Metabolic Syndrome and Early Death
Getting to the Heart of the Problem

Paul W. Franks, Tommy Olsson

This editorial appraises an article in the current issue of *Hypertension* that examines the prospective relationships between features of the metabolic syndrome (MetS) and early death in a population-based cohort form Northern Italy. We also discuss, in light of that study’s findings, how relevant conventional definitions of the MetS are for identifying individuals at high risk of early death.

The MetS describes a constellation of metabolic and cardiovascular disease risk factors. Although varying definitions of the MetS exist, all of the commonly used definitions include a measure of obesity, hyperglycemia, hypertension, and dyslipidemia. These definitions are based on “expert” opinion and not on evidence derived from prospective studies, which would be preferable. Thus, it remains uncertain whether the component features of the MetS or the thresholds at which each component is defined as present or absent are informative and optimal for predicting risk of disease or early death. It is also undetermined whether MetS represents a distinct pathophysiological entity. Notwithstanding these issues, the syndrome is extensively used in research studies, and many advocate its use in clinical practice to identify people at high risk of cardiovascular disease and early death.

The idea that cardiovascular risk factors with a common etiology cluster in certain individuals at high risk of cardiovascular disease was first popularized by Reaven6 in the 1980s, although the origins of the MetS date back much earlier. Reaven’s emphasis was on elucidating the underlying pathophysiology of cardiovascular disease, for which he postulated that insulin resistance plays a pivotal role, and not on developing a diagnosis of MetS, which could be used in clinical practice.

Superficially, at least, MetS relates strongly with cardiovascular morbidity and early death; this is perhaps unsurprising, because so too do each of the component features of the syndrome. However, for the MetS to have greater clinical or scientific utility than the singular components requires that the level of risk conveyed by MetS exceeds the total level of risk conferred when all of the MetS components are considered simultaneously; in other words, the whole should exceed the sum of its parts. If this were true, it would support the view that the components of the MetS have a common etiology and that ≥2 of the components positively interact. If, however, the level of risk was equal for the syndrome and the sum of its components, a common etiology might exist, but the components could not, on average, be said to interact. Alternatively, if the total risk was less for MetS compared with the sum of its components, the likely explanation would be that the risk conveyed by ≥2 of the components overlap. In this last example, using MetS to identify high-risk individuals would be inefficient and could unnecessarily complicate the choice of treatments.

Whether the objective is to test the validity of existing definitions of MetS or to define a new evidence-based definition, large prospective studies of population-based cohorts with baseline measures of the MetS components and well-defined end points are necessary. In this issue of *Hypertension*, Mancia et al report data from the Pressioni Arteriose Monitorate E Loro Associazioni Study, a longitudinal observation cohort study of cardiovascular risk factors and mortality conducted in a population-based cohort of 2013 adults from the town of Monza in Northern Italy. The main objective of this study was to assess the relationship between MetS and early death during 12 years of follow-up. Sixteen percent of the cohort fulfilled the National Cholesterol Education Program Adult Treatment Panel III definition of the MetS.1 The adjusted hazard rate ratios for cardiovascular and all-cause mortality associated with MetS in the entire study population were 1.7 and 1.4, respectively, which were both of modest statistical significance. Mancia et al determined that not all of the components of the MetS significantly contribute to the prediction of mortality. For those that do (ie, blood pressure and hyperglycemia), the pathological processes that link elevations in these traits with fatal events are well described elsewhere, and it is clear that both factors can independently and, in combination, severely damage vital organs and tissues.

Mancia et al also examined the contributory role of cardiac function assessed using echocardiography (left ventricular hypertrophy and left ventricular mass index) and elevated ambulatory blood pressure to mortality risk, both of which were present to a greater degree in people with MetS than in those without. When the risk of death associated with MetS was calculated only in people with left ventricular hypertrophy (n=266), the hazard rate ratios increased to 3.0 and for all-cause death to 8.2. These estimates were highly statistically significant. This observation suggests that in people with left ventricular hypertrophy, MetS results in a substantial increase in the risk of dying from noncardiovascular causes, which would include neoplasms, neurodegenera-
The mechanisms that might underlie this observation are not discussed in the report, and the possibility that confounding by unknown factors explains this association cannot be excluded. Furthermore, because neither the independent association between cardiac function and mortality nor the effect of MetS on mortality risk among those with normal cardiac function were reported, it is difficult to determine whether these are independent risk factors for mortality or whether they interact to exponentially increase the level of risk.

