

# Metabolically healthy versus unhealthy obesity and risk for diabetes mellitus and cardiovascular diseases

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Obesity presents one of the biggest issues of modern-day life for a wide variety of medical specialties, starting with the cardiologist and ending with the diabetologist or the bariatric surgeon. However, in the last few years a new entity has emerged, the metabolically healthy obese (MHO) individual. This category encompasses obese individuals without the presence of metabolic diseases such as type 2 diabetes mellitus, dyslipidemia, or hypertension. Several studies have thus been undertaken to determine the risk of these MHO individuals for diabetes mellitus or cardiovascular diseases compared with the 'unhealthy' obese. Data are still controversial on this matter, but one trend seems to be emerging: MHO is but a transient phase

in the path toward insulin resistance and metabolic syndrome. *Cardiovasc Endocrinol* 6:23–26 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

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## Introduction

According to the WHO, health represents a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity. In contrast, obesity, plaguing more than 600 million people as far as 2014 and on an ascending trend, is associated with mental, physical, and social implications (<http://www.who.int/mediacentre/factsheets/fs311/en/>). This indicates that obesity is linked to a vast number of consequences, and last but not the least it entails huge costs to alleviate some of these issues.

Obesity, as defined by a BMI over 30 kg/m<sup>2</sup>, holds an incomplete view of this matter. It is intended for those 20 years or older. Moreover, not just those obese but those overweight too are at high risk of cardiovascular disease (CVD). Can we really base our risk stratification merely on an estimative scale concerning the weight and height of an individual? Obesity and overweight are both chronic conditions that are the result of an energy imbalance over time. The cause of this energy imbalance can be due to a combination of several factors that vary from person to another, including individual behaviors, environmental factors and genetics, all contributing to the complexity of the obesity epidemic. Another determinant of increased adiposity is waist circumference, over 102 cm in men and over 88 cm in women for the White race (with different cutoff points in Asian populations) ([http://apps.who.int/iris/bitstream/10665/44583/1/9789241501491\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/44583/1/9789241501491_eng.pdf?ua=1)).

However, from an evolutionary point of view, overweight has served as an adaptive mechanism protecting individuals from starvation by storing excess energy into fat

cells during periods of abundance. Yet the effects of excess weight on mortality and morbidity have been recognized for more than 2000 years, although not by the name of atherosclerosis. It was Hippocrates who noted that 'sudden death is more common in those who are naturally fat than in the lean'.

It should come as no surprise that, according to an article published by Mokdad *et al.* [1], poor diet, together with inactivity and obesity, occupies a second place in preventable mortality caused by health-impairing behaviors in the USA, after smoking. However, their mortality estimate for obesity has proven controversial and is the subject of some debate [1]. Yet, one should take into consideration that an increase in BMI by 1 U raises the risk for coronary heart disease by 15.8% in men and 14.3% in women [2].

## Definitions of metabolically healthy obese

Obesity is at the core of metabolic disorder, and over the last three decades the worldwide prevalence of obesity has nearly doubled; the mean BMI has increased worldwide by 0.4 kg/m<sup>2</sup> per decade for men and 0.5 kg/m<sup>2</sup> per decade for women. Nevertheless, waist circumference, body composition, and other metabolic indicators are now competing with BMI for defining the best cardiometabolic risk. It was the first 'cardiometabolic health alliance' led by professor Laurence Sperling, who stated that metabolic syndrome should be classified by subtype and stage, which translates to specific evidence-based management algorithms to improve clinical outcomes [3]. Despite this, no uniform definition of what should be considered 'metabolically healthy' has so far been

established. Investigators often define participants with metabolic healthy obesity (MHO) by the absence of metabolic syndrome, the absence of insulin resistance, or, less often, the absence of abdominal adiposity or high cardiorespiratory fitness. But the phenotype of MHO, described by the presence of obesity in the absence of metabolic risk factors, has gained a lot of interest. First of all, some studies argue that a specific subgroup of obese individuals is resistant to metabolic complications such as arterial hypertension or insulin resistance, and recent data from a cross-sectional study support the notion that MHO is accompanied by a more favorable inflammatory status than is metabolically unhealthy obesity (MUO). However, MHO individuals present a higher all-cause mortality compared with normal-weight metabolically healthy individuals [4].

