



# Metabolically Healthy Obesity: Criteria, Epidemiology, Controversies, and Consequences

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## Abstract

**Purpose of Review** To present a comprehensive overview regarding criteria, epidemiology, and controversies that have arisen in the literature about the existence and the natural course of the metabolic healthy phenotype.

**Recent Findings** The concept of metabolically healthy obesity (MHO) implies that a subgroup of obese individuals may be free of the cardio-metabolic risk factors that commonly accompany obese subjects with adipose tissue dysfunction and insulin resistance, known as having metabolic syndrome or the metabolically unhealthy obesity (MUO) phenotype. Individuals with MHO appear to have a better adipose tissue function, and are more insulin sensitive, emphasizing the central role of adipose tissue function in metabolic health. The reported prevalence of MHO varies widely, and this is likely due the lack of universally accepted criteria for the definition of metabolic health and obesity. Also, the natural course and the prognostic value of MHO is hotly debated but it appears that it likely evolves towards MUO, carrying an increased risk for cardiovascular disease and mortality over time.

**Summary** Understanding the pathophysiology and the determinants of metabolic health in obesity will allow a better definition of the MHO phenotype. Furthermore, stratification of obese subjects, based on metabolic health status, will be useful to identify high-risk individuals or subgroups and to optimize prevention and treatment strategies to compact cardio-metabolic diseases.

**Keywords** Obesity · Metabolic syndrome · Metabolically healthy obesity · Metabolically unhealthy obesity · BMI · Visceral adiposity

## Introduction

Obesity is defined by excess body fat and is a current health epidemic associated with increased risk for type 2 diabetes and cardiovascular disease (CVD) [1, 2]. In clinical practice, obesity is assessed by the body mass index (BMI), calculated as weight (in kilograms) divided by height (in meters squared), and categorized using the WHO classification [3] (Table 1). Population studies have shown a progressive increase in cardio-metabolic risk with increasing BMI [4].

However, although obese subjects, as a group, are at increased risk for cardio-metabolic complications compared with normal-weight subjects, not all obese individuals will ultimately develop these complications [5].

Evidently, the BMI does not take into account the heterogeneity of body fat distribution, associated with increased risk for CVD. Accumulating evidence suggests that for the evaluation of the risk associated with obesity in an individual patient, body fat distribution must be taken into consideration as it is a key driver of cardio-metabolic risk associated with any given amount of body fat [5, 6].

Adipose tissue is commonly categorized into two main types: white adipose tissue (WAT) that stores energy in the form of triglycerides, and brown adipose tissue (BAT) that is responsible for energy dissipation during cold exposure (i.e., non-shivering thermogenesis) and is primarily located in the interscapular region [7]. WAT makes up the main mass of adipose tissue in human adults and is located mainly in subcutaneous regions and surrounding internal organs (visceral adipose tissue, VAT). Fat deposition in visceral depots makes

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**Table 1** WHO classification of obesity

Classification	BMI (kg/m <sup>2</sup> )	Health Risk
Underweight	< 18.5	Increased
Normal weight	18.5–24.9	Least
Overweight	25.0–29.9	Increased
Obesity grade I	30.0–34.9	High
Obesity grade II	35.0–39.9	Very high
Obesity grade III	> 40.0	Extremely high

obese individuals more prone to complications than subcutaneous fat. Evidently, excess visceral fat deposition is a key phenotype associated with a cluster of metabolic abnormalities, including hypertension, atherogenic dyslipidemia, and impaired glucose metabolism that confer an increased risk for type 2 diabetes (T2DM) and CVD [6].

The clustering of metabolic abnormalities, occurring in the same individual, has been termed metabolic syndrome (MS) or insulin resistance syndrome [8, 9]. Insulin resistance, a core feature of the MS, is strongly associated with visceral obesity and may link the individual components of the syndrome. A number of clinical criteria have been put forward by various organizations to define the MS and to identify high-risk individuals [10–14] (Box 1).

However, the clinical usefulness of the MS has been questioned after reports that the syndrome does not predict CVD risk better than the sum of its components [15]. The inability of MS to be used as a CVD risk calculator has led to the introduction of the cardio-metabolic risk, which is the global risk of CVD resulting from the presence of traditional risk factors together with the possible added contribution of emerging factors such as visceral obesity /ectopic fat and features of the MS [16].

It must be noted that insulin resistance refers to the anabolic actions of insulin on energy metabolism in its target tissues, i.e., the muscles, liver, and adipose tissue, but it does not involve the mitogenic effects of insulin, such as the stimulation of cell growth and the anti-apoptotic effects. Thus, in individuals with MS/insulin resistance syndrome, the underlying insulin resistance is accompanied by compensatory hyperinsulinemia, implying that such individuals exhibit not only the metabolic manifestations from the insulin resistance but also the mitogenic manifestations of hyperinsulinism, including acanthosis nigricans and skin tags [17].

