABI decline >0.15 or b) medical record confirmed hospitalization for symptomatic lower extremity PAD (critical limb ischemia, revascularization, amputation). Most studies have reported that an ABI < 0.90 is 69% to 79% sensitive and 83% to 99% specific for angiogram-measured lower extremity atherosclerosis.[14]

Progression of PAD could occur in either leg. However, if PAD developed in both legs, PAD was only counted once for that individual. We did not consider development of a high ABI as indicative of PAD, since previous study shows that many people with a high ABI do not have PAD.[14,16–18] For example, previous studies have reported PAD prevalences of only 56% and 62%, respectively, among patients with a high ABI who were referred to vascular laboratory cohorts.[16–17] Because development of ABI > 1.40 is not the same as developing lower extremity atherosclerosis, participants whose baseline ABI increased from normal to > 1.40 were not considered to have definite PAD.

Statistical Analysis

We compared characteristics of MESA participants with and without MetS at baseline using chi-square tests for categorical variables and analysis of variance (or Kruskal-Wallis when appropriate) for continuous variables. We tested for effect modification by creating interaction terms between MetS status and sex and race/ethnicity, respectively. We found no significant interactions in univariate or multivariable models. Therefore, analyses were performed for the entire cohort combined. In univariate analyses, we compared the prevalence of each component of MetS between participants who developed PAD and those who did not develop PAD. We used relative risk regression (generalized linear Poisson model with robust error variance) to estimate the risk ratios (RRs) and 95% confidence intervals (CIs) of developing PAD among participants with and without MetS at baseline, adjusting for age, sex, race, education, smoking status (current, former, never), number of pack-years smoked, statin use, education, blocks walked last week, urinary albumin creatinine ratio, exercise, LDL cholesterol, and baseline ABI. These analyses were repeated

using the ethnic-specific criterion for elevated waist circumference in the metabolic syndrome definition.[3] We repeated the Poisson regression model, replacing MetS status with each individual component of the MetS, entered as a categorical variable and as a continuous variable, respectively. We did not perform stepwise regression analysis because our original hypotheses did not include identifying which individual component of MetS would improve the model's fit. Rather, the objective of our analysis was to evaluate the association of MetS and each individual components of MetS with PAD incidence after adjusting for a set of well-established, clinically relevant potential risk factors. To assess whether inflammatory biomarkers may account for the relationship of MetS and incident PAD, CRP, fibrinogen, and IL-6 levels were added to the fully adjusted model. We also repeated analyses of waist circumference and triglycerides, respectively, with development of PAD adjusting for the inflammatory biomarkers. Analyses were conducted with SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC). $P<0.05$ was considered statistically significant.

RESULTS

Among 4,817 participants eligible for these analyses, 1,382 (29%) had MetS at baseline. Participants with MetS were older, included a lower proportion of men, had a higher BMI, had higher total cholesterol levels, and had lower walking activity at baseline than participants without MetS (Table 1). As anticipated, participants with MetS had higher values for waist circumference and triglyceride level, lower HDL values, and higher systolic blood pressure, diastolic blood pressure, total cholesterol, and fasting glucose at baseline compared to participants without MetS (Table 1). A higher proportion of participants with MetS were taking anti-hypertensive medications and statin medications as compared to participants without MetS. Mean baseline values of fibrinogen, CRP, and IL-6 were higher in participants with MetS compared to the participants without MetS at baseline. Mean follow-up was 3.2 years ± 0.30 in participants with and without MetS at baseline, respectively.

A total of 53 participants developed PAD during follow-up, 23 with MetS at baseline and 30 without MetS at baseline. Among the 23 participants with MetS at baseline who developed PAD during follow-up, 20 met criteria for PAD based on a significant decline in ABI and three met criteria for PAD based on hospitalization for PAD-related symptoms. Among the 30 participants without MetS at baseline who developed PAD during follow-up, 23 met criteria for PAD based on a significant decline in ABI and seven met criteria for PAD based on hospitalization for PAD-related symptoms.

