Defining the Metabolic Syndrome Construct: Multi-Ethnic Study of Atherosclerosis Cross-sectional Analysis

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Running Title: Different Metabolic Syndrome Constructs

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Abstract

Objective: It is controversial if the clustering of certain metabolic abnormalities should be separately designated as the metabolic syndrome (MetSyn). We operationalized the “syndrome” concept and tested whether MetSyn was compatible with these operational constructs.

Research Design and Methods: The baseline cross section of the Multi-Ethnic Study of Atherosclerosis recruited a population-based cohort of 6781 persons, aged 45-84 years, from 6 communities in the United States. MetSyn components (waist circumference, blood pressure, fasting serum HDL-cholesterol, triglycerides, plasma glucose), HOMA insulin resistance (fasting glucose×insulin) and intimal-medial thickness (IMT) in the common and internal carotid arteries by B-mode ultrasound were measured.

Results: 1. Higher syndrome component count is associated with higher HOMA levels (trend p < 0.001). 2. Given the prevalence of individual components, the non-prevalence of any component or the co-prevalence of 4 or 5 components is greater than expected ($\chi^2$ p<0.001). 3. After accounting for the additive association of each component, the current definition of MetSyn (co-prevalence of 3 or more components) does not have supra-additive association with thicker IMT in the common carotid (men: p = 0.075, women p = 0.949) or internal carotid artery (men: p = 0.106, women: p = 0.121).

Conclusions: 1. MetSyn did not have supra-additive association with IMT, but 2. its components clustered greater than chance expectation and 3. higher component count was associated with greater insulin resistance. MetSyn was compatible with two of three “syndrome” constructs tested.
Introduction:
A recent joint statement by the ADA and EASD (1) questioned the designation of the clustering of certain metabolic factors as a “syndrome”, igniting a debate (2, 3). The commonly used description of “syndrome” as a “cluster of abnormalities”, does not lend to straightforward operationalization. Factor analysis has been previously used to evaluate whether the metabolic syndrome abnormalities (obesity, dyslipidemia, hypertension, impaired fasting glucose) load factors as a group (4, 5). However, without biological insight, factor loadings are opaque and depend on the model parameterization (6).

We propose three different ways to operationalize the notion of “syndrome”, with different signification, as follows.

Construct 1: Each component of the metabolic syndrome is additively diagnostic of insulin resistance, the putative etiology (4, 7, 8). Proposed Metric: A graded association of individual components and component count with insulin resistance, e.g., as measured by the homeostasis model assessment (HOMA) (9). Practical significance: The component count may be used to diagnose underlying insulin resistance, which is not routinely assayed.

Construct 2: “Unusual” clustering of components may manifest an unknown underlying etiology. Proposed metric: Observed component coprevalence compared to that expected by their individual prevalences. Practical significance: Research effort is needed in identifying the underlying etiology.

Construct 3: Coprevalence of components implies greater pathology than the summation of the independent associations of each component. Proposed metric: Supra-additive association of component coprevalence with pathology. Practical significance: Aggressive treatment of any risk factors would also reduce the supra-additive cluster risk.

We used baseline data from the Multiethnic Study of Atherosclerosis (MESA) to explore whether the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III) definition of the metabolic syndrome (10, 11) is compatible with any of the above syndrome constructs.

Methods
The design of the MESA study has been previously described (12). The study was approved by institutional review boards of all participating centers. At baseline (2000 - 2002), 6814 White, African-American, Chinese or Hispanic men and women who were free of clinical cardiovascular disease were recruited. The majority (3199 men, 3581 women) had complete data required for classification by the modified NCEP-ATP-III definition (10, 11) for these analyses. Subjects completed standardized medical history questionnaires. Fasting blood measurements of glucose, insulin and a lipid panel were performed. Umbilicus-level waist circumference was measured using a standard tape measure with 4oz tension. Resting seated blood pressure was measured three times using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida). The average of the last two measurements was used in analysis. The metabolic syndrome is the presence of three or more of the components (10, 11): (1) Waist ≥ 102 (men) or ≥ 88 cm (women), (2) Triglycerides ≥150 mg/dL, (3) HDL-Cholesterol ≤ 40 (men) or ≤ 50 mg/dL (women), (4) blood pressure ≥ 130/85 mmHg or on anti-hypertensive treatment, and (5)
fasting plasma glucose $\geq 100$ mg/dL or on anti-hyperglycemic treatment.

HOMA was calculated as fasting plasma insulin ($\mu$U/ml) $\times$ glucose (mmol/l)/22.5 (9). The maximum intimal-medial thickness (IMT) was measured at 12 bilateral locations for the internal carotid arteries (IIMT) and 4 locations for the common carotid arteries (CIMT) using B-mode ultrasound and averaged.

