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Metabolic Syndrome, Inflammation and Risk of Symptomatic Peripheral Artery Disease in Women: A Prospective Study

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Abstract

Background—Metabolic syndrome (MetS) is associated with incident myocardial infarction and stroke and is linked with subclinical inflammation. However, prospective data pertaining to MetS and future peripheral artery disease (PAD) are sparse with few studies examining the role of inflammation. We therefore evaluated the relationship between MetS, inflammation, and incident PAD.

Methods and Results—We conducted a prospective cohort study among 27,111 women free of baseline cardiovascular disease participating in the Women's Health Study. Subjects were followed for incident symptomatic PAD (n=114; median cohort follow-up=13.3 years). We used Cox proportional hazards models to compare PAD risk among women with and without MetS. We also evaluated relationships between MetS and subclinical inflammation as measured by high sensitivity C-reactive protein (hsCRP) and soluble intercellular adhesion molecule-1 (sICAM-1) and adjusted for these biomarkers in multivariable models. Women with MetS had a 62% increased risk of future PAD (HR 1.62; 95% CI 1.10–2.38). After multivariable adjustment, MetS remained significantly associated with PAD (adj HR 1.48; 95% CI 1.01–2.18) with a 21% risk increase per additional MetS-defining trait (adj HR 1.21; 95% CI 1.06–1.39). Median levels of hsCRP were 4.0 versus 1.5 mg/L ($p<0.0001$) and 374 versus 333 ng/mL for sICAM-1 ($p<0.0001$) in women with and without MetS, respectively. When hsCRP and sICAM-1 were added to multivariable models, risk associated with the MetS was substantially attenuated and no longer significant (HR 1.14, 95% CI 0.75–1.73).

Conclusion—MetS is associated with an increased risk of future symptomatic PAD in women. This risk appears largely mediated by the effects of inflammation and endothelial activation.

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Clinical Summary

Metabolic syndrome (MetS) is associated with myocardial infarction and stroke and is linked with subclinical inflammation. We conducted a prospective cohort study among 27,111 women free of baseline cardiovascular disease to evaluate the relationship between Metabolic Syndrome (MetS), inflammation, and incident peripheral artery disease (PAD). We found that MetS was associated with significantly increased risk of PAD after multivariable adjustment (HR 1.48 (95% confidence interval 1.01–2.18), similar to previously documented associations between the MetS and coronary disease or stroke. However, when inflammatory biomarkers were added to multivariable models, risk associated with the MetS was attenuated and no longer significant. Our findings were comparable in women who were non-diabetic at baseline. Taken together, our data provide evidence that the MetS confers an increased risk of incident PAD among initially healthy women and that this increased risk is largely mediated through the effects of inflammation and endothelial activation.

Keywords

Peripheral artery disease; metabolic syndrome; inflammation; endothelial dysfunction; women

INTRODUCTION

The metabolic syndrome (MetS), a cluster of cardiovascular risk factors associated with insulin-resistance and obesity, has been consistently associated with a moderate increase in the incidence of coronary heart disease, stroke and cardiovascular mortality^{1–6}. Much less information is available on the relationship between the MetS and incident lower extremity peripheral artery disease (PAD) with most data deriving from cross-sectional reports^{7–10}. One of two previously published prospective evaluations suggested that the MetS is a predictor of end-stage PAD (lower extremity amputation or revascularization), but that this risk increase is largely attributable to the impact of diabetes alone¹¹. Another recent analysis did not find a significant association of MetS with incident PAD, although a strong and independent relationship between the MetS and cerebrovascular disease was noted¹². This potential difference in the relationship between the MetS and coronary heart disease and stroke on one hand and PAD on the other may be due to the absence of large prospective studies for incident PAD or to differences in atherogenic mechanisms affecting these distinct vascular beds¹³.

Systemic inflammation, assessed through plasma levels of high sensitivity C-reactive protein (hsCRP), is an important predictor of cardiovascular morbidity and mortality^{14–17} and may be an important mediator of the association between the MetS and cardiovascular disease^{3, 5}. Furthermore, both inflammation and endothelial injury or activation (as measured by soluble cellular adhesion molecule-1, sICAM-1) have recently been shown to be strongly and independently associated with incident PAD¹⁸. These factors may therefore explain potential associations between the MetS and PAD; however, few prospective data have been available. In an attempt to clarify these issues, we assessed the relationships between the MetS, inflammation and future symptomatic PAD defined as intermittent claudication or lower extremity artery revascularization in a large cohort of initially healthy women.

