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Invited Commentary

Invited Commentary: Limitations and Usefulness of the Metabolically Healthy Obesity Phenotype

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The fraction of the obese population who appear to be free of the metabolic abnormalities that usually accompany excess adiposity has garnered a great deal of attention recently. The so-called "metabolically healthy obesity" concept is thought to offer a refinement of the traditional obesity definitions that are based solely on anthropometry. The commentary by Rey-López et al. (*Am J Epidemiol*. 2015;182(9):737–741) in this issue of the *Journal* highlights several limitations of the "metabolically healthy obesity" concept and calls into question its usefulness as a public health metric. We discuss several of the issues raised by these authors and offer some perspective on why the utility of this concept remains unresolved.

metabolically healthy obesity; metabolic syndrome; obesity

Abbreviations: BMI, body mass index; MHN, metabolically healthy normal weight; MHO, metabolically healthy obesity; MUN, metabolically unhealthy normal weight; MUO, metabolically unhealthy obesity.

The subset of obese individuals without the metabolic abnormalities that commonly accompany excess adiposity (e.g., dysliplidemia, glucose dysregulation, and inflammation) accounts for as much as 30% of the obese US adult population, according to one definition (1). This subset has been called persons with "metabolically healthy obesity" (MHO). The MHO concept is currently embroiled in controversy. Consensus on the definition of what constitutes metabolic health among the obese is yet to be achieved (2–4), and the implications of this phenotype for clinical and public health practice are unclear (3, 5). A commentary in this issue of the *Journal* by Rey-López et al. (6) calls into question the very utility of the concept of metabolic health among obese persons, particularly for public health practice. The authors raise a number of important issues in this debate that warrant additional consideration.

HOW DO WE DEFINE MHO?

As mentioned by Rey-López et al. (6), the lack of an accepted definition of what it means to have MHO is a significant issue. The metabolic milieu driven by visceral adipose tissue is believed to be the key mediating factor in the relationship between obesity and chronic diseases (3, 7, 8), but the lack of a consistent definition of metabolic health among the obese hinders comparisons of findings across studies and causes confusion. As mentioned by the authors, the prevalence of the MHO phenotype varies widely according to the definition of metabolic health (3), but perhaps less well recognized is that it also varies by how obesity is assessed (9). It is well-accepted that body mass index (BMI; weight (kg)/height $(m)^2$) is an imperfect measure of excess adiposity among individuals, as it fails to accurately account for body composition and adipose tissue distribution (10), which are believed to be at the root of the links between obesity and chronic disease (11). Shea et al. (9) found a higher prevalence of MHO for obesity determined through percentage of body fat (MHO prevalence: 47.7%), calculated by means of dual-energy x-ray absorptiometry, than for BMI-based obesity (MHO prevalence: 34.0%). Many researchers have noted the limitations of relying on BMI for classification of excess adiposity and have called for more accurate measures of body fat to evaluate the associated health risks irrespective of stratification by metabolic health (10). Inconsistencies regarding

the health effects of MHO and the effects of interventions in this group (e.g., whether persons with MHO benefit from lifestyle interventions) cannot be resolved until a standard definition of the condition is agreed upon. However, a key factor supporting the utility of the MHO classification is that it provides a system for identifying the physiological heterogeneity of what it means to be obese.

ARE PEOPLE WITH MHO TRULY METABOLICALLY HEALTHY?

We also agree with Rey-López et al. (6) that the dichotomizaton of inherently continuous risk factors is problematic. It has been reported that obese persons who appear to be metabolically healthy (falling within "normal ranges" of selected cardiometabolic risk factors) tend to have higher mean levels of risk factors than persons of normal weight (12, 13), and this likely confers an increased risk of subsequent disease compared with persons with relatively lower risk factor levels. Chang et al. (13), who investigated this topic in some detail, reported that an observed increase in coronary artery calcification among people with MHO appeared to be mediated by elevated metabolic parameters (lipid levels, blood pressure, glucose level, and insulin resistance) that were within normal ranges.

Also mentioned in the commentary by Rey-López et al. (6) was evidence that metabolic health may be transient among obese individuals (14), which appears to be accumulating (12, 15, 16). Work by our group showed that among persons free from the "metabolic syndrome" (excluding waist circumference), those who were obese had more than fourfold the risk of normal-weight persons of developing the metabolic syndrome over 9 years of follow-up (15). More recently, we reported that MHO individuals who lose weight tend to have better cardiometabolic profiles than MHO individuals who maintain or gain weight over time (12). In the review cited by Rey-López et al., Kramer et al. (17) reported a 24% increased risk of all-cause mortality and cardiovascular events among persons with MHO in studies that included at least 10 years of follow-up, but an attenuated and statistically nonsignificant association was found in studies with shorter follow-up periods. All of this work points to the conclusion that, compared with metabolically healthy normal-weight (MHN) adults, MHO adults are at increased risk for adverse outcomes over the long term.