**Statistical Methods**

Analyses were stratified by sex, because the criteria the metabolic syndrome are sex-specific.

**Construct 1:**

Association of each component with HOMA was tested using non-parametric rank sum tests. Sensitivity analyses excluded persons taking antidiabetic medications. The association of HOMA with the number of coprevalent components was tested using the Kusick non-parametric trend test. Receiver Operating Characteristic (ROC) analysis for the metabolic components count used the upper quartile of HOMA to define insulin resistance (13).

**Construct 2:**

The prevalence of each metabolic component was calculated by the number of other coprevalent components. Trends in prevalences were tested by the Kruskal and Goodman gamma statistic. Expected co-prevalences of 0, 1, ... 5 components were calculated based on the marginal prevalences of each metabolic component (appendix) and compared against the observed distribution using $\chi^2$ statistics.

For constructs 1 and 2, stratified analyses were done to confirm if the qualitative conclusions differed by race/ethnicity.

**Construct 3:**

CIMT and IIMT were analyzed on the log-scale. Coefficients for multiple linear regression were adjusted for age and race/ethnicity. In model series 1, the population was restricted to those who had no prevalent components, exactly one component, or three or more components. (Those who had exactly two components neither have the defined metabolic syndrome, nor reflect the individual component contributions.) Regression models specified separate coefficients for the five isolated components and a coefficient for the metabolic syndrome cluster, compared to the referent group that has no prevalent component. The difference between the linear combination of the five component coefficients and the cluster coefficient was tested for statistical significance. In model series 2, persons with all five metabolic syndrome components co-prevalent were included with those with exactly one, or none, of the components prevalent. In confirmatory model series 3, all components (irrespective of being isolated) were included, and the metabolic syndrome cluster variable was also included as a single interaction variable. However, this model series does not account for all possible 2-component clusters, and hence the coefficients of the individual components cannot be interpreted as unambiguously as in model series 1 and 2. Racial/ethnic heterogeneity of supra-additivity was tested using omnibus F-tests of the race-metabolic syndrome interaction variables in models including a race/ethnicity specific coefficient for each isolated component and the metabolic syndrome cluster.

In separate models adjusted for age and racial/ethnic group, an interaction coefficient was estimated to test whether the presence of each of 26 possible coprevalent component combinations was associated with IMT above
and beyond the sum of the component coefficients.

Results

The proportions of MESA participants with the individual components of the metabolic syndrome were: large waist circumference – 38% men, 69% women; high triglycerides – 32% men, 29% women; low HDL-C – 40% men, 49% women; high BP 59% men, 59% women; high fasting plasma glucose – 49% men, 36% women; with 40% of men and 46% of women having 3 or more components.

Insulin Resistance as an underlying “common denominator”

For each metabolic syndrome component, median HOMA was higher if the component was present (all differences p <0.001, Online Appendix Table 1). Table 1 shows that an increasing number of coprevalent components was associated with higher HOMA levels in men and women (all trends, p < 0.001). This was true in race/ethnicity stratified analysis (all groups, p < 0.001, Online Appendix Table 2).

For the number of coprevalent components as the diagnostic for insulin resistance, the area under the ROC curve (AUC) was 0.80 (95% CI: 0.78, 0.81) for men and 0.80 (95% CI: 0.79, 0.82) for women. The metabolic syndrome (≥3 components) results in sensitivity and specificity levels of 74% and 29% in men, and 82% and 34% in women, respectively. A moderate to good diagnostic efficiency was present in men and women of all four race/ethnicities (AUC range 0.74 to 0.86 for different groups, detailed in Online Appendix Table 3).

Clustering of Metabolic Syndrome components

In both men and women, there is a graded relationship between the prevalence of any given component and the number of other components (for all components, p< 0.001, Online Appendix Figure 1).

The observed distribution of co-prevalence of components was significantly different from the co-prevalence expectation given the prevalence of each of the individual components (Figure 1, p < 0.001 for men and women). Specifically, non-prevalence of any component, and co-prevalence of 4 and 5 components were observed more frequently than expected (i.e., tails of the distribution were heavier), suggesting that clustering is not a chance event. Similarly, significantly heavier-tailed distributions were observed for men and women in analyses stratified by race/ethnicity (all groups, p<0.001). In all men, the five largest contributors to $\chi^2$ were (1) no components, (2) all components (3) obesity, high triglycerides, low HDL-C, and high BP, without high glucose (all more frequent than expected), and (4) isolated high BP and low HDL-C, and (5) isolated high BP and high triglycerides are less frequently observed than expected. The five highest deviating clusters in all women include (1)- (4) as in men, with the cluster of isolated obesity and high triglycerides less frequently observed than expected.