**How Efficient Is MetS for the Prediction of Disease and Early Death?**

One argument often lodged in favor of the MetS is that it can be used to define those at the highest risk of disease or death. This is obviously important in a world where health care resources are limited and the prioritization of high-risk individuals for treatment is necessary. However, with these issues in mind, the most efficient predictive model (ie, the one containing the fewest most easily measured components) is preferred. Optimally defining this model requires that studies are conducted to determine whether and where on the continuum of each component’s distribution the relationship with the disease outcome departs from linearity, possibly with the aim of identifying a value above which the risk of disease increases exponentially. This point could then be used as a cutoff for treatment. In the case of hyperglycemia, a 2-hour postchallenge blood glucose concentration of ≈200 mg/dL (11.1 mmol/L) approximates the point at which the risk of microvascular disease rises exponentially and is, thus, used in the diagnosis of type 2 diabetes. The thresholds used to define the MetS, however, are not, by and large, supported by similar levels of evidence.

Notwithstanding the clinical utility of categorical disease traits, most disease thresholds are pathophysiologically artificial; rarely do they represent a true biological point of inflection. The relationship between blood pressure and cardiovascular disease, for example, is dose dependent, such that blood pressure and cardiovascular risk increase proportionately across the spectrum of blood pressure, and no detectable increase in risk occurs at the thresholds for hypertension. Body mass index, waist circumference, and lipid concentrations also bear linear relationships with key cardiovascular disease end points. Falsely dichotomizing continuously distributed variables which, as is the case with all features of the MetS, are prone to measurement error, will result in varying degrees of misclassification, such that some individuals who are truly “diseased” are misclassified as “healthy,” and vice versa. Some of those who do not require treatment consequently receive therapies that cause unnecessary adverse effects, whereas others who do require treatment go without. A second problem with categorizing continuously distributed variables that are linearly related with the outcome is that doing so reduces the ability to detect this association primarily because it reduces statistical power. Thus, categorizing continuously distributed variables that are linearly related with the outcome is that doing so reduces the ability to detect this association primarily because it reduces statistical power. Thus, categorizing continuously distributed variables that are linearly related with the outcome is that doing so reduces the ability to detect this association primarily because it reduces statistical power.
ing variables of this nature increases the probability of false-negative findings.

Because there are caveats to artificially categorizing disease-related traits, it is worth considering whether MetS expressed on a continuum could be used in both clinical research and clinical practice. For example, MetS could be expressed as a continuously distributed score, and in some circumstances it would be possible to treat proportionate to the level of this score. Alternatively, if resources are scarce, and traditional treatment regimes are favored, the fraction of the population identified for treatment could be determined by available economic resources and a cutoff applied to the continuum at the point to which resources will stretch (Figure 1).

An additional limitation of conventional definitions of the MetS is that they can result in a heterogeneous classification of MetS. Using the Adult Treatment Panel III definition as an example, there are 10 unique phenotypes that can be described using this criteria (Figure 2). Although some of these phenotypes are biologically related, the manifestation of MetS in such a variety of forms could complicate appropriate treatment, because no pharmacotherapy is presently available that has a ubiquitous effect. Furthermore, a catchall definition, which optimally predicts all of the key outcomes, will lack specificity. As such, the ideal definition for the prediction of type 2 diabetes, for example, would likely place greater emphasis on obesity and hyperglycemia, whereas the optimal definition for coronary heart disease might focus more on dyslipidemia and hypertension.

The only truly compelling reason for considering the use of MetS in clinical practice or research is that, ultimately, to do so might improve health. The effect of the syndrome as a whole is rarely greater or equal to the summed effects for each of its parts. This suggests that the MetS is not truly a syndrome, and some of the components of the MetS are bystanders that provide no unique predictive information and muddy the water. If this is true, then combining all of the features of the MetS together is neither logical nor efficient. An alternative would be to include only the features that are uniquely informative and to weight each of these components by an empirical value.

Mancia et al determined through their analyses that, although MetS is a significant predictor of early death, the 2 components that apparently explain the association between MetS and mortality are hyperglycemia and high blood pressure. This suggests that in populations of Central European descent, these are 2 relevant risk factors on which we should focus for the prevention or deferment of cardiovascular-related death.

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References
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