Metabolically healthy obesity: facts and fantasies

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Although obesity is typically associated with metabolic dysfunction and cardiometabolic diseases, some people with obesity are protected from many of the adverse metabolic effects of excess body fat and are considered "metabolically healthy." However, there is no universally accepted definition of metabolically healthy obesity (MHO). Most studies define MHO as having either 0, 1, or 2 metabolic syndrome components, whereas many others define MHO using the homeostasis model assessment of insulin resistance (HOMA-IR). Therefore, numerous people reported as having MHO are not metabolically healthy, but simply have fewer metabolic abnormalities than those with metabolically unhealthy obesity (MUO). Nonetheless, a small subset of people with obesity have a normal HOMA-IR and no metabolic syndrome components. The mechanism(s) responsible for the divergent effects of obesity on metabolic health is not clear, but studies conducted in rodent models suggest that differences in adipose tissue biology in response to weight gain can cause or prevent systemic metabolic dysfunction. In this article, we review the definition, stability over time, and clinical outcomes of MHO, and discuss the potential factors that could explain differences in metabolic health in people with MHO and MUO — specifically, modifiable lifestyle factors and adipose tissue biology. Better understanding of the factors that distinguish people with MHO and MUO can produce new insights into mechanism(s) responsible for obesity-related metabolic dysfunction and disease.

Introduction

Obesity is often associated with a constellation of metabolic abnormalities, including insulin resistance, prediabetes, atherogenic dyslipidemia (high plasma triglyceride [TG] and low HDL-cholesterol [HDL-C] concentrations), nonalcoholic fatty liver disease, and the metabolic syndrome, which are important risk factors for type 2 diabetes (T2D) and cardiovascular diseases (CVDs) (1, 2). However, not all people with obesity have metabolic complications, raising the question of whether those who are metabolically healthy represent a unique subset of people with obesity or are simply a group that is in transition to developing metabolically unhealthy obesity (MUO) later. In this article, we explore the premise that very few people with obesity are truly metabolically healthy, and evaluate putative modifiable factors (diet, physical activity, and sleep) and adipose tissue factors involved in determining the metabolic effects of excessive adiposity. To this end, we will provide a background to review the definition, prevalence, stability, and clinical outcomes of metabolically healthy obesity (MHO), followed by a discussion of potential factors that could explain the differences in metabolic health in people with MHO and MUO.

Definition of metabolically healthy obesity

There is no universally accepted standard for defining MHO, and more than 30 different definitions have been used in different studies (ref. 3 and Table 1). In most studies, MHO was defined as having ≤2 of the following five metabolic syndrome components: high systolic and diastolic blood pressures, high plasma TG concentration, low HDL-C concentration, high fasting blood glucose, and a large waist circumference; or ≤1 abnormal component excluding waist circumference (4). Additional criteria, including high plasma total cholesterol, LDL-cholesterol, and C-reactive protein concentrations, 2-hour blood glucose concentrations during an oral glucose tolerance test, and indices of insulin sensitivity/resistance (based on the homeostasis model assessment of insulin resistance [HOMA-IR] score [ref. 5], the Matsuda index [an index of whole-body insulin sensitivity] [ref. 6], the glucose infusion rate during a hyperinsulinemic-euglycemic clamp procedure [HECP] [ref. 7], and the insulin suppression test [ref. 8]), have also been used to determine MHO (9–24). In some studies, even people with impaired glucose tolerance, T2D, and history of CVD were considered metabolically healthy because they did not have a sufficient number of the specified metabolic abnormalities to be identified as MUO (15, 25–28). Accordingly, people who are reported as having MHO are often not truly healthy, but simply have fewer cardiometabolic abnormalities than those defined as MUO. Therefore, a more rigorous and universally accepted definition of MHO is needed to determine the true prevalence and long-term consequences of MHO and to conduct studies elucidating the mechanisms that protect some people with obesity from the adverse metabolic effects of excess body fat.

We propose a set of robust criteria to identify people with MHO (Table 2), based on (a) the absence of cardiometabolic diseases, (b) a healthy cardiometabolic blood profile, (c) normal blood pressure, (d) normal intrahepatic TG content, and (e) normal insulin sensitivity. We have divided these criteria into those that can be readily obtained in a typical outpatient clinical setting (basic criteria) and those that require more sophisticated testing

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Table 1. Examples of variability in criteria used to identify metabolically healthy obesity

