MECHANISMS IN ENDOCRINOLOGY

Are metabolically healthy obese individuals really healthy?

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Abstract

Obesity has become one of the major public health concerns of the past decades, because it is a key risk factor for type 2 diabetes, cardiovascular diseases, dyslipidemia, hypertension, and certain types of cancer, which may lead to increased mortality. Both treatment of obesity and prevention of obesity-related diseases are frequently not successful. Moreover, a subgroup of individuals with obesity does not seem to be at an increased risk for metabolic complications of obesity. In this literature, this obesity subphenotype is therefore referred to as metabolically healthy obesity (MHO). Importantly, individuals with MHO do not significantly improve their cardio-metabolic risk upon weight loss interventions and may therefore not benefit to the same extent as obese patients with metabolic comorbidities from early lifestyle, bariatric surgery, or pharmacological interventions. However, it can be debated whether MHO individuals are really healthy, especially since there is no general agreement on accepted criteria to define MHO. In addition, overall health of MHO individuals may be significantly impaired by several psycho-social factors, psychosomatic comorbidities, low fitness level, osteoarthritis, chronic pain, diseases of the respiratory system, the skin, and others. There are still open questions about predictors, biological determinants, and the mechanisms underlying MHO and whether MHO represents a transient phenotype changing with aging and behavioral and environmental factors. In this review, the prevalence, potential biological mechanisms, and the clinical relevance of MHO are discussed.

Introduction

The current obesity epidemic affects more than 20% of the general population in modern societies and contributes to higher mortality due to an increase in type 2 diabetes, hypertension, cardiovascular disease, stroke, as well as several types of cancer (1, 2, 3, 4, 5, 6, 7).

Although prevention of obesity-related diseases and treatment of obesity itself are important tasks, both at the individual and population level, many strategies to reduce body weight and the obesity-associated risk have not been successful (8, 9, 10). In addition, not all obese individuals
can be included into treatment programs. Therefore it could help to reduce the medical and socioeconomic burden associated with obesity treatment if those patients who will benefit the most from diet and exercise, pharmacological or bariatric surgery interventions could be identified early (11). Metabolically healthy obesity (MHO) may represent a subgroup of obese individuals in which excessive body fat accumulation does not lead to adverse metabolic effects including insulin resistance, impaired glucose tolerance, dyslipidemia, and hypertension (12, 13, 14, 15). MHO prevalence ranges from ~10 to 30% of obese individuals (13).

Noteworthy, it has been shown in different independent studies that metabolically healthy obese individuals may not significantly improve their obesity-related cardiovascular and metabolic risk by anti-obesity treatment strategies (16, 17, 18, 19, 20). It has been recently reported that 60 sedentary obese postmenopausal women, who have been defined as metabolically healthy obese, respond differently to a 6-month restricted caloric diet compared with at-risk obese people despite similar weight loss (18). In the MHO group, insulin sensitivity deteriorated by ~13%, whereas the same intervention improved insulin sensitivity significantly in the high-risk obese subgroup (18). In another study of 103 men and women with MHO, a lifestyle intervention also did not improve insulin sensitivity despite significant reductions in visceral fat mass (16). Although one previous study found improved insulin sensitivity and reduced cardiovascular risk parameters upon a 3–6 months multimodal lifestyle intervention program, the degree of insulin sensitivity in the metabolically high-risk obese group did not reach the level of MHO study participants (20). However, in these short-term intervention reductions and incidence of type 2 diabetes, cardiovascular events or mortality could not be assessed (14).

In a recent population-based prospective cohort study, including a total of 61299 men and women without evidence of cardiovascular disease at baseline, it has been demonstrated that individuals with MHO are not at increased risk of acute myocardial infarction compared with normal-weight, metabolically healthy study participants (21). On the other hand, the risk for cardiovascular events was increased among metabolically unhealthy individuals across the whole range of BMI (21). Additional observational studies support the finding that individuals with MHO are at lower risk for cardiovascular disease and all-cause mortality (22), although this is not confirmed in all observations (23). Interestingly the study also demonstrated that obesity even in the MHO subgroup is associated with an increased risk for the development of heart failure (21). Taken together, this study convincingly demonstrates that it is necessary to stratify obese patients according to MHO vs metabolically high-risk obesity, in particular with respect to the prediction of cardiovascular disease (24). Moreover, benefits of lifestyle interventions in healthy obese individuals are questionable (25, 26).

Based on such findings and under the pressure of limited healthcare resources, future guidelines for obesity treatment should distinguish between MHO and metabolically high-risk obese individuals (10, 11). Until now, current guidelines still recommend lifestyle intervention for all obese individuals independently of their individual obesity-associated cardiometabolic risk (27). In particular, for the bariatric surgery treatment decision, the individual risk:benefit ratio should take a stratification of the obesity-associated metabolic risk into account.

