Metabolic Syndrome and Risk of Incident Peripheral Artery Disease
The Cardiovascular Health Study

Abstract—Prior studies evaluating metabolic syndrome (MetS) and incident peripheral artery disease (PAD) have been limited by use of modified MetS criteria and restriction to clinical PAD end points. We investigated MetS and risk of developing a low ankle-brachial index (ABI) and clinical PAD in the Cardiovascular Health Study, a population-based cohort of adults aged ≥65 years. Participants with MetS met at least 3 of 5 Adult Treatment Panel III criteria. Baseline C-reactive protein-MetS or fibrinogen-MetS were defined as presence of 3 of 6 components, with elevated C-reactive protein (>3 mg/L) or fibrinogen (>341 mg/dL) as a sixth component. Incident low ABI, defined as ABI <0.9 and decline of ≥0.15, was assessed among a subset of 1899 individuals with 2 ABI measurements 6 years apart. Over a median follow-up of 13.7 years, 4632 individuals were followed up for clinical PAD, defined as revascularization or diagnosed claudication. Adult Treatment Panel III MetS was associated with both incident low ABI (risk ratio, 1.26; 95% confidence interval [CI], 1.00–1.58) and clinical PAD (hazard ratio, 1.47; 95% CI, 1.11–1.94). Incorporating C-reactive protein or fibrinogen into Adult Treatment Panel III criteria identified an additional 16% to 20% of individuals as having MetS, and both C-reactive protein-MetS and fibrinogen-MetS were associated with incident low ABI (risk ratio, 1.36; 95% CI, 1.07–1.72 and risk ratio, 1.43; 95% CI, 1.13–1.81, respectively) and clinical PAD (hazard ratio, 1.56; 95% CI, 1.17–2.08 and hazard ratio, 1.55; 95% CI, 1.17–2.07, respectively). Among Adult Treatment Panel III MetS criteria, risk of PAD was most strongly associated with hypertension. (Hypertension. 2014;63:413-419.) * Online Data Supplement

Key Words: cohort studies • inflammation • metabolic syndrome • peripheral artery disease

The metabolic syndrome (MetS) is defined by a combination of criteria including elevated triglycerides, reduced high-density lipoprotein, high blood pressure, impaired fasting glucose, and increased abdominal girth.1–3 Prevalence of the MetS has been consistently associated with incident coronary artery disease, stroke, and cardiovascular mortality.4–7 To our knowledge, there are only 2 published prospective studies evaluating associations of MetS and incident peripheral artery disease (PAD); however, both are limited by the use of clinical PAD alone as an end point.8,9 These studies also used modified MetS criteria by substituting the presence of diabetes mellitus for impaired fasting glucose and body mass index for increased abdominal girth. Given the moderate correlation between atherosclerosis across different vascular beds,10 it remains uncertain whether MetS is similarly associated with PAD.

Atherogenic risk factors such as impaired fibrinolysis, oxidative stress, hypoadiponectinemia, and increased thrombogenicity often cluster with the MetS.11,12 Although traditional definitions of MetS incorporate measures of insulin resistance, they do not account for measures of inflammation. Inflammatory markers such as C-reactive protein (CRP) and interleukin-6 are elevated in MetS.6,11,13 Some have proposed that inflammation be included into the definition of the MetS,14 but whether inflammation provides additional information to standard MetS criteria is unclear.

The Cardiovascular Health Study (CHS) offers a unique opportunity to examine associations between MetS and incident PAD in a large, well-defined population with long-term follow-up. We investigated the association of MetS and its individual components with the risk of developing a low

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ankle-brachial index (ABI) as well as symptomatic clinical PAD. We also investigated how a modified MetS definition that includes inflammation is associated with incident PAD.

Methods

Study Participants

The CHS is a community-based, longitudinal observational study of adults ≥65 years at baseline that was designed to evaluate risk factors for the development and progression of cardiovascular disease. The study’s primary objectives and design have been reported previously. Briefly, participants were recruited from randomly sampled Medicare eligibility lists in Sacramento, CA; Forsyth County, NC; Washington County, MD; and Allegheny County, PA. Eligibility also required an expectation to remain in the area for 3 years after recruitment. Prevalent PAD was defined as history of myocardial infarction, angina, angioplasty, amputation, or thrombolysis for the indication of PAD. Other PAD events, or as part of regular review of Centers for Medicare & Medicaid Services records for the International Classification of Diseases, ninth revision codes 440.2 (atherosclerosis of the native arteries of the extremities) and 443.9 (peripheral vascular disease, unspecified). After a potential PAD event was identified, medical records were then reviewed, and a final decision was adjudicated by the Morbidity Subgroups of the CHS Clinical Events Subcommittee.