Cutoff for abnormal values	Wildman (9)	Karelis (10)	Aguilar-Salinas (12)	Lynch (183)	Meigs (11)	Meigs (11)	Calori (17)
Blood pressure (mmHg)							
≥130/85	X	–	–	–	X	–	–
>130/85	–	–	–	X	–	–	–
>140/90	–	–	X	–	–	–	–
Blood pressure medications	X	–	X	X	X	–	–
Fasting TG (mg/dL)							
≥150	X	X	–	–	X	–	–
Total cholesterol (mg/dL)							
≥200	–	X	–	–	–	–	–
LDL-cholesterol (mg/dL)							
≥130	–	X	–	–	–	–	–
HDL-cholesterol (mg/dL)							
<40 in men or <50 in women	X	–	–	–	X	–	–
<50 in men and women	–	X	–	–	–	–	–
<40 in men and women	–	–	X	–	–	–	–
Lipid medications	X	–	–	X	–	–	–
Fasting TG/HDL-cholesterol ratio							
>1.65 in men or >1.32 in women	–	–	–	X	–	–	–
Fasting glucose (mg/dL)							
≥100	X	–	–	–	–	–	–
>100	–	–	–	X	–	–	–
≥126	–	–	X	–	–	–	–
100–125	–	–	–	–	X	–	–
Glucose 2-h into oral glucose tolerance test (mg/dL)							
≥200	–	–	X	–	–	–	–
Diabetes medications	X	–	X	X	–	–	–
Waist circumference (cm)							
>102 in men or >88 in women	–	–	–	–	X	–	–
HOMA-IR							
≥75th percentile in study population	–	–	–	–	–	X	–
>1.95	–	X	–	–	–	–	–
≥2.5	–	–	–	–	–	–	X
>5.13 (i.e., ≥90th percentile in study population)	X	–	–	–	–	–	–
C-reactive protein (mg/L)							
≥90th percentile in study population	X	–	–	–	–	–	–
Metabolically healthy	≤1 of above	≤1 of above	0 of above	0 of above	≤2 of above	0 of above	0 of above

Examples of other criteria used to identify MHO include: (a) Absence of hypertension, dyslipidemia, type 2 diabetes, and cardiovascular disease (82). (b) ≤2 of the National Cholesterol Education Program (NCEP) adult treatment panel (ATP) III metabolic syndrome criteria: waist circumference >102 cm in men and >88 cm in women; systolic blood pressure ≥135 mmHg or diastolic blood pressure ≥85 mmHg; fasting plasma glucose concentration ≥110 mg/dL; HDL-C concentration <40 mg/dL in men and <50 mg/dL in women; fasting plasma TG concentration ≥150 mg/dL; or treatment with antihypertensive, lipid-lowering, or glucose-lowering medications (4). (c) ≤2 of the NECP ATP III metabolic syndrome criteria revised by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) scientific statement (184) to redefine abnormal fasting glucose concentration as ≥100 mg/dL. (d) ≤2 of the AHA/NHLBI metabolic syndrome criteria revised to define waist circumference cutoff values based on population and country-specific standards (185). (e) ≤1 metabolic syndrome criteria excluding waist circumference (33, 38). (f) Zero metabolic syndrome components, except for waist circumference (50, 186). (g) Plasma C-reactive protein concentration <3 mg/L in addition to different metabolic syndrome components with or without criteria for HOMA-IR and LDL-cholesterol (16, 60). (h) HOMA-IR values: ≤2.7 (16), lowest tertile in participants with obesity (187), <25th percentile (HOMA-IR ≤1.27) (43) or <90th percentile (47) of participants without diabetes. (i) "Insulin sensitive," defined as OGTT-derived Matsuda index (6) >2.1 (18); or as ≥75th percentile of people with obesity (19); or as glucose infusion rate during a hyperinsulinemic-euglycemic clamp procedure of >8 mg/kg lean body mass/min at insulin infusion rate of 40 mU/m^2 body surface area/min (20), >70 μmol/kg body mass/min at insulin infusion rate of 40 mU/m^2 body surface area/min (21), ≥ upper tertile (≥10.5 mg/kg fat-free mass/min) at insulin infusion rate of 50 mU/m^2 body surface area/min (22), or ≥ upper quartile (≥12.62 mg/kg fat-free mass/min) at insulin infusion rate of 75 mU/m^2 body surface area/min (23) of people with obesity in the study; or as steady-state glucose concentration <100 mg/dL during fixed-rate infusion of octreotide, glucose, and insulin (24).

Table 2. Proposed criteria for defining metabolically healthy obesity

Basic criteria:	
Absence of diagnosis or therapy of cardiometabolic diseases	Absence of prediabetes, T2D, hypertension, dyslipidemia, NAFLD, CKD, or CVD; or treatment with blood pressure, lipid, or diabetes medications
Healthy cardiometabolic profile:	
Fasting TG	<95 mg/dL
HDL-C	≥40 mg/dL in men and ≥50 mg/dL in women
Fasting glucose	<100 mg/dL
2-hour OGTT glucose	<140 mg/dL
Blood pressure	<130/85 mmHg
Advanced criteria:	
Intrahepatic lipid content (for those not already diagnosed as having NAFLD)	<5% of liver volume by imaging or <5% of hepatocytes with intracellular TG by histology
Insulin sensitivity	GIR >8 mg/kg FFM/min during an HECP (insulin infusion rate: 40 mU/m^2/min)

CKD, chronic kidney disease; CVD, cardiovascular disease; FFM, fat-free mass; GIR, glucose infusion rate; NAFLD, nonalcoholic fatty liver disease; HECP, hyperinsulinemic-euglycemic clamp procedure; OGTT, oral glucose tolerance test; T2D, type 2 diabetes.

