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Association Between High-Sensitivity Troponin T and Cardiovascular Risk in Individuals with and without Metabolic Syndrome: The ARIC Study

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YP and VN conceived the study, and all authors reviewed the proposal and provided important input in the design of the study and analysis. WS performed analysis with input from YP and VN. All authors were involved in the interpretation of the data. YP, WS and VN drafted the manuscript. All authors reviewed the manuscript and provided feedback to help with the critical revision of the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Abstract

Background—Metabolic syndrome (MetS) is associated with increased cardiovascular disease (CVD), but there is heterogeneity in this risk. We evaluated whether high-sensitivity troponin T (hs-cTnT), a marker associated with CVD, can stratify risk in MetS.

Methods—We evaluated associations between MetS (and groups with similar number of MetS components) and incident heart failure hospitalization (HF), coronary heart disease (CHD), stroke and death using hs-cTnT categories after adjusting for risk factors/markers between 1996–2011 in 8204 individuals in the Atherosclerosis Risk In Communities study.

Results—The mean age of the population was 63 years (56% women, 19% blacks). hs-cTnT levels were higher with MetS and with increasing MetS components. In individuals with MetS, higher hs-cTnT levels were associated with increased hazard ratios (HRs) for HF, CHD and death. Within each number of MetS components, higher hs-cTnT was associated with progressively higher HF, CHD and death hazards. The association was particularly strong for HF. With increasing hs-cTnT categories, the HRs (95% confidence interval) for HF in individuals with MetS increased gradually from 1.68 (1.31–2.16) to 3.76 (2.69–5.26) [P-trend <0.001], compared to those with MetS and hs-cTnT <5 ng/L; and respective HRs with increasing hs-cTnT categories in those with all 5 MetS components ranged from 2.22 (1.17–4.21) to 4.23 (1.89–9.50) [P-trend 0.004], compared to those with all 5 MetS components and hs-cTnT <5 ng/L. However, mostly there were no significant interactions of hs-cTnT with MetS or its components.

Conclusion—hs-cTnT is useful for identifying MetS patients with increased hazards for CHD, death and particularly HF.

Keywords

Metabolic syndrome; high-sensitive troponin T; risk stratification; heart failure; coronary heart disease

Introduction

The National Cholesterol Education Program's Adult Treatment Panel III defines metabolic syndrome (MetS) as the presence of at least 3 out of 5 following components – elevated blood pressure (BP), elevated triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C) levels, impaired fasting glucose and elevated waist circumference.¹ MetS has been shown to be associated with increased risk for cardiovascular disease (CVD) such as coronary heart disease (CHD) and heart failure, and all-cause mortality.² Given that MetS is associated with heart failure, the American College of Cardiology/ the American Heart Association (ACC/AHA) has categorized persons with MetS to have “Stage A” heart failure i.e. at increased risk for clinical heart failure.^{3,4} On the other hand, there is substantial heterogeneity in risk among those with MetS.⁵ Therefore, identifying individuals with MetS

who are at higher risk for CVD and heart failure development may help in targeting these individuals with intensive treatment and prevention strategies. Furthermore, this may also allow researchers to identify higher risk individuals for clinical trials.

Cardiac troponin T measured with a high-sensitivity assay (hs-cTnT), is a sensitive marker of subclinical myocardial injury⁶ and has shown to be strongly associated with mortality and CVD events including incident CHD, incident heart failure hospitalization (HF) and incident stroke in several population studies,^{7,8} including the Atherosclerosis Risk In Communities (ARIC) study.⁹

Recently we have shown that hs-cTnT can help identify individuals with higher CVD and HF risk across systolic BP categories.¹⁰ When stratified by systolic BP, individuals with higher levels of hs-cTnT had increased hazards for incident CVD events, particularly HF, when compared to individuals with undetectable hs-cTnT. We hypothesized that much like for systolic BP, hs-cTnT can help identify individuals with MetS who are at higher risk for incident CVD including CHD, stroke and HF as well as death. In other words, there will be varying levels of hs-cTnT in individuals with MetS, and those with higher hs-cTnT levels will have greater risk for incident events when compared to individuals with MetS who have lower hs-cTnT levels. We further hypothesized that within groups with presence of similar number of MetS components, the risk for incident events would be stronger with higher hs-cTnT levels.

Materials and Methods

Study population

The ARIC study is a prospective cohort study of 15,792 individuals aged 45–64 years on initial evaluation (Visit 1, 1987–89) from four U.S. communities. Details related to the study design have been described previously.¹¹ Study participants have been examined at 4 additional follow-up visits since the initial evaluation. Among 11,656 participants at Visit 4 (1996–1998), which was the baseline for this analysis, we excluded individuals with race other than black or white (n= 31), blacks from the Washington County, Maryland and Minneapolis, Minnesota centers, with predominantly white population (n= 38), and those with prevalent diabetes and CVD, missing data on MetS or prior CVD, resulting in 8204 individuals (Supplemental Figure 1).