METHODS

Participants

All study subjects were participants of the Women's Health Study, a completed randomized trial evaluating the risks and benefits of low dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. Details of the study design have been described previously^{19–21}.

Briefly, beginning in 1993, 39,876 female health professionals in the United States who were 45 years or older and free of cardiovascular disease, cancer or other major illnesses were randomized to receive 100 mg aspirin every other day, 600 IU vitamin E every other day, both agents or placebo. The trial initially had a beta carotene arm that was terminated early²². Information on baseline variables was collected using mailed questionnaires. Follow-up questionnaires asking participants about study outcomes and other information were sent every six months during the first year and every 12 months thereafter.

For the purpose of this study, we excluded 11,935 participants because they did not provide a baseline blood sample, 7 participants with confirmed pre-randomization PAD, and 823 participants with missing information on body mass index (BMI), blood pressure or history of hypertension. Thus, the final study population for the present analysis consisted of 27,111 women. Written informed consent was obtained from all participants. The study was approved

by the institutional review board of Brigham and Women's Hospital, Boston, and was monitored by an external data and safety monitoring board.

Laboratory analyses

All blood analyses were performed in a core laboratory certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization Program. Total cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides were ascertained with direct measurement assays (Roche Diagnostics). Triglyceride levels were measured enzymatically, with correction for endogenous glycerol, using a Hitachi 917 analyzer and reagents and calibrators from Roche Diagnostics (Indianapolis, Indiana). Plasma hsCRP was measured with a validated high-sensitivity immunoturbidimetric method (Denka Seiken, Niigata, Japan). The interassay coefficients of variation using two levels of control materials ranged from 1.07 to 5.20%. sICAM-1 was measured by quantitative sandwich ELISA (R&D Systems, Minneapolis, Minn) with a reproducibility of 8.89% and 6.39% at concentrations of 171.8 and 289.1 ng/mL, respectively.

Definition of the MetS

According to the Adult Treatment Panel (ATP) III guidelines, women with three or more of the following traits are defined as having the MetS: (1) waist circumference ≥ 88 cm; (2) triglycerides ≥ 150 mg/dL; (3) HDL-C < 50 mg/dL; (4) blood pressure $\geq 130/85$ mm Hg; and (5) abnormal glucose metabolism as identified by a fasting blood glucose ≥ 100 mg/dL^{23, 24}. For the present study, we used a modified ATP III definition of the MetS previously validated in this cohort³. Since waist circumference was not available at baseline, a BMI cutpoint for obesity of > 26.7 kg/m² was used as a surrogate. When waist circumference was collected at the six-year follow-up, this value corresponded to the same percentile for BMI as did a waist circumference of 88 cm. In addition, prior data in the WHS have demonstrated that BMI is equivalent to waist circumference in predicting major cardiovascular events²⁵ and a recent meta-analysis of MetS and vascular risk found no heterogeneity of effects whether waist circumference, waist-to-hip ratio or BMI was used⁶. Triglyceride level and HDL-C were ascertained as described above. Blood pressure at baseline was self-reported by WHS participants all of whom were female health professionals, a group in which self-report of blood pressure has proven highly accurate²⁶. Subjects meeting the blood pressure criterion for MetS included those who reported a diagnosis of hypertension by a physician, a systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 85 mmHg at baseline. Because fasting glucose levels were not available, we used a diagnosis of diabetes at baseline or during follow-up to identify individuals with impaired glucose metabolism.

