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Commentary: Obesity and cardiovascular disease risk among the young and old—is BMI the wrong benchmark?

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The positive relationship between body mass index (BMI) and cardiovascular disease (CVD) mortality has been reported from analyses of data from many large prospective cohort studies.[1–5] There is less agreement, however, as to the shape of the curve[1] and to what degree the risk of mortality from CVD increases with greater BMI. This has also led to a debate on the proper epidemiological methods for analysis and on the optimal BMI range for lowest risk. The reference category of lowest risk should ideally be defined in a population free of existing disease since clinical and pre-clinical disease can cause weight loss and bias rates of CVD upwards in lower BMI categories. The lowest risk group should also be defined among non-smokers because smoking-induced weight loss can again artificially inflate the rates of CVD among lower BMI categories. These methodological issues have been carefully addressed in most prospective studies, including the study by Park *et al.*[6] in this issue of the Journal. What has not previously been described as carefully is the extent to which the relationship between BMI and CVD mortality is modified by age.

Results from large prospective cohort studies have generally showed an increased risk of CVD mortality with increasing BMI.[1–5] Investigators from one of the longest running prospective studies—the Framingham Heart Study[2]—reported the risk of myocardial infarction and CHD death by BMI, based on the 44 year follow-up of 2453 US men aged 30–74 years at study entry. Compared with the reference group with BMI < 25, the relative risk (RR) for men in the overweight category (BMI 25–29.9) was 1.21 (95% CI 1.05–1.40) while for men in the obese category of BMI $\geqslant 30$, the RR was 1.46 (95% CI 1.20–1.77). The authors did not report estimates stratified by age.

An analysis from the America Cancer Society's Cancer Prevention Study I, based on data from 62 116 never-smoking US men, was stratified by age into five categories ranging from 30–44 years to $\geqslant$85 years and used a proportional hazards model to estimate the RR of CVD mortality according to BMI

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category.[3] The RR for a one unit increment in BMI decreased with increasing age, from RR of 1.10 (95% CI 1.04–1.16) for men aged 30–44 years to RR 1.03 (95% CI 1.02–1.05) for age 65–74 years. For men ⩾85 years, the BMI–CVD mortality relationship was not statistically significant. Of note, a similar pattern of decreasing RR with age was found for women in this study.

In the recent analysis of the nationally representative survey data from the National Health and Nutrition Examination Survey (NHANES), Flegal *et al*.[4] reported estimates of excess (all-cause) deaths associated with overweight and obesity in the US. In their overall study population of men and women, the authors reported decreasing magnitudes of association with increasing age for high BMI compared with reference BMI of 18.5–25.0. For example, the RR for BMI ⩾ 35 was 1.83 (95% CI 1.27–2.62) among those aged 25–59 years, 1.63 (95% CI 1.16–2.30) among those 60–69, and 1.17 (95% CI 0.94–1.47) for age 70 and older. The paper also stimulated discussion on methodological approaches to estimating the risks of BMI in the overweight and obese ranges associated with mortality in general, and CVD mortality specifically. Analytic approaches to reduce possible reverse causation[7] and the idea that BMI may reflect adiposity less well in the elderly than it does in the young[8] are among the issues which need to be considered carefully in any such analyses.

There is some evidence that the BMI–CVD mortality relationship may vary by ethnicity and cause-specific CVD mortality. Recently, investigators of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) reported the results from a cohort of 43 889 Japanese men aged 40–79 years at baseline and followed-up prospectively for 9–11 years.[9] Compared with a reference category of BMI 23–24.9 m^2/kg, there was no elevated risk associated with BMI ⩾ 27.0 for total CVD mortality, but there was a strong elevated risk for the subgroup of men who died of coronary heart disease (RR = 2.05; 95% CI 1.35–3.13), but not stroke (RR = 0.78; 0.52–1.18). These results were not further stratified by age.

In this issue of the journal, Park *et al*.[6] present their findings on the relationship between BMI and cardiovascular mortality in a different Asian population. In this prospective study of 246 146 non-smoking Korean men aged 20–69 at baseline, with 8 years of follow-up, the obesity-related relative risk of death from stroke and all CVD combined was stronger in younger men than in older men. The authors provide several possible explanations for their findings. The first is the bias which could be introduced by the use of a limited number of age categories across a wide age range. The second is the classic epidemiologic issue that while relative risks may be lower in the older age categories, the absolute risk of cardiovascular mortality associated with higher BMI may in fact exceed that of the lower age categories. Thus, the risk difference may be equal or be greater in the older age groups even though the relative risk is lower. Finally, the authors note that as age increases, waist circumference may be a better predictor than BMI of cardiovascular risk.

Given the potential implications of findings which suggest that obesity may be somehow less important with advancing age, in terms of cardiovascular risk and mortality, it is worthwhile to consider these and other possible explanations for the results reported. Certainly, the choice of cut-off points for age categorization of a given study population might be expected to influence the effect estimates on which they are based. However, the authors' finding of a consistent decrease in relative risk across four age categories ranging from 20–39 to 60–69 years argues against the effect being solely due to arbitrary age cut-off points. Other studies have also found that the relative risk of some CVD outcomes associated with BMI may be less strong in older men compared with younger men. In our [ER] findings from the Health Professionals Follow-up Study,[5] among men <65 years of age, BMI was a better predictor of coronary heart disease. In contrast, among men 65 years and older, the waist-to-hip ratio was a better predictor. One explanation may be that BMI becomes a less accurate reflection of fat mass in men with increasing age.[10] Waist circumference or waist-hip ratio may reflect visceral fat better than BMI does.

Finally, the vulnerability to obesity-related development of CVD mortality may be due, in part, to genetics, early life exposures, and other factors as yet undetermined. Men who are most vulnerable to obesity-related cardiovascular mortality are of course removed from follow-up at earlier ages. As a result, with increasing age, the study population may progressively contain proportionately fewer individuals among the obese who are most vulnerable. This explanation is not likely to account for the whole age modification phenomena, because in some populations circumference measures are still strong predictors of CVD risk in older age groups. Furthermore, the association between measures of adiposity and biological markers of CVD risk exists across all age strata. For decades we have known that abdominal obesity, especially when measured by computed tomography scan or other more technical measures, is associated with dyslipidemia, hypertension, hypercoaguable states, hyperglycemia and now also adipokine related insulin resistance,[11,12] all factors which left untreated increase CVD risk to some extent at all ages.

It is important from a clinical and epidemiological perspective that going forward we use age-appropriate methods to assess adiposity because most developing and developed countries of the world are undergoing both an aging of the population as well as an epidemic of obesity. The fact that BMI may not accurately reflect the true biological ramifications of adiposity at older ages should not deter efforts to prevent weight gain in older populations.

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