Laboratory Analyses

Please refer to Methods in online-only Data Supplement.

Classification of MetS

MetS was defined as meeting 3 of the following 5 criteria consistent with the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity: (1) large waist circumference (women ≥88 cm, men ≥102 cm), (2) elevated triglycerides (≥150 mg/dL), (3) low high-density lipoprotein (men <40 mg/dL, women <50 mg/dL), (4) impaired fasting glucose (≥100 mg/dL and <126 mg/dL), and (5) high blood pressure (≥130 and ≥85 mm Hg or use of medications for hypertension). We categorized 8 individuals who were positive for 3 or more criteria as having MetS even if information was missing on the others; these individuals were excluded in analyses of number of positive components. Use of fibrates and statins was missing on the others; these individuals were excluded in analyses of number of positive components. Use of fibrates and nicotinic acid at baseline was rare (1.8%) in this cohort and was not included in our definition. Consistent with prior research evaluating an incorporated definition of inflammation and MetS, inflammation-MetS (CRP-MetS or fibrinogen-MetS) was defined as having 3 or more of 6 components, including elevated markers of inflammation as a sixth component. Elevated CRP was defined as ≥3 mg/L. Elevated fibrinogen corresponded to a value in the highest tertile of our study population (>341 mg/dL).

Incident Low ABI

We used general linear models with log link, Poisson error structure, and robust standard errors to calculate relative risks for developing a low ABI according to the presence or absence of MetS, each MetS component, and each inflammatory marker. Models were adjusted for age, sex, race, clinic site, alcohol consumption, cigarette smoking (current status and pack-years of smoking), prevalent cardiovascular disease, low-density lipoprotein, estimated glomerular filtration rate (eGFR), and physical activity levels. Prevalent cardiovascular disease was defined as history of myocardial infarction, angina, angioplasty, bypass surgery, or stroke. Models evaluating the presence or absence of MetS were additionally adjusted for CRP and fibrinogen. To evaluate whether the association of MetS and PAD was modified by either sex or race, we fit models that included cross-product terms and robust standard errors to calculate relative risks for developing a low ABI in each sex and race group.
relative risk of developing a low ABI associated with the presence of 1, 2 to 3, or 4 to 5 MetS components compared with participants with no MetS components present.

To assess the individual and joint associations of MetS and inflammation markers with incident low ABI, we cross-classified participants on MetS status (presence/absence) and inflammation status (low/high). CRP and fibrinogen were considered separately and low/high categories were dichotomized at 3 mg/L for CRP and the highest tertile of the distribution for fibrinogen (341 mg/dL). We calculated the relative risk of incident ABI for each category compared with the group without MetS and low inflammation levels.

Finally, adjusted relative risks were calculated incorporating CRP or fibrinogen into the MetS definition (CRP-MetS and fibrinogen-MetS) to determine whether this improves risk prediction of a low ABI. A c-statistic (area under the receiver operating characteristic curve) of the modified MetS definition for a low ABI was also calculated to determine the added impact of inflammatory markers.

**Incident Clinical PAD**

To evaluate the association between MetS, individual MetS components, inflammatory markers, and incident clinical PAD, we calculated hazard ratios (HRs) and 95% confidence interval (CI) using Cox proportional hazards models. Participants who did not develop clinical PAD were censored at the earliest of loss to follow-up, death, or the end of follow-up for this analysis (June 2007), and time-to-event was calculated as the interval between enrollment and either incident PAD or censorship.

**Results**

Baseline characteristics of participants followed up for clinical PAD stratified by the presence or absence of MetS are shown in Table 1.

There were 253 cases of incident low ABI among the 1899 participants with follow-up ABI measurements. There were 208 incident cases of clinical PAD among the 4632 participants followed up for this outcome over a median duration of 13.7 years.