available in a research setting (advanced criteria). We propose a lower plasma TG concentration "cut-point" than that used for diagnosing the metabolic syndrome (i.e., <95 mg/dL vs. <150 mg/dL), based on the plasma TG concentration that marks the point of transition from large buoyant LDL particles to highly atherogenic, small, dense LDL particles (29). We also propose the inclusion of an assessment of insulin sensitivity, defined as the glucose infusion rate needed to maintain euglycemia during an HECP, because many people with obesity who are resistant to insulin can have a normal fasting plasma glucose concentration and normal oral glucose tolerance due to a compensatory increase in plasma insulin (30). We chose a glucose infusion rate cutoff value that was used previously to define MHO (20) and is similar to the mean value reported in people with a BMI of 25 kg/m^2 who are metabolically healthy (31).

Prevalence of metabolically healthy obesity

The prevalence of MHO depends on the criteria used to define metabolic health, whether people with T2D or CVD were excluded from the cohort a priori, and the sex, age, BMI range, and racial or ethnic background of the study population. Differences in these variables are likely responsible for the large variability in reported prevalence, ranging from 6% (32) to 60% (33) of adults with obesity when the criteria for metabolic health were based on measured variables (see Supplemental Tables 1–4; supplemental material available online with this article; https://doi.org/10.1172/JCI129186DS1), and up to 75% when based primarily on self-reported data (34). In general, MHO is more common in women than in men (35–38), in younger than in older adults (35, 36, 39), in people with BMIs less than 35 kg/m^2 than in people with BMIs of 35 kg/m^2 or higher (40), and in people of European ancestry than in those from Africa, South America, and South Asia (Indian ancestry) (39, 41). An estimate of the prevalence of MHO based on the stringency of selection criteria from studies conducted in North American and European cohorts is shown in Figure 1 and

Supplemental Tables 1–4. The prevalence of MHO, defined as "normal" insulin sensitivity (based on the HOMA-IR score) and absence of any metabolic syndrome components (excluding waist circumference), is approximately 7%, whereas half of all people with obesity can be classified as MHO when defined as ≤2 metabolic syndrome components (including waist circumference). However, it is likely that these results overestimate the prevalence of MHO in the general population, because many studies excluded people with existing cardiometabolic diseases, such as T2D and CVD (9, 11, 13, 28, 42–44).

Stability of metabolically healthy obesity over time

The normal decline in metabolic health associated with increasing age, the metabolic insult of prolonged excess adiposity, and the tendency to gain weight throughout middle age likely influence the stability of MHO. The data from longitudinal studies suggest that approximately 30% to 50% of people with MHO convert to MUO after 4 to 20 years of follow-up (25, 28, 42, 45–48). The major factors associated with the conversion of MHO to MUO are a decline in insulin sensitivity and an increase in fasting blood glucose (49). The risk of transitioning from MHO to MUO is greater in those with a high BMI, older age, evidence of more severe metabolic dysfunction (i.e., number of abnormal metabolic criteria and values that are closer to the upper limit of the normal range, and the presence of hepatic steatosis) (28, 50–52), a poor lifestyle index (a composite of diet composition, leisure time physical activity, and cigarette smoking) (53), and weight gain during the observation period (54, 55).

Clinical outcomes of metabolically healthy versus unhealthy obesity

In general, the risks of T2D, CVD, and all-cause mortality are greater in people with MUO than in those with MHO and greater in those with MHO than in those who are metabolically healthy and lean (MHL) (14, 28, 56–60). Moreover, the risks of these adverse outcomes are directly related to the number and severity of metabolic abnormalities (57, 61–66).

Type 2 diabetes

The data from most studies show that the risk of developing T2D is 5- to 20-fold greater in people with MUO than in those who are MHL (56). The risk of developing T2D is much lower in those with MHO than MUO, but is still about 4-fold greater than in those who are MHL (56), and is directly related to the number of metabolic abnormalities at baseline (61–63). In studies with a 6-year follow-up, the risk of developing T2D relative to MHL individuals was still increased in people with MHO without any metabolic syndrome components at baseline (61), but was not increased when metabolic status remained stable throughout the study (67).