It is believed that visceral rather than subcutaneous adiposity is associated with resistance to insulin action. Furthermore it is recognized that it is not merely an increase in adipose tissue mass that directly leads to attenuation of insulin action but rather adipose tissue dysfunction and the resultant ectopic lipid deposition and pro-inflammatory state that both may activate the insulin resistance mechanism in insulin target tissues, ultimately leading to the manifestations of the MS [5, 6].

In this context, a subgroup of obese individuals does not appear to be at increased cardio-metabolic risk. These individuals are said to have the “metabolically healthy or insulin-sensitive obese” (MHO) phenotype, in contrast to metabolically unhealthy or insulin-resistant obese (MUO) individuals that exhibit the phenotype of MS [18].

The aim of this review is to appraise the literature regarding the concept of “metabolic health” in obese individuals. We will analyze the diagnostic criteria and the epidemiology of this obese sub-phenotype and critically discuss the controversies and the implications regarding the actual existence and the natural history of this entity.

## Criteria

The term MHO applies to individuals who are obese (BMI > 30 kg/m<sup>2</sup>) and in whom cardio-metabolic risk factors are (largely) absent. The use of the term “metabolic health” implies that individuals are not at an increased risk of cardio-metabolic complications compared with normal-weight individuals [18]. Currently, there are not universally accepted criteria to identify individuals with MHO. In addition to BMI, the criteria used in most studies to define metabolic health are frequently based on 1) absence of the MS and 2) insulin sensitivity. The absence of MS in obese individuals has most commonly been used to define MHO. Although various definitions of the MS have been considered, most investigators include measures of blood pressure, triglycerides, HDL-cholesterol, and plasma glucose levels [18–21] (Table 2). However, the absence of the MS alone does not exclude the presence of individual risk factors. More importantly, the absence of all components of the MS has rarely been considered for the diagnosis of MHO. Also, the influence of lifestyle, gender, ethnicity, and age on the phenotype of MS is generally accepted but these variables are not included in the current criteria. Furthermore, not all metabolic health definitions include insulin resistance indices, whereas others consider inflammatory markers and cardio-respiratory fitness [22–25]. In addition, using BMI to define obesity can also be misleading. First, BMI cannot distinguish between fat and lean tissue or provide information on body fat distribution. Thus, an individual with high BMI may have increased muscle mass and be physically fit or may have increase fat mass but very little accumulation in visceral fat depots [26].

The need for harmonizing MHO definitions has been addressed recently by the BioShare-EU project, an international collaboration between European and Canadian institutes and cohort studies [27]. In the Healthy Obese Project, data from more than 163,000 individuals in ten population-based cohort studies from different countries in Europe have been evaluated to characterize clinical and metabolic factors associated with MHO and compare key characteristics defining MHO. In

**Table 2** Criteria used for the definition of metabolically healthy obesity

Criteria	Meigs [18]	Karelis [17]	Aguilar-Salinas [19]	Wildman [20]
WC, cm	≥ 102 (M) ≥ 88 (F)	-	-	-
FPG, mg/dL	≥ 100 or treatment	-	< 126 and no	≥ 100 or treatment
BP, mmHg	≥ 130/85 or treatment	-	< 140/90 and no	≥ 130/85 or treatment
TG, mg/dL	≥ 150	< 150	≥ 150	≥ 150
HDL, mg/dL	< 40 (M) < 50 (F)	≥ 50	≥ 40	< 40 (M) < 50 (F)
HOMA-IR	-	< 1.95	-	90th percentile
Others	-	TC < 200 mg/dL LDL < 100 mg/dL	-	hsCRP < 90th percentile
MHO criteria:	< 3 of the above	≥ 4 of the above	All of the above	< 2 of the above
BMI, kg/m <sup>2</sup>	≥ 30	≥ 30	≥ 30	≥ 30

WC, waist circumference; FPG, fasting plasma glucose; BP, blood pressure; TG, triglycerides; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; MHO, metabolically healthy obesity; BMI, body mass index

addition to the current WHO classification of obesity, (BMI > 30 kg/m<sup>2</sup>), the harmonization effort in the Healthy Obesity Project used four parameters based on the NCEP ATP III criteria [10] to define the metabolic phenotype (Table 3).

## Epidemiology

### Prevalence of MHO

The main problem in estimating the prevalence of MHO is the lack of consensus regarding its definition. Evidently, the proportion of obese subjects diagnosed to have MHO varies considerably depending on the criteria used to define MHO. Thus, using data from the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of MHO varied between 47% when classified based on the absence of the MS as defined by the ATP III criteria, 32% based on insulin sensitivity (using HOMA-IR cut-off of 2.5), and 10% if classified based on all components of the MS being absent. Furthermore, there seems to be only partial overlap between various definitions in identifying those with MHO, thus only approximately one-third of those diagnosed being MHO

based on insulin sensitivity were also identified as being MHO based on absence of MS [28]. Furthermore, the findings that approximately half of obese subjects are MH when classified using DEXA for the measurement of body fat percentage compared with approximately one-third using BMI suggest that caution should be used how obesity is defined [29].

