Comments and Responses

Metabolically Healthy Overweight and Obesity

TO THE EDITOR: Kramer and colleagues (1) conclude that "there is no healthy pattern of increased weight." However, all of the studies included in this analysis define unhealthy obesity as the presence of at least 2 components of the metabolic syndrome. Thus, by definition, persons with just 1 risk factor (such as hypertension, elevated fasting glucose levels, or hypercholesterolemia) would be considered "metabolically healthy." It is not surprising that this group has an elevated risk for cardiovascular events. We believe that this meta-analysis adds to the confusion on the topic by defining "healthy obesity" by criteria that we would consider anything but healthy.

Previous studies that have used a far more stringent definition of "healthy obesity"—that is, the absence of any medical, mental, or functional risk factors or limitations associated with excess weight (Edmonton Obesity Staging System stage 0) (2–4)—show virtually no increased mortality risk in overweight and obese persons, even over a 200-month follow-up period. In contrast, obese persons with just 1 metabolic or other risk factor are considered to have Edmonton Obesity Staging System stage 1 or 2 obesity and have clearly elevated mortality risk (3, 4).

Mislabeling "unhealthy obese individuals" as supposedly "healthy" further promotes weight bias and reinforces the widespread misconception that health can be measured simply by stepping on a scale. Rather, we should not assume that everyone with excess body fat is at high risk and in immediate need of treatment. Instead, we should look at individual risk factors (smoking, high blood pressure, dysglycemia, dyslipidemia, and others) to determine whether a given person needs medical attention. After all, 1 size does not fit all!

Jean-Philippe Chaput, PhD
University of Ottawa
Ottawa, Ontario, Canada

Arya M. Sharma, MD, PhD
University of Alberta
Edmonton, Alberta, Canada

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TO THE EDITOR: Kramer and colleagues' (1) data suggest that metabolically healthy obese persons have increased cardiovascular and all-cause mortality risk compared with their normal-weight counterparts. However, the relative risk (RR) reported for the metabolically healthy obese group is approximately one half that reported for the metabolically unhealthy obese group (1.24 vs. 2.65, respectively). This finding suggests that metabolically healthy obese persons are relatively protected from some adverse outcomes of obesity.

Cross-sectional studies suggest that metabolic health in obesity is associated with "healthy" adipose tissue that is capable of storing fat away from insulin-sensitive tissues, primarily the liver (2, 3). Longitudinal studies with long-term follow-up are vital to determine whether a snapshot of metabolically healthy obesity is stable and whether it ultimately translates into decreased risk for cardiovascular disease, type 2 diabetes, cancer, and all-cause mortality at an older age.

The main obstacle to advancing our understanding of the metabolically healthy obese phenotype and its metabolic risks is the inconsistent definition of "metabolic health" across studies. In this meta-analysis, it is defined as the absence of the metabolic syndrome (defined by criteria from the Adult Treatment Panel III, the International Diabetes Federation, or versions of these) or the presence of fewer than 2 abnormalities. Defining metabolic health on the basis of different criteria results in reported prevalence for the phenotype from less than 10% of the obese population to almost 50% (2, 3). We and others have reported considerable differences in metabolic characteristics (4) and all-cause mortality (5) among metabolically healthy obese persons, defined on the basis of different sets of criteria. Furthermore, although inclusion of metabolically unhealthy normal-weight persons in the meta-analysis is important and emphasized the increased risk for metabolic abnormality at any body mass index (BMI), some well-conducted longitudinal studies were excluded; the meta-analysis thus includes only 4 studies with more than 10 years of follow-up.

In summary, standardization of the definition of metabolic health is required before the metabolically healthy obese phenotype is dismissed. Without being totally "healthy," some obese persons still seem healthier than others.

Dorit Samocha-Bonet, PhD
Garvan Institute of Medical Research and Faculty of Medicine, University of New South Wales
Sydney, New South Wales, Australia

Antony D. Karelis, PhD
Université du Québec à Montréal
Montreal, Québec, Canada

Rémi Rabasa-Lhoret, MD, PhD
Institut de Recherches Cliniques de Montréal
Montreal, Québec, Canada

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TO THE EDITOR: Kramer and colleagues (1) report that obese persons are at long-term risk for cardiovascular events and total mortality regardless of their metabolic status. The discrimination of participants according to a metabolic score is an oversimplified dichotomous classification that does not reflect the huge heterogeneity of obesity. Metabolically healthy persons, as classically defined, may still have metabolic disorders.

