Do Different Metabolic Syndrome Definitions Predict Cerebrovascular Events and Coronary Heart Disease Independent of Their Components?  
9 Years Follow-Up of the Tehran Lipid and Glucose Study

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Background and Purpose—The purpose of this study was to examine whether metabolic syndrome (MetS), applying different definitions, predicts incident coronary heart disease (CHD) and cerebrovascular events (CVAs) independent of its components.

Methods—Among 2548, aged ≥50 years, World Health Organization, International Diabetes Federation, and Joint Interim Statement criteria were used to define MetS. Cox proportional hazards regression was implemented to estimate hazard ratios of incident CVA and CHD.

Results—During 9.3 years of follow-up, 72 and 343 cases of CVA and CHD events occurred. The multivariate hazard ratios (95% CI) of incident CVA and CHD were 2.71 (1.57–4.68) and 2.07 (1.63–2.64) for MetS as defined by the Joint Interim Statement, respectively. There was no difference among the 3 definitions of MetS regarding the prediction of the CVA incidence. However, MetS as defined by the Joint Interim Statement predicted CHD better than the International Diabetes Federation definition. After adjustment for components, MetS lost its association with CHD and CVA; in this model, the elevated blood pressure and high fasting plasma glucose (International Diabetes Federation definition) showed significant risk for CVA events; regarding CHD events, the elevated blood pressure, high fasting plasma glucose, and, for World Health Organization definition, obesity and dyslipidemia remained as predictors.

Conclusions—All definitions of MetS were associated with CVA and CHD events. After adjusting its components, MetS lost its association with incident CVA and CHD; however, elevated blood pressure for both CVA and CHD events and high fasting plasma glucose for CHD events remained as independent predictors in all definitions. (Stroke. 2012;43:1669-1671.)

Key Words: coronary heart disease ■ hypertension ■ metabolic syndrome ■ stroke

Metabolic syndrome (MetS) has become a leading health concern due to its association with cardiovascular disease. Despite presentation of a common definition for MetS, some studies have raised concerns about the necessity to combine these risk factors into a syndrome and determine its association with cardiovascular disease.1,2

The aim of this study is to compare the different definitions of MetS versus its components in prediction of incident cerebrovascular accident (CVA) and coronary heart disease (CHD) and to examine whether the MetS per se has any risk independent of its components.

Methods
From overall Tehran Lipid and Glucose Study1 participants, aged ≥50 years, we excluded those with a history of prior cardiovascular disease (n=435) as well as those with missing data on all of covariates, leaving 2818 subjects, of whom 2548 subjects were monitored until March 2009 for a median follow-up of 9.3 years. Outcome measurements have been described elsewhere.3 In the current study, CHD (International Classification of Diseases, 10th Revision rubric I20–I25) and CVA (International Classification of Diseases, 10th Revision rubric I60–I69, G45) were used to define outcomes. MetS was defined according to modified World Health Organization,4 the Joint Interim Statement (JIS),1 and International Diabetes Federation4 definitions using the Iranian cutoff for high waist circumference.2

Statistics
Cox proportional hazards regression was developed to estimate hazard ratios (HRs) for incident CHD and CVA. To compare the magnitude of HRs for different MetS definitions and their components, a paired homogeneity test was performed.
The study sample consisted of 2548 subjects with a mean age of 60.3 years (SD 7.4). The prevalence of MetS was 55.9%, 38.7%, and 34.7% as defined by JIS, International Diabetes Federation, and World Health Organization, respectively. During 9.3 years of follow-up, 72 and 343 cases of CVA and CHD occurred, respectively. The incidence rate of CVA was 330 (CI, 262–416; stroke: 275 [CI, 214–355] and transient ischemic attack: 55 [CI, 31–97]); the corresponding rate for CHD was 1636 (CI, 1472–1819) per 100 000 person-years.

Table 1 highlights the HR of CHD and CVA for MetS and its components. In risk factor-adjusted analysis, the HR of CHD and CVA were 2.07 (1.63–2.64) and 2.71 (1.57–4.68) for MetS as defined by JIS, respectively. There was a significant difference between the magnitudes of the HRs for JIS and International Diabetes Federation definitions in risk prediction of CHD. However, we did not show any superiority between MetS definitions in prediction of CVA.

Among MetS components, all the components, applying different definitions, were associated with increased risk of CHD. However, CVA incidence was correlated with high fasting plasma glucose, elevated blood pressure, and high waist (or obesity using the World Health Organization definition), but not with high triglycerides and low high-density lipoprotein cholesterol. Comparisons between effect size of MetS (defined by JIS) and its components showed that MetS defined by JIS convey higher risk of CHD than high waist circumference, high triglycerides, and low high-density lipoprotein cholesterol.

As shown in Table 2, after we adjusted for the all MetS components, the HRs of incident CHD and CVA were reached to a nonsignificant level for all definitions regarding both CHD and CVA. In this model, the elevated blood pressure and high fasting plasma glucose (International Diabetes Federation definition) showed significant risk for CVA. Considering CHD events, the elevated blood pressure, high fasting plasma glucose, and, additionally for World Health Organization definition, obesity and dyslipidemia remained as predictors.