Cardiovascular disease

The risk of CVD events (new-onset angina, fatal and nonfatal myocardial infarction, sudden cardiac death, fatal and nonfatal
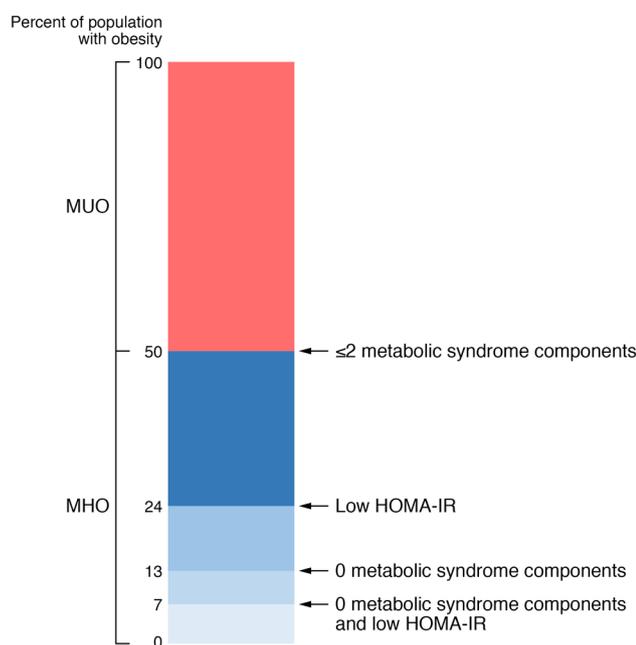
Figure 1. Estimated prevalence of metabolically healthy and metabolically unhealthy obesity among people with obesity in North America and Europe based on the number of metabolic syndrome criteria and an assessment of insulin sensitivity (using the homeostasis model assessment of insulin resistance [HOMA-IR] score). Data were derived from 33 studies involving a total of 123,548 people with obesity as described in the Supplemental Material (available online with this article; https://doi.org/10.1172/JCI129186DS1).

heart failure, and peripheral vascular disease) is lower in people with MHO than in those with MUO, but is still higher in people with MHO than in those who are MHL (57–59). A meta-analysis that pooled data from 18 studies followed over a median of 10 years found that the risk of CVD events was about 50% greater in people with MHO at baseline than in people who were MHL (14). The risk of developing CVD events is directly associated with the number of metabolic abnormalities at baseline (57) and whether the MHO phenotype remains stable or converts to MUO (28). For example, in one study, the risk of CVD events in participants who maintained a stable MHO phenotype over a median of 12 years was not different from that in participants who were MHL (28).

All-cause mortality
The risk of all-cause mortality is less in people with MHO than in people with MUO (60). The risk of all-cause mortality in people with MHO relative to those who are MHL depends on the number and severity of metabolic abnormalities and the stability of metabolic health (64–66). The combined data from five large cohort studies that followed participants for an average of 13 years found that people with MHO and no metabolic syndrome components (excluding waist circumference) did not have an increased risk of all-cause mortality compared with the MHL group; however, the risk of all-cause mortality was greater in participants with MHO versus MHL when participants with one abnormal metabolic risk factor (excluding waist circumference) were included in the MHO group (66).
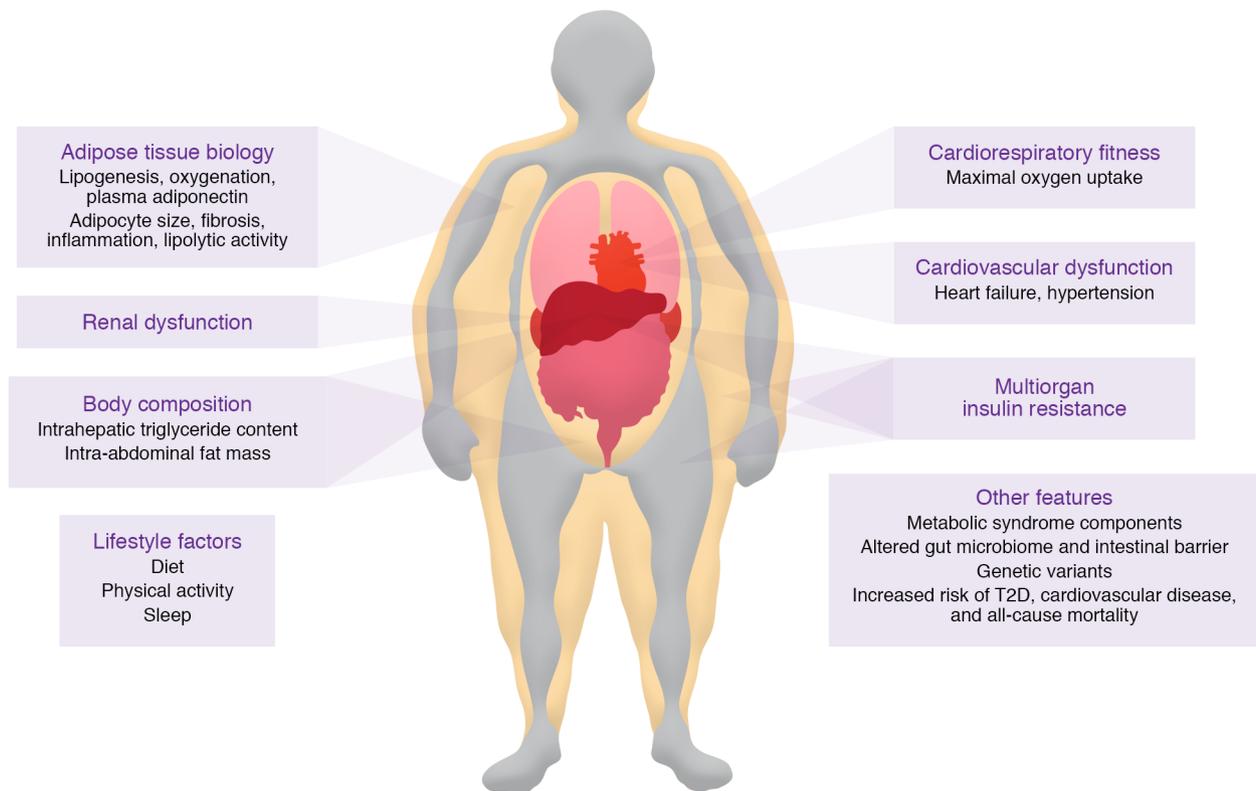
Selected characteristics of metabolically healthy and unhealthy obesity
The characteristics that have been associated with MUO are shown in Figure 2. Among these features, multiorgan insulin resistance (impaired insulin-mediated suppression of hepatic glucose production, suppression of adipose tissue lipolytic activity, and stimulation of muscle glucose uptake) is likely the most important underlying factor responsible for the development of cardiometabolic diseases (68). In people without diabetes, whole-body insulin sensitivity, assessed with the HECP, is inversely correlated with BMI; however, there is considerable heterogeneity in insulin sensitivity at any given BMI value so that a small subset of people with obesity are as insulin sensitive as people who are lean (31, 69). Insulin sensitivity is greater in people with MHO than in those with MUO, and many participants identified as having MHO are more insulin resistant than those who are MHL, manifested by greater fasting plasma insulin concentrations, blood glucose concentrations during an oral glucose tolerance test, and HOMA-IR values (9, 27, 70–72). The factors responsible for the greater preservation of insulin action in people with MHO than in those with MUO are not clear, but could be related to differences in potentially modifiable lifestyle factors and alterations in adipose tissue biology (73). In this section we review each of these areas with a major focus on adipose tissue biology.