The prevalence of MHO has been examined in the BioShare-EU project. Among 11,465 men and 16,612 women with obesity, age-standardized prevalence on MHO was 12% across all cohorts, with great variation between cohorts from different regions of Europe. For men, the highest prevalence of MHO (19%) was found in the CHRIS study from Italy, followed by the KORA study (13.5%) from Germany. MHO prevalence was in general higher in women compared with that in men. The BioShare-EU project also demonstrated that the prevalence of MHO decreases significantly with age in both genders, independent of geographic region and MHO criteria applied [27]. These data are at least suggestive that MHO represents a transient phenotype. A systematic review, based on the prevalence of different variables among studies, reported that the prevalence of MHO ranged from 6 to 75%, and this may vary according to several socio demographic variables such as gender, age, and race/ethnicity. Thus, the

**Table 3** Criteria for harmonizing MHO definitions in the BioShare-EU project

Criteria	Thresholds
Blood pressure	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or use of antihypertensives
Blood glucose	≥ 110 mg/dL or use of antidiabetic medications
HDL-cholesterol	< 40 mg/dL in men or < 50 mg/dL in women or treatment
Triglycerides	> 150 mg/dL or medication for elevated triglycerides
Diagnosis of CVD	Yes

Metabolically healthy obesity is defined as having BMI ≥ 30 kg/m<sup>2</sup>, none of the criteria of MS, and no cardiovascular disease

prevalence of MHO was higher in women and younger aged subjects, and regarding race/ethnicity, the prevalence was higher in Asian populations compared with Caucasians or multi-ethnic groups [30].

The observed differences in MHO prevalence reported in the comparative studies and meta-analyses highlight the need for larger-scale population-representative studies, improved obesity classification, and a global consensus on standardized MHO criteria.

### The Natural History of MHO—Is MHO a Stable Condition?

A major point of content of the MHO concept relates to its natural history and whether MHO represents a stable or a transient phenomenon. MHO was initially thought as a static condition, but although some individuals can maintain their metabolic health status over time, it is becoming increasingly evident that MHO status is transient in nature [31]. This has been confirmed by studies with follow-up up to 10 years, the majority of which suggested that between one-third and half of individuals with MHO convert to an unhealthy phenotype [31, 32, 33, 34]. Very few studies have been conducted over longer time periods. In the Whitehall III study, about half of initially healthy obese individuals converted to an unhealthy phenotype over 20 years [31]. This number was larger in the Nurses' health study, where only 16% and 6% of women with MHO remained metabolically healthy after 20 and 30 years, respectively [28]. Interestingly, metabolic health is also a transient phenomenon among normal-weight individuals. Thus, while about 60% of individuals with normal weight were found to remain metabolically healthy after 10 years of follow-up in a number of cohort studies, only about 30% remained metabolically healthy after 20 years in the Nurses' Health Study and about 15% remained metabolically healthy after 30 years of follow-up [32, 33, 34]. Again, the use of different definitions of MHO makes comparisons across studies problematic. Evidently, however, MHO appears to be a transient phenotype.

Since accumulating evidence suggests that MHO is not a stable condition, researchers have focused on the variables that can predict metabolic transition from MHO to MUO. Thus, a study from Spain reported that increase in BMI, waist circumference, and waist-to-hip ratio was among the factors that predicted the transition from MHO to MUO [35, 36]. On the other hand, adherence to a healthy lifestyle including a healthy diet, high level of physical activity, and no smoking, were among the factors that helped prevent the transition. Another study demonstrated that nearly two-thirds of Japanese Americans with MHO developed MUO over 10 years. A higher conversion was associated with female gender, greater visceral adiposity, higher fasting insulin levels, and lower HDL-cholesterol levels at baseline. The features

that appear to preserve metabolic health in individuals with MHO include a healthier lifestyle, less visceral and ectopic fat deposition, lower levels of inflammation, and greater insulin sensitivity [37, 38]. Therefore, sustaining these factors in MHO individuals may help prevent the progression to MUO phenotype. Collectively, these findings suggest that MHO may evolve over time to MUO.

### MHO and Long-Term Health Outcomes. Does the MHO Phenotype Have a Favorable Prognosis?

Several studies have indicated that individuals with MHO are at a lower risk of T2DM, CVD, and mortality compared with subjects with MUO and are not at elevated risk compared with normal-weight individuals. However, not all studies support this view, and so the prognostic value of MHO remains a subject of debate [39, 40].