### Discussion

In this study, we demonstrated that all MetS definitions were associated with the increased risk of CHD and CVA events. After further controlling for MetS components, MetS lost its association with incident CVA and CHD. However, elevated blood pressure for both CVA and CHD events and high fasting plasma glucose for CHD remained as independent predictors in all definitions.

In 2010, Mottillo et al. in a systematic review stressed the “need for longitudinal studies that examine the risk associated with the MetS after its individual components have been adjusted for.” Recently, Gupta et al. showed that MetS, independent of its individual components, was associated with increased risk of stroke and all-cause mortality but not with CHD. In the current, after controlling for MetS components, none of the MetS definitions were associated with increased risk of CVA and CHD; however, the effects of elevated blood pressure remain robust after simultaneous adjustment in all of MetS definitions.

In this study, triglycerides and high-density lipoprotein cholesterol were associated with incident CHD but not with CVA. The results of epidemiological studies that have evaluated the relationship between triglycerides and high-density lipoprotein cholesterol and ischemic CVA are inconsistent.

### Table 1. Hazard Ratios (95% CIs) Showing the Relationship of Different Definitions of MetS and Their Individual Components With Incidence of CVA and CHD

<table>
<thead>
<tr>
<th>MetS Name</th>
<th>No. (%)</th>
<th>CVA Adjusted HR (95% CI)</th>
<th>P Value</th>
<th>CHD Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mets_JIS</td>
<td>1424 (55.9)</td>
<td>2.71 (1.57–4.68)*</td>
<td>0.000</td>
<td>2.07 (1.63–2.64)† ‡</td>
<td>0.000</td>
</tr>
<tr>
<td>Mets_IDF</td>
<td>986 (38.7)</td>
<td>2.04 (1.27–3.27)‡</td>
<td>0.003</td>
<td>1.69 (1.36–2.10)§</td>
<td>0.000</td>
</tr>
<tr>
<td>High waist circumference</td>
<td>1197 (47.0)</td>
<td>1.73 (1.08–2.79)</td>
<td>0.024</td>
<td>1.50 (1.20–1.86)†</td>
<td>0.000</td>
</tr>
<tr>
<td>High fasting blood sugar</td>
<td>1032 (40.5)</td>
<td>2.01 (1.25–3.22)</td>
<td>0.004</td>
<td>1.77 (1.43–2.19)</td>
<td>0.000</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>1545 (60.6)</td>
<td>3.98 (2.01–7.88)</td>
<td>0.000</td>
<td>2.10 (1.63–2.70)</td>
<td>0.000</td>
</tr>
<tr>
<td>High triglycerides</td>
<td>1532 (60.1)</td>
<td>1.13 (0.68–1.88)*‡</td>
<td>0.639</td>
<td>1.59 (1.24–2.03)†</td>
<td>0.000</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>1537 (60.3)</td>
<td>1.31 (0.80–2.15)‡</td>
<td>0.285</td>
<td>1.40 (1.10–1.75)†</td>
<td>0.005</td>
</tr>
<tr>
<td>Mets_WHO</td>
<td>884 (34.7)</td>
<td>1.87 (1.17–3.00)†</td>
<td>0.009</td>
<td>2.07 (1.67–2.57)</td>
<td>0.000</td>
</tr>
<tr>
<td>Obesity</td>
<td>2051 (80.5)</td>
<td>2.19 (1.04–4.59)</td>
<td>0.038</td>
<td>1.87 (1.34–2.59)</td>
<td>0.000</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1646 (64.6)</td>
<td>1.02 (0.62–1.68)†</td>
<td>0.929</td>
<td>1.71 (1.32–2.20)</td>
<td>0.000</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>1146 (45.0)</td>
<td>3.27 (1.91–5.59)</td>
<td>0.000</td>
<td>2.13 (1.70–2.67)</td>
<td>0.000</td>
</tr>
<tr>
<td>Dysglycemia</td>
<td>1080 (42.4)</td>
<td>1.57 (0.98–2.51)</td>
<td>0.060</td>
<td>1.94 (1.56–2.40)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Multivariable models were adjusted for age as a time dependent variable, sex, total cholesterol, smoking behavior, and family history of premature cardiovascular disease.

MetS indicates metabolic syndrome; CVA, cerebrovascular accident; CHD, coronary heart disease; HR, hazard ratio; JIS, Joint Interim Statement; IDF, International Diabetes Federation; HDL-C, high-density lipoprotein cholesterol; WHO, World Health Organization.

* † ‡ §Paired homogeneity test shows significant difference (P<0.05) between the pairs with the same symbol.
In the Atherosclerosis Risk in Communities Study, there was no association between these lipid parameters and incident stroke.

As a limitation, it should be emphasized that the results of this study were determined in Middle East white residents in the capital city of Iran, and further studies should be conducted to determine whether our findings are applicable to other populations.

These findings suggest limited use of all MetS definitions for predicting incident CHD and CVA events in an Iranian population independent of its components.

Disclosures
None.

References
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