The additive association of metabolic syndrome components with subclinical atherosclerosis

Figure 2 shows that the association of CIMT or IIMT with the co-prevalence of three or more (model series 1), or all five components (model series 2), is no greater than the added isolated component associations (i.e., no supra-additive interaction) either in men or women. Note that the small non-significant (p = 0.66) negative association of CIMT with isolated glycemia among women is conditioned on the absence of all other components. There are no significant racial/ethnic differences in the lack of supra-
additive interaction of the metabolic syndrome cluster above the five isolated components. The lack of supra-additive association of the metabolic syndrome with IMT variables was confirmed in models estimating the marginal rather than isolated component effects (model series 3).

Using the Bonferroni criterion level (alpha=0.05/26=0.0019), no positive additive interaction was found for any of the combinations of two or more metabolic components in relation to either CIMT or IIMT.

Discussion
We showed that the metabolic syndrome qualified as a “syndrome” under some, but not all constructs hypothesized in the present study.

Construct 1 postulated a common denominator for the components of the syndrome. We confirmed the graded association of HOMA with the number of components. If direct measurement of insulin resistance is not feasible, the metabolic syndrome as defined may be used as a clinical diagnosis of insulin resistance.

The assumption of the primacy of insulin resistance is controversial, as abdominal obesity has been suggested as an essential etiological basis for the metabolic syndrome (14). Nevertheless, the metabolic syndrome could be used as a marker of insulin resistance. If treatment of insulin resistance per se may not impact on the syndrome components, the practical significance of this finding is not clear.

Construct 2 postulated that clustering was not by chance, and thus was hypothesis generating. We presented a metric and directly tested for the hypothesis of clustering that allowed for additive component count, because components of syndromes are used additively by clinicians (15, 16). We showed that the components were correlated, such that component counts of 4 or 5, and correspondingly, zero components, occurred more frequently than chance expectation. Data reduction techniques such as factor analysis generate new linear combinations of components (reviewed by Lawlor et al. (6)), and do not test the syndrome construct hypothesis. Though factor analysis may be useful for generating latent phenotypes (6, 17), this was outside the scope of our analyses.

Practically, the detection of any one component should alert the clinician to seek other abnormalities. Clustering generates the hypothesis of a common source for the abnormalities. This source may be biochemical, such as insulin resistance, but our analyses do not exclude the possibility that other sources are responsible for the clustering, such as psychosocial causes.

For construct 3, "syndrome" implied that coprevalence of components was associated with a supra-additive association with pathology, more than expected by summing individual component contributions. This understanding of the “syndrome” construct has been mentioned in a recent debate(1-3). This construct was also implicit in the demonstration by Golden et al (18) that 18 of the 57 six-component-combinations were associated with supra-additive carotid IMT. Surprisingly, this was not found in our analyses, which show no supra-additive association. However, our results may not be directly comparable to those of Golden at al (18), which used hyperinsulinemia (≥110 pmol/L) and BMI ≥25 kg/m² as metabolic components, and more stringent criteria for hypertension (≥140 mmHg systolic), high triglycerides (≥200 mg/dL), high glucose (≥110) and low HDL in women (≤40 mg/dL), in
a younger population (45-64 years). Carotid bulb IMT, needed to exactly replicate the analyses of Golden et al. (18), was not measured in MESA. In analysis that used the metabolic criteria of Golden et al. (18) among individuals 45-64 years, our conclusion regarding construct 3 for common, internal, or mean IMT remained unchanged (results not shown). It is possible that there are differences between the cohorts studied, and that construct 3 may be valid in some populations. Further, in our analysis, the association of each component with IMT conditioned on the absence of all other components was somewhat weak, with a non-significant negative association in one instance. The weak association of isolated components should result in an enhanced power to detect supra-additive association of clustered components, yet no supra-additive association was seen in our analysis.

Interestingly, supra-additive association with a harmful outcome is not expected in other clinically useful “syndromes”. For example, the only prognosticator for acute rheumatic fever sequelae is carditis (19), and not the other components of the Duckett-Jones criteria (15), thus there is no proven supra-additive risk for component clustering. To examine supra-additive association of clustering with upstream etiology, we can consider the example of the Down’s syndrome using an 8-component syndrome definition (16). In a series of 19,000 live births, there was no incremental association of trisomy 21 with the component counts beyond 5, suggesting a saturation of the association of cause at higher scores, which is statistically equivalent to a sub-additive effect of clustering.