Lifestyle factors
Diet. The relationship between dietary intake and metabolic health has been evaluated in large population studies by using the food frequency questionnaires or 24-hour dietary recall data. The ability of these methods to reliably assess dietary intake has been questioned (74, 75). The results from most studies do not show a difference in total dietary energy intake or macronutrient distribution between people with MHO and MUO (76–78). In addition, data from the US National Health and Nutrition Examination Survey showed no difference in diet quality, assessed as the consumption of Mediterranean-style and DASH-style diets, between people with MHO and MUO (79). A higher total Healthy Eating Index score, which assesses diet quality in relation to the 2005 US National Dietary Guidelines, was found in MHO than in MUO women who were 19–44 years old, but this score was not different in women with MHO and MUO who were 45–85 years old or in adult men with MHO and MUO (80). There is evidence from some (76, 77, 80–82) but not all (27, 77) studies that the consumption of specific types of foods differs between MHO and MUO groups; MHO was associated with a lower intake of sugar, sugar-sweetened beverages, and saturated fat and a higher intake of whole fruits, whole grains, and protein from vegetable sources.

Physical activity and cardiorespiratory fitness. Increased physical activity improves insulin sensitivity and metabolic syndrome abnormalities (83). The amount and intensity of physical activity in MHO and MUO populations have been studied by the doubly labeled water method, accelerometry, and activity questionnaires. No differences in total daily energy expenditure or energy expended during physical activity, measured by the doubly labeled water method, were detected between people with MHO and MUO (20, 84). In contrast, studies that measured physical activity by using accelerometers or questionnaires showed that people with

Figure 2. Putative characteristics of people with metabolically unhealthy obesity that are distinct from those of people with metabolically healthy obesity. However, the evidence to support a difference in many of these characteristics between people with MUO and MHO is not definitive because of inadequate data or conflicting results from different studies.

MHO spend more time in moderate to vigorous physical activities and less time in sedentary activities than people with MUO (35, 85–87). The results from a meta-analysis that pooled data from 15 studies found that cardiorespiratory fitness, assessed as maximum oxygen consumption during exercise, was greater in people with MHO than in those with MUO (87), but the average difference between groups was very small (1–2 mL/kg/min).

Sleep. Insufficient sleep duration and poor sleep quality have adverse effects on metabolic function (88) and are associated with obesity (89, 90). The results from nearly all studies that have assessed sleep duration and quality in people with MHO and MUO are not adequate to reliably evaluate potential differences between people with MHO and MUO, because the data are derived from questionnaires rather than direct assessments of sleep duration and quality. In general, sleep duration and the proportion of short sleepers (<7 hours per day) were not significantly different in people with MHO and those with MUO (72, 85, 91–93).

Adipose tissue biology

The expansion of adipose tissue and TG mass with weight gain (a) is not uniformly distributed among different adipose tissue depots and the liver; (b) is due to an increase in adipocyte size or adipocyte number, or both; (c) requires adequate blood supply to maintain tissue oxygenation; (d) promotes extracellular matrix (ECM) remodeling to provide the scaffolding needed to support the expanded adipocyte mass; (e) causes an increase in adipose tissue–resident immune cells and both adipose tissue and system-

ic markers of inflammation; (f) affects adipocyte lipolytic activity and the rate of release of fatty acids into the circulation; and (g) alters the production of adiponectin, the major adipocyte secretory protein involved in regulating insulin sensitivity.