Table 2 shows the baseline prevalence of each component of the MetS among participants who developed PAD during follow-up vs. those who did not develop PAD during follow-up. Baseline prevalence of hypertension, but not other baseline components of the MetS, was associated with an increased incidence of PAD at three-year follow-up.

Twenty-three participants (1.7%) with MetS developed PAD, compared to 30 participants (0.87%) without MetS (P=0.017). After adjusting for age, sex, race, smoking status (never, former, current), smoking pack-years, education, statin use, LDL cholesterol, blocks walked in the past week, and baseline ABI, those with MetS at baseline had a higher incidence of

PAD during follow-up (risk ratio=1.76 [95% Confidence Interval (CI), 1.01 to 2.91], P=0.040). These results were not substantively changed when the MetS syndrome was defined using ethnic-specific thresholds to define an increased waist circumference (risk ratio = 1.75, 95% Confidence Interval=1.02 to 3.00, P=0.038).

Next, we evaluated the association of each individual component of MetS with PAD incidence, adjusting for age, sex, race, smoking (smoking status and pack-years), education, blocks walked in the past week, and baseline ABI. As shown in Table 3, none of the individual MetS components was associated with incident PAD when each was entered as a categorical variable. Risk ratios for large waist circumference, triglycerides, and hypertension were similar to the risk ratio for MetS and nearly achieved statistical significance. However, when entered as a continuous variable, higher waist circumference and higher triglyceride levels were associated with higher PAD incidence (Table 3).

Table 4 shows associations of MetS with incident PAD, adjusting for age, sex, race, education, smoking status, pack-years of cigarettes, LDL cholesterol, statin use, urinary albumin creatinine ration, total intentional exercise, blocks walked during the past week, and baseline ABI. The significant adjusted association of MetS with PAD did not substantively change after additional adjustment for CRP, fibrinogen, and IL-6 levels (Table 4). In exploratory analyses, higher waist circumference and higher levels of triglycerides were associated with an increased incidence of PAD, respectively. These associations remained statistically significant even after adjustment for inflammatory biomarkers (Supplementary Table 1).

DISCUSSION

Findings reported here suggest that among individuals free of clinically evident cardiovascular disease, those with MetS are at increased risk for developing PAD at three year follow-up. These results were independent of potential confounders including age, physical activity, education, statin use, baseline ABI, LDL cholesterol, and BMI. Adjustment for CRP, fibrinogen, or IL-6 did not attenuate the association of MetS with new onset PAD, suggesting that the association of MetS and PAD is not mediated by these biomarkers.

Individual components of the MetS were associated significantly with an increased incidence of PAD after adjustment for confounders when individual components were analyzed as continuous variables, but not when they were analyzed as categorical variables. This is likely because analyzing the individual MetS components as continuous variables provides greater statistical power than analyzing them as categorical variables. However risk ratios for three of the individual components of MetS were similar to the risk ratio for MetS and p values for these three individual components were nearly statistically significant. These results demonstrate that the simultaneous presence of three or more MetS individual components is a stronger risk factor for PAD than individual components of MetS. Similarly, the simultaneous presence of multiple atherosclerotic disease risk factors is associated with a higher incidence of PAD than presence of a single atherosclerotic disease risk factor.[19]

PAD is a growing public health problem. Recent evidence shows that PAD affects more than 200 million men and women worldwide.[20] PAD is associated with increased risk of cardiovascular events, functional decline, and mobility loss compared to people without PAD.[21–23] Identifying risk factors for PAD will help target therapeutic interventions to prevent PAD and its adverse consequences. Diabetes, cigarette smoking, and hypertension have been identified as the most important risk factors for PAD.[2,24] Our results suggest that efforts to prevent PAD should also focus on preventing MetS. However, further study is needed.