However, should this construct come to be generally accepted for metabolic abnormalities, our results indicate that the metabolic syndrome is not “syndromic” in terms of carotid IMT as pathology. The practical implication is that every metabolic component should be vigorously treated on its own, with no expectation of a putative supra-additive risk reduction for subclinical carotid atherosclerosis.

Our analysis suffers from certain limitations. HOMA is not the gold standard for the measurement of insulin resistance. However, the random error associated with the estimation of insulin resistance by HOMA would be more likely to dilute the findings resulting from the analysis of construct 1. We have used IMT, an intermediate cardiovascular outcome which is available in MESA. A valid outcome measure for construct 3 needs longitudinal follow-up for incident diabetes, myocardial infarction or death. This limitation must be borne in mind while comparing the results of Golden et al. (18) that found construct 3 to be valid for a slightly different measure of IMT in a different population using different metabolic components.

In summary, while we could not observe a supra-additive interaction resulting from the simultaneous presence of metabolic syndrome components in terms of intimal-medial thickening of the carotid artery, co-prevalence of multiple components of the metabolic syndrome was more frequent than expected by chance alone. Detection of any of the components of the syndrome in a patient should raise the index of suspicion in the health care provider that the other components may also be present. This clustering is consistent with the presence of a common underlying cause. If the underlying cause is insulin resistance, our results suggest that the metabolic syndrome provides a good proxy diagnostic for insulin resistance, which is not assessed in routine clinical tests. However, it remains to be determined if identification of insulin resistance will result
in a more effective therapeutic approach than that aimed at the individual components of the metabolic syndrome.

**Acknowledgement:**
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**Appendix:**
Calculation of expected component coprevalences:
Let \( p_1, p_2, \ldots, p_5 \) (\( q_1, q_2, \ldots, q_5 \)) be the marginal prevalence (non-prevalence) of the five components of the metabolic syndrome. The expected co-prevalences are given by

0 components: \( \prod_i (q_i) \)
1 component: \( \sum_i \{ \prod p_i q_{j \neq i} \} \)
2 components: \( \sum \sum_{j \neq i} \{ \prod p_i p_j q_{k \neq i,j} \} \)
3 components: \( \sum \sum \sum_{i,j,k} \{ \prod q_i q_j p_{k \neq i,j} \} \)
4 components: \( \sum_i \{ \prod q_i p_{j \neq i} \} \)
5 components: \( \prod_i (p_i) \)
References


10. NIH, Third report of the National Cholesterol Education Program Expert Panel on the detection, evaluation and treatment of high blood cholesterol in adults. 2001, National Institutes of Health: Bethesda, MD.


Table 1: The Association of the Homoeostatic Model Assessment of Insulin Resistance (HOMA) With the Number of Metabolic Syndrome Components in the Multi-Ethnic Study of Atherosclerosis (2000-2002)

<table>
<thead>
<tr>
<th># Metabolic Syndrome Components</th>
<th>Median HOMA (interquartile range) in HOMA units</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>All</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Exclude diabetes meds</td>
<td>0.75</td>
</tr>
<tr>
<td>n=375</td>
<td>(0.53,0.99)</td>
</tr>
<tr>
<td>n=717</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.65</td>
</tr>
<tr>
<td>n=391</td>
<td>(0.46,0.89)</td>
</tr>
<tr>
<td>n=683</td>
<td></td>
</tr>
<tr>
<td>Exclude diabetes meds</td>
<td>0.65</td>
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<tr>
<td>n=391</td>
<td>(0.49,0.89)</td>
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<tr>
<td>n=675</td>
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<td>All</td>
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<td>n=391</td>
<td>(0.46,0.89)</td>
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<td>Exclude diabetes meds</td>
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Figure legends:

Figure 1
Expected co-prevalence of metabolic syndrome components based on the prevalence of individual components, compared to the observed co-prevalences in the Multi-Ethnic Study of Atherosclerosis (2000-2002)
Figure 2:
Percentage greater common and internal carotid artery intimal-medial thickness (IMT) in subjects with metabolic syndrome components (individual or co-prevalent) as compared to age and race-adjusted subjects with no metabolic syndrome components in the Multi-Ethnic Study of Atherosclerosis (2000-2002). Ob – abdominal obesity, TG – high triglyceride level, HDL – low HDL cholesterol level, HBP – high blood pressure, Glu – high fasting plasma glucose. The cutpoints for these components are detailed in the text. Left arrow within stacked bars represents a negative association. All associations of single components are conditional to the absence of all other components. Under this condition, note that the direction of the isolated Glu association with common carotid IMT is non-significantly negative in women, and the association of isolated high TG with common carotid IMT is zero in men.