The Metabolic Syndrome  
More Than the Sum of Its Components?

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See related article, pages 1078–1083.

The metabolic syndrome is a clustering of metabolic abnormalities, which include insulin resistance or diabetes, obesity, hypertension, and dyslipidemia. Although the mechanisms of the underlying abnormalities remain to be clarified, the pathogenesis includes both genetic predisposition and modifiable risk factors such as sedentary lifestyle and dietary intake. Recent estimates suggest that approximately 24% of US adults have the metabolic syndrome.1

In several studies, the metabolic syndrome has been shown to increase the risk of cardiovascular diseases2; however, the strength of its association with stroke is weaker than that for coronary heart disease.3 In the guidelines for the primary prevention of stroke from the American Heart Association/ American Stroke Association, the metabolic syndrome is listed as a less–well-documented risk factor.4 But, given the high prevalence of the metabolic syndrome, studying its association with stroke is certainly relevant for 2 reasons: first, to obtain a better etiologic understanding of the causes of stroke; second, to identify individuals at high risk for stroke. This translates into 2 distinct scientific questions: is the metabolic syndrome by itself a risk factor for stroke?5,6 and can we predict which individuals are at increased risk for stroke based on information about the metabolic syndrome? To answer these questions from observational data, one needs 2 distinct model-building strategies that require differences in assumptions of biological associations and statistical considerations.5,6

In this issue of Stroke,7 Wang and colleagues investigated the association of the metabolic syndrome and stroke during a 14-year follow-up period. In particular, they focused on whether the metabolic syndrome plays a role in stroke prediction beyond its individual components. The results indicate that the metabolic syndrome by most definitions is associated with the risk of stroke, with relative risks ranging from 1.5 to 1.7 in age- and gender-adjusted models. The exclusion of participants with existing myocardial infarction and the addition of information on smoking, alcohol consumption, and total cholesterol, which may be viewed in part as confounding factors, only minimally changed these estimates. When, in a last modeling step, the individual components of the metabolic syndrome were entered into the models, the relative risk estimates changed considerably, only leaving statistically significant associations for 2 of the 6 metabolic syndrome definitions.

Furthermore, Wang and colleagues also evaluated the ability of the various models in predicting stroke. The c-statistic value of the models, a measure of how well a model can discriminate between individuals who do or do not have the disease, ranged from 0.59 to 0.63. These results indicate that the metabolic syndrome does not help to identify individuals at increased risk for stroke regardless of whether or not individual components of the syndrome were entered into the models.

How can this surge of information from the study by Wang and colleagues be interpreted? For the evaluation of causal risk factors, biological knowledge about the disease and causal associations between the individual risk factors themselves, as well as with the disease, are necessary to construct regression models.8 Besides the main risk factor of interest, models include information on biologically relevant confounders. In many cases, we have an understanding of how a risk factor relates to a particular disease because the mechanism is either known or a hypothesis has been formulated. For example, it is believed that part of the association between body mass index and stroke is mediated by hypertension.9 Because increased body mass index is a risk factor for hypertension. In such situations, a second model is presented that adjusts not just for the set of confounders but for information on potential biological mediators as well. If, after adjustment and modeling considerations,9 the risk factor is still associated with the disease, one can conclude that above and beyond the mediating pathways, the risk factor still relates to the outcome, potentially suggesting additional biological mechanisms.

Prediction models, on the other hand, follow a different rationale. The ultimate aim of such models is to maximize the ability to predict future disease or to correctly classify individuals in high- or low-risk groups for the disease. Here, the overall ability of the model to predict disease or discriminate between risk classes is evaluated, and individual relative risk estimates are of less importance unless the order of statistical predictors is of interest. Thus, these models do not necessarily depend on biological relationships and can include proxy measures for risk factors or risky behaviors.

Disentangling methodological concepts of risk factors and prediction, one can conclude from the study by Wang and colleagues that the metabolic syndrome is a risk factor for stroke.
stroke even after adjustment for potential confounding factors. This is concordant with the results of other studies of different vascular outcomes for the metabolic syndrome.\textsuperscript{2,3} If we recognize a role for the metabolic syndrome that is independent of its individual components, we can assume that potential interventions may modify the risk of stroke above and beyond intervening on individual risk factors, such as hypertension.\textsuperscript{10} Wang and colleagues evaluated this question by adding all the individual components of the metabolic syndrome to the models. The interpretation of such models, however, is difficult because the estimates of individual components of the metabolic syndrome are now represented in the relative risks of the individual factors as well as the metabolic syndrome (ie, the summary measure). Without evaluating whether or not specific biological mechanisms may explain the association between the metabolic syndrome and stroke, it remains unclear if the metabolic syndrome should be viewed as an etiologic entity above and beyond its individual components.\textsuperscript{11}

With regard to prediction, none of the models in the study by Wang and colleagues allows good discrimination of individuals who will or will not have a stroke, regardless of whether the metabolic syndrome and/or its individual components are included, as indicated by the low \( c \)-statistic. The Framingham Risk Score is probably the most powerful tool for risk prediction of vascular outcomes\textsuperscript{12} including stroke\textsuperscript{13} at an individual level and as such should be considered a gold standard when establishing a new prediction tool. The Framingham Score includes detailed information on factors like smoking, low-density lipoprotein cholesterol, and blood pressure that are much more discriminatory than the very crude categorizations of factors included in the definition of the metabolic syndrome. In addition, one has to keep in mind that the \( c \)-statistic is a measure of discrimination, which may not be the preferred measure for predicting future events.\textsuperscript{14,15} Furthermore, because the \( c \)-statistic does not capture information on absolute risk, more global measures of model fit, such as likelihood statistics, will help to determine whether using information on the metabolic syndrome will help in classifying individuals into risk groups.

For the stroke community, the study by Wang and colleagues adds important information and supports previous studies and recommendations.\textsuperscript{4,11} First, to reduce the risk of stroke, physicians should target individual stroke risk factors for modification and/or treatment and, second, using information on the metabolic syndrome will not improve prediction of stroke as compared with detailed information on well-established individual stroke risk factors.

## Disclosures

None.

## References


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