MetS affects approximately 35% of adults age 20 and older in the U.S. and will be increasingly common as the U.S. population survives longer with chronic disease.[3–4] Previous studies evaluating associations of MetS with new-onset PAD have yielded conflicting results.[26–29] For example, Wild et al. found no association between MetS and development of symptomatic PAD in a cohort of 762 community dwelling men and women in northern Europe (mean age 65 years; 34% with MetS) who were followed for up to 15 years. However, the study by Wild et al evaluated only symptomatic PAD, defined by new onset of intermittent claudication, rest pain, ulcer, gangrene, vascular surgery or amputation.[26] Skilton et al. found no association of MetS with new onset PAD in a prospective cohort study of 3592 persons (age 30–65 years at baseline; 12% with MetS) followed for 9 years.[27] Incident PAD was defined as an ABI < 0.90 at nine-year follow-up among participants without PAD at baseline.[27] Wang et al. reported that MetS was associated with incident PAD, defined as revascularization or amputation, in 1,212 Finnish participants (mean age 65 years, 61% MetS at baseline) who were followed for a median of 14 years.[24] However, this association was attenuated and no longer significant after additional adjustment for diabetes mellitus. In contrast, Conen et al. found that MetS was associated with incident symptomatic PAD (intermittent claudication or revascularization) in a prospective study of 27,111 women in the Women's Health Study who were free of cardiovascular disease at baseline (mean age 53 years; 26% with MetS at baseline) and followed for a median of 13.3 years.[25] Similarly, Garg et al reported that MetS was associated with new onset PAD among 4,632 participants in the Cardiovascular Health Study who were followed for a median of 13.7 years.[28] Garg et al defined new onset PAD as either a significant decline in the ABI to < 0.90 or hospitalization for PAD during follow-up. Therefore, the association of MetS with PAD remains unclear.

The current report differs from prior studies on MetS and PAD in the following ways. First, we found that MetS was associated with incident PAD even over relatively short-term follow-up (three years). Second, the MESA cohort included a racially diverse cohort of men and women. Third, the definition of new onset PAD in the MESA cohort was based both on clinically-severe PAD (i.e hospitalizations for PAD), and clinically meaningful declines in the ABI, which may or may not be associated with symptoms. Only one other study, by Garg et al,[28] assessed the association of MetS with a combined PAD outcome that included both decline in the ABI and clinically severe PAD associated with hospitalizations.

Previous research has shown that people with MetS have elevated levels of inflammatory and hemostatic biomarkers.[4,5] Higher levels of CRP, fibrinogen, and IL-6 are associated with incident PAD.[6–9] Therefore, one potential explanation for findings reported here is that

elevated levels of inflammation mediate the association of MetS with PAD. Consistent with this theory, Conen et al. reported that the association between MetS and incident PAD was mediated by elevated levels of CRP and sICAM-1.[25] However, our data suggest that the association of MetS and PAD is not mediated by circulating levels of CRP, fibrinogen, or IL-6. Similarly, Garg et al reported that neither circulating levels of CRP or fibrinogen mediated the association of MetS with PAD in the Cardiovascular Health Study. However, it is possible that inflammatory markers within atherosclerotic plaque may mediate the association of MetS with PAD. Other biologic pathways by which MetS could potentially lead to PAD include the renin-angiotensin system, which promotes insulin resistance, and nuclear peroxisome proliferator-activated receptors that regulate genes promoting atherosclerosis and influencing lipid metabolism and glycemic control.[29] Further study is needed to identify the biologic pathway by which MetS promotes insulin resistance.

This study has limitations. First, data are observational. Relationships reported cannot be construed as causal. Second, there is potential for residual confounding by unmeasured characteristics. Third, there is the potential for residual confounding by cardiovascular disease risk factors, which were more common among participants with MetS. Fourth, participants were followed for three years. Findings could change with longer follow-up. Fifth, the prevalence of components of the MetS varies across populations, thus the generalizability of our findings to other populations may be limited. Sixth, our ABI definition of new onset PAD required both a new onset of ABI < 0.90 combined with a drop in ABI of at least 0.15. Participants who developed a new onset of ABI < 0.90 without a concomitant ABI decline of at least 0.15 did not meet our ABI criteria for PAD. However, measurement error of the ABI is approximately 0.15. Our ABI definition of PAD is an accepted definition[30] and enhances the specificity of this outcome measure. Seventh, the sensitivity of the ABI for PAD is modest.[14] However, the resulting mis-classification is likely to have biased our findings toward the null, particularly since the sensitivity of the ABI for PAD is lower among people with insulin resistance.[14] Eighth, MetS has been criticized in part because identification and treatment of MetS may not be more important than identifying and treating the individual components that comprise MetS.[31–33]