### MHO Phenotype and Risk of Type 2 Diabetes

Some studies have reported that individuals with MHO are at higher risk of type 2 DM than metabolically healthy subjects with normal weight [41–43], whereas other studies have refuted these results [44, 45]. In this context, a recent meta-analysis has determined that subjects with MHO were at more than 4 times greater risk of developing T2DM over time than healthy normal-weight adults, although the risk was about half that of MUO individuals [46]. Compared with Caucasians, Asians have a lower BMI, but a higher risk of developing T2DM for a given BMI. In a Korean population study, the authors reported that subjects with MHO are at a higher risk of T2DM [47]. The risk in the MHO group varied according to the degree of systemic inflammation (as determined by high-sensitivity C-reactive protein (hsCRP) levels), as well as the degree of fatty liver disease (determined by the fatty liver index, a simple scoring system that detects fatty liver disease) [48]. These findings suggest that MHO subjects are metabolically heterogeneous (see the “MHO Phenotype and Risk of Subclinical CVD” section) in terms of developing T2DM.

### MHO Phenotype and Risk of Subclinical CVD

Several studies have assessed the risk of subclinical atherosclerosis in MHO subjects. They have reported that overweight or obese middle-aged metabolically healthy women had greater subclinical CVD burden, including carotid artery intima-media thickness (IMT), aortic pulse wave velocity, and coronary and aortic calcification compared with normal-weight women [48, 49]. Another study reported that individuals with MHO (defined by the degree of insulin sensitivity using euglycemic hyperinsulinemic clamp) had a metabolic and CVD risk profile, including carotid IMT that was intermediate between those of normal weight insulin-sensitive

subjects and insulin-resistant obese subjects [50]. Interestingly, the association between MHO and carotid IMT was modified by cardio-respiratory fitness [51]. Similarly, MHO subjects were at a different risk of coronary atherosclerosis progression, as measured by CAC score, according to the presence of ultrasound-based fatty liver disease [52]. Again, the above findings indicate that MHO subjects may be heterogeneous in terms of subclinical CVD risk.

We have recently compared the profile of circulating monocyte subsets (macrophage precursors) as measured by using flow cytometry, between three groups of adult individuals: a group with MHO, another group with MUO, and a control group of healthy normal-weight individuals. The proportion of pro-inflammatory monocyte subsets in the group of MHO subjects was found to be lower than in the subjects with MUO but higher than that in the normal control group [53], suggesting that MHO individuals are not devoid of cardio-metabolic risk.

### MHO Phenotype and Long-Term CVD Risk

The long-term association of MHO and CVD has been investigated by several studies, and the results were conflicting. While some studies reported no increased risk of CVD among MHO individuals, several other studies have shown an increased CVD risk in this group [54–59, 60]. Thus, in the Framingham Offspring Study, 11-year follow-up of 2902 men and women showed that MHO subjects do not have an increased risk for CVD [54]. Similarly, a report from the Women's Ischemia Syndrome Evaluation (WISE) Study showed that the presence of MS, but not BMI, predicted 3-year risk of cardiovascular death among women referred for angiography [55]. Furthermore, a large prospective study of 25,626 women age 45 years and older, followed up to 10 years, found that MHO individuals were not at increased risk of CVD [56]. This study also showed that the presence of the MS conferred a higher risk of developing CVD than BMI. In a similar way, a study of 5314 middle-aged to elderly individuals from the prospective population-based Rotterdam study reported that the presence of obesity without MS did not confer a higher risk of CVD [57]. However, MS was strongly associated with CVD risk and was associated with increased risk in all BMI categories. In fact, the presence of MS explained 71.3% of the risk attributed to BMI in association with CVD. In contrast with these studies, in a 17-year follow-up study, including men and women aged 35–55 years, the authors reported that MHO subjects were at increased risk of incident CVD, compared with normal-weight subjects without MS [58]. Moreover, these authors revealed a gradual increased CVD risk for overweight and obese individuals compared with normal-weight subjects, irrespective of the presence or absence of MS. Similarly, a short follow-up (median 3.6 years) study of 71,527 men and women aged 20–100 years

showed that both in individuals with and without MS, there was increased incidence of CVD going from normal weight to overweight to obesity [59]. Furthermore, in this study, MS explained only 12% of the risk attributed to BMI in association with CVD. In a recent large prospective study of approximately 3.5 million individuals, accruing 165,302 CVD events during 5.4-year average follow-up, the authors found that individuals who are obese and classified as metabolically healthy (either no metabolic abnormalities, 1 or 2) are still at an increased risk for CHD, cerebrovascular disease, and heart failure compared with normal weight, with no metabolic risk factors, individuals [60].

More recently, among 6809 participants of the Multi-Ethnic Study of Atherosclerosis (MESA), the authors investigated the joint association of obesity ( $\geq 30$  kg/m<sup>2</sup>) and MS with CVD and mortality across a median of 12.2 years [61]. They reported that baseline MHO was not associated with incident CVD, compared with healthy normal-weight individuals. However, almost half of those MHO developed MS during follow-up (unstable MHO) and then had significantly higher odds of CVD, compared with those with stable MHO or healthy normal weight, although lower than those with MUO from baseline. Higher duration of MS was also significantly associated with CVD in a dose-response manner. The association between obesity and CV was strongly mediated by MS. These results imply that although stable MHO may be a lower risk state, the lack of reliable predictors for stability and the increased risk of transitioning to MUO from continuing obesity limit the use of MHO to predict future risk in the clinical setting. In addition, three meta-analyses came to the similar conclusion that MHO is not necessarily a low-risk condition and suggest that clinicians should be hesitant to reassure patients that the metabolically benign phenotype is safe, as increased risk of CVD and death has been shown [51, 62].

