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EDITORIAL

Metabolically healthy obese and MAFLD: does weight status alone matter?

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There is convincing evidence that indicates the adverse effects of obesity on health, and obesity is considered a crucial risk factor for a wide range of metabolic diseases, including type 2 diabetes mellitus, cardiovascular disease and metabolic dysfunction-associated fatty liver disease (MAFLD) [1]. In addition to a reduced life expectancy, disabilities, and an impaired quality of life, obesity causes a substantial economic burden on health care systems.

Observations that a proportion of individuals with obesity (~10–15%) do not entail apparent cardiometabolic abnormalities led to the notion of metabolically healthy obesity (MHO) [2]. Given the magnitude of obesity, a nuanced understanding of the extent to which the MHO phenotype carries risks for health is pivotal to avoiding inappropriate public health messages. Although there is no standardized operational definition of MHO, normal glucose and lipid metabolism profile levels in addition to blood pressure values—usually serve as the criteria to diagnose MHO [2].

The associations between the MHO phenotype and fatty liver disease (FLD) and fibrosis remain uncertain, but these associations have been examined in few studies. In *Hepatology International*, Man and colleagues [3] determined that overweight and obesity were strongly and progressively associated with an increased incidence of FLD and advanced fibrosis, even in the absence of metabolic abnormalities. This study was conducted using health check-up data from a large cohort of 31,010 adults with no evidence of FLD and advanced fibrosis at baseline during a median follow-up of 2.2 years. The diagnosis of FLD and fibrosis progression was based on B-type ultrasound and noninvasive fibrosis scores. A recent meta-analysis showed that ultrasonography allows for reliable detection of ≥ 5% histologically defined hepatic steatosis compared to histology [4].

These findings are consistent with a previous study from Korea that was conducted in 77,425 individuals with no FLD and metabolic abnormalities at baseline who were followed up for an average of 4.5 years. The results of this study showed a statistically significant graded relationship between body mass index (BMI) and FLD [5]. Further support for this conclusion arises from multiple Mendelian randomization analyses, which indicated that genetically driven BMI causally increases FLD risk [6]. These results imply that overweight and obese individuals, irrespective of their metabolic status, carry an excess risk of FLD and fibrosis progression and suggest that there is no healthy pattern of increased weight.

Notably, another study of 14,384 South Koreans from an occupational cohort showed that MHO subjects are at risk of fatty liver but not of preclinical atherosclerosis [7]. These findings suggest that there could be differential impacts of fat mass, fat distribution and function or other cardiometabolic risk factors among different metabolic diseases [8]. However, further studies are required to clarify this aspect.

This study has several positive clinical and public health implications and thus merits thorough consideration. Fundamental questions arising from this work are whether MHO represents a marker of true resilience and whether individuals with MHO remain metabolically healthy throughout life or are a transient phenotype of metabolically unhealthy obesity (MUO) on the pathway to FLD. In longitudinal cohorts, half to three-fourths of MHO individuals will develop MUO and increased health risks [9]. Notably, liver fat accumulation was found to be an early and sensitive predictor of the transition from MHO to MUO [10]. Thus, this work provides new evidence that the so-called "MHO" is not a reliable indicator of a lower clinical risk of FLD. Instead, MHO signals an opportunity for early intervention and the primary prevention of FLD and fibrosis via weight reduction and lifestyle interventions, whereas secondary prevention through

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the treatment of already existing risk factors might be the only viable option for those with MUO.

However, normal weight status did not necessarily imply metabolic health, and being metabolically unhealthy, regardless of BMI, largely conferred an augmented risk for FLD development and fibrosis [11–13]. These findings collectively add additional support for the utility of MAFLD definition that includes overweight and obese as a sole criterion for the diagnosis of MAFLD. It also emphasizes the role of metabolic health, particularly among nonobese individuals [14, 15]. The MAFLD definition thus provides clinicians with a holistic patient-centered approach to manage fatty liver attributed to metabolic dysfunction [16, 17].

This study had some limitations, including a lack of information on the homeostasis model assessment of insulin resistance (HOMA-IR) and high sensitivity C reactive protein (hsCRP). Previous studies have shown that the HOMA index might be a more sensitive and effective measure of metabolic health status in the obese population [18]. In addition, MHO is associated with an elevated hsCRP (a marker of underlying low grade systemic inflammation) compared to metabolically healthy weight individuals [19]. These limitations are compensated for by numerous strengths. The main strengths of this study are the large sample size, the prospective design, the use of both BMI and waist circumference to identify obesity, and the testing of both FLD and FLD with fibrosis progression. In addition, the authors have undertaken a sex-specific analysis and demonstrated that the association between MHO and FLD was more profound in females than in males. Large prospective and mechanistic studies are warranted to further explore the pathophysiological basis of this finding.

In conclusion, the study by Man et al. [3] adds further evidence to support the notion that obesity even in the absence of classical metabolic risk factors is not a benign condition but is linked with subclinical vascular inflammation, FLD and fibrosis progression. The MHO phenotype is a fallacy, particularly in subjects with hepatic steatosis, and using this term may mislead individuals to believe obesity can be healthy and desirable. Identifying individuals with obesity, with no metabolic abnormalities represents an opportunity for early intervention via lifestyle modifications to help prevent the progression to adverse liver and cardiometabolic outcomes.

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Declarations

Conflict of interest Authors Ziyan Pan and Mohammed Eslam has no competing interests or any conflict of interest relevant to this work.

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