Table 2 shows the relative risk for developing a low ABI and HR for clinical PAD by baseline MetS, each MetS component, and elevated CRP or fibrinogen. MetS was associated with both outcomes in the multivariate model. Additional adjustment for CRP and fibrinogen did not appreciably attenuate the association between MetS and either a low ABI (RR, 1.25; 95% CI, 0.99–1.57) or clinical PAD (HR, 1.42; 95% CI, 1.07–1.88). Additional adjustment for eGFR slightly attenuated the association between MetS and either a low ABI (RR, 1.19; 95% CI, 0.94–1.50) or clinical PAD (HR, 1.31; 95% CI, 0.96–1.77).
Incorporating Inflammation With MetS on Risk of Incident PAD

Joint associations of MetS and either fibrinogen or CRP with the development of an incident low ABI and clinical PAD are shown in Tables S2 and S3, respectively. There was no evidence of synergistic associations for development of an incident low ABI. The combination of MetS and an elevated fibrinogen or CRP resulted in a higher likelihood of developing clinical PAD compared with having only one of these.

To determine whether including CRP or fibrinogen in the definition of MetS increased the predictive value of MetS for developing a low ABI, we created 2 modified definitions of MetS: CRP-MetS and fibrinogen-MetS (Table 3). The prevalence of CRP-MetS was 50.0% (949 of 1899), with 233 of 1183 (19.7%) without MetS reclassified as CRP-MetS. Participants with CRP-MetS had increased risk for an incident low ABI (RR, 1.36; 95% CI, 1.07–1.72 versus no CRP-MetS). The prevalence of fibrinogen-MetS was 47.6% (904 of 1899), with 188 of 1183 (15.9%) without MetS reclassified as fibrinogen-MetS. Participants with fibrinogen-MetS also had a significantly increased risk for an incident low ABI (RR, 1.43; 95% CI, 1.13–1.81) when compared with participants without fibrinogen-MetS. Compared with the c-statistic for MetS alone (0.540), the addition of fibrinogen significantly improved discrimination (c, 0.565; P=0.03) but the addition of CRP did not (c, 0.556; P=0.18).

CRP-MetS and fibrinogen-MetS were also associated with risk of developing clinical PAD (Table 3). The HRs were 1.56 (95% CI, 1.17–2.08) for CRP-MetS and 1.55 (95% CI, 1.17–2.07) for fibrinogen-MetS. The c-statistics for both CRP-MetS (0.566) and fibrinogen-MetS (0.567) related to the development of clinical PAD were similar to the c-statistic for MetS alone (0.556). Comparing the area under the curve for MetS versus MetS-inflammation, the P values were 0.37 and 0.29 for MetS versus MetS-CRP and MetS versus MetS-Fib, respectively.

Discussion

In a cohort of community-dwelling older adults, MetS was associated with the development of PAD, defined either by a low ABI or the development of clinically manifest PAD, after the adjustment for traditional risk factors and markers of inflammation. Hypertension was the only MetS component independently associated with incident PAD. Inflammatory
markers CRP and fibrinogen were also independently associated with incident PAD.

Our findings contrast with the 2 previously published studies on the prospective associations of MetS and incident PAD. The Edinburgh Artery Study (EAS) found no association between MetS and incident PAD. In the Women’s Health Study, a younger cohort of females free of baseline cardiovascular disease participating in a clinical trial, MetS was associated with an increased risk of incident PAD. This association, however, was strongly attenuated after adjustment for inflammatory markers CRP and soluble intracellular adhesion molecule-1 and no longer significant.

The CHS cohort comprised older individuals with a significantly higher baseline prevalence of hypertension and may, in part, explain discrepancies between our findings and those reported in the EAS and Women’s Health Study. Additionally, these 2 prior studies used adapted definitions of MetS and, consequently, did not capture the true prevalence of participants meeting criteria for this syndrome. Waist circumference was not available in either study and body mass index was used instead, which may not capture visceral adiposity. In addition, the Women’s Health Study defined glucose intolerance as the presence or absence of diabetes mellitus, and diabetes mellitus is a well-established PAD risk factor. Thus, overt diabetes mellitus may have driven associations in this study. Additionally, the primary end point for both studies was limited to symptomatic PAD. Prior studies have reported that anywhere from 20% to 50% of individuals with PAD are asymptomatic. The presence of PAD as assessed by ABI as we did here, regardless of the presence of symptoms, is strongly associated with increased cardiovascular morbidity and mortality. It is unclear why these findings were not consistent across race. Our null findings in black participants may simply be the result of small event numbers or chance. Further study with primary attention to racial differences is needed.

