

## Letter to the Editor

### Original article:

Title: Obesity severity and duration are associated with incident metabolic syndrome: Evidence against metabolically healthy obesity from the Multi-Ethnic Study of Atherosclerosis

Authors: Morgana Mongraw-Chaffin , Meredith C. Foster , Rita R. Kalyani , Dhananjay Vaidya , Gregory L. Burke , Mark Woodward, and Cheryl A.M. Anderson

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### Letter authors:

Wahyu Wulaningsih<sup>1,2,3</sup>, Johnathan Watkins<sup>3</sup>

### Affiliations:

<sup>1</sup>Medical Research Council Unit for Lifelong Health and Ageing, University College London, London WC1B 5AH, UK

<sup>2</sup>Division of Haematology/Oncology, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta 55292, Indonesia

<sup>3</sup>PILAR Research and Education, Cambridge CB1 2JD, UK

**Corresponding author:** Wahyu Wulaningsih  
MRC Unit for Lifelong Health and Ageing at UCL  
33 Bedford Place  
London WC1B 5JU United Kingdom  
Phone: +44(0)20 7670 5700  
Fax: +44(0)20 7580 1501  
Email: [w.wulaningsih@ucl.ac.uk](mailto:w.wulaningsih@ucl.ac.uk)

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## **Abstract**

There is an emerging interest on a subgroup of obese individuals with favourable metabolic profile or metabolically healthy obesity (MHO). We discussed two recent publications challenging the existence of this obesity subtype.

The notion that being obese can be 'healthy' has gained emerging interest in the past decade. The term metabolically healthy obesity (MHO) refers to a subgroup of obese individuals suggested to have favourable metabolic profile in comparison to those with metabolically unhealthy obesity (MUO).[1] However, MHO is not a benign condition, with increased risk for cardiovascular events compared to the non-obese counterpart.[2] A growing perspective sees MHO as a transient state towards metabolic syndrome rather than a distinct phenotype,[3,4] but until recently, there had not been exhaustive evidence supporting this claim.

The past month saw two major publications challenging the existence of MHO which we consider pivotal to the field. Mongraw-Chaffin and colleagues performed an analysis of repeated BMI measurements in the Multi-Ethnic Study of Atherosclerosis (MESA),[5] and reported a positive association between obesity duration and severity and incident metabolic syndrome among obese individuals. Ryden and colleagues performed a transcriptomic analysis on the subcutaneous white adipose tissue of 51 obese participants of a clinical trial evaluating gastric bypass surgery outcomes [6], and reported similar gene expression response to insulin between metabolically healthy and unhealthy obese individuals. Despite the different approaches used, these two studies arrived at a similar conclusion – that there is a full if not partial overlap of those belonging to the metabolically healthy and unhealthy obese groups.

Several issues arise when interpreting these findings. First, criteria used to classify individuals into metabolically healthy and unhealthy vary. MESA used the presence of metabolic syndrome, whereas the study by Ryden and colleagues classified obese individuals by insulin sensitivity measured during a hyperinsulinemic euglycemic clamp. Given the wide range of MHO prevalence (6-75%) depending on the definition [7], a consensus is needed to define metabolic health. Participant inclusion also posed limitations. Mongraw-Chaffin and colleagues included participants with any documented MHO at any point of measurements for the primary analysis, and we appreciate that the authors mentioned the lack of information on previous history of metabolic syndrome. In the other study, only patients due to undergo a gastric bypass surgery were included, thereby limiting generalisability to severely obese individuals.

Secondly, the role of lifestyle, such as smoking and physical activity, has not been explicitly addressed, although nicotine consumption did not differ between insulin-sensitive and -resistant patients in the study by Ryden and colleagues. There is indication that physical activity may differentiate MHO and MUO,[8] and adverse obesity-related lifestyles may have masked the effect of obesity duration or severity.

Finally, these studies have yet to answer the question whether MHO is a universal pathway between being non-obese and metabolically unhealthy obese, or whether it represents individuals with slower progression towards developing metabolic syndrome. Further investigations combining longitudinal and experimental approaches may shed light into whether a 'one-for-all' intervention against obesity is indeed plausible.

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