Metabolic syndrome, high sensitivity troponin T and baseline variables

MetS was defined according to the National Cholesterol Education Program's Adult Treatment Panel III.¹ Individuals were classified as having MetS if they had three or more of the followings from ARIC Visit 4: elevated BP (systolic BP $\geq$ 130 mmHg or diastolic BP $\geq$ 85 mm Hg and/or use of anti-hypertensive medications); elevated TG ($\geq$ 150 mg/dL); low HDL-C (men $<$ 40 mg/dL, women $<$ 50 mg/dL); impaired fasting glucose ($\geq$ 100 mg/dL); and elevated waist circumference (men $>$ 102 cm, women $>$ 88 cm).

Details about the hs-cTnT assay used have been previously reported.⁹ Briefly, hs-cTnT was measured in 2010 from blood samples collected during ARIC Visit 4 (1996–98) with a high-sensitivity assay, Elecsys Troponin T (Roche Diagnostics®), on an automated Cobas e411

analyzer. The limit of detection for hs-cTnT is 5 ng/L (i.e., the lowest concentration of hs-cTnT that can be reliably quantified in a given sample) and the limit of measurement is 3 ng/L (i.e., the highest apparent hs-cTnT levels in an analyte-free sample). The 99th percentile value for the hs-cTnT measured in a healthy reference population was 14 ng/L (Roche Diagnostics®, data on file).

Medical history, demographic data, fasting lipids, anthropometric and BP measurements were obtained using standardized protocols. Certified technicians used a random-zero sphygmomanometer to measure 2 BP readings in the sitting position after 5 minutes of rest and the mean BP of the 2 measurements was recorded.¹² Total cholesterol, HDL-C, TG and glucose were determined by enzymatic methods after overnight fasting.¹³ Diabetes was defined as a fasting blood glucose level ≥ 126 mg/dL, non-fasting blood glucose level ≥ 200 mg/dL, or a self-reported physician diagnosis of/ or treatment for diabetes. Estimated glomerular filtration rate was computed from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.¹⁴ Anthropometric measurements were taken in standard scrub attire with no shoes. Waist circumference was measured by obtaining the horizontal measurement of maximum girth at the level of the umbilicus, with results measured to the nearest centimeter, rounding down.¹⁵ Weight was measured using a scale that was zeroed daily and calibrated quarterly.

Cardiovascular disease and death

Incident CHD was defined as hospitalization for myocardial infarction, definite coronary death, coronary revascularization procedure, or silent myocardial infarction as confirmed by electrocardiogram.¹⁶ Stroke was defined as sudden onset of neurological symptoms lasting for >24 hours or leading to death, without evidence for a non-stroke cause.¹⁷ Incident heart failure hospitalization (HF) was defined as the first heart failure hospitalization identified with *International Classification of Diseases Code* of 428.x (*Ninth Revision*) or I50 (*Tenth Revision*) in any position on the hospital discharge list or on a death certificate with death from HF in any position.¹⁸ Deaths were confirmed by review of hospital discharge records for inpatient deaths and death certificates for out of hospital deaths.

Statistical Analysis

In our analyses, we included individuals with and without MetS and also those without presence of any MetS components, similar to our prior work on BP.¹⁰ We first assessed baseline characteristics according to the presence of MetS. In cross sectional analyses we then examined the overall prevalence of MetS and each of its components at ARIC Visit 4. We also examined hs-cTnT levels (measured at ARIC Visit 4) among individuals with and without MetS, and also according to the number of MetS components. We examined whether there was a linear trend for higher hs-cTnT levels with progressively increasing presence of MetS components.

To examine the relationship of MetS and its components to subclinical myocardial injury, we estimated the odds ratio (OR) for detectable levels of hs-cTnT (i.e., ≥ 5 ng/L)^{9,10} according to the presence of MetS and its components using logistic regression models. For individuals with MetS, we constructed models adjusted for age, gender and race (model 1) and then

additionally adjusted for all MetS components together (model 2) as MetS components can be correlated with each other. We also calculated the correlation coefficients among all MetS components and hs-cTnT.