The association between inflammation and incident PAD has been demonstrated previously. Both CRP and fibrinogen have been reported to be associated with the development of incident PAD. Our results corroborate those of prior studies by also showing an independent association between inflammation and the development of PAD. It is unclear, however, why CRP was only significant for the development of clinical PAD and fibrinogen only significant for the development of a low ABI. As mentioned previously, the CHS cohort is different at baseline from other well-studied cohorts in terms of age and prevalence of hypertension. As a result, it may be that different biomarkers are relevant in different populations. Alternatively, these results may signify that inflammation is important in development of both outcomes, and the disparity found between fibrinogen and CRP is simply reflective of chance.

To our knowledge, this is the first prospective study to evaluate the incorporation of inflammation markers into a MetS definition with incident PAD. Findings from the Women’s Health Study suggested that increased inflammation and endothelial activation might serve as a mechanistic link between MetS and incident PAD. Our results suggest that the relationship between MetS and incident PAD is independent of common inflammatory pathways represented by markers such as CRP and fibrinogen, but the addition of inflammation to the definition of MetS identified larger numbers of older adults at risk and, at least for MetS-Fib, significantly improved discrimination between individuals who did and did not develop a low ABI.

Hypertension was the only MetS component independently associated with incident PAD. Prior studies have documented a strong cross-sectional association between hypertension and PAD. In CHS participants, hypertension was previously reported as a risk factor for ABI decline. eGFR has been previously reported to be closely correlated to hypertension in CHS participants and may explain why findings were slightly attenuated after adjusting for this. It is also possible that eGFR may be a mediator. Our findings underscore the particular role of hypertension in the development of PAD in older individuals with MetS. Current American College of Cardiology and American Heart Association guidelines recommend all individuals aged ≥65 years be screened for PAD. Because hypertension is extremely prevalent and a strong risk factor for PAD development in older age, our results only further justify the need to screen all individuals aged ≥65 years.

Our study has limitations. The CHS participants are all aged ≥65 years; therefore, our results may not be generalizable to younger aged cohorts. Follow-up ABI data were not available for many participants, and this may have introduced bias to analyses involving ABI decline, although results were generally similar for analyses of incident clinical PAD that were not limited by attrition.
Perspectives

MetS is associated with the development of both a low ABI and clinical PAD. Incorporating measures of inflammation into the definition of MetS may help identify more at-risk individuals and provide additive information in predicting incident PAD. Lifestyle modification strategies such as aggressive blood pressure control, dietary changes, regular exercise, and weight loss may be useful targets to evaluate in intervention studies to determine if these reduce the risk of PAD in individuals with MetS. Considering the strong association of hypertension with incident PAD in MetS, studies are needed to determine if strict blood pressure control provides particular benefit to reduce the risk of PAD.

Sources of Funding

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Disclosures

None.

References

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lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA*. 2001;285:2481–2485.


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**Novelty and Significance**

**What Is New?**

- We examined the combined effects of 2 important abnormalities that lead to atherosclerosis—the constellation of increasingly common metabolic abnormalities termed metabolic syndrome and 2 blood tests that reflect inflammation.

- We determined how each abnormality influences 2 measures of blockages in arteries of the legs in older adults.

**What Is Relevant?**

- Hypertension is a key component of metabolic syndrome and very common in these older adults.

**Summary**

Both metabolic syndrome and inflammation lead to blocked arteries in the leg. Using inflammation to define metabolic syndrome helps to identify people at risk.
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Metabolic Syndrome and Risk of Incident Peripheral Artery Disease: The Cardiovascular Health Study

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Supplemental Methods

Laboratory Analyses

Blood was drawn in the morning after an overnight fast, and samples were analyzed at the Central Blood Analysis Laboratory at the University of Vermont. Quality assurance procedures and results for blood procurement, processing, shipping, storage, and sample analysis have been reported previously. Serum total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides, glucose, and creatinine were measured by enzymatic methods. Low-density lipoprotein cholesterol (LDL) was calculated for those with triglycerides <400 mg/dL using the Friedewald equation. CRP was measured by a validated high-sensitivity enzyme-linked immunosorbent assay (ELISA). Cystatin C was measured by means of a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring) with a nephelometer (BNII; Dade Behring). Glomerular filtration rate (eGFR) was estimated with the use of the CKD-EPI cystatin C equation (eGFRcys) without demographic coefficients: eGFRcys = 76.7 × cys C−1.19.