Outcome Ascertainment

Participants are surveyed annually for multiple health outcomes, including symptomatic PAD events, defined as intermittent claudication and/or peripheral artery surgery inclusive of catheter-based interventions. Case confirmation occurred by telephone interview during which the presence of vascular claudication was established by use of the Edinburgh Claudication Questionnaire. This instrument is a modified version of the World Health Organization/Rose Claudication Questionnaire, which has previously been validated in a community outpatient setting with 92% sensitivity and 99% specificity for physician-diagnosed intermittent claudication²⁷. In addition, medical records were obtained to assess the concordance of reported symptoms with diagnostic testing when available. Reports of peripheral arterial surgery were confirmed after review of operative notes or procedural reports in the case of peripheral angioplasty or stenting. Of 456 self-reported PAD events occurring as of November 23, 2007, 114 were confirmed utilizing these methods. Among disconfirmed events, venous disease, lower extremity arthritis, lumbar disc disease, and peripheral neuropathy were the

main causes of non-ischemic leg pain. There were 73 unrefuted events in women who were unreachable for telephone interview, deceased, or unwilling to participate. Only confirmed events were considered in the analysis. Among women with confirmed PAD, there were 111 cases of intermittent claudication, 56 of these women undergoing revascularization. In addition, there were 3 cases of peripheral artery revascularization without antecedent claudication.

Statistical analyses

Baseline characteristics were compared according to the presence or absence of the MetS using Wilcoxon rank sum tests for continuous variables and chi square tests for categorical variables. Age-adjusted incidence rates were calculated using internal standardization.

The divergence of PAD incidence over time between groups with 0, 1–2 and ≥ 3 MetS traits was estimated using Kaplan-Meier survival curves, and the log-rank test computed to compare curves. To account for potential confounders, we constructed multivariable Cox proportional hazards models to estimate the adjusted hazard ratio (HR) of PAD for women with 1–2 and ≥ 3 MetS traits by creating indicator variables for these two categories and adding terms for potential confounders. Cox models were also used to compare the risk according to presence versus absence of the MetS. The HR per increasing number of MetS-defining traits was estimated by using the number of traits (ranging from 0–5) as an ordinal variable in the model. For each woman, person-years of follow-up were calculated from the date of return of the baseline questionnaire to the date of incident PAD, death or to November 23, 2007, whichever came first. All risk estimates are presented as HRs with the 95% confidence interval (CI).

Crude models were first adjusted for age and smoking status and then additionally adjusted for total cholesterol and exercise. We also assessed the effect of hormone replacement therapy on incident PAD, and as it was neither a significant predictor nor a confounder for the association between the MetS and PAD, hormone replacement therapy was not included in the final models. To assess whether the increased risk associated with the MetS is mediated by inflammation and/or endothelial activation, we included hsCRP and sICAM-1 in the model building process. Both hsCRP and sICAM-1 were log-transformed to normalize the variable distribution and better meet the assumption of linearity in risk across increasing levels of these biomarkers. We fitted separate models adjusting for each biomarker in a first step, and subsequently added both markers to the same model. Finally, to evaluate whether the risk associated with MetS is independent of baseline diabetes, we repeated the main analyses among women without established diabetes on entry into the study.

Effect modification was assessed using multiplicative interaction terms. The proportional hazards assumption was examined for all models by including a MetS by logarithm of time interaction variable into the model²⁸. No violation of this assumption was detected. All analyses were carried out using SAS version 9 (SAS Institute Inc, Cary, NC). A two-tailed p value <0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics of the study population according to MetS status are shown in Table 1. Overall, 6,920 (25.5%) participants had the MetS. Compared to women without the MetS, those with MetS were significantly older ($p<0.0001$), more likely to smoke ($p=0.009$) and less likely to exercise on a regular basis ($p<0.0001$). Among participants with the MetS, an HDL-C <50 mg/dL was the most prevalent individual MetS-defining trait (88.0%), followed by elevated BMI (81.2%), elevated blood pressure (77.8%), elevated triglycerides (77.7%), and dysglycemia as identified by baseline or incident diabetes (28.2%).

During a median (interquartile range) follow-up of 13.3 (12.5–13.8) years, 114 symptomatic PAD events occurred. There were 44 and 70 events among women with and without the MetS, respectively. Age-adjusted incidence rates in these two groups were 0.43 and 0.30 events per 1000 person-years of follow-up, respectively. Figure 1 provides the cumulative incidence curves for PAD after classifying subjects according to presence of 0, 1–2, and ≥ 3 MetS traits and shows the increasing risk of PAD with higher number of traits. Multivariable regression analysis confirmed these relationships (Figure 2). Compared to women without any MetS traits, those having one or two criteria had a 2.5-fold increased PAD risk, and women with established MetS had a 3-fold increased risk independent of age, smoking, total cholesterol, and physical activity.

