Furthermore, a review of current literature suggests that the approach of using only effect sizes when comparing the utility of risk factors may be obsolete—particularly in light of more efficient statistical approaches such as net reclassification index and incremental discrimination index (2,3)—the techniques that enable comparisons based on number of subjects correctly allocated with the enhanced risk or not.

However, we agree that despite these further analyses, the eventual interpretation may remain unchanged, as evidenced by findings of a recent study (4) among >19,000 hypertensive patients, where there was an absence of any synergy among the individual components of MS on the risk of coronary outcomes associated with MS. However, in that study, the risk of stroke and all-cause mortality associated with MS, independent of its components, was found to be significant. We believe these apparent contradictions in the current literature are likely to be minimized by interrogating prospective data, to evaluate whether the risk of myocardial infarction (both in terms of magnitude and the number of patients correctly identified) is more closely associated with MS or with the presence of each of the individual risk factors, separately and in combination.

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Reply

Drs. Gupta and Poulter raise an interesting point about our study (1) and about estimating the risk of myocardial infarction (MI) associated with metabolic syndrome (MS), after adjusting for all its individual components (as continuous variables). The idea of controlling for all components and MS simultaneously to assess each of the effects comparatively seems intuitive. However, there are statistical assumptions in constructing such a model. Controlling for component factors that were used to define MS would likely substantially alter the association between MS and MI risk. Indeed, when adjusting for all of the individual MS components, the odds of MS on MI risk is <1 (odds ratio: 0.79; 95% confidence interval: 0.68 to 0.91); however, the effects of diabetes mellitus (odds ratio: 2.52; 95% confidence interval: 2.24 to 2.83) and hypertension (odds ratio: 2.22; 95% confidence interval: 2.05 to 2.39) remain robust after simultaneous adjustment. Prior investigations have used a similar approach to that of our study in assessing the effects of MS and component factors (2,3).

We agree that alternative analytical approaches may be used to determine the agreement between MS and component factors classification versus MI (e.g., net reclassification). However, this approach is usually applied to prospective cohort data, and not to retrospective case-control data. Nonetheless, as the investigators recognize, the general pattern of results and eventual interpretation is unlikely to change. Moreover, an important advantage of estimating the effect size is that it may be used to estimate population attributable risk (PAR), an approach used previously in the first INTERHEART study (a global case-control study of risk factors for acute myocardial infarction) paper, which showed that 90% of risk of MI is explained by 9 modifiable risk factors (4). An assessment of the PAR of MS on MI is particularly important in the current study, since the use of a dichotomous definition of MS based on ≥3 risk factors leads to a substantially lower prevalence of MS than its component factors (e.g., 10% for MS compared with 19.6% for diabetes and 23.4% for hypertension). This finding partly explains our observation that the PAR of MS is substantially lower than the PAR of several component factors considered separately, including diabetes and hypertension, and indicates that MS accounts for a smaller number of MI cases in a population compared with several of its constituent components. Thus, our findings highlight an important limitation of MS diagnosis.

We also agree that a cohort study might provide more rigorous data. However, an important strength of the INTERHEART study is that it is a large international study of 52 countries using a standardized protocol, and it is the first large study to show that the risk of MI associated with MS is qualitatively similar across sex, global regions, and ethnic groups. A cohort study with similar objectives would require an enormous sample size and 2 decades of follow-up. Although not impossible, such a study would be extremely costly to conduct.

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