Body composition. Percentage body fat is not different in people with MHO and MUO when the groups are matched on BMI and sex (19–21, 23, 94). However, there are marked differences in adipose tissue distribution and intrahepatic TG content between MHO and MUO cohorts. People with MHO have less intra-abdominal adipose tissue (IAAT) than people with MUO (21, 23, 76, 95–97), but still have two to three times more IAAT than people who are MHL (19, 22). Although women with MHO tend to have a greater amount of lower-body (subcutaneous thigh or leg) fat mass than women with MUO (20, 48, 95, 96), lower-body fat mass is not different between men with MHO and MUO (48, 96). Intrahepatic TG content is greater in people with MUO than in those with MHO (98), and those with steatosis have greater multiorgan insulin resistance (99) and higher plasma TG concentrations (100) than those with normal intrahepatic TG content, even when matched on BMI, percentage body fat, and IAAT volume (101). Taken together, these data show that excess adiposity per se is not responsible for the differences in metabolic health between people with MHO and MUO, but differences in adipose tissue distribution distinguish between MHO and MUO phenotypes.

Adipogenesis and lipogenesis. Studies that assessed adipogenesis/lipogenesis in people with MHO and MUO have focused primarily on the subcutaneous abdominal adipose tissue (SAAT)

depot. The relationship between adipogenesis (i.e., proliferation and differentiation of preadipocytes) in SAAT and metabolic health is unclear. Adipogenic capacity in SAAT, assessed by in vitro differentiation assays and expression of genes involved in preadipocyte proliferation and differentiation, is greater in people with MHO than in those with MUO (102–105). However, adipocyte proliferation rates, determined in vivo by measurement of the incorporation of ingested deuterium into the DNA of adipocytes isolated from SAAT, have been reported as either not different (106) or lower (107) in people who were overweight/obese and insulin sensitive than in people who were overweight/obese and insulin resistant. The capacity for lipogenesis in SAAT, assessed as expression of genes involved in lipogenic pathways (CD36, GLUT4, ChREBP, FASN, and MOGAT1), is greater in people with MHO than MUO (101, 102, 108, 109). Moreover, the expression of these genes is positively correlated with insulin sensitivity (108, 109), and increases more after moderate weight gain in people with MHO than MUO (110). Collectively, these data refute the notion that impaired adipogenesis contributes to insulin resistance in people with MUO (111), but demonstrate that increased adipose tissue gene expression of lipogenic pathways is associated with metabolic health.

Adipocyte size. Adipocyte size is typically measured by one of three methods: (a) histological analysis of adipose tissue; (b) collagenase digestion of adipose tissue to generate free adipocytes that are measured by microscopy; and (c) adipose tissue osmium tetroxide fixation and cell size analysis using microscopy or a Multisizer Coulter Counter. The median adipocyte diameters in SAAT measured by each of these methods correlate with whole-body adiposity (112). However, the frequency of small cells (20–50 μm range) varies considerably among the three methods (112). The highest frequency of these small cells, which are believed to be immature or differentiating adipocytes, but could be large lipid-laden macrophages (113), is observed when cell size is assessed by the osmium fixation method (112, 114). The results from several studies show an inverse correlation between average or peak subcutaneous abdominal adipocyte size and insulin sensitivity, and that adipocyte size is greater in people with MUO than in those who are metabolically healthier (21, 114–118). However, other studies did not detect a difference in average subcutaneous adipocyte size in MHO and MUO participants (102, 105, 119). Two studies identified two distinct populations of adipocytes based on size and found a higher ratio of small to large subcutaneous abdominal adipocytes in people who were insulin resistant than in those who were insulin sensitive (102, 114). In summary, the majority of studies show that mean adipocyte size is smaller in people with MHO than MUO. However, the observation that adipose tissue contains distinct small- and large-cell populations with variable cell numbers confounds the interpretation of overall mean cell size. Accordingly, more sophisticated analytical methods that quantify adipocyte cell sizes and number are needed.

Oxygenation. The oxygenation of adipose tissue depends on the balance between the rate of oxygen delivery to adipose tissue cells (adipocytes, preadipocytes, mesenchymal stem cells, fibroblasts, vascular endothelial cells, and immune cells) and their rate of oxygen consumption. The delivery of oxygen to adipose tissue is likely lower in people with obesity than in people who are lean