The prevalence of MHO in the population is estimated at around 10–20% of obese individuals [5], and according to the National Health and Nutrition Examination Survey, a nationally representative sample of adults living in the USA, 32% of obese adults over the age of 20 could be included in the MHO category [6].

How does MHO compare to metabolically abnormal obese? Is there a difference in adipose tissue metabolism, muscle characteristics, or simply gene expression? Individuals with MHO, although having high fat mass, have high insulin sensitivity, low ectopic fat, low triglycerides, low inflammation, high high-density lipoprotein cholesterol (HDL-C), low intima-media thickness, high adiponectin, and low apolipoprotein B. According to the Wildman criterion an MHO individual is described as fulfilling one or none of the following components: blood pressure more than 130/85 mmHg or use of anti-hypertensive drugs, triglycerides more than 1.7 mmol/l or use of lipid-lowering drugs, fasting glucose more than 5.6 mmol/l or use of medications for diabetes, homeostasis model assessment-estimated insulin resistance above the 90th percentile, C-reactive protein above the 90th percentile, or HDL-C less than 1.3 mmol/l [6].

#### **Metabolically healthy obese and cardiovascular disease**

The Kramer *et al.*'s [7] meta-analysis compared metabolically healthy normal-weight (MHNW) individuals with MHO individuals and showed that there was an increased risk for cardiovascular (CV) events in the MHO group. Compared with MHNW individuals, obese persons are at increased risk for adverse long-term outcomes even in the absence of metabolic abnormalities, suggesting that there is no healthy pattern of increased weight. However, the duration of exposure to the metabolic-BMI phenotypes was not described in the studies [7].

Excess weight is first associated with the development of subclinical metabolic and vascular dysfunction that eventually leads to an increased incidence of CV events and mortality over the long term. Previous reports that

evaluated MHO individuals over short-term follow-up or that compared these individuals with control groups not fully characterized for CV risk might have contributed to the concept of a 'benign obesity' phenotype that is not associated with adverse outcomes. Even within the same category of metabolic status (healthy or unhealthy), certain CV risk factors (blood pressure, waist circumference, low HDL-C level, insulin resistance) progressively increase over time from normal weight to overweight to obese. These findings contradict the notion that increased BMI can be harmless [7].

Van der A *et al.* [8] followed up 22 654 individuals aged between 20 and 59 years who were metabolically healthy but had abdominal obesity with normal glucose levels, blood pressure, and lipid profile for an average period of 13.4 years. Metabolically healthy abdominal obese individuals had 40% higher mortality compared with metabolically healthy nonabdominal obese ones. Moreover, the metabolically healthy abdominal obese had lower mortality compared with the metabolically unhealthy abdominal obese, but without statistical significance [8].

Yet, one should bear in mind that metabolically healthy abdominal obese do not represent 'healthy' individuals. When compared with metabolically unhealthy abdominal obese persons they are less severely obese, lead a healthier lifestyle, and have a more positive health perception. But their risk for all-cause mortality is significantly increased versus that of metabolically healthy nonobese. This leads to the conclusion that enlarged waist circumference without metabolic disorders is an intermediate stage and it is important to avoid abdominal obesity [8].

#### **Metabolically healthy obese and diabetes mellitus**

The extent to which the MHO phenotype is associated with a lower risk for adverse health outcomes remains the subject of debate. When it comes to metabolic status phenotypes and diabetes mellitus, MHO and metabolically unhealthy normal-weight individuals appear to have an equivalent risk. The MHO have higher risk for CVD and this risk is no different from that in the MUO. This suggests that obesity outweighs the impact of metabolic status for risk for CVD. However, the pattern is different for type 2 diabetes where, although the MHO group had higher risk compared with the normal-weight metabolically healthy phenotype, as reported previously, their risk was significantly lower than that of the MUO group. Thus, for type 2 diabetes, for which metabolic health is an important predictor, the risk in the MHO group is lower than that in the MUO group. The MHO phenotype carries less risk for diabetes mellitus when compared with the MUO phenotype, even though the risk is greater than that in MHNW individuals [9].