A significant limitation of many of the recent studies in obese subjects is the lack of information on the role of physical activity and cardio-respiratory fitness (CRF). Evidence suggests that when CRF is included in the models, individuals with MHO and relatively preserved CRF have an excellent prognosis, because fitness may be more important than fatness for predicting long-term prognosis [63]. Therefore, it appears that only those with MHO and low levels of CRF may have significantly increased risk of CVD. Indeed, in a systematic review in 7 of 7 studies that included assessments for physical activity (PA)/exercise or CRF, MHO was not associated with increased risk of CVD mortality and 6 of these 7 studies showed no increased risk of nonfatal CVD [64]. Without good assessment of PA and, preferably, assessment of CRF, the true risks associated with MHO may not be adequately assessed.

Clearly, the data on long-term impact of MHO on cardio-metabolic health and mortality risk are conflicting, which may be at least partly due to differences in study design, obesity

classification, MHO definitions, and reference groups. Also, the relative impact of metabolic health and body weight status on cardio-metabolic health outcomes and mortality is yet to be fully clarified and requires further investigation.

## Controversies

The concept that an individual can be obese yet metabolically healthy has been highly controversial and widely debated in the literature. Based on epidemiological evidence that MHO individuals 1) tend to develop cardio-metabolic complications and transition to unhealthy phenotype more frequently than their normal-weight counterparts and 2) have greater incidence of CVD mortality and morbidity outcomes, the critics have dispelled MHO as an unhelpful and misleading construct [65•]. On the other hand, the proponents maintain that MHO is a novel concept that stratifies obese individuals according to their metabolic status [66•].

The lack of a standard definition of metabolic health and obesity as well as the dynamic nature of MHO may have contributed to these contradictory reports. It appears that a subgroup of MHO individuals may have a better prognosis. The characteristics of which have been described in the literature [23]. However, the currently used criteria are insufficient to detect these individuals.

## Characterization and Determinants of Metabolic Health Status

Accumulating evidence from several recent studies has increased our understanding of the potential biological, environmental, and genetic factors as determinants of metabolic health that distinguish MHO from obesity per se and from MUO.

## Role of Adipose Tissue Function in Metabolic Regulation

Metabolically healthy state reflects normal metabolic regulation, which in turn is largely dependent on normal adipose tissue function, in response to nutrient supply. The normal adipocytes have two main functional roles: First, adipocytes store triglycerides, synthesized from fatty acids and glucose after food digestion, under the anabolic action of insulin. Second, during fasting, triglycerides undergo lipolysis, under the catabolic action of glucagon, and release FFAs, through the portal circulation, to the peripheral tissues, in order to be used as energy fuel (through  $\beta$ -oxidation) by the peripheral cells [66•, 67–69]. This lipo-regulatory function is controlled by the adipocytes themselves through the secretion of adipokines such as adiponectin and leptin, which enhance  $\beta$ -

oxidation of FFAs in the mitochondria of the peripheral cells [70].

Dysfunction of adipose tissue, regarding its lipid storage and lipo-regulatory role, may change the dynamics between FFA release and their oxidation in peripheral tissues. It should be noted that the non-adipose tissue cells have limited capacity for storing FFAs in the form of triglycerides, so the FFAs that arrive to peripheral tissues should be mainly oxidized. If this capacity is exceeded, then bioactive lipid metabolites accumulate into these cells, causing lipo-toxicity and leading to insulin resistance (as will be seen below) [71].

In conditions of excess nutrient intake, the storage capacity of adipose tissue depends on the number of normally functioning adipocytes and the capacity to expand through adipocyte hyperplasia. Evidently, the maximal expandability of subcutaneous adipose tissue is limited and, for every individual, is depended on genetic and environmental factors [72].

If the adipose tissue cannot exert its normal storage and lipo-regulatory function, this may then lead to the development of metabolic deregulation with resultant insulin resistance and its cardio-metabolic consequences [73]. This may occur under the following circumstances: 1) in the extreme phenomenon of “supersizing,” when the existing adipocytes are overwhelmed with energy surplus that far exceeds their normal storage capacity, resulting in overflow of lipids to peripheral tissues [74]; 2) in congenital or acquired forms of lipodystrophy in which the number of adipocytes is too low to store even normal fat intake that is then stored in non-adipose tissues [75]; 3) in the case of visceral obesity when, under conditions of excess nutritional intake, the adipocytes become hypertrophic and dysfunctional, leading to lipid deposition in peripheral tissues. This applies to MS/insulin resistance syndrome [76]; and 4) if there is mitochondrial dysfunction, due to aging or genetic factors that results in reduced capacity for  $\beta$ -oxidation of FFAs and accumulation of non-oxidized lipids in peripheral tissue cells [77].