When examined according to presence or absence of the MetS or per number of individual traits (Table 2), we found similar results. The hazard ratio for symptomatic PAD among women with the MetS versus those without MetS was 1.62 (95% CI 1.10–2.38) on univariable analysis and 1.48 (95% CI 1.01–2.18) after adjustment for age and smoking status. Additional adjustment for total cholesterol and exercise had virtually no effect on these risk estimates. Adjustment for low density lipoprotein cholesterol instead of total cholesterol did not change our results (data not shown). When assessed as an ordinal risk factor, after multivariable adjustment there was a 21% (95% CI 6 to 38%; $p=0.004$) greater hazard of PAD per additional MetS-defining trait.

Both hsCRP and sICAM-1 were strongly associated with MetS and increasing number of MetS traits. Median levels of hsCRP were 4.0 mg/L and 1.5 mg/L ($p<0.0001$) among women with and without the MetS, respectively. The corresponding levels of sICAM-1 were 374 ng/mL and 333 ng/mL ($p<0.0001$). Among participants with 0 to 5 MetS-defining traits, median hsCRP levels gradually increased from 1.0 to 5.9 mg/L ($p<0.0001$) and median sICAM-1 levels from 321 to 413 ng/mL ($p<0.0001$).

To address whether elevated hsCRP or sICAM-1 levels might account for the relationship of MetS and incident PAD we sequentially added these variables to multivariable models (Table 2). After inclusion of hsCRP, the adjusted HR for the MetS was reduced to 1.23 (95% CI 0.82–1.85). A similar effect was observed after inclusion of sICAM-1; the adjusted HR for MetS in this model was 1.30 (95% CI 0.87–1.95). When both biomarkers were added to the same model, the association was markedly attenuated (adjusted HR 1.14; 95% CI 0.75–1.73). Findings were similar when assessed according to number of MetS-defining traits (Table 2). In analyses stratified by age, smoking status or approximate tertiles of hsCRP and sICAM-1, we found consistent results (data not shown). None of the p -values for effect modification by these factors was statistically significant ($p>0.14$ for all interactions tested).

Finally, we evaluated the risk associated with the individual MetS-defining traits. The HRs (95% CIs) for PAD associated with elevated BMI, elevated triglycerides, hypertension, low HDL-C and dysglycemia were 0.98 (0.65–1.46), 1.39 (0.96–2.01), 1.50 (1.02–2.19), 1.60 (1.10–1.33) and 2.05 (1.26–3.36), respectively. By comparison, the HR associated with current smoking was 12.7 (7.6–21.2). Whether MetS had an effect independent of established diabetes was evaluated among 26,364 women free of diagnosed diabetes at baseline. Among this subgroup, 105 symptomatic PAD events occurred. Similar to the main analyses, the multivariable adjusted hazard ratio for MetS was 1.43 (95% CI 0.95–2.16; $p=0.09$), and this risk estimate was reduced to 1.15 (95% CI 0.73–1.78) after additional adjustment for hsCRP and sICAM-1.

DISCUSSION

In this prospective study of initially healthy, middle-aged women, similar to previously published data for coronary and cerebrovascular disease, we found that the MetS is associated with a moderate increase in risk of future symptomatic PAD. This finding persisted after adjustment for age, smoking status, total cholesterol and physical activity (adj HR 1.48; 95% CI 1.01–2.18). Furthermore, the magnitude of effect was comparable in women who were non-diabetic at baseline. Risk relationships were largely attenuated after control for hsCRP and sICAM-1 suggesting that in this generally low risk population of women, the excess risk associated with MetS may be mediated through heightened inflammation and/or endothelial activation.

Most prior cross-sectional reports have demonstrated a positive association between MetS and prevalent PAD. Among participants in the National Health and Nutrition Examination Survey (NHANES), MetS was linked to a high likelihood of prevalent PAD (OR 4.8; 95% CI 2.2–34.0) and presence of PAD increased with levels of CRP⁸. In another study from NHANES²⁹, insulin resistance as measured by the homeostasis model (HOMA-IR) was also associated with prevalent PAD (OR 2.1 for highest vs. lowest HOMA-IR quartile; 95% CI 1.1–4.0) independently of traditional risk factors including other components of the MetS. However, in this population having a high prevalence of cardiovascular risk factors and established cardiovascular disease, adjustment for CRP did not attenuate this relationship. In a third cross-sectional study of patients with diagnosed vascular disease, MetS was more common in those having PAD (57%) compared to atherosclerosis affecting other vascular beds (40%, 43%, and 45% for coronary disease, cerebrovascular disease, and aortic aneurysm, respectively)⁷.