**Definition of MHO**

To answer the question whether metabolically healthy obese individuals are really healthy, it is important to acknowledge that the criteria to classify MHO and cut-off values for each parameter describing MHO vary from study to study (13, 16, 28, 29). Most studies define MHO as the absence of any metabolic disorder including type 2 diabetes, dyslipidemia, and hypertension in an obese individual (BMI > 30 kg/m²; reviewed in references (13, 14, 30)). Although the influence of lifestyle, physical fitness, ethnicity, gender, or age on the MHO phenotype is widely accepted, current definitions do not include these variables (13). Variable associations between MHO and reduced risk for cardiovascular diseases and mortality (13, 21, 22, 23) highlight the need for harmonized classification criteria (13). Until very recently, there have been no standardized criteria to define MHO individuals, except for the presence of obesity (BMI ≥ 30 kg/m²) (13, 18). The need to harmonize MHO definitions has been recently addressed by the BioShare-EU project (13), an international collaboration between European and Canadian institutes and cohort studies. In the Healthy Obese Project, data from more than 163 000 individuals in ten population-based cohort studies (age range 18–80 years) from different countries in Europe have been evaluated to compare key characteristics defining MHO and to characterize clinical and metabolic factors associated with MHO (13). Across all cohorts, the prevalence of obesity was ~17% with a range from 11.6% in a cohort from Italy to 26.3% in the KORA-cohort from Germany (13). The harmonization effort in the Healthy Obese
Project used criteria to define the metabolic syndrome to characterize MHO (Table 1). In addition to the current World Health Organization (WHO) classification of obesity (BMI ≥ 30 kg/m²) (31), four parameters were used to define the metabolic phenotype based on the NCEP ATP III criteria (32). Specifically, the definition of metabolic syndrome in obese included: elevated blood pressure, defined as i) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or antihypertensive treatment; ii) fasting blood glucose ≥ 6.1 mmol/l, history of type 2 diabetes, or use of glucose-lowering agents; and iii) HDL serum concentrations < 1.3 mmol/l (in men) or < 1.7 mmol/l (in women), fasting triglyceride serum concentrations ≥ 1.7 mmol/l or drug treatment to alter HDL or triglycerides (Table 1). The collaborators also applied a set of less strict criteria to define MHO (Table 1) (13).

In the past, different definitions have been used to identify MHO individuals. Previous definitions of MHO included parameters such as insulin sensitivity determined by euglycemic–hyperinsulinemic clamps or with HOMA-IR, blood pressure, lipid parameters, and circulating C-reactive protein (reviewed in references (11, 14)). Different MHO definitions are a major limitation for the comparison between different observational studies and for the interpretation of associations between MHO, cardiovascular disease, and mortality (reviewed in reference (14)). For example, different HOMA-IR cut-offs derived from arbitrary decisions have been used to categorize MHO (Table 1) (23, 33, 34, 35, 36, 37). Different MHO criteria may indeed identify different obese sub-populations with only little overlap (14). In the NHANES III, ~44% of the obese study participants have been categorized as MHO, applying the NCEP ATP III criteria for metabolic syndrome (32), whereas only 20% met the strict predefined HOMA-IR cut-off < 2.5 (33). Such divergent definitions also support the concept that MHO does not describe a fixed or permanent phenotype. In one cross-sectional data, we find a continuous relationship between insulin sensitivity as determined by euglycemic–hyperinsulinemic clamps and BMI in lean and obese individuals (Fig. 1), which have been defined as metabolically healthy following the NCEP ATP III criteria (38). At any given BMI (Fig. 1), there are obese individuals with either extreme insulin sensitive or extreme insulin-resistant healthy obesity, but there is no cut-off clearly separating distinct insulin-sensitive and -resistant subgroups (38). This observation is further supported by data from 2472 participants of the Tübingen Family Study and the Tübingen Lifestyle Intervention Program (15, 39). Despite the strong association between BMI and waist circumference, large variations have been found in insulin sensitivity (determined using HOMA-IR) for individuals with the same BMI (14). Noteworthy, similar continuous relationships between increasing BMI and deterioration of components of the metabolic syndrome have been reported in children and adolescents (40). Therefore, these data suggest that MHO represent the extreme phenotype of continuous relationships between increased BMI and different metabolic deteriorations and does not reflect a distinct biologically defined phenotype (11). However, defining the MHO phenotype still represents an important tool to study the mechanisms of how fat accumulation on obesity causes or contributes to metabolic and cardiovascular diseases (12, 24).

### Epidemiology

In children and adolescents, prevalence of MHO has been recently defined in 21.5–31.5% (depending on the classification system) of obese 8- to 17-year-old individuals with a BMI above the 85th percentile (41). The prevalence

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**Table 1** Criteria used for the definition of metabolically healthy phenotypes in different studies. (This table was modified from references (13, 14).) Importantly, studies include participants with normal body weight and obesity.

<table>
<thead>
<tr>
<th>Criteria</th>
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<tr>
<td>Insulin sensitivity</td>
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<td>Gir &gt; 70 µmol/kg per min (38)</td>
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<tr>
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<td>&lt; 2.5 (23, 33, 35, 36, 37)</td>
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<td>Matsuda-index</td>
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<tr>
<td>Lower quartile/tertile</td>
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<td>Upper 25% of distribution</td>
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Is MHO a fixed or transient phenotype?

In all cohorts systematically studied for the occurrence of MHO, even in the oldest age groups, metabolically healthy

Figure 1
Identification of insulin sensitivity in metabolically healthy obese individuals. Individuals for whom euglycemic–hyperinsulinemic clamp data were available to determine insulin sensitivity have been selected by the following criteria: fasting plasma glucose <7.0 mmol/l, HbA1c <6.0%, no medical history of hypertension, systolic blood pressure (SBP) <140 