JAMA Network Open

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Metabolically Healthy Obesity Redefined

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Obesity is a leading preventable cause of cardiometabolic diseases and mortality, and the increasing prevalence of obesity has become a major public health concern.[1] Defined as a body mass index (BMI) greater than or equal to 30 (calculated as weight in kilograms divided by height in meters squared), obesity is often associated with metabolic abnormalities, including glucose intolerance, type 2 diabetes, dyslipidemia, hypertension, nonalcoholic fatty liver disease, increased inflammation, and metabolic syndrome—all of which increase the risk of cardiovascular diseases (CVD) (ie, coronary heart disease, stroke, and heart failure).[2] Yet, not all individuals meeting the criteria for obesity exhibit metabolic complications. Obesity phenotypes have been observed in which a subset of obese persons may be considered as having metabolically healthy obesity (MHO) with no evidence of existing cardiometabolic disease. In contrast to MHO, there are also obese persons having metabolically unhealthy obesity (MUO) and an excess risk of adverse cardiometabolic and CVD outcomes. However, the debate continues as to whether individuals with MHO are truly free of adverse CVD outcomes when compared with metabolically healthy nonobese individuals. The evidence has been inconsistent. A review article showed that in some studies, those with MHO have a similar risk of CVD as those who are metabolically healthy and nonobese,[3] but in other studies, people with MHO appear to have an increased risk of CVD than the metabolically healthy individuals who are not obese.[3,4] Furthermore, it is debated whether any form of obesity can ever be considered healthy or whether the MHO phenotype is merely a stage in transition to developing MUO over time. Part of the contention may be related to how MHO is defined. To date, there is no universally accepted standard for defining MHO and more than 30 different definitions have been used to operationalize the phenotypes in studies.[3] This large number of differing approaches may explain why the prevalence, stability, and clinical outcomes of MHO are inconsistent across studies and lend to a continued unresolved debate.

The present study by Zembic et al[5] sought to derive a more precise definition of MHO and investigate its association with CVD mortality and total mortality using data from the third National Health and Nutrition Examination Survey (NHANES-III) and the UK Biobank. In previous investigations of MHO, metabolic health was defined a priori using either the cluster of indicators of the metabolic syndrome (dyslipidemia, elevated blood pressure, dysregulated glucose, and abdominal obesity) or insulin resistance, with inconsistent results.[3] Zembic et al[5] used systematic approaches (area under the receiver operating characteristic and Youden index) to identify anthropometric and metabolic parameters with clinically relevant cutoffs associated with the outcomes of interest among individuals with obesity. The present study found that MHO was best defined by the following criteria: (1) systolic blood pressure less than 130 mm Hg and no use of blood pressure–lowering medication, (2) waist-to-hip ratio (WHR) less than 0.95 (women) and less than 1.03 (men), and (3) no prevalent type 2 diabetes. This new definition places an emphasis on the WHR and does not account for dyslipidemia. Although easy to measure, BMI is considered an insufficient measure of body fat content because it fails to account for muscle mass and bone density and does not reflect fat distribution. Waist circumference is commonly used to capture abdominal obesity in prior MHO definitions; however, WHR is a more effective measurement of central adiposity, with WHR having the strongest gradient with incident CVD because not all excess weight is the same and will differ in its association with health risks. Central abdominal obesity is a key component of the metabolic syndrome leading to cardiovascular abnormalities and is thought to play a specific role in insulin resistance and dyslipidemia.[6] The WHR provides a measure of central vs peripheral body fat

distribution, but waist circumference does not. In the present study, WHR estimated the probability of CVD better than waist circumference among individuals with obesity, making WHR an important component for accessing atherogenic risk among this population. The present study also suggests that, although still relevant to metabolic syndrome risk, the effect of dyslipidemia on CVD death and mortality risk may be weaker among individuals with obesity.

Based on the new definition, MHO was not associated with CVD mortality and total mortality in the NHANES-III and again when validated in the UK Biobank. The MHO phenotype was also prevalent with more than 40% of individuals with obesity in the NHANES-III cohort meeting the criteria. In addition, individuals with MHO as identified in this study were healthier, more educated, and less likely to have low income than those of the metabolically unhealthy groups, regardless of BMI category. The authors rigorously tested their new definition against previous criteria and established a meaningful approach to disentangle obesity-related metabolic health phenotypes by mortality risk. The current definition was only applied to outcomes of CVD death and total mortality and may have low specificity among people with a BMI greater than or equal to 40. The results of the study and the new MHO definition, therefore, may not be generalizable to other cardiovascular outcomes and will require future studies testing the robustness of the new definition against associations with incident coronary heart disease, stroke, and heart failure.

Zembic et al[5] make a case that clarifying MHO classification may help to explain why those classified by prior definitions as having MHO were often linked to an increased risk of mortality compared with individuals of normal weight. Previous definitions may have been insufficient and, clearly, misclassification of exposure status is problematic. Therefore, the present study provides the much-needed evidence to support establishing a standardized definition of MHO as the first step in understanding obesity phenotypes. There are several other issues to address to help move this area of research forward.

Previous evidence has shown that MHO is likely an unstable phenotype.[7] Underestimating risk based on MHO at a single time is still an issue because some of these individuals will transition to MUO over the years of follow-up. In many individuals with MHO, the likelihood of transitioning to MUO is substantial and likely directly related to weight gain, aging, and acquiring a poor lifestyle index. The current literature has yet to adequately differentiate the key lifestyle factors experienced between MHO and MUO, but factors such as physical activity, smoking, and diet indices would clearly modify the MHO-CVD relationship and portent to the risk of individuals with MHO developing MUO over time. Studies simply adjusting for some of these lifestyle factors reported that MHO was not associated with CVD and mortality, suggesting the benefits of the MHO state may be independent, although diet assessments and objective measures of cardiorespiratory fitness were consistently missing. Regardless, it would seem that the benefits of MHO are conditional at best on avoiding weight gain, maintaining ideal WHR with good levels of lifestyle factors (ie, diet, physical activity, and smoking), and avoiding development of metabolic syndrome.

Metabolic dysfunction associated with obesity has important clinical and public health implications. As the evidence continues to mount suggesting that BMI classifications alone are insufficient in capturing an individual's current or future health status, it is clear that a more robust and universally used definition of obesity phenotypes is needed. The present study provides a prototype of how that definition can be derived, but more rigorous tests and evidence using similar techniques are needed, particularly in prospective studies. Once a standardized definition is recognized, we can begin to enumerate the prevalence of people with MHO and MUO, identify factors that can contribute to the stability of MHO over time, and gain mechanistic insight into the factors that differentiate people with MHO and MUO that are not solely related to metabolic outcomes.

ARTICLE INFORMATION

Published: May 7, 2021. doi:10.1001/jamanetworkopen.2021.8860

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Conflict of Interest Disclosures: Dr Rodriguez reported receiving grants from the National Institutes of Health and Amgen outside the submitted work. No other disclosures were reported.

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