Individuals were followed for incident events including HF, CHD, all types of stroke and death from any cause, until December 31, 2011. All prevalent diagnoses of HF, CHD and all types of stroke were excluded for this analysis. We performed 2 sets of analyses to examine the hazard ratios (HR) for HF, CHD, stroke and death. In one analysis we stratified individuals by presence of MetS (or presence of same number of MetS components) and used hs-cTnT <5 ng/L as the reference for each group (i.e., separately for those with MetS, without MetS, and for those with same number of MetS components). For example, we selected all individuals with 1 MetS component and used those with hs-cTnT <5 ng/L as the reference (Table 4), while in the second analysis, we used those without MetS or without presence of any MetS component and hs-cTnT <5 ng/L as the reference group (Supplemental Table 5). Within the first set of analysis, we additionally performed sensitivity analysis after excluding individuals with incident CHD or myocardial infarction to assess the relationship between hs-cTnT and HF independent of CHD/myocardial infarction. Similar to prior analysis,^{9,10} we further categorized hs-cTnT $\geq$ 5 ng/L as 5–8, 9–13 and $\geq$ 14 ng/L. In addition, we examined individuals by presence of similar number of MetS components (i.e. from 0–5) and assessed if those with hs-cTnT $\geq$ 5 ng/L have higher HRs for HF, CHD, stroke and death. We used Cox-proportional hazard models and confirmed the proportional hazards assumption using time-dependent covariates and likelihood ratio statistics. These analyses were adjusted for age, gender, race, ARIC center, estimated glomerular filtration rate, total cholesterol, current cigarette smoking, log-transformed C-reactive protein and log-transformed N terminal pro-B-type natriuretic peptide. We examined if there was a linear trend for increasing HRs across higher hs-cTnT levels. Finally, we assessed interaction between hs-cTnT (either <5 or $\geq$ 5 ng/L; or 5–8, 9–13 and $\geq$ 14 ng/L) and MetS (or its components) for their association with HF, CHD, stroke and death.

Categorical variables were analyzed using Chi-square tests and continuous variables were analyzed using analysis of variance. A 'p' value for trend across groups was calculated by the Jonckheere-Terpstra test for continuous variables and by the Cochran-Armitage trend test for categorical variables. All presented tests were 2-tailed and a 'p' value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.3 (Cary, NC). Written informed consent was provided by all study participants and the institutional review boards at the participating sites approved the study protocol.

Results

The mean age (standard deviation) of the population was 63 (6) years; 19% were blacks and 57% were women (Table 1). The mean levels of blood glucose was 99 (9) mg/dL, systolic and diastolic BP 126 (19) mmHg and 71 (10) mmHg, respectively, HDL-C 51 (17) mg/dL and waist circumference 100 (14) cm, respectively. Median (25th, 75th percentile) level of TG was 118 (86, 166) mg/dL. MetS was present in 45% of the cohort; the prevalence of individual MetS components is shown in Supplemental Table 1. Detectable levels of hs-

cTnT (i.e., ≥ 5 ng/L) were present in 49.7% and 45.0% of individuals with and without MetS, respectively. The mean hs-cTnT levels were higher in individuals with MetS compared to those without MetS (Table 2). Although modest, hs-cTnT levels were higher as the number of MetS components increased (P trend for hs-cTnT levels across progressively higher MetS components was <0.001) (Table 2).

The correlation coefficients among MetS components and hs-cTnT are presented in Supplemental Table 2. The OR for having detectable hs-cTnT in individuals with MetS compared to those without MetS was 1.28 (95% CI, 1.17–1.41) when adjusted for age, gender and race (model 1, Table 3). When MetS components were considered individually, elevated BP, reduced HDL-C levels and elevated waist circumference and glucose each had significant increased odds for having detectable hs-cTnT (i.e., ≥ 5 ng/L) compared to individuals without these respective factors in models adjusted for age, gender and race (model 1). When all of the 5 MetS components were adjusted for each other and age, gender and race (model 2), the associations remained significant but attenuated for elevated BP, reduced HDL-C and elevated waist circumference, and became non significant for elevated glucose. Elevated BP had the strongest association for having detectable hs-cTnT (OR 1.41, 1.28–1.55). The association of elevated TG with hs-cTnT was not significant when modeled alone or when adjusted for other MetS components.

There were 772 overall incident heart failure hospitalizations, 971 CHD, 357 stroke and 1570 deaths, with incidence rates of 7.3, 9.5, 3.3 and 14.4 per 1000 person-years, respectively. The incidence rates by MetS and hs-cTnT levels are shown in Supplemental Table 3. Numerically, individuals with MetS and hs-cTnT ≥ 5 ng/L had higher incident event rates compared to those with MetS and hs-cTnT <5 ng/L (Supplemental Figures 2–5).