## Ectopic Fat Deposition and Insulin Resistance

In conditions of positive energy balance, the subcutaneous adipose tissue may fail to expand further through hyperplasia in order to store safely the excess energy. Then, fat is deposited in visceral adipocytes that, because their hyperplastic potential is limited, soon become hypertrophic and dysfunctional. As a result, there is an overflow of FFAs into the portal circulation and uptake by the liver or muscle cells and other peripheral tissue cells [78]. As mentioned earlier, the FFAs inside the peripheral non-adipose tissue cells should be oxidized in the mitochondria, because their storage capacity for triglycerides is limited. Thus, the increased flux of FFAs into, for example, the muscle cells, in the absence of adiponectin, far exceeds the ability for their oxidation in the mitochondria, and this is followed by saturation of their storage pathway to

become triglycerides, ultimately leading to intracellular accumulation of intermediate lipid metabolites. The latter then may activate the mechanism of insulin resistance in these cells [79]. It is believed that the mechanism of lipid-induced insulin resistance in these insulin target tissue cells would serve as a protective mechanism against further intracellular lipid accumulation that, if not stopped, could lead to cellular stress and apoptosis (lipo-apoptosis) [80].

In this context, accumulation of lipid metabolites in the liver (hepatic steatosis) would lead to hepatic insulin resistance and consequent increase in hepatic production of glucose and triglycerides. On the other hand, lipid accumulation into muscle cells may cause muscle insulin resistance. Moreover, ectopic lipid deposition in the pancreatic islets may induce  $\beta$ -cell dysfunction and apoptosis, ultimately leading to the development of T2DM in genetically susceptible individuals [81–84].

### Low-Grade Inflammation and Insulin Resistance

There is evidence that dysfunctional hypertrophic adipocytes may secrete various pro-inflammatory cytokines including  $IL-1\beta$  and  $TNF-\alpha$  as well as chemokines such as MCP-1. The latter may attract circulatory monocytes into adipose tissue where they become activated adipose tissue macrophages (ATMs). These ATMs are polarized to a pro-inflammatory, M1-like phenotype and secrete pro-inflammatory cytokines, ultimately leading to systemic low-grade inflammation [85]. The pro-inflammatory cytokines in turn, acting in a paracrine way, in insulin target tissue cells, may activate intracellular inflammatory pathways (such as  $NF-\kappa\beta$ ) that are known to induce insulin resistance on these cells [85, 86]. This may provide another mechanism for the inflammation-induced component of insulin resistance. In conclusion, therefore, ectopic fat deposition and low-grade inflammation constitute the two main mechanisms that may contribute to the development of insulin resistance and the manifestations of the MS in subjects with visceral obesity and dysfunctional adipose tissue.

### Role of Lifestyle Factors and Cardio-Respiratory Fitness

Evidence exists that lifestyle habits might partly explain the heterogeneity of obesity in terms of metabolic abnormalities. It was reported that adopting four healthy habits, i.e., moderate alcohol intake, not smoking, 30 min of exercise daily, and eating 5 or more servings of vegetables and fruits daily, even individuals classified as overweight or obese by BMI can have the same overall mortality risk as normal-weight subjects [87].

Mechanistically, lifestyle may modulate whole body energy metabolism as suggested by the evidence that concurrent physical activity increases mitochondrial oxidation of free fatty acids in the peripheral tissues during high calorie intake

[88]. In this context, MHO individuals were shown to have a lower fasting respiratory quotient, that is, higher cardio-respiratory fitness, compared with MUO subjects [89]. Also, the same study showed that insulin sensitivity is positively associated with the ability to extract energy from fat [89]. Higher levels of cardio-respiratory fitness have been independently associated with healthier metabolic profiles and reduced CVD risk [25]. Thus, a high fitness level despite being obese—a phenotype frequently referred to as “fit and fat”—is associated with less visceral and intrahepatic fat deposition which could mediate the beneficial effects of physical activity. Indeed, a recent study has shown that MHO participants had a better fitness level than MUO counterparts. In conclusion, a higher cardio-respiratory fitness level should be considered to be a characteristic of the MHO phenotype [64].