because of decreased systemic arterial oxygen content associated with pulmonary dysfunction (120, 121), decreased adipose tissue capillary density and perfusion (122–125), an increased number of interstitial immune cells (126), and possibly greater oxygen diffusion distance due to hypertrophied adipocytes and increased ECM content (127). However, the adequacy of adipose tissue oxygenation in people with obesity is not clear, because interstitial adipose tissue oxygen partial pressure (pO_2), not intracellular pO_2, is measured and because of conflicting data from different studies depending on the method used (120, 123–125, 128–130). Studies that used a Clark-type electrode or a fiber optic system to assess interstitial SAAT pO_2 in situ found that pO_2 was lower in people who are obese than in those who are lean (123, 124, 128, 129). In contrast, studies that used an optochemical sensor to measure pO_2 in SAAT interstitial fluid extracted by microdialysis ex vivo found that pO_2 was higher in people with obesity than in those who were lean despite decreased adipose tissue blood flow in people with obesity, suggesting decreased adipose tissue oxygen consumption in the obese group (125, 130). A direct assessment of arteriovenous oxygen balance across SAAT demonstrated that both oxygen delivery and consumption were decreased in people with obesity compared with those who were lean or overweight; however, obesity was not associated with evidence of adipose tissue hypoxia, assessed as oxygen net balance and the plasma lactate-to-pyruvate ratio across SAAT (120). We are aware of three studies that evaluated interstitial SAAT pO_2 in people with MHO and MUO. Two studies measured pO_2 in situ and found that pO_2 was greater (128), or not different (129), in the MHO compared with MUO groups. The third study measured pO_2 ex vivo in SAAT interstitial fluid extracted by microdialysis and found it was lower in MHO than in MUO (130). We are not aware of any studies that evaluated metabolic indicators of adipose tissue hypoxia, namely adipose tissue HIF1α protein content, in people with MHO and MUO. In summary, currently there is not adequate evidence to conclude there is a physiologically important decrease in adipose tissue oxygenation in people with MUO compared with MHO.

ECM remodeling and interstitial fibrosis. The ECM of adipose tissue is composed of structural proteins (primarily collagens I, III, IV, V, and VI) and adhesion proteins (fibronectin, elastin, laminin, and proteoglycans). Compared with people who are lean, people with obesity have increased expression of genes for collagen I, IV, V, and VI and histological evidence of increased fibrosis, particularly pericellular fibrosis in omental adipose tissue and SAAT (131–135). In addition, we recently found that adipose tissue expression of connective tissue growth factor (CTGF), a matricellular protein that regulates tissue fibrosis, is positively correlated with body fat mass and inversely correlated with indices of whole-body, liver, and skeletal muscle insulin sensitivity (136). Adipose tissue expression of collagen genes and collagen content are also inversely correlated with insulin sensitivity in people with obesity, and decrease with weight loss (129, 137–139). These data support the notion that adipose tissue fibrosis is associated with MUO, as has been demonstrated in rodent models (140).

Immune cells and inflammation. Obesity is typically associated with chronic, low-grade, noninfectious inflammation, which has been purported to be a cause of insulin resistance (141, 142). It has been proposed that alterations in adipose tissue immune cells

are an important cause of the chronic inflammation and insulin resistance associated with obesity (141, 143). Macrophages are the most abundant immune cell in adipose tissue, and adipose tissue macrophage content is increased in people with obesity compared with people who are lean (126). Moreover, adipose tissue macrophage content and crown-like structures (macrophages surrounding an extracellular lipid droplet) are greater in both SAAT and IAAT in people with MUO than in those with MHO; the increase in macrophage content is primarily due to an increase in M1-like (proinflammatory) macrophages (21, 144–147). Differences in adipose tissue proinflammatory CD4+ T lymphocytes between people with MHO and MUO have also been reported. The percentages of total CD4+ T cells that are proinflammatory Th17 and Th22 cells are lower in both SAAT and IAAT in people with MHO than MUO (22, 148). In addition, in one study, antiinflammatory CD4+ Th2 cells in both SAAT and IAAT correlated directly with insulin sensitivity, assessed by the insulin suppression test (149).

In conjunction with the alterations in adipose tissue immune cells, adipose tissue expression of inflammation-related genes is also greater in people with MUO than in those with MHO (21, 129, 145, 146, 150, 151), but there is inconsistency in the specific genes that are upregulated among studies, and the differences in gene expression markers between MUO and MHO groups are often small (21, 129, 145, 146, 150, 151). Plasma concentrations of markers of inflammation, primarily C-reactive protein, plasminogen activator inhibitor-1 (PAI-1), IL-6, and TNF-α, are either higher in those with MUO than MHO (21, 23, 42, 96, 152–154) or not different between the two groups (155–157). The variability in results is likely related to the definitions used to identify MUO and MHO, the specific inflammatory markers evaluated in different studies, and the sample size needed for adequate statistical power because of small mean differences in plasma concentrations between groups.

The variability and small difference in adipose tissue expression of inflammatory markers in people with MHO and MUO and both the variability and small differences in plasma markers of inflammation between people with MUO and MHO question the importance of adipose tissue production and secretion of inflammatory cytokines in mediating the difference in systemic insulin resistance observed in people with MUO and MHO. Nonetheless, it is possible that other immune cell–related mediators, such as adipose tissue macrophage-derived exosomes (158), are involved in the pathogenesis of metabolic dysfunction.