Other Covariates

For the purpose of exclusion, diabetes mellitus was defined as a fasting blood glucose level of ≥126 mg/dl, non-fasting glucose of ≥ 200 mg/dL, or the use of anti-diabetic medication, including both oral medications and insulin. Field center staff directly measured weight and standing height, and body mass index was calculated as measured weight in kilograms divided by standing height in meters squared. Physical activity levels referred to the self-reported number of blocks walked per week. Alcohol consumption was grouped according to self-reported number of drinks per week (none, <7 drinks weekly, 7–13 drinks weekly, and ≥14 drinks weekly). We separated smoking into three categories (current, former, and never) and calculated pack-years of smoking at baseline based upon reported age at onset, age at cessation, and average use.
Supplemental References
## Supplemental Results

**S1:** Relative risk for developing a low ABI according to number of metabolic syndrome (MetS) components at baseline

<table>
<thead>
<tr>
<th>MetS components</th>
<th># Cases / Total (%)</th>
<th>Model 1* (95% CI)</th>
<th>Model 2† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9/158 (5.7)</td>
<td>1.00 (1.00)</td>
<td>1.00 (1.00)</td>
</tr>
<tr>
<td>1</td>
<td>53/464 (11.4)</td>
<td>1.78 (0.93-3.41)</td>
<td>1.76 (0.91-3.41)</td>
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<tr>
<td>2-3</td>
<td>137/964 (14.2)</td>
<td>2.35 (1.26-4.37)</td>
<td>2.27 (1.22-4.21)</td>
</tr>
<tr>
<td>4-5</td>
<td>54/313 (17.3)</td>
<td>2.98 (1.49-5.94)</td>
<td>2.89 (1.44-5.82)</td>
</tr>
</tbody>
</table>

* Model 1 adjusted for age, sex, race, clinic site, alcohol, smoking (current status & pack-years), blocks walked, prevalent CVD, LDL
† Model 2 adjusted for age, sex, race, clinic site, alcohol, smoking (current status & pack-years), blocks walked, prevalent CVD, LDL, C-reactive protein, fibrinogen
**S2: Relative risk of developing a low ABI by the combination of metabolic syndrome (MetS) and inflammatory markers**

<table>
<thead>
<tr>
<th>Elevated inflammation marker*</th>
<th>MetS</th>
<th>C-reactive protein</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td># Cases / Total (%)</td>
<td>Relative Risk (95% CI)†</td>
</tr>
<tr>
<td>(-)</td>
<td>(-)</td>
<td>90/790 (11.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>(-)</td>
<td>(+)</td>
<td>46/338 (13.6)</td>
<td>1.13 (0.82-1.57)</td>
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<tr>
<td>(+)</td>
<td>(-)</td>
<td>50/393 (12.7)</td>
<td>1.02 (0.75-1.40)</td>
</tr>
<tr>
<td>(+)</td>
<td>(+)</td>
<td>67/378 (17.7)</td>
<td>1.38 (1.02-1.86)</td>
</tr>
</tbody>
</table>

*Elevated inflammation marker defined as >3 mg/L for C-reactive protein and >341 mg/dL for fibrinogen

† Relative risks are adjusted for age, sex, race (black, non-black), clinic site, alcohol, smoking (current status & pack-years), blocks walked per week, prevalent CVD, LDL
### S3: Relative risk of developing clinical PAD by the combination of metabolic syndrome (MetS) and inflammatory markers

<table>
<thead>
<tr>
<th>Elevated inflammation marker*</th>
<th>MetS</th>
<th>C-reactive protein</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Cases; Person-Years</td>
<td>Hazard Ratio (95% CI)†</td>
<td># Cases; Person-Years</td>
</tr>
<tr>
<td>(-) ( - )</td>
<td>56</td>
<td>1.00</td>
<td>72</td>
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<tr>
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<td>24510</td>
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<td>26060</td>
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<tr>
<td>(-) ( + )</td>
<td>38</td>
<td>1.45 (0.96-2.20)</td>
<td>56</td>
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<td></td>
<td>11168</td>
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<td>(+) ( - )</td>
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*Elevated inflammation marker defined as >3 mg/L for C-reactive protein and >341 mg/dL for fibrinogen
† Relative risks are adjusted for age, sex, race (black, non-black), clinic site, alcohol, smoking (current status & pack-years), blocks walked per week, prevalent CVD, LDL