Despite such evidence from cross-sectional reports, few prospective comparisons of MetS and incident PAD have been available. A small prospective study in a Finnish cohort demonstrated a 2-fold increased hazard of end-stage PAD (n=57 amputations or revascularization procedures) among those with MetS. However, this relationship appeared largely due to prevalent diabetes¹¹. After analyses adjusting for diabetes or excluding diabetic subjects, the authors conclude that MetS does not predict PAD beyond the risk associated with established diabetes. However, in this evaluation of end-stage PAD, diabetes-related chronic conditions such as neuropathic ulcers and concurrent infection rather than ischemia *per se* may have been major contributors as nearly 50% of events were amputations. A dominant effect of pre-existing diabetes was not confirmed in our analysis which included milder cases of PAD (intermittent claudication and limb ischemia).

The Edinburgh Artery Study did not find a significant association between the MetS and incident PAD (HR 0.89; 95% CI 0.57–1.28)¹². Compared to our study population, the Edinburgh cohort was older (mean age 65 years), of mixed gender, and had a high prevalence of baseline smoking (25.3%), and asymptomatic disease (17% with enrollment ABI<0.9). Nonetheless, these null findings from a higher risk group in contrast to our positive results among low risk women invoke the intriguing possibility that MetS has a greater impact on atheroma initiation than progression in individuals with extant subclinical disease. This hypothesis requires corroboration in other cohorts but is supported by results of a recent meta-analysis of MetS and incident cardiovascular events in which MetS had a larger effect (HR 1.96 vs. 1.43; p=0.04) in studies of individuals at lower baseline cardiovascular risk (<10%)⁶.

As demonstrated in prior reports^{3–5, 12, 30, 31}, our data also confirm that markers of inflammation and endothelial activation are strongly associated with MetS. We found an increase in plasma levels of hsCRP and sICAM-1 per additional MetS-defining trait such that

women with the MetS had substantially higher plasma levels than those without MetS. Furthermore, the addition of either hsCRP or sICAM-1 individually to multivariable models substantially attenuated the effect of MetS on subsequent PAD, while inclusion of both markers virtually abolished this association. Our findings thus suggest that in this relatively healthy population of women, inflammation and endothelial activation may be potential mediators of the heightened PAD risk conferred by this risk factor cluster.

The present data also emphasize the importance of smoking in the pathogenesis of PAD. Smoking women had a 12.7-fold increased risk of developing PAD compared to non-smokers, and therefore smoking was by far the strongest risk factor in this population. While prior risk estimates for the association between smoking and PAD are somewhat weaker than in the current study³², our finding may reflect a heightened risk of smoking in women that requires further investigation. The relative magnitude of smoking as a risk factor compared not only to MetS but also diabetes in this study underscores the importance of abstinence from smoking for the prevention of PAD.

Our results should be interpreted in the context of several potential limitations. First, our study included women who are of predominantly Caucasian origin, and our findings may not be generalizable to other groups. Second, the use of symptomatic PAD as our primary *a priori* end point by definition excludes subclinical disease, which may have otherwise been detected through abnormal pulse examination or ankle-brachial index³³. However, we believe our data to be not only relevant from a mechanistic perspective but also of clinical importance for the following reasons. First, claudication and limb ischemia requiring revascularization are the principal clinical manifestations of PAD. Second, all events evaluated in this analysis were confirmed by a validated claudication questionnaire and medical record review. Third, women enrolled in this study are health professionals and are therefore less likely to encounter barriers to medical care, which may otherwise have led to underdiagnosis. Although potential misclassification resulting from atypical or occult disease may have occurred, this, if anything, would have biased our results toward the null. On the other hand, a low ankle brachial index has been shown to strongly and independently predict the occurrence of cardiovascular events independent of claudication symptoms, highlighting the importance of this endpoint³⁴. Nevertheless, we believe that the use of confirmed symptomatic PAD is not only valid but also represents an important clinical endpoint for this disease. Finally, a modified version of the official ATP III MetS definition was used in this analysis. The criteria for MetS have been variable and continue to evolve over time. Our use of baseline or incident type 2 diabetes instead of fasting glucose levels as a MetS defining trait likely underestimated the number of women who satisfied the MetS criteria. Again, this could have biased our results toward the null. The definition used in the current report has previously associated with incident cardiovascular disease in this cohort³. Furthermore, it is important to note that our study was undertaken in order to describe a potential etiologic role for this risk factor cluster in the development of PAD rather than to validate the utility of the syndrome for risk prediction.