Lipolytic activity. Acute experimental increases in plasma free fatty acid (FFA) concentration, induced by infusion of a lipid emulsion, impair insulin-mediated suppression of hepatic glucose production and insulin-mediated stimulation of glucose disposal in a dose-dependent manner (159, 160). However, the influence of endogenous adipose tissue lipolytic activity and plasma FFA concentration on insulin sensitivity in people with obesity is not clear because of conflicting results from different studies. Specifically, the basal rates of FFA release into the systemic circulation and plasma FFA concentration have been reported as either greater (21, 161, 162) or not different (101, 163, 164) in people who are overweight/obese and insulin resistant compared with those who are insulin sensitive. The importance of circulating FFA as a cause of insulin resistance in MUO is further questioned by studies that found no difference in basal, postprandial, and 24-hour plasma FFA concen-

trations in people with obesity compared with those who are lean and more insulin sensitive (122, 165). The reason(s) for the differences between studies are not clear, but could be related to the considerable individual day-to-day variability in FFA kinetics and plasma FFA concentration and differences in compensatory hyperinsulinemia and insulin-mediated suppression of adipose tissue lipolytic rate in people with insulin resistance (122, 165, 166). Differences in the percentage of women between study cohorts will also affect the comparison of FFA kinetics and concentrations between MHO and MUO groups, because the rate of the appearance of FFA in the bloodstream in relationship to fat-free mass or resting energy expenditure is greater in women than in men (167, 168), yet muscle (169) and liver (170, 171) insulin sensitivity are greater in women. Taken together, these studies suggest that differences in subcutaneous adipose tissue lipolytic activity do not explain the differences in insulin sensitivity between people with MHO and MUO. However, it is still possible that differences in lipolysis of IAAT and portal vein FFA concentration (172) or differences in the effect of FFA on tissue (muscle or liver) insulin action contribute to the differences in insulin resistance between the two groups.

Adiponectin. Adiponectin, the most abundant protein secreted by adipose tissue, is inversely associated with percentage body fat and directly associated with insulin sensitivity in both men and women (173). Plasma adiponectin concentrations are often higher in people with MHO than MUO (12, 174–176). The reasons for the lower adiponectin concentration in MUO than MHO are unclear but could be related to chronic hyperinsulinemia in people with MUO, which suppresses adipose tissue adiponectin production (177, 178), thereby generating a feed-forward cycle of decreased adiponectin secretion caused by insulin resistance and increased insulin resistance caused by decreased adiponectin secretion.

Conclusions

There is considerable heterogeneity in the metabolic complications associated with obesity. About 50% of people with obesity are metabolically healthy when healthy is defined as the absence of the metabolic syndrome, whereas only approximately 5% are metabolically healthy when healthy is defined as the absence of any metabolic syndrome components and normal insulin sensitivity assessed by HOMA-IR. The risk of developing cardiometabolic diseases in people with obesity is directly related to the number and severity of metabolic abnormalities. Accordingly, people with MHO are at lower risk of future T2D and CVD than people with MUO, but most people with MHO are at a higher risk than people who are MHL. However, people with MHO who do not have any metabolic abnormalities and remain MHO over time might not have an increased risk of developing cardiometabolic diseases compared with those who are MHL. These findings support the need for a rigorous and universal definition of MHO (proposed in Table 2) to allow reliable integration of data from different studies and facilitate research needed to identify the factor(s) involved in protecting some people with obesity from the adverse metabolic effects of excess adiposity.

The precise mechanisms responsible for preserved metabolic health in people with MHO are not known. The studies to date have not demonstrated important differences in lifestyle factors (diet composition, physical activity, and sleep) between MHO and

MUO. However, this does not mean that lifestyle is not an important regulator of metabolic health, but rather underscores the limitations in the assessment of lifestyle factors and in the definition of MHO in the current studies. It is likely that there is an important genetic contribution to the metabolic phenotype in people with obesity. Although GWAS have identified genetic variants that are associated with increased adiposity in conjunction with a healthy metabolic profile (179), a better understanding of the genetic aspects of MHO will likely provide new insights into the mechanisms responsible for metabolic disease. The influence of the gut microbiome on metabolic health is a rapidly emerging area of research. The potential for adverse and beneficial effects of the gut microbiome on metabolic health could be related to the composition and diversity of the microbiota and the ability of the gut barrier function to prevent leakage of bacteria and bacterial products across the intestine (180–182). In addition, studies conducted in human subjects demonstrate an increase in markers of inflammation and interstitial fibrosis in adipose tissue in people with MUO compared with MUO. However, these studies are not able to determine whether these abnormalities are a cause or a consequence of insulin resistance and related metabolic dysfunction.

The heterogeneity in the metabolic complications associated with obesity has important clinical implications, particularly in the current era of precision medicine and cost-effectiveness. The classification of obesity by BMI status alone does not provide adequate insight into current health status, the potential risk of future adverse clinical outcomes, or who might benefit most from weight loss therapy. The available data suggest that more intensive, and presumably more expensive, weight management therapies should be prioritized for those with MUO over those with MHO. However, this approach requires a more robust diagnosis of MHO and additional data to understand the relationship between MHO and the risk of other obesity-related complications, beyond metabolic outcomes alone.

Acknowledgments

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