Results comparing the associations of detectable hs-cTnT when individuals with and without MetS were considered separately are presented in Table 4. Compared with individuals without MetS and hs-cTnT <5 ng/L, the HRs (95% CI) for incident heart failure hospitalization was 1.60 (1.24–2.05) in those without MetS and hs-cTnT ≥ 5 ng/L (Table 4). The corresponding HR for those with MetS was 1.94 (1.54–2.43). For CHD significant association was present only in those with MetS and hs-cTnT ≥ 5 ng/L (1.59, 95% CI, 1.30–1.95). The associations were essentially null for stroke. The hazard for death was higher in individuals with detectable hs-cTnT, either without (1.42, 1.21–1.67) or with MetS (1.29, 1.09–1.53, Table 4). When detectable levels of hs-cTnT were further categorized, results were broadly similar and strongest for HF (Table 4). There were significant linear trends ($P<0.05$) for progressive higher risk of HF and death, both with and without MetS; for CHD only with MetS; for stroke only without MetS (Table 4). Sensitivity analysis for HF outcome showed similar results after excluding incident CHD and myocardial infarction (Supplemental Table 4).

When compared to individuals without MetS and hs-cTnT <5 ng/L, the HRs for incident HF hospitalization were 1.60 (95% CI: 1.24–2.05) in those without MetS and hs-cTnT ≥ 5 ng/L; 1.28 (1.00–1.64) in those with MetS and hs-cTnT <5 ng/L and 2.51 (2.01–3.14) in those with MetS and hs-cTnT ≥ 5 ng/L (Supplemental Table 5). Although attenuated, results were similar for CHD. There were no significant associations for stroke, and associations for

death were significant only in groups with detectable hs-cTnT (Supplemental table 5). When assessed across higher hs-cTnT levels, although there were higher hazards for HF and CHD in individuals without MetS, the strength of association generally was numerically stronger in those with MetS (Supplemental Table 5). The association was strongest for HF. For example, compared to individuals without MetS and hs-cTnT <5 ng/L, those with MetS and hs-cTnT 14 ng/L had approximately 5 times increased hazards for HF.

Next we present results comparing the associations by detectable hs-cTnT separately in groups with presence of same number of MetS components (Table 4). There were increased hazards for HF in individuals with hs-cTnT 5 ng/L compared to those with hs-cTnT <5 ng/L in groups with same number of MetS components, with highest risk for those with all 5 MetS components (2.47, 1.39–4.42, Table 4). Results were attenuated for CHD and death, and essentially null for stroke. When detectable levels of hs-cTnT were further categorized, generally there were progressively stronger hazards with higher hs-cTnT categories (Table 4). Associations were robust and stronger for HF than for CHD or death, and almost null for stroke. Within each group with presence of same number of MetS components, generally there were significant linear trends with higher hs-cTnT levels. Conversely, the linear trend with progressive increase in presence of MetS components within each hs-cTnT category was not as robust (Table 4). Results were similar in analyses with references as groups with hs-cTnT <5 ng/L and absence of any MetS component (Supplemental Table 5). Again, the association was strongest for HF. For example, compared with individuals without any MetS component and hs-cTnT <5 ng/L, those with presence of all 5 MetS components and hs-cTnT 14 ng/L had 8.7 times increased hazards for HF (Supplemental Table 5).

We did not find significant interactions between hs-cTnT and MetS in their association with any of the outcomes when hs-cTnT was used as cutoff of 5 ng/L and MetS (all p for interaction >0.05). When interaction was examined between MetS and greater number of hs-cTnT categories as in Table 4, the interaction was significant only for stroke (p=0.049) and death (p=0.0315). Similarly there was no significant interaction between hs-cTnT (analyzed as cutoff of 5 ng/L or more categories as in Table 4) and MetS components for HF, CHD, stroke or death (all p for interaction >0.05).

Discussion

In this study we found that MetS was associated with increased hazards for HF, CHD and death, especially in individuals with greater subclinical myocardial injury, and that these associations were relatively attenuated and frequently non-significant in those without subclinical myocardial injury (i.e., undetectable hs-cTnT). The associations of MetS components for HF, CHD and death were generally stronger with higher levels of hs-cTnT within groups with similar numbers of MetS components. The hazards were strongest in those with all 5 MetS components and highest levels of hs-cTnT. The association was particularly strong for HF. However, formal test of interactions between MetS or its components and hs-cTnT were not significant for most outcomes.