In conclusion, similar to the previously noted relationship between the MetS and incident coronary heart disease and stroke, this study demonstrated a modest positive association with future PAD in a population of otherwise low risk women. Substantially increased plasma levels of hsCRP and sICAM-1 were evident in subjects with MetS and a strong influence of these factors on the relationship between MetS and PAD was noted suggesting a possible pathophysiologic role. Prospective data from other cohorts are greatly needed not only to corroborate our results but also to further elucidate mechanistic links between risk factor clustering and onset of this disease.

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DISCLOSURES

Dr. Conen reports no disclosures; Dr. Rexrode reports no disclosures. Dr. Creager reports having research support from Sanofi-Aventis and Merck and is a consultant for BioMarin and Genzyme. Dr. Ridker reports having received research funding support from multiple not-for-profit entities including the National Heart, Lung, and Blood Institute, the National Cancer Institute, the American Heart Association, the Doris Duke Charitable Foundation, the Leducq Foundation, the Donald W Reynolds Foundation, and the James and Polly Annenberg La Veia Charitable Trusts. Dr. Ridker also reports having received investigator-initiated research support from multiple for-profit entities including Astra-Zeneca, Novartis, Pharmacia, Roche, Sanofi-Aventis, and Abbott, as well as non-financial research support from Amgen. Dr. Ridker is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Siemens and AstraZeneca, and has served as a research consultant to Schering-Plough, Sanofi/Aventis, AstraZeneca, Isis, Dade, Merck, Novartis, and Vascular Biogenics. Dr. Pradhan reports having received research support from Sanofi-Aventis.

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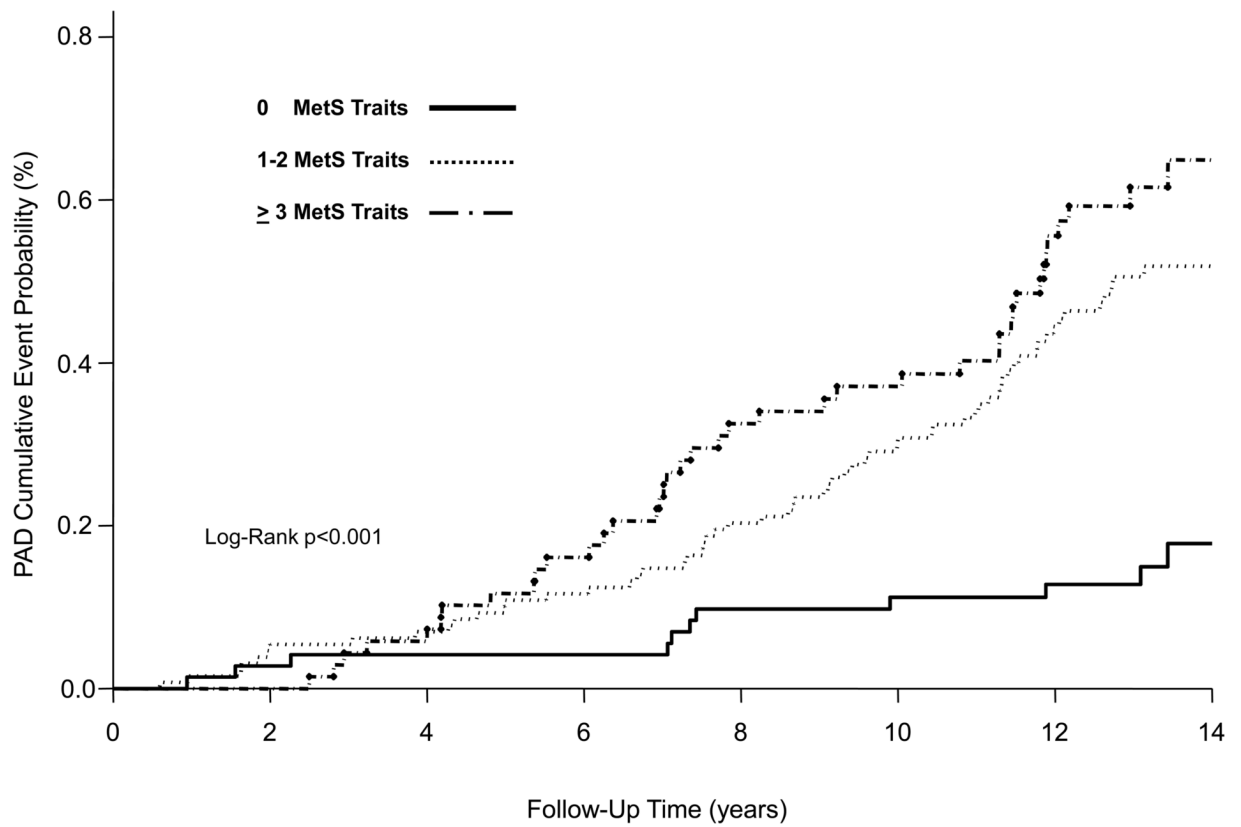