In conclusion, among people who are free of clinically evident cardiovascular disease, those with MetS are at increased risk for developing PAD. Further study is needed to determine whether weight loss among people with MetS can prevent the development of PAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Among 4,817 men and women in the MESA cohort, 29% had metabolic syndrome at baseline.
- Metabolic syndrome was associated with higher risk of peripheral artery disease.
- Metabolic syndrome conferred a 1.78-fold increased risk of peripheral artery disease.
- Individual metabolic syndrome components did not predict peripheral artery disease.
- Inflammation did not explain the higher risk associated with metabolic syndrome.

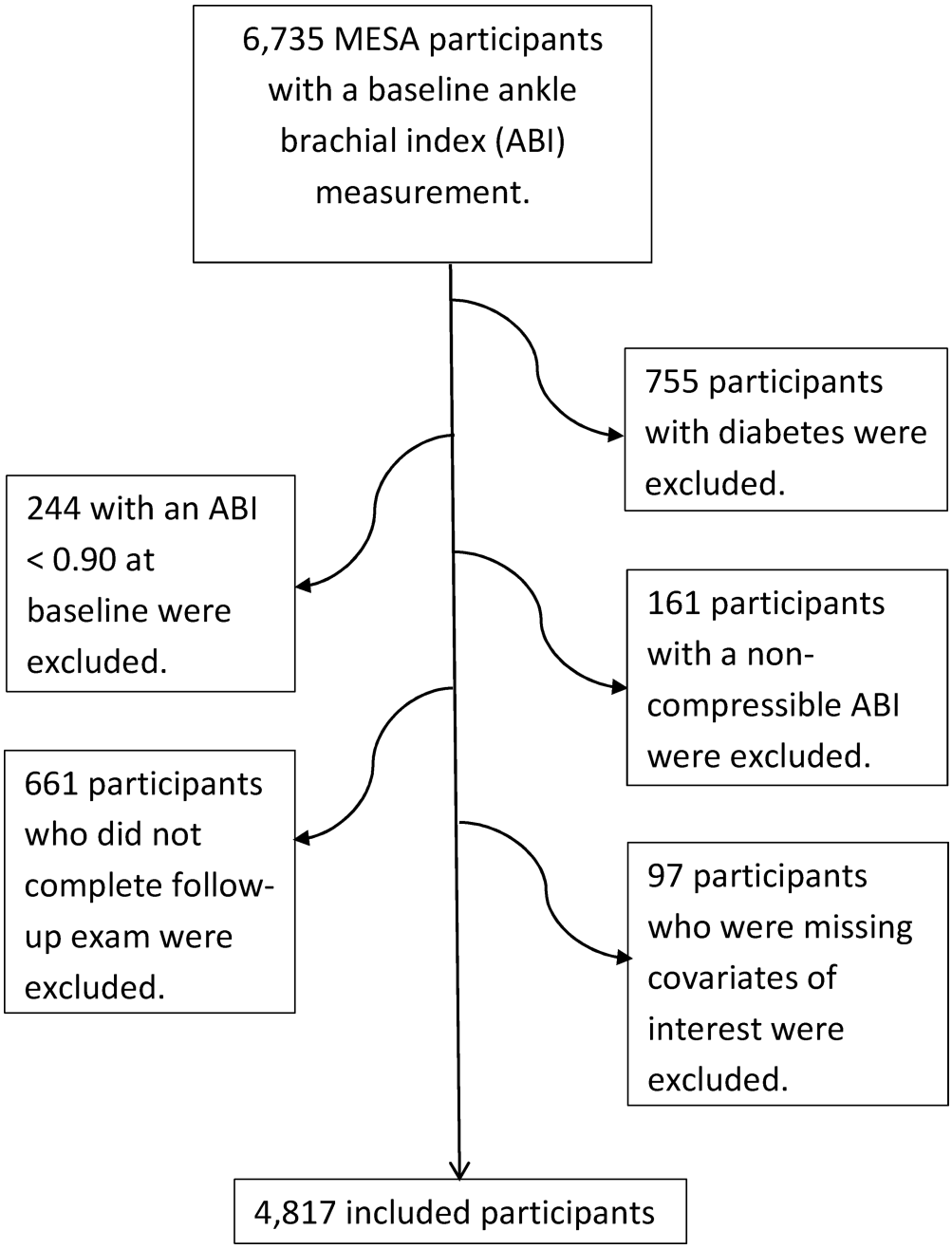

Figure 1. Flow Diagram of Study Participants

Depiction of number of MESA participants excluded from analyses and reasons for exclusion.

Table 1

Baseline characteristics of women and men according to presence or absence of metabolic syndrome, MESA (2000–2002)[¶]

Characteristic	All participants (n=4817)		
	MetS	No MetS	P value*
N	1382	3435	
Age (years)	62.3 (9.7)	60.6 (10.1)	<0.001
Male (%)	41.2	48.3	<0.001
Race/ethnicity (%)			
White	41.1	42.9	<0.001
Chinese	9.6	13.4	
African American	23.9	25.4	
Hispanic	25.4	18.3	
Education (%)			
< high school	19.9	13.2	<0.001
High school graduate or some college	49.6	44.2	
College graduate or higher	30.5	42.6	