Insulin resistance, a key component of MetS, has been hypothesized to have a direct pathogenic mechanism for myocardial injury.¹⁹ The ACC/AHA classifies MetS as a risk

factor for heart failure.^{3,4} All individuals with ACC/AHA classification of stage A heart failure (i.e., at risk for HF development) may not go on to develop clinical heart failure. Therefore, in patients with MetS, identifying subgroups at increased risk for heart failure is useful. Approaches have been used to stratify CVD risk in individuals with MetS. For example, presence of clusters of MetS components rather than MetS per se has been proposed as markers of arterial aging and CVD events.²⁰ Similarly, high-sensitivity C-reactive protein has been proposed to risk stratify individuals with MetS.²¹ However, there has not been many approaches to stratifying HF risk. The value of hs-cTnT in predicting CVD events including HF has been emerging. There is limited data related to hs-cTnT and MetS. In one analysis, obese children with MetS were found to have higher hs-cTnT levels than obese children without MetS.²² On the other hand, obesity was associated with increased hs-cTnT levels only among individuals without MetS in another study.²³ In the current study, we found that hs-cTnT levels were higher in individuals with MetS than those without MetS. However, among individuals with MetS, those with greater subclinical myocardial injury had particularly increased hazards for HF. Among individuals with MetS, we found that the rate of HF was 5.4 per 1000 person-years in persons without detectable hs-cTnT and it was 13.7 per 1000 person-years in those with detectable hs-cTnT. In addition, although the hazards for HF development increased with presence of more MetS components in individuals with hs-cTnT < 5, there was a tendency towards stronger associations in those with hs-cTnT ≥ 5 ng/L. Furthermore, we showed that highest hs-cTnT levels (≥ 14 ng/L) was associated with 3 and 5 times higher hazards for HF in those without and with MetS, respectively as compared with those with undetectable hs-cTnT and without MetS.

We have previously shown that higher hs-cTnT levels across various clinically relevant systolic BP categories were associated with increased hazards for CVD and the association was particularly strong for HF.¹⁰ Furthermore, individuals with “normal” systolic BP (example 120–129 mmHg) and higher hs-cTnT levels had greater CVD risk than those with higher systolic BP of 150–159 mmHg but lower hs-cTnT level. In a separate analysis from the ARIC study, presence of pre-diabetes (hemoglobin A1c of 5.7–6.4%) as well as diabetes (hemoglobin A1c ≥ 6.5%) was associated with increased risk for elevated hs-cTnT levels and increased risk for HF, CHD and death compared to those without diabetes (hemoglobin A1c < 5.7%).²⁴ Combined together, these studies suggest that perhaps a surrogate of sub-clinical myocardial injury, such as hs-cTnT is a better marker of advanced pathophysiological processes than the mere presence of risk factors and can therefore complement risk factor information in MetS identifying higher risk individuals.

Study Strengths and Limitations

To our knowledge, this is the first study to examine if subclinical myocardial injury in individuals with MetS can stratify risk for CVD, HF and death. Strengths of this study include a well-characterized large cohort of blacks and whites with a large representation of women and long follow up period of about 12 years. The lack of echocardiographic data can be viewed as a possible limitation when evaluating HF outcomes. However, validation of HF hospitalizations showed positive predictive value of discharge and death certificate codes were 93% for acute decompensated HF and 97% for chronic HF.¹⁸ MetS in younger

population could be related to presence of more obesity and dyslipidemia, and less hypertension than older population. Since the average age of our study population was 63 years, our findings may not directly apply to younger population. Despite increased hazards for CHD, HF and death, it should also be noted that results of most interaction analyses were not statistically significant. As an observational non-blinded study, residual confounding could still be possible despite adjustment for multiple variables.

Future Directions

Our findings could have important research and clinical implications. For example, hs-cTnT can be helpful to identify patients further advanced in the pathophysiological cascade of adverse events. Therefore, hs-cTnT may provide opportunities to identify and perhaps, in the future with additional studies, personalize treatment of high-risk MetS patients or guide inclusion in clinical trials (identifying higher risk subjects). For example, perhaps future clinical trials can examine if novel drugs, such as empagliflozin (which has been shown to reduce the risk of HF and mortality in patients with diabetes)²⁵ can reduce HF risk in patients with MetS selected based on evidence of subclinical myocardial injury. However, clearly all of this will need to be carefully tested in future studies before any conclusions on the potential value of hs-cTnT in current day clinical practice can be proposed.

Conclusion

Elevated hs-cTnT in individuals with MetS components or MetS are at greater hazards for incident HF, CHD and death. Future clinical trials could consider using hs-cTnT to identify individuals with MetS at higher risk for incident CHD, HF and death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ARIC	Atherosclerosis Risk In Communities Study
BP	blood pressure
CVD	cardiovascular disease
CHD	coronary heart disease

hs-cTnT	cardiac troponin T measured using a high-sensitivity assay
HDL-C	high-density lipoprotein cholesterol
HF	incident heart failure hospitalization
MetS	metabolic syndrome
TG	triglyceride