### Role of Genetic Factors

There is a considerable inter-individual variation in the response to excess energy intake. The amount and distribution of body fat and the number of adipocytes appear to be controlled by various factors, including sex and age but also genetic factors and epigenetic influences [90]. Both genome-wide association studies (GWAS) and gene-expression studies showed that body fat distribution is influenced by a number of genetic loci and developmental genes, independently of BMI. Indeed, WHR, a surrogate measure of fat distribution, shows significant heritability of up to  $\sim 60\%$ , even after adjusting for BMI. Recent GWAS for measures of body fat distribution revealed numerous loci harboring genes potentially regulating the distribution of adipose tissue (subcutaneous vs visceral adipose tissue). Also, developmental genes may at a very early stage determine specific fat distribution at later life. Indeed, genes such as *TBX15* not only manifest differential expression in various fat depots but also correlate with obesity and related traits. Moreover, recent GWAS identified several polymorphisms in developmental genes (including *TBX15*, *HOXC13*, *RSPO3*, and *CPEB4*) strongly associated with body fat distribution [91–93].

Genetic associations and effects clearly differ between sexes, in particular for distribution of adipose tissue to the legs and trunk. The distribution of body fat in women has previously been suggested as a causal factor leading to lower risk of cardiovascular and metabolic disease, as well as cardiovascular mortality for women in middle age. To this effect, genetic studies have identified SNPs that are associated with a favorable body fat distribution, i.e., with higher BMI but lower risk of cardiovascular and metabolic disease, emphasizing the strong sexual dimorphism in the genetic regulation of fat distribution traits [92, 93].

Besides genes, epigenetic changes, that is, inheritable modifications of gene expression, can also contribute to metabolic disturbances [94]. Thus, during endometrial life, maternal

metabolic deregulation could favor in the offspring the development of MS phenotype in adult life [95].

### Role of Chronic Stress

Under acute stress conditions, the human body activates the stress system, including the hypothalamic-pituitary-adrenal (HPA) axis, as well as the sympatho-adrenal system (SNS) with resultant increase in the secretion of glucocorticoids and catecholamines, respectively. The aim of these stress hormones is to ensure enough energy supply to the brain and peripheral tissues in the form of glucose and FFAs, respectively, to be used for a “fight or flight” response that is crucial for the survival of the individual [96]. In order for this to occur, a state of transient insulin resistance has to be induced by the stress hormones, in insulin target cells, to allow the mobilization of stored energy [97].

In today’s society, stress is more likely to be psychological and chronic rather than physical and transient but elicits the same stress response on a chronic basis with resultant chronic insulin resistance and hyperinsulinemia. However, psychological stress is not tied to an increased energy demand and the mobilized energy is restored as fat in central fat depots, resulting in central obesity and its cardio-metabolic consequences [98].

### Implications and Conclusions

It is evident that it is not the amount of adipose tissue but rather an adequate number of normally functioning adipocytes capable of expanding through hyperplasia, in response to excess nutrient intake, that determine normal metabolic regulation and consequently a metabolically healthy state. A metabolically healthy individual may have increased subcutaneous hyperplastic adiposity, in conditions of excess calorie intake, and be obese by BMI criteria, but as long as he/she can maintain normal metabolic regulation and insulin sensitivity may be characterized as having the MHO phenotype [99] (Fig. 1).

It is, therefore, expected that an individual with MHO should have no evidence of ectopic lipid deposition (normal liver enzymes and U/S, normal adiponectin, and increased cardio-respiratory fitness) or of low-grade inflammation (low hsCRP), neither evidence of insulin resistance/hyperinsulinism (absence of metabolic or mitogenic manifestations of the MS phenotype, normal HOMA-IR) [100]. Obviously, MHO cannot be a static state but rather a dynamic condition that may evolve to MUO as a result of changes in lifestyle or aging.

On the other hand, a MUO subject should have the metabolic and mitogenic manifestations as well as the metabolic abnormalities of the insulin resistance and MS [8]. Again, MUO state is not static as it may convert to MHO, as it has

been shown after bariatric surgery [100], or following treatment with the PPAR $\gamma$ -agonist pioglitazone that is known to promote adipocyte differentiation and generation of new, insulin-sensitive adipose cells [101].

In conclusion, the existence and clinical utility of the MHO phenotype has been questioned and widely debated. While the lack of a universally accepted MHO definition and the usefulness of BMI to accurately classify obesity are clearly pertinent issues, pathophysiological evidence supports the notion that metabolically healthy obesity is a novel concept. The MHO phenotype constitutes an interesting human model demonstrating the central role of adipose tissue function in metabolic health. This evidence favors the need for a conceptual shift from adipose tissue mass to adipose tissue function and lipo-regulation. However, the diagnosis of MHO at one time point does not always translate into a life-long reduced cardio-metabolic risk, although maintaining MHO is clearly beneficial for reducing CVD risk.