Figure 1. Cumulative Incidence for PAD According to Number of MetS Traits
Kaplan-Meier cumulative incidence curves for symptomatic PAD according to 0, 1–2, or ≥ 3 metabolic syndrome traits. MetS denotes metabolic syndrome.

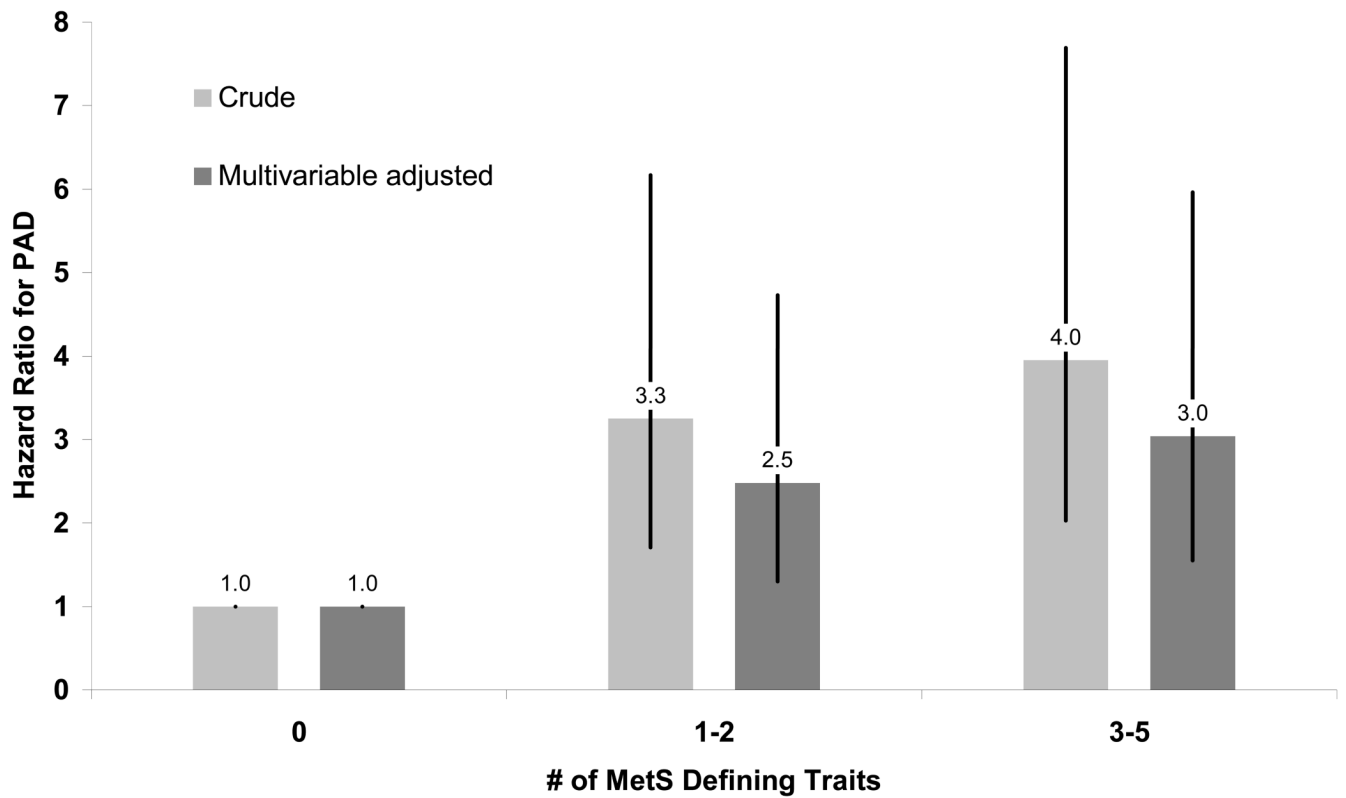


Figure 2. Hazard Ratio for PAD According to Number of MetS Traits

Data are crude (light bars) and multivariable-adjusted (dark bars) hazard ratios. Multivariable models were adjusted for age, smoking status, total cholesterol and exercise. Error bars represent 95 percent confidence intervals. MetS denotes metabolic syndrome.

Table 1
Baseline Characteristics of the Study Population According to Presence or Absence of Metabolic Syndrome

	Metabolic syndrome		P-value
	Absent (n=20191)	Present (n=6920)	
Age, years	53 (49, 58)	54 (50, 60)	<0.0001 0.009
Smoking, %			
Current	11.3	12.5	
Past	37.2	35.7	
Never	51.6	51.8	
Exercise frequency in times/week, %			
Rarely/never	34.1	46.6	
<1	19.1	20.9	
1-3	33.9	26.0	
>3	13.0	6.7	
Body mass index, kg/m ²	23.7 (21.9, 25.8)	29.9 (27.4, 33.5)	<0.0001
HDL-Cholesterol, mg/dL	56 (48, 66)	42 (36, 47)	<0.0001
Triglycerides, mg/dL	103 (75, 140)	193 (153, 260)	<0.0001
Total cholesterol, mg/dL	205 (182, 232)	217 (191, 244)	<0.0001
Metabolic Syndrome Traits			
Body mass index >26.7 kg/m ² , %	17.1	81.2	<0.0001
HDL-Cholesterol <50 mg/dL, %	29.5	88.0	<0.0001
Triglycerides ≥150 mg/dL, %	20.1	77.7	<0.0001
