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Metabolically Healthy Overweight and Obesity

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IN RESPONSE:

One reason to do a meta-analysis is to confirm the findings observed in smaller individual studies and document the magnitude of effect in a larger study population to enable a more accurate estimate of effect. This approach is particularly important when evaluating a low- or moderate-risk population (such as metabolically healthy obese persons) because it enhances statistical power to detect differences in outcomes that individual studies could not identify. However, we recognize that the pooling of several studies requires that their data be relatively homogeneous, which partly limits the questions that a single meta-analysis can answer.

Drs. Chaput and Sharma and Dr. Samocha-Bonet and colleagues point to the controversies in the literature over the definition of metabolic health. In this context, although a standard definition of metabolic health does not currently exist, the definition applied in our meta-analysis was that which was most prevalent in our systematic review of 1443 studies that make up this literature. Of note, although Kuk and colleagues (1) did not find differences in cardiovascular death, their study, which used a more stringent definition of health, showed increased cancer mortality in healthy obese persons; this finding reinforces the concept that a healthy pattern of obesity may not exist. In addition, the literature that Dr. Esser and associates cited showing increased inflammation in healthy obese persons concurs with this concept. Indeed, even when interpreted most conservatively, our meta-analysis clearly shows the complexity of estimating a person's risk and that metabolic status and adiposity should be taken into consideration.

In response to Dr. Lesser's comment, it is relevant to reiterate that the statistical method used in our meta-analysis (random-effects model [profile likelihood method]) is most appropriate when risk estimates are close to nonsignificance because this approach better accounts for the imprecision in the estimate of between-study variance (2). Thus, even when this robust model was used, the healthy obese group had an RR of 1.24, which translates to a significant increase in absolute risk at a population level as discussed in our review. However, we agree that the definition of obesity based on BMI does not consider the distinction between LBM and WF, which could further characterize the adiposity profile and have implications for outcomes.

Potential Conflicts of Interest: None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-1059.

We also recognize that pooling unadjusted estimates does not account for other covariates possibly associated with mortality. In this context, we agree with Dr. Cho and coworkers and Dr. Flegal that age and sex are important covariates. However, we believe that this limitation does not invalidate our results for 2 reasons. First, the age distribution was similar across the studies included in the meta-analysis (mostly middle-aged participants approximately 45 to 55 years), which reduces the confounding effect of age in the meta-analysis estimates; in addition, age did not differ among the BMI-metabolic phenotypes in most of the included studies. Second, certain metabolic factor thresholds are sex-based in their definition (that is, waist circumference and high-density lipoprotein cholesterol level), which again reduces a possible sex confounder effect in our estimates. Thus, considering that the confounding effect of these covariates was partly muted and that the adjusted estimates shown in the studies used heterogeneous models that would make the pooling of adjusted data difficult to interpret, we used unadjusted estimates while acknowledging their limitations.

With respect to the subgroup analyses that were restricted to studies with at least 10 years of follow-up (mentioned by Dr. Cho and coworkers), this approach allows more time for events to occur, which is the most appropriate strategy in evaluating a low- or moderate-risk population. Ecological bias is possible in any subgroup analyses; however, for the reasons noted earlier, we believe that this factor probably did not affect our findings.

Overall, there are still several unanswered questions about the effect of obesity on health. In providing evidence that obesity should be recognized as harmful regardless of metabolic status, our metaanalysis should ideally lead to further studies of the long-term effects of excess adiposity and their implications for health.

References

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