Finally, understanding the molecular mechanisms underlying adipose tissue plasticity and lipo-regulation may lead to novel therapeutic strategies to prevent the development of metabolic disease. In the meantime, in order to keep metabolically healthy, one should not lose sight of Hippocrates’ saying that “walking and keeping fit is man’s best medicine”.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

### Appendix

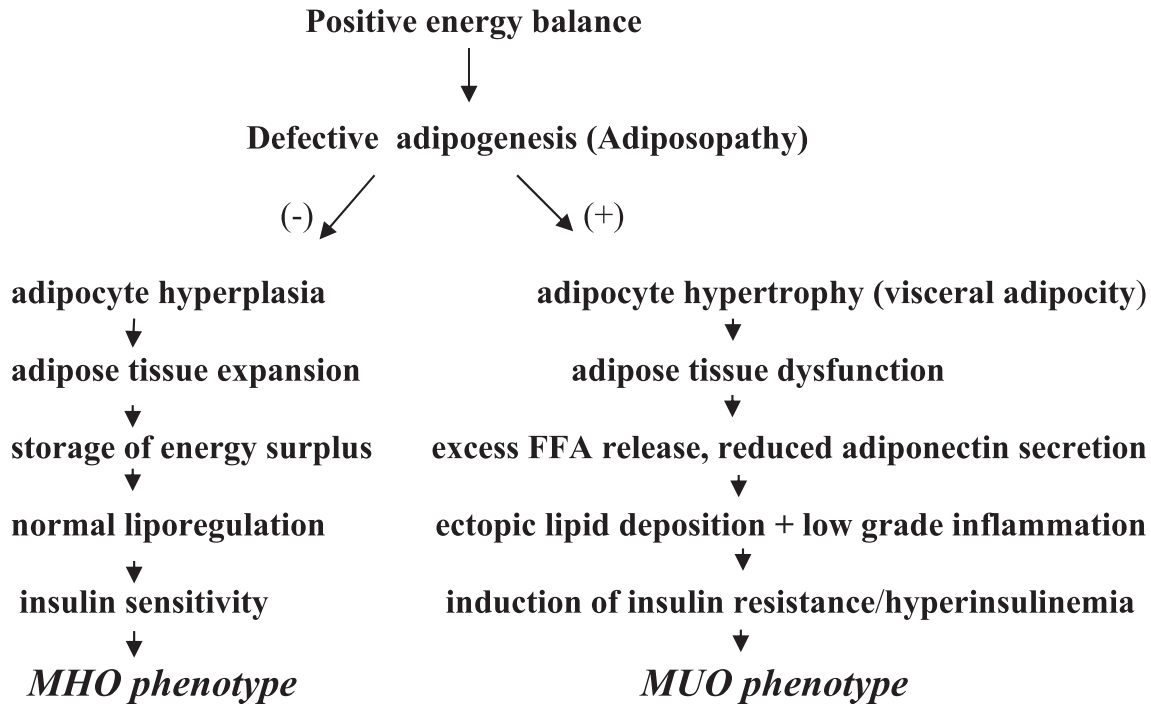
#### Box 1 Definition criteria of MS

The definition of MS is based on clustering of metabolic abnormalities in the same individual. Different sets of criteria have been proposed by different health organizations. All versions included central obesity by waist circumference, hypertension, and dyslipidemia. The first formal definition was proposed by WHO that, in addition to the three common criteria, included evidence of insulin resistance (by IGT, IFG, or T2DM) [9]. In 2001, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) proposed a new set of criteria, requiring for the diagnosis 3 of the following 5 parameters: abdominal obesity, hypertriglyceridemia, reduced HDL, hypertension, and fasting hyperglycemia [11]. Insulin resistance was not included in the criteria. In 2005, the international diabetes federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), in an attempt to reconcile the different



definitions, suggested waist circumference as prerequisite plus two of the criteria proposed by ATP III for diagnosis [12]. There was a disagreement, however, regarding the definition of abdominal obesity by waist circumference threshold, and the IDF required a narrower waist circumference (WC) that would equate to BMI = 25 kg/m<sup>2</sup>, whereas the AHA/NHLBI required a larger WC threshold (BMI = 30 kg/m<sup>2</sup>) [13]. Recently, a unifying definition has been proposed by the IDF, AHA/NHLBI, WHO,

International Atherosclerosis Society, and International Society for the Study of Obesity that includes 3 of the following 5 criteria: 1) elevated WC (specific thresholds based on population/country), 2) elevated serum TG (> 150 mg/dL) or medication, 3) reduced HDL (< 40 and < 50 mg/dL) in males and females, respectively, or medication, 4) elevated BP (systolic > 130, diastolic > 85 mmHg) or antihypertensive therapy, and 5) elevated fasting blood glucose (> 100 mg/dL) or medication [14]



**Fig. 1** Under conditions of positive energy balance, defective adipogenesis (adiposopathy) may lead to adipocyte hypertrophy and dysfunction in the visceral fat depots with resultant ectopic lipid deposition and low-grade inflammation that both can induce insulin resistance and ultimately lead to the manifestations of the MS and the

MUO phenotype. On the other hand, under the same conditions, normal adipogenesis is associated with adipose tissue expansion, through adipocyte hyperplasia of the subcutaneous fat depots and safe storage of energy and thus maintenance of normal lipo-regulation and insulin sensitivity that characterize the MHO phenotype

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