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Forum

# Metabolically Healthy Obesity: Personalised and Public Health Implications

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**Obesity is a heterogeneous condition; thus, metabolic abnormalities and cardiometabolic risk vary among obese individuals, with a significant proportion considered to be metabolically healthy. However, whether these individuals are truly healthy remains controversial and, therefore, a better understanding of such phenotypes may offer opportunities to improve current obesity diagnosis, intervention, and treatment.**

## Obesity and Metabolically Healthy Obesity

Worldwide obesity prevalence is increasing, with future projections predicting that over 1 billion people, or approximately 20% of the entire adult population of the world, will be obese by 2030 [1]. The current epidemic is one of the greatest public health issues of this century, given its association with increased risk of developing metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD), among other chronic conditions, leading to increased risk of premature death and higher all-cause mortality. However, it appears that not all obese subjects may in fact be at increased risk. A subgroup of 'metabolically healthy obese' (MHO) individuals has been described whose excess adiposity exists in the absence of the major obesity-associated metabolic abnormalities, including insulin resistance, hypertension, and dyslipidaemia [2].

MHO prevalence estimates vary widely (10–40% of all obese subjects) [2]. Notwithstanding study design differences, such as age, ethnicity, geography, and sample size, differences in how both metabolic health and obesity are classified are the most likely causes of such disparity. No standard metabolic health definition has been adopted, with some based solely on the presence of MetS or some of its individual components, whereas others include raised inflammatory status. The reported disparities in MHO prevalence underscore the need for consensus on a standard definition. However, even when MHO definition was harmonised (obesity without any MetS component and no previous CVD diagnosis) in a recent examination of ten cohort studies involving 163 517 individuals from seven European countries, varying MHO prevalence was reported (7–28% in women and 2–19% in men) [3].

Many questions remain regarding MHO definitions and determinants, as well as MHO stability over time and associated cardiometabolic and mortality risk. Furthermore, given that current approaches to treat obesity have limited success, this begs the question of whether stratifying obese individuals based on their metabolic health subtype may offer new opportunities for a more personalised approach in obesity diagnosis, intervention, and treatment.

## MHO Stability

Initially considered a static condition, accumulating evidence now suggests that MHO status is transient. Longitudinal follow-up (median 7.8 years) of the San Antonio Heart Study revealed that almost half (47.6%) of MHO subjects at baseline transitioned to metabolically unhealthy obesity (MUO) [4]. Those who converted were older, had greater adiposity, and lower HDL cholesterol levels than those with stable MHO. The authors further attempted to characterise the factors that distinguished those who progressed to MHO from those who progressed to MUO. Interestingly, body mass index (BMI), waist circumference, and weight gain were not significant predictors. By contrast, lipid profiles were the strongest determinants of the type of metabolic state that is likely to develop with weight gain. Ten-year follow-up of the Tehran Lipid and Glucose Study revealed that 43.3% of the metabolically healthy abdominally obese became MUO [5]. Baseline insulin resistance, triglycerides, and high-density lipid (HDL) cholesterol were significant predictors of change. Consistent with these findings, an 8-year follow-up of the English Longitudinal Study of Ageing demonstrated that 44.5% of the MHO individuals became MUO [6]. Relative to the stable MHO individuals, those who transitioned to MUO were more likely to have raised triglycerides and C-reactive protein, high glycated haemoglobin and blood pressure, and increased abdominal adiposity. Recent research showed that MHO individuals display more favourable lipoprotein subfraction profiles [7] and that systemic inflammation may explain the increased risk of T2DM observed among MHO individuals [8]. Collectively, these data underscore the importance of maintaining healthy lipoprotein and/or lipid and inflammatory profiles in the context of achieving and preserving optimal cardiometabolic health. Further longitudinal investigation of the sustainability and predictors of the MHO phenotype combined with characterisation of persistent metabolic health status may uncover potential intervention targets.

## MHO and Long-Term Outcomes

The concept that any obesity phenotype may be considered healthy is controversial. Prospective studies tracking the development of cardiometabolic disease and mortality in MHO have produced conflicting results. How MHO is defined and the transient nature of this phenotype may be partly responsible. Guo and Garvey examined the relative impact of metabolic health and body-weight status on long-term health outcomes using data from two large cohorts (Coronary Artery Risk Development in Young Adults Study and the Atherosclerosis Risk in Communities Study, with 18.7 and 20 years follow-up, respectively) [9].

They reported lower risk for diabetes, coronary heart disease (CHD), stroke, and mortality among the MHO compared with the MUO, but increased diabetes risk relative to the metabolically healthy lean subjects. Results of the 17-year follow-up of the Whitehall II cohort study indicated increased risk of both incident CVD and T2DM among MHO individuals relative to their healthy normal-weight counterparts [10]. However, relative to the MUO subjects, MHO individuals were at a lower risk of T2DM but not of CVD. Thus, MHO may not be as benign as initially thought and largely depends on the reference group.

The individual and combined contributions of metabolic health status and BMI on cardiometabolic health outcomes and mortality are yet to be fully clarified and require further investigation. Recent data from a 20-year follow-up suggest that cumulative incidence rates for CHD, stroke, and survival probability in individuals with suboptimal health ($\leq$ two risk factors) were intermediate between the healthy and unhealthy subgroups, with no effect of BMI [9], suggesting that metabolic health is more important with regards to development of adverse cardiometabolic outcomes. It is clear that high-risk groups, such as MUO, would benefit from risk stratification that identifies obese individuals who may gain most from weight-loss interventions with subsequent improvements in metabolic health profile and reduction in development of cardiometabolic disease. However, interventions aimed at improving metabolic health with or without obesity could be additionally advantageous for other intermediate-risk subgroups, including metabolically unhealthy lean individuals and those with uncomplicated obesity.