DIVERSE SCIENTIFIC APPROACHES ARE CRITICAL

Although we agree with the points made by Rey-López et al. about compromised health in MHO individuals, we disagree with their statement that "public health will benefit very little, if at all, from complex biological definitions of obesity and systems for characterizing obesity" (6, p. 739). The examples of breakthroughs in mechanistic understanding of disease that have resulted in improved therapies and prevention efforts are too long to list. We fail to understand how attention paid to the MHO phenotype somehow distracts public health researchers from the goal of reducing obesity in populations.

The authors express their concern about a division between epidemiology and biology (6), yet dismissal of metabolic health with regard to obesity's influence on disease serves only to widen this divide. As previously noted and in the reviews cited by Rey-López et al. (17–19), MHO individuals have elevated risk of chronic disease compared with MHN individuals. However, it is important to note that in the studies cited, the risk associated with MHO was much lower than that associated with metabolically unhealthy obesity (MUO) and tended to be lower than that in metabolically unhealthy normal-weight (MUN) individuals. Although the MHO phenotype does not appear to be benign, it is obviously different from the MUO and MUN phenotypes. The mechanisms driving these phenotypes, as well as their impact on health and disease, need to be understood. The MHO phenotype has clear utility in understanding the etiology of obesity-related chronic disease (3, 5).

WHAT'S IN A NAME?

An unfortunate weak point in this field is the nomenclature that we now seem to be stuck with—specifically the use of the word "healthy" to describe obese persons whose clinical measurements are under particular cutpoints for traditional cardiovascular disease risk factors. While MHO may be associated with some reduced level of risk for metabolic and cardiovascular diseases compared with MUO, there are a number of other conditions that it may not offer protection from. Greater fat mass is thought to exert mechanical effects on the body, independently of metabolic health, that increase the risk of a number of chronic conditions, including knee osteoarthritis (20), sleep apnea (20), and gastroesophageal reflux disease (21). Thus, without additional context, use of the term MHO may end up deemphasizing obesity's effects on these conditions. Clearly obese persons suffering from these conditions would not be considered "healthy," even if their metabolic markers fell well within a normal range. A focus on the MHO phenotype therefore has the potential to lead to confusion regarding the management and treatment of obesity. Perhaps adding to the confusion is the fact that overweight persons (BMI $\geq$25 and <30) with no traditional cardiometabolic risk factors are not recommended for weight loss treatment (22), despite the fact that they are at elevated risk of becoming obese.

However, observations that persons with MHO are at somewhat increased risk for chronic disease compared with MHN individuals support the current guidelines for obesity treatment that state that the obese are recommended for weight loss, without regard to the presence or absence of cardiovascular risk factors (22). Nevertheless, on the surface, the term "healthy" may indicate to health-care providers a patient who is not in need of treatment. Indeed, persons in the MHO category have risk factor levels that do not exceed the cutpoints used as indicators for medication therapies. In most clinical settings in the United States, pharmaceutical treatment is easier to implement than weight loss therapy, and the implications for billing for these types of therapies are also different. In the face of these obstacles, the word "healthy" could result in less attention being paid to supporting the behavior changes needed to combat obesity and could leave MHO individuals with fewer resources to combat their excess weight. To improve clinical utility, perhaps clinicians should

consider alternatives to the use of the phrase "metabolically healthy" to describe this population—perhaps incorporating the gradations of risk observed in epidemiologic studies of disease outcomes (e.g., the "high-risk" vs. "moderate-risk" obese) or focusing on the need for pharmaceutical treatment of risk factors (e.g., the "medicated" vs. "unmedicated" obese).

INDIVIDUAL HEALTH VERSUS PUBLIC HEALTH GOALS

While the concept of the MHO phenotype was, to our knowledge, never intended for public health messaging, the assertion that it is "irrelevant" seems premature. However, we heartily agree that the widespread nature of the problem of obesity and the complexity of the myriad societal and environmental factors that encourage obesity require population-level approaches (23). Although care must be used in communicating complex definitions of obesity, consideration of the potential for metabolic heterogeneity among obese persons does not preclude a public health goal of shifting the population distribution of BMI in order to reduce the health effects of excess adiposity. It is clear that much work remains to be done in this area, and understanding of the implications of excess adiposity for the etiology and burden of disease, even in large populations, would benefit from refinements of the definition of obesity (3).

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