The challenge is to understand how metabolic health is defined and what health outcome is taken into

consideration? Given the prevalence of the MHO phenotype in obese populations, emphasis is being increasingly placed on understanding the characteristics and potential mechanisms underlying their healthy metabolic profile. MHO does not appear to be a benign condition, making it important to promote prudent weight loss in overweight/obese individuals and control of modifiable risk factors.

Furthermore, considering a worldwide prevalence of ~200 million people with MHO, the absolute risk increase of 0.7% over 10–11 years associated with this condition converts to 1.4 million incident deaths or CV events over this time [6].

The analysis of the 33 939 young men (mean age:  $30.9 \pm 5.2$  years) of the Metabolic, Lifestyle and Nutrition Assessment in Young Adults cohort published by Twig *et al.* [10] showed that, among young men, an abnormal BMI is associated with increased risk for diabetes, independent of the cluster of metabolic abnormalities. In fact, compared with MHNW young adults, those who were overweight or obese, with no Adult Treatment Panel-III, metabolic abnormalities had nearly two- and four-fold higher risk for incident diabetes, respectively.

As the definition of MHO varies among studies and is inconsistent whether it encompasses individuals with one or even two metabolic abnormalities, the study of Twig *et al.* [10] argues against using such definitions as metabolic ‘healthiness’ given that an increase of 35–67% in diabetes risk is observed in patients with one metabolic abnormality compared with MHO individuals. This is especially important in young adults, in whom diabetes risk attributed to increased levels of fasting plasma glucose, triglycerides, or white blood cells could be demonstrated already within what is currently considered to be the normal range for these parameters. Their results reflect that inflammatory burden as reflected by the white blood cell count may not be a required mediator for diabetes onset among obese young adults. The independent role of obesity in mediating diabetes incidence even among individuals with normoglycemia, no evidence of dyslipidemia, and with normal blood pressure is controversial. Although obesity seems to mediate the incidence of diabetes, independent of the classic risk factors, it may still be mediated by significant insulin resistance and/or  $\beta$ -cell dysfunction that have not yet resulted in dysglycemia or dyslipidemia. In addition, it has also been demonstrated that diabetes risk associated with a positive family history of the disease may be mediated, at least in part, by obesity [11]. Thus, overweight and obesity allow for an increased risk for diabetes at any BMI status, including young obese adults with no other recognizable diabetes risk factors [10].

Particular focus should be placed upon individuals with metabolic unhealthy status despite normal weight. This group had a similar rate of events as that in their

metabolically unhealthy overweight and obese peers [6]. A possible explanation could be that this group might represent the most severe subtype along the phenotypic spectrum of individuals genetically predisposed to CVD, such that they have poor metabolic features, even without excess weight. This concept is supported by the surprising observation that this group had the highest weighted mean difference in low-density lipoprotein cholesterol and glucose levels compared with the MHNW group (even higher than their metabolically unhealthy overweight and obese peers) [7].

### Social implications

Current guidelines recommend lifestyle modifications directed at minimizing visceral fat accumulation as a fundamental public health measure. However, it is not completely elucidated whether MHO individuals would also benefit from traditional lifestyle interventions that focus on dietary changes and increased physical activity. A study published by Karelis *et al.* [12] suggested that MHO people react differently from a metabolic point of view to a 6-month calorie-restricted diet compared with ‘at risk’ obese individuals despite achieving similar weight loss, thus supporting the theory that MHO and non-MHO individuals require different treatment approaches. Although the public health message regarding obese patients remains promoting a healthy lifestyle, the controversial results surrounding interventions for MHO individuals justify prioritizing, for cost-efficacy reasons, intensive interventions in metabolically abnormal obese individuals and monitoring MHO individuals for early detection of the development of metabolic abnormalities [13].

### Conclusion

Debate has been raging whether MHO individuals are truly ‘healthy’ or whether they remain healthy as the years go by. Yet, there is growing evidence that obese adults without metabolic risk factor clustering (the healthy obese) progress to unhealthy obesity over time. Ultimately, the natural course of MHO is progression toward metabolic deterioration [14]. However, further studies are necessary to better understand the protective metabolic and genetic factors that contribute to the creation of the so-called MHO individual.

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#### Conflicts of interest

There are no conflicts of interest.

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