## Prevention, Intervention, and Potential Implications of MHO

The UK Foresight obesity systems map highlights the sheer complexity of, and inter-relationships between, the social, biological, and environmental determinants of obesity. Although multifaceted, the key determinants can be summarised by several subsystems, including food production, food consumption, physiology, individual activity, physical activity environment, and both individual and social psychology. Such diversity suggests a number of potential intervention points, both at the individual and population level. It is obvious that 'one size fits all' strategies to prevent and/or reduce obesity and body weight, which do not take the degree of heterogeneity of this condition or interindividual differences in responsiveness to dietary or lifestyle interventions into account, have had limited success. Current first-line obesity management is weight loss through a combination of dietary and physical activity behaviour changes. Unfortunately, this does not work for most people. Recently, the American Association of Clinical Endocrinologists suggested a complication-centric approach to weight-loss management, advocating more aggressive therapeutic approaches for those patients with obesity-related complications [11]. Thus, stratifying obese individuals according to their metabolic health phenotype may have clinical implications in terms of developing more tailored obesity treatments. Whether such an approach would deliver on this promise remains to be seen. The significant diversity in the reported prevalence of MHO across Europe suggests that additional factors, such as environment and genetics, also have a role. While we await data regarding genetic susceptibility to MHO, limited and inconsistent data on the environmental determinants of MHO exist. Recent evidence suggests that, despite no difference in overall dietary intake between metabolic health subtypes, favourable lifestyle factors, including healthy diet pattern, higher dietary quality, better compliance with food pyramid recommendations, and having moderate levels of physical activity, are all positively associated with MHO [12–14]. Furthermore, recent characterisation of stable and unstable MHO indicates that a healthy lifestyle index may influence transition to MUO [15]. Collectively, these later findings may represent new potential intervention targets for future personalised obesity treatment.

## Concluding Remarks and Future Perspectives

There is absolutely no suggestion that some, but not other, obese individuals should receive treatment, but it is tempting to speculate that stratifying obesity according to metabolic health status may be more advantageous. First, this may allow earlier identification of obese individuals with the greatest risk of adverse metabolic and cardiovascular outcomes (i.e., MUO). Second, these individuals could then be prioritised for more appropriate tailored treatment focussed on improving their metabolic health profile and reducing excess adiposity and cardiometabolic risk. For example, developing interventions to improve dietary quality or promote healthier lifestyle indices may be particularly beneficial to MUO individuals. Notwithstanding the additional costs and resources required to implement such an approach in an already constrained public healthcare system, taking future obesity projections and associated costs arising from increased healthcare, absenteeism, and lost productivity into account, such a personalised approach, if successful, could reap long-term benefits on outcomes and cost-effectiveness of care. For now, this is speculative and, although improving, the evidence relating to how metabolic health background may affect responsiveness to antiobesity dietary or lifestyle interventions is insufficient and mixed. Thus, further research using larger, well-designed intervention studies with longitudinal follow-up is warranted, because improved understanding of the MHO phenotype may open up new avenues in personalised obesity research.

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## References

1. Kelly, T. *et al.* (2008) Global burden of obesity in 2005 and projections to 2030. *Int. J. Obes.* 32, 1431–1437
2. Phillips, C.M. (2013) Metabolically healthy obesity: definitions, determinants and clinical implications. *Rev. Endocr. Metab. Disord.* 14, 219–227
3. van Vliet-Ostaptchouk, J.V. *et al.* (2014) The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. *BMC Endocr. Disord.* 14, 9
4. Achilike, I. *et al.* (2015) Predicting the development of the metabolically healthy obese phenotype. *Int. J. Obes.* 39, 228–234
5. Eshtiaghi, R. *et al.* (2015) Natural course of metabolically healthy abdominal obese adults after 10 years of follow-up: the Tehran Lipid and Glucose Study. *Int. J. Obes.* 39, 514–519
6. Hamer, M. *et al.* (2015) Stability of metabolically healthy obesity over 8 years: the English Longitudinal Study of Ageing. *Eur. J. Endocrinol.* 173, 703–708
7. Phillips, C.M. and Perry, I.J. (2015) Lipoprotein particle subclass profiles among metabolically healthy and unhealthy obese and non-obese adults: does size matter? *Atherosclerosis* 242, 399–406
8. Jung, C.H. *et al.* (2015) The risk of incident type 2 diabetes in a Korean metabolically healthy obese population: the role of systemic inflammation. *J. Clin. Endocrinol. Metab.* 100, 934–941
9. Guo, F. and Garvey, W.T. (2016) Cardiometabolic disease risk in metabolically healthy and unhealthy obesity: stability of metabolic health status in adults. *Obesity* 24, 516–525
10. Hinnouho, G.M. *et al.* (2015) Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. *Eur. Heart J.* 36, 551–559
11. Garvey, W.T. *et al.* (2014) American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. *Endocr. Pract.* 20, 977–989
12. Bell, L.K. *et al.* (2015) The relationship between dietary patterns and metabolic health in a representative sample of adult Australians. *Nutrients* 7, 6491–6505
13. Camhi, S.M. *et al.* (2015) Healthy eating index and metabolically healthy obesity in U.S. adolescents and adults. *Prev. Med.* 77, 23–27
14. Phillips, C.M. *et al.* (2013) Defining metabolically healthy obesity: role of dietary and lifestyle factors. *PLoS ONE* 8, e76188
15. Schroder, H. *et al.* (2014) Determinants of the transition from a cardiometabolic normal to abnormal overweight/obese phenotype in a Spanish population. *Eur. J. Nutr.* 53, 1345–1353