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Table 1

Baseline characteristics

Characteristics	Total population [N=9206]	MetS present [N=4191]	MetS absent [N=5015]	P value
Age, years	62.7 (5.7)	63.1 (5.6)	62.4 (5.7)	<0.001
Black	1746 (19.0)	794 (18.9)	952 (19.0)	0.963
Women	5240 (56.9)	2459 (58.7)	2781 (55.4)	0.002
Current smokers	1395 (15.2)	563 (13.4)	832 (16.6)	<0.001
Body mass index, kg/m ²	28.2 (5.3)	30.6 (5.3)	26.2 (4.5)	<0.001
Blood glucose, mg/dL	99.0 (9.4)	103.6 (9.0)	95.2 (7.9)	<0.001
Total cholesterol, mg/dL	201.3 (36.2)	204.9 (38.3)	198.3 (34.2)	<0.001
HDL-C, overall, mg/dL	51.2 (16.7)	43.7 (12.8)	57.5 (16.9)	<0.001
HDL-C, men, mg/dL	43.7 (13.6)	37.1 (9.5)	48.7 (14.1)	<0.001
HDL-C, women, mg/dL	56.9 (16.6)	48.3 (12.8)	64.6 (15.7)	<0.001
LDL-C, mg/dL	123.1 (33.2)	127.0 (33.9)	119.9 (32.2)	<0.001
Non-HDL-C, mg/dL	150.1 (37.2)	161.2 (37.2)	140.8 (34.6)	<0.001
Total cholesterol/HDL-C ratio	4.29 (1.42)	4.99 (1.41)	3.70 (1.13)	<0.001
Triglycerides, mg/dL	118 (86, 166)	161 (115, 210)	98 (74, 126)	<0.001
Systolic blood pressure, mm Hg	126.4 (18.7)	131.0 (18.5)	122.6 (18.0)	<0.001
Diastolic blood pressure, mm Hg	71.1 (10.2)	72.4 (10.4)	70.0 (10.0)	<0.001
Hypertension	4013 (43.8)	2508 (60.2)	1505 (30.1)	<0.001
NTproBNP, pg/mL	69.8 (34.8, 133.8)	67.5 (32.8, 136.0)	71.2 (36.5, 131.4)	0.180
High sensitivity C reactive protein, mg/L	2.24 (1.0, 5.0)	3.05 (1.4, 6.1)	1.67 (0.81, 4.0)	<0.001
Serum creatinine, mg/dL	0.7 (0.6, 0.8)	0.7 (0.6, 0.9)	0.7 (0.6, 0.8)	<0.001
eGFR, mL/min per 1.73 m ²	95.3 (15.1)	93.8 (16.1)	96.6 (14.1)	<0.001
Antihypertensive medication use	3587 (39.0)	2310 (55.1)	1277 (25.5)	<0.001
Waist circumference, overall, cm	100.3 (14.0)	107.1 (12.8)	94.6 (12.3)	<0.001
Waist circumference, men, cm	101.8 (11.1)	107.8 (10.0)	97.2 (9.6)	<0.001
Waist circumference, women, cm	99.2 (15.7)	106.6 (14.4)	92.6 (13.8)	<0.001
Prevalent CHD	1543 (16.8)	862 (20.6)	681 (13.6)	<0.001
Prevalent Stroke	531 (5.77)	282 (6.73)	249 (4.97)	<0.001
Prevalent peripheral artery disease	274 (5.29)	140 (6.14)	134 (4.62)	0.015
Family history of CHD	3764 (45.3)	1830 (48.6)	1934 (42.6)	<0.001
Family history of stroke	2671 (32.2)	1302 (34.4)	1369 (30.3)	<0.001

CHD, coronary heart disease; eGFR, Estimated glomerular filtration rate; HDL-C, High-density lipoprotein cholesterol; MetS, metabolic syndrome; LDL-C, low-density lipoprotein cholesterol, NTproBNP, N-terminal pro-B-type natriuretic peptide

Data presented as mean $\pm$ standard deviation or median (25th, 75th percentile) for continuous variables and n (%) for dichotomous variables.

P value is comparing individuals with and without MetS

Table 2

Levels of hs-cTnT by presence of MetS and its components

hs-cTnT (ng/L)						
	N	Mean	SD	Median	25 th , 75 th percentile	
Overall	9206	16.67	4	3, 7		
MetS present	4191	22.42	5	3, 8		
MetS absent	5015	9.46	4	3, 7		
MetS components	0	810	5.4	4.02	4	3, 6
	1	1846	5.9	7.22	4	3, 7
	2	2359	6.6	11.98	4	3, 7
	3	2247	6.5	7.10	5	3, 8
	4	1433	8.0	36.90	5	3, 8
	5	511	7.6	8.94	5	3, 9
P trend for hs-cTnT levels across increasing MetS components						<0.001

hs-cTnT, cardiac troponin T measured using a high-sensitivity assay; MetS, metabolic syndrome; SD, standard deviation