In Kramer and colleagues' meta-analysis, metabolically healthy obese persons had an intermediate risk for total mortality and cardiovascular events, higher than that for metabolically healthy lean and overweight persons but lower than that for metabolically unhealthy overweight and obese persons. However, the metabolically healthy obese group was only at increased risk in the studies with more than 10 years of follow-up. Variation in some components of the metabolic syndrome over time may have influenced these results. Indeed, metabolically healthy obesity is a transient state for one third of patients who may progress to metabolic risk and type 2 diabetes (2). Kramer and colleagues speculate that metabolically healthy obese persons probably have subclinical levels of risk factors that worsen over time (1).

A proinflammatory state is recognized as an important component of the metabolic syndrome, which is mainly associated with abdominal obesity. We recently showed that metabolically unhealthy obese persons have a less favorable inflammatory profile in their visceral adipose tissue than metabolically healthy obese persons, which results from the infiltration by proinflammatory adipose tissue macrophages with increased nucleotide-binding oligomerization domain–like receptor family pyrin domain–containing 3 inflammasome activity and interleukin-1β production. Furthermore, metabolically unhealthy obesity was associated with fewer anti-inflammatory T-regulatory lymphocytes in visceral adipose tissue (3).

Of interest, Wildman and associates (4) report that overweight and obese women without clustering of cardiometabolic risk factors still have abnormal levels of inflammatory markers. In our study, metabolically healthy obese persons similarly had an intermediate inflammatory pattern in their visceral adipose tissue, with lower levels of interleukin-1β production and gene expression than metabolically unhealthy obese persons but higher levels of these inflammatory markers than metabolically healthy lean persons (3). This finding agrees with Kramer and colleagues' data on mortality and cardiovascular events (1).

Chronic silent inflammation may contribute to the elevated risk for cardiovascular events and overall mortality (1, 5) and may be a potential mechanism linking abdominal obesity and cardiovascular risk. Differences in the inflammatory pattern of visceral adipose tissue may explain why metabolically healthy obese persons still have an elevated cardiovascular risk that is intermediate between that of metabolically healthy lean and overweight persons and metabolically unhealthy overweight and obese persons.

Nathalie Esser, MD
André J. Scheen, MD, PhD
Nicolas Paquot, MD, PhD
University Hospital of Liege
Liege, Belgium

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TO THE EDITOR: Kramer and colleagues (1) and Hill and Wyatt (2) suggest that healthy obesity is a myth. However, there are problems with the data and, more important, with the concepts. Two large studies (3, 4) included in Kramer and colleagues' review represent approximately 90% of participants followed for 10 years. Compared with metabolically healthy normal-weight participants, metabolically healthy obese participants in 1 study had a mortality rate just short of significance and in the other study had an RR of 1.00—hardly "strong evidence" (2).

That obesity has come to be defined as higher BMI rather than demonstrated excess body fat (weight of fat divided by total weight [WF/W]) is misleading and confuses the argument. The assumption that adiposity (increased WF/W above some given value) is a factor for health risk and probably for earlier mortality seems to underlie Kramer and colleagues' review. Unfortunately, the anthropometrically calculated BMI does not separate or define the components of its 2-compartment model: lean body mass (LBM) and total body fat (WF).

The authors tend to equate elevated BMI with "increased adiposity"; this incorrectly assumes LBM to be constant at any given height, so that any difference in BMI is taken to represent a difference in WF/W. When body fat is measured directly, the calculated

LBM of persons of a cohort of similar height and sex varies at least ± 20% from the group mean and a person's deviation from average weight at this height can be all WF, all LBM, or any combination of the 2 (5). Consequently, for healthy persons of identical height, weight, and BMI, a ± 20% range of LBM may be associated with a remarkable range of fat content (WF/W), roughly between 10% and 40% (5).