Body mass index (kg/m^2)	30.8 (5.1)	26.7 (4.8)	<0.001
Total walking (MET-min/wk), median (IQR)	945.0 (330.0 to 1935.0)	1050.0 (435.0 to 2047.5)	0.003
Ankle-brachial index	1.12(0.1)	1.13 (0.1)	0.018
Smoking status (%)			
Never	52.1	51.2	0.448
Former	35.0	36.8	
Current	12.9	12.0	
Cigarette smoking (pack-years)	11.9 (27.9)	10.1 (18.9)	0.009
Waist circumference (cm)	105.2 (12.0)	93.4 (13.2)	<0.001
Total cholesterol (mg/dl)	196.8 (37.2)	194.3 (33.5)	0.022
LDL cholesterol (mg/dl)	117.4 (31.5)	118.2 (30.1)	0.403
Triglyceride levels (mg/dl)	181.7 (90.0)	104.4 (58.1)	<0.001
HDL cholesterol (mg/dl)	43.3 (10.5)	55.4 (15.1)	<0.001
Systolic blood pressure (mmHg)	133.1 (20.1)	121.2 (19.9)	<0.001
Diastolic blood pressure (mmHg)	73.8 (10.5)	71.0 (10.0)	<0.001
Fasting glucose (mg/dl)	95.2 (12.0)	86.8 (8.6)	<0.001
Anti-hypertensive medication use N (%)	721 (52.2)	815 (23.7)	<0.001
Statin use, N (%)	238 (17.2)	405 (11.8%)	<0.001
Urinary albumin creatinine ratio (mg/g), median (IQR)	6.0 (3.6 to 12.4)	4.4 (3.0 to 7.7)	<0.001
Total intentional exercise, MET-min/week [median (IQR)]	663.7 (0.0 to 1755.0)	1000.0 (262.5 to 2235.0)	<0.001
Fibrinogen (mg/dl)	356.1 (73.2)	335.0 (69.2)	<0.001
C-reactive protein (mg/l), median (IQR)	2.9 (1.3 to 5.7)	1.4 (0.6 to 3.3)	<0.001
Interleukin-6 (pg/ml), median (IQR)	1.4 (0.9 to 2.1)	1.0 (0.7 to 1.6)	<0.001

[¶]Data are expressed as mean (SD) unless otherwise indicated.