Table 3

Odds ratio for presence of detectable hs-cTnT (hs-cTnT < or = 5)

MetS and its components	Odds ratios for hs-cTnT ≥ 5 ng/L	
	Model 1	Model 2
Elevated blood pressure	1.44 (1.31–1.58)	1.41 (1.28–1.55)
Elevated triglycerides	1.02 (0.93–1.13)	0.92 (0.83–1.02)
Reduced HDL-C	1.15 (1.05–1.26)	1.12 (1.02–1.24)
Elevated waist circumference	1.21 (1.10–1.34)	1.14 (1.02–1.26)
Elevated fasting glucose	1.15 (1.05–1.26)	1.08 (0.98–1.19)
MetS present	1.28 (1.17–1.41)	-

HDL-C, high-density lipoprotein cholesterol; hs-cTnT, cardiac troponin T measured using a high-sensitivity assay; MetS, metabolic syndrome

Note that with Model 1 each row is modeled separately whereas Model 2 has included all MetS components simultaneously. i.e., Model 1: adjusted for age, gender and race. Model 2: adjusted for each of the 5 MetS components (i.e., elevated blood pressure, elevated triglyceride, reduced HDL-C, elevated waist circumference and elevated fasting glucose), age, gender and race

MetS components include elevated blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg and/or use of antihypertensive medication; Elevated triglycerides (≥ 1.69 mmol/L); Low HDL-C (men <1.03 mmol/L, women <1.29 mmol/L); Impaired fasting glucose (≥ 100 mg/dL); and Large waist circumference (men >102 cm, women >88 cm). Presence of 3 out of 5 of these components was defined as presence of MetS

Numbers marked in bold indicates statistically significant findings

Table 4

Associations between MetS, its components with CVD and death by hs-cTnT categories (reference groups: hs-cTnT<5 ng/L and by presence of MetS/ or similar number of MetS components present)

MetS components [n with outcomes/n at risk]	hs-cTnT<5 ng/L [n=4322]	hs-cTnT 5 ng/L [n=3882]	hs-cTnT 5-8 ng/L [n=2441]	hs-cTnT 9-13 ng/L [n=993]	hs-cTnT 14 ng/L [n=448]	P-trend across higher hs-cTnT
HF	[258/4322]	[514/3882]	[250/2441]	[149/993]	[115/448]	<0.001
0[36/784]	reference	1.61 (0.73-3.54)	1.41 (0.59-3.35)	1.85 (0.60-5.69)	3.84 (0.92-16.01)	0.304
1[124/1705]	reference	1.32 (0.88-1.99)	1.10 (0.70-1.74)	1.59 (0.90-2.80)	2.88 (1.46-5.65)	0.013
2[179/2101]	reference	1.82 (1.28-2.59)	1.60 (1.09-2.34)	2.19 (1.38-3.48)	3.24 (1.80-5.82)	<0.001
3[201/1968]	reference	1.96 (1.40-2.74)	1.61 (1.11-2.34)	2.06 (1.32-3.22)	4.19 (2.63-6.70)	<0.001
4[161/1224]	reference	1.69 (1.17-2.44)	1.58 (1.06-2.35)	1.72 (1.05-2.83)	2.68 (1.47-4.86)	0.009
5[71/422]	reference	2.47 (1.39-4.42)	2.22 (1.17-4.21)	2.35 (1.14-4.83)	4.23 (1.89-9.50)	0.004
P trend			<0.001	0.201	0.232	
MetS absent [339/4590]	reference	1.60 (1.24-2.05)	1.38 (1.05-1.82)	1.91 (1.36-2.68)	3.04 (1.99-4.62)	<0.001
MetS present [433/3614]	reference	1.94 (1.54-2.43)	1.68 (1.31-2.16)	2.05 (1.52-2.77)	3.76 (2.69-5.26)	<0.001
CHD	[359/4322]	[612/3882]	[329/2441]	[180/993]	[103/448]	<0.001
0[54/784]	reference	1.18 (0.64-2.17)	1.23 (0.65-2.33)	1.01 (0.38-2.64)	1.13 (0.24-5.23)	0.926
1[157/1705]	reference	1.03 (0.72-1.47)	1.02 (0.70-1.50)	0.99 (0.59-1.68)	1.17 (0.61-2.26)	0.968
2[237/2101]	reference	1.18 (0.88-1.58)	1.04 (0.75-1.44)	1.46 (0.98-2.16)	1.63 (0.95-2.81)	0.119
3[257/1968]	reference	1.67 (1.25-2.24)	1.45 (1.05-2.01)	1.82 (1.23-2.71)	2.84 (1.84-4.40)	<0.001
4[192/1224]	reference	1.29 (0.93-1.79)	1.35 (0.95-1.91)	1.18 (0.75-1.85)	1.18 (0.64-2.19)	0.421
5[74/422]	reference	2.52 (1.41-4.48)	2.19 (1.16-4.14)	2.64 (1.33-5.23)	4.06 (1.77-9.32)	0.005
P trend			<0.001	0.023	0.037	
MetS absent [448/4590]	reference	1.13 (0.91-1.40)	1.07 (0.85-1.34)	1.24 (0.92-1.66)	1.40 (0.93-2.09)	0.302
MetS present [523/3614]	reference	1.59 (1.30-1.95)	1.48 (1.18-1.84)	1.67 (1.28-2.18)	2.22 (1.61-3.06)	<0.001
Stroke	[143/4322]	[214/3882]	[109/2441]	[71/993]	[34/448]	<0.001
0[23/784]	reference	1.33 (0.52-3.40)	1.22 (0.43-3.43)	1.28 (0.32-5.17)	3.47 (0.63-18.95)	0.553
1[76/1705]	reference	1.10 (0.66-1.83)	0.88 (0.49-1.58)	1.54 (0.77-3.09)	1.97 (0.78-4.97)	0.231
2[88/2101]	reference	1.61 (0.98-2.67)	1.40 (0.81-2.43)	1.90 (0.97-3.72)	3.12 (1.42-6.89)	0.036