This factor leads to great uncertainty in categorizing persons for health risk within the commonly defined BMI groups. Some persons with high WF/W may be among the lower BMI groupings. Although the overweight or obese BMI groups probably include greater proportions of those with high WF/W, they also include some persons with higher LBM but normal or low WF/W. Are some persons with a high fat content perhaps overrepresented as metabolically unhealthy in normal and overweight BMI groups and some with high LBM overrepresented as metabolically healthy in the obese BMI group? Does the size of LBM also affect health risk? Would that alter the approach of Kramer and colleagues and other investigators?

Finally, the 10-year interval seems minimal. Most participants were in their mid-50s (3, 4); death rates before age 65 years are very low.

Gerson T. Lesser, MD
New York University School of Medicine
New York, New York

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TO THE EDITOR: We were surprised that Kramer and colleagues (1) used crude, unadjusted data from individual studies for their pooled estimates. In the Discussion, the authors acknowledge this limitation and indicate that smoking and physical activity could confound the observed associations. Although we agree with this statement, the authors do not mention that age and sex are also important confounders that deeply influence BMI and the rate of mortality and cardiovascular disease.

The effects of confounding by all of these factors can be substantial, and we believe that evaluation of the association between BMI and mortality or cardiovascular disease is meaningful only after adjustment at least for age, sex, and smoking. Furthermore, meta-regression analyses cannot overcome the limitations introduced by lack of within-study adjustment (2).

In addition to the use of unadjusted measures of association, we were concerned by the subgroup analyses that were restricted to studies with more than 10 years of follow-up, because they may also be affected by ecological bias (2). Overall, we believe that the conclusions of this review, based on crude data and across-study subgroup comparisons, do not provide solid evidence on the effect of BMI categories by metabolic health status on mortality and cardiovascular end points, which is still an open question.

Juhee Cho, PhD
Sungkyunkwan University
Seoul, South Korea

Yoosoo Chang, MD
Seungho Ryu, MD, PhD
Kangbuk Samsung Hospital, Sunkgyunkwan University School of Medicine
Seoul, Korea

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TO THE EDITOR: Kramer and colleagues (1) took data from observational studies, calculated new unadjusted RRs, and summarized the unadjusted risks. All of the summarized studies had published RRs that were adjusted for confounding factors, such as age and sex. Kramer and colleagues did not use those published RRs but instead calculated new unadjusted RRs for each study from counts of sample sizes and events. As a result, the unadjusted RRs for individual studies in this review do not match those published in the original studies.

The differences are sometimes large. For example, Kramer and colleagues included results from a study by Kuk and Ardern (2) that used data from NHANES III (the Third National Health and Nutrition Examination Survey), a complex sample survey. The original publication presented hazard ratios that were adjusted for age, sex, income, ethnicity, smoking status, and alcohol consumption and that incorporated sample weights. Kuk and Ardern found RRs of 1.24 for metabolically unhealthy normal-weight participants and 0.45 for metabolically healthy overweight participants relative to metabolically healthy normal-weight participants. The corresponding unadjusted RRs for that study that Kramer and colleagues provided were 2.52 and 0.96, respectively, but were not adjusted for the complex sample design or for any confounding factors, not even age.

Kramer and colleagues list the use of pooled unadjusted estimates as a limitation of their study and note that their procedure did not account for physical activity or smoking but do not mention the

potentially more serious limitation of failing to adjust for age and sex. The procedure that they followed is more appropriate for summaries of randomized trials than for summaries of observational studies. The lack of adjustment for confounding by age, sex, smoking status, or other factors makes their summary unadjusted results difficult to interpret. A summary of adjusted risks, such as that previously provided by Fan and associates (3) on the same topic or subsequently provided by Roberson and coworkers (4), could have been useful.

Katherine M. Flegal, PhD
National Center for Health Statistics, Centers for Disease Control and Prevention
Hyattsville, Maryland

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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.

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 meta-analysis should ideally lead to further studies of the long-term effects of excess adiposity and their implications for health.

Caroline K. Kramer, MD, PhD
Bernard Zinman, CM, MD
Ravi Retnakaran, MD
Mount Sinai Hospital, University of Toronto
Toronto, Ontario, Canada

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

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