The phrase “metabolically healthy obesity” first entered the scientific lexicon in the early 2000s, when some observational data indicated insulin resistance was not a universal or inevitable finding among all persons with obesity. Analyses from the National Health and Nutrition Examination Survey (NHANES) 1999-2004 illustrated the phenomenon that more than one-third of persons with obesity (as defined by Quetelet index [body mass index] ≥30.0 kg/m²) failed to exhibit common clinical manifestations of obesity, including hypertension, dyslipidemia, or insulin resistance, whereas more than 20% of persons of normal body composition (as defined by BMI <25 kg/m²) exhibited 2 or more of these abnormalities. Some prospective studies also reported similar risks for coronary heart disease or overall mortality among “metabolically healthy” persons with obesity compared with their normal-weight counterparts. The implication then was that a subset of persons with overweight or obesity may be protected from adverse health effects, and that efforts at weight loss or maintenance in these “protected” persons might not be necessary.

Since then, however, numerous authors and analyses have questioned the premise of metabolically healthy obesity. First, do hypertension, dyslipidemia, and insulin resistance capture the totality of the metabolic derangements in obesity? The short answer is “no,” as adipose tissue is a complex, highly active endocrine organ that expresses and secretes myriad proteins that have wide-ranging metabolic effects in the body. As a result, the more stringent the threshold for metabolic health, the smaller the subgroup deemed metabolically healthy, and the less clinically relevant the construct becomes. Second, obesity is a chronic, relapsing, progressive disease process. In that construct, “metabolic healthy” obesity is a transient state, one in which individuals sustain their metabolic health for finite periods before developing adverse health outcomes.

In this issue of *AJKD*, Wang et al demonstrate that incident chronic kidney disease (CKD) is one adverse health outcome from which persons with overweight and obesity do not escape. Using a large population-based cohort from the United Kingdom, and applying pragmatic definitions of metabolic health, the authors demonstrate a graded relation between BMI and incident CKD, whether defined by reduced estimated glomerular filtration rate (eGFR), albuminuria, or both. Over a mean follow-up of 5.4 years, the risk of incident CKD was 30% (95% CI, 28%-33%) and 66% (95% CI, 62%-70%) higher in individuals who were overweight (BMI 25-<30 kg/m²) and had obesity (BMI ≥30 kg/m²) but were without evidence of baseline hypertension, dyslipidemia, or insulin resistance, relative to similarly unaffected persons of “ideal” weight (BMI 18.5-<25 kg/m²). Notably, the risk of incident albuminuria was nearly tripled for persons with obesity, concordant with putative mechanistic pathways that can lead to glomerular damage in obesity, such as hyperfiltration, hypoadiponectinemia, activated renin-angiotensin-aldosterone system, and macrophage activation, among others. These results mirror those related to coronary heart disease from the same cohort, in which individuals with obesity but without evidence of hypertension, dyslipidemia, or insulin resistance experienced a 50% higher risk of coronary heart disease and a doubling of the risk of heart failure.

The study by Wang et al has several strengths. The authors used a very large and well-characterized data set with several years of follow-up. They required persistent findings of reduced eGFR or albuminuria, reducing misclassification. In addition to the usual covariates, the authors also adjusted for socioeconomic factors using the Townsend index. Moreover, they conducted analyses in which they considered death as a competing risk. Key limitations were generally acknowledged. Despite its widespread use in population-based studies, BMI is an imperfect proxy for obesity. It fails to distinguish body weight related to intracellular water (largely housed in the skeletal muscle), extracellular water (which tends to accumulate in advanced CKD), and adipose tissue. Race or ethnicity was missing in more than half of participants, and the proportion of non-White participants among those with documented race or ethnicity was very low. Thus, we cannot extrapolate these findings to more diverse populations. Nevertheless, these findings are informative and should change the way we think about those persons currently considered “fat but fit.”

First, we should abandon the term “metabolically healthy obesity.” Obesity defined by elevated BMI is neither necessary nor sufficient to cause hypertension, dyslipidemia, insulin resistance, or other features of cardiometabolic disease related to adiposity. We should work to better understand how obesity (and more specifically, adiposity) contributes to these conditions and the degree to which age, sex, race/ethnicity, and other factors modify the links between obesity and cardiometabolic disease. Next, we should redouble efforts to identify other patient-specific features (including genetic, biochemical, and neuropsychiatric) and neighborhood- or environment-specific features (including those related to socioeconomic status, educational attainment, and family and social
supports) that predict cardiometabolic disease. While arresting or reversing the ascending body weight trajectory in developed (and in many developing) countries would go a long way toward reducing the burden of type 2 diabetes, coronary heart disease, heart failure, and CKD, clinical and translational investigators need to better understand what triggers these conditions and in whom. Finally, these findings are of utmost relevance to primary care providers, who have an important role in kidney protection at earlier stages of CKD in order to decrease the incidence of advanced CKD.

We often see patients in our clinical practice who have reduced eGFR and/or albuminuria and no other risk factors for CKD except obesity. Or we may see persons with known causes of CKD (eg, IgA nephropathy or polycystic kidney disease) who have obesity. In all cases, we should counsel our patients regarding the hazards of overweight and obesity, diabetes, coronary heart disease, heart failure, and CKD, and a Deputy Editor. Accepted in revised form August 9, 2021.

References