Elevated blood pressure, % [‡]	24.0	77.8	<0.0001
Dysglycemia, % [‡]	1.6	28.2	<0.0001
History of baseline diabetes	0.6	7.3	
Incident diabetes	1.0	20.9	

Data are median (interquartile range) or percentages

HDL High density lipoprotein

* The following question was used to categorize exercise frequency: "How often do you engage in strenuous (aerobic) physical activity (e.g. swimming, aerobics, cycling, running)?"

[‡] Defined as blood pressure ≥130/85 mmHg or history of a physician's diagnosis of hypertension

[‡] Dysglycemia defined by history of diabetes at baseline or incident diabetes during follow-up

Table 2
Hazard Ratio for Incident PAD According to Presence of Metabolic Syndrome and Per Number of Metabolic Syndrome Defining Traits

	No. Events	Metabolic Syndrome (Yes/No)		Per Additional Metabolic Syndrome Defining Trait	
		HR for PAD (95% CI)	P-Value	HR for PAD (95% CI)	P-Value
Crude model (n=27111)	114				
Multivariable model 1* (n=27089)	113	1.62 (1.10–2.38)	0.013	1.26 (1.12–1.43)	0.0002
Multivariable model 2† (n=27079)	113	1.48 (1.01–2.18)	0.046	1.21 (1.06–1.38)	0.004
Multivariable model 3‡ (n=26900)	108	1.48 (1.00–2.19)	0.048	1.21 (1.06–1.39)	0.004
		1.14 (0.75–1.73)	0.55	1.11 (0.96–1.28)	0.18

* Adjusted for age and smoking status.

† Additionally adjusted for total cholesterol and exercise.

‡ Additionally adjusted for plasma levels of hsCRP and sICAM-1.