*P values for comparisons between MetS and No MetS.

Metabolic syndrome (MetS) was defined as the presence of 3 or more of the following risk factors: increase waist size (men >102cm, women >88cm), high triglycerides (>= 150mg/dl or treated), low HDL cholesterol (men <40mg/dl, women <50mg/dl, or treated), hypertension (DBP >=85 or SBP >=130 or treated), elevated fasting glucose (fasting glucose 100–<126mg/dl). IQR=inter-quartile range. MESA denotes the Multi-Ethnic Study of Atherosclerosis.

Table 2

Baseline prevalence of individual component among men and women with metabolic syndrome, MESA (2000–2002)*

Metabolic syndrome component	Participants, N (%)		
	All (n=4,817)	Developed PAD during follow-up (N=53)	Did not develop PAD during follow-up (N=4,764)
Large waist circumference (> 88 cm in women or > 102cm in men)	2471 (51.3)	33 (62.3)	2438 (51.2)
High triglyceride levels (>= 150mg/dl or treated)	1340 (27.8)	17 (32.1)	1323 (27.8)
Low HDL-C levels (women:<50 mg/dl, men: <40 mg/dl, or treated)	1608 (33.4)	20 (37.7)	1588 (33.3)
Hypertension (blood pressure >=130/85 or treated)	2505 (52.0)	41 (77.4)	2464 (51.7)[1]
Elevated fasting glucose levels (100 – < 126mg/dl)	718 (14.9)	8 (15.1)	710 (14.9)

*Values shown are number of participants (percent).

HDL-C = High density lipoprotein cholesterol. PAD= peripheral artery disease.

[1]P<0.001 for comparison between participants who developed PAD vs. those who did not develop PAD.

Table 3

Adjusted associations between each metabolic syndrome component and risk for developing peripheral artery disease among participants without peripheral artery disease at baseline in the MESA cohort (N=4,817)*

	Adjusted Risk Ratios (95% CI) for association of each metabolic syndrome component, with incident PAD			
Models	***Categorical variable***	***P- value***	**Continuous variable**	**P value**
Waist circumference	1.70 (0.94 to 3.05)	0.077	1.03 (1.01 to1.04)	<0.001
High triglycerides	1.71 (0.95 to 3.06)	0.071	2.23 (1.16 to 4.29)	0.016
Low HDL cholesterol	1.35 (0.75 to 2.45)	0.315	0.98 (0.96 to 1.01)	0.129
Elevated systolic blood pressure	1.67 (0.83 to 3.32)	0.150	1.00 (0.99 to 1.02)	0.836
Elevated fasting glucose	0.83 (0.39 to 1.77)	0.622	**	

*Risk ratios are shown for each component of the metabolic syndrome, adjusting for age, sex, race, education, smoking status, pack-years of cigarette, statin use, blocks walked last week, and baseline ABI. Incident PAD was defined as declining from a normal ABI (0.90 –<1.40) at baseline to the presence of the following conditions at visit 3: a) a decline of ABI to <0.90 at visit 3 combined with an ABI decline greater than 0.15 or b) or confirmed symptomatic low extremity PAD (critical limb ischemia, revascularization, amputation) between baseline and visit 3.

**Model did not converge.

Table 4

Adjusted associations of metabolic syndrome with incident peripheral artery disease with and without adjustment for biomarkers (N=4,817).

Model	**Risk Ratio (95% CI) for association of metabolic syndrome with incident PAD**	***P- value***
Metabolic Syndrome	1.78 (1.04 to 2.82)	0.031
Metabolic Syndrome + fibrinogen + Log(IL6) + Log(CRP)	1.76 (1.05 to 2.92)	0.042

Each model was adjusted for age, sex, race, education, smoking status, pack-years of cigarette, LDL cholesterol, statin use, urinary albumin creatinine ratio, total intentional exercise, blocks walked last week, and baseline ABI.

CRP=C-reactive protein. IL6=Interleukin-6.