MetS components [n with outcomes/n at risk]	hs-cTnT <5 ng/L [n=4322]	hs-cTnT 5 ng/L [n=3882]	hs-cTnT 5–8 ng/L [n=2441]	hs-cTnT 9–13 ng/L [n=993]	hs-cTnT 14 ng/L [n=448]	P-trend across higher hs-cTnT
3 [81/1968]	reference	1.04 (0.63–1.73)	1.12 (0.66–1.92)	1.09 (0.56–2.15)	0.46 (0.15–1.44)	0.454
4 [64/1224]	reference	1.59 (0.89–2.82)	1.43 (0.76–2.68)	2.21 (1.09–4.46)	0.81 (0.25–2.63)	0.084
5 [25/422]	reference	0.48 (0.19–1.20)	0.53 (0.18–1.52)	0.41 (0.12–1.42)	0.49 (0.11–2.30)	0.462
P trend			0.795	0.379	0.083	
MetS absent [187/4590]	reference	1.35 (0.97–1.88)	1.14 (0.78–1.65)	1.68 (1.07–2.63)	2.63 (1.50–4.58)	0.003
MetS present [170/3614]	reference	1.14 (0.81–1.62)	1.13 (0.78–1.65)	1.35 (0.86–2.10)	0.66 (0.33–1.34)	0.187
All-cause death	[584/4322]	[986/3882]	[472/2441]	[314/993]	[200/448]	<0.001
0 [120/784]	reference	1.46 (0.95–2.23)	1.22 (0.76–1.95)	1.96 (1.11–3.45)	2.71 (1.29–5.68)	0.022
1 [313/1705]	reference	1.29 (1.00–1.68)	1.07 (0.80–1.43)	1.67 (1.18–2.36)	2.29 (1.49–3.52)	<0.001
2 [405/2101]	reference	1.47 (1.17–1.86)	1.26 (0.98–1.63)	1.62 (1.19–2.21)	3.10 (2.16–4.45)	<0.001
3 [392/1968]	reference	1.31 (1.04–1.65)	1.17 (0.90–1.51)	1.34 (0.97–1.84)	2.13 (1.49–3.02)	<0.001
4 [239/1224]	reference	1.31 (0.97–1.76)	1.23 (0.89–1.71)	1.44 (0.98–2.13)	1.52 (0.91–2.54)	0.235
5 [101/422]	reference	1.21 (0.77–1.89)	0.95 (0.56–1.63)	1.49 (0.86–2.59)	1.69 (0.84–3.41)	0.221
P trend			0.875	0.586	0.329	
MetS absent [838/4590]	reference	1.42 (1.21–1.67)	1.19 (1.00–1.43)	1.71 (1.39–2.11)	2.76 (2.14–3.57)	<0.001
MetS present [732/3614]	reference	1.29 (1.09–1.53)	1.16 (0.96–1.40)	1.41 (1.13–1.77)	1.88 (1.44–2.45)	<0.001

CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; hs-cTnT, cardiac troponin T measured using a high-sensitivity assay; MetS, metabolic syndrome

Data presented as HR (95% CI)

Numbers marked in bold indicates statistically significant findings

Model adjusted for age, gender, race, center, estimated glomerular filtration rate, total cholesterol, current cigarette smoking, C-reactive protein (log) and N-terminal pro-B-type natriuretic peptide (log)