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## Does the Metabolic Syndrome Exist

Response to Grundy

A key question in the debate concerning the metabolic syndrome (1,2) is whether the risk accompanying it is more than the sum of its parts. Grundy (1) asserts that “risk factors are multiplicative, i.e., risk for ASCVD [atherosclerotic cardiovascular disease] from risk factors rises geometrically, not linearly, as the number of risk factors increases. Therefore, total risk is more than a summation of the individual factors.” The study by Yusuf et al. (3) is offered to support this statement, but this study is a standardized case-control study of 27,098 participants in 52 countries representing several major ethnic groups to assess the relation between BMI, waist and hip circumferences, and waist-to-hip ratio to myocardial infarction overall and for each group. The metabolic syndrome is not even mentioned in the article.

In the same issue of *Diabetes Care*, Sunderström et al. (4) published a study evaluating the risk factors for cardiovascular death in >2,000 individuals followed for 30 years after being studied at age 50. More than 1,000 of them were reexamined at age 70 and followed for 9 more years. Sunderström et al. showed that the “metabolic syndrome did not predict cardiovascular mortality independently of its individual components at any age” and concluded that “the metabolic syndrome might be viewed as a clinically handy summary measure of nontraditional risk factors rather than as a strong biological entity.” Thus, this evidence suggests that the answer to the key question posed above is that the risk of the metabolic syndrome for cardiovascular

events is no more than the sum of its parts. Whether the metabolic syndrome serves an important function to alert physicians and patients of the importance of addressing these risk factors is a separate issue.

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## Does the Metabolic Syndrome Exist?

Response to Davidson

In response to Davidson (1), who questions whether the metabolic syndrome conveys more risk for cardiovascular disease (CVD) than that contained in its risk components, I suggest that this debate is partly confused by ambiguity over the issues of prediction versus causation. The argument based on prediction contends that among the diagnostic components of the syndrome (elevated blood pressure, low levels of HDL cholesterol, high triglycerides, elevated glucose, and abdominal obesity), most of the predictive power is contained in blood pressure and HDL cholesterol. Therefore, in epidemiological studies, the short-term risk for CVD for the syndrome as a whole, assessed by current diagnostic criteria, does not substantially exceed the risk contained in two of its risk factors. Consequently, from a predictive perspective, the metabolism syndrome is really nothing more than a higher blood pressure and a lower HDL. The argument from causation holds that these predictors of risk do not necessarily reflect the true causes of the risk. Indeed, there are other types of data to indicate that several risk factors of the syndrome, such as elevations in VLDL, a prothrombotic state and a proinflammatory state also contribute to risk. It is possible to say that for causation, robust predictors are confounded by other risk factors, some of which are not routinely measured. In fact, there is still uncertainty as to whether a low HDL cholesterol is truly a direct cause of CVD or is only a marker for risk. Further, clinical trials indicate that reducing blood pressure does not fully reverse the risk predicted by a higher blood pressure; hence risk associated with a higher blood pressure must be confounded by other factors. The clinical implications of this distinction between prediction and causation are considerable. At present, it cannot be assumed that treatments directed toward the predictors will produce the expected reduction in risk; rather, it is important to identify the true causes of CVD associated with the metabolic syndrome so that they can be better targeted for therapy.

A second line of debate is whether the risk factors of the metabolic syndrome, or indeed for all CVD, are additive or synergistic in their effect on CVD risk. Synergism in effect is referred to as multiplicative risk. Several epidemiological studies and the risk algorithms developed from these studies support the synergism associated with multiple risk factors. If multiple risk factors are synergistic in their effects, as epidemiology indicates, then the risk associated with multiple risk factors is greater than what would be obtained by simple addition of their individual effects. Finally, the metabolic syndrome is a progressive condition. It typically worsens with advancing age. Hence, risk is compounded by aging. This means that risk predicted at any one time underestimates the long-term risk associated with the syndrome.

These multiple lines of evidence support my contention that the CVD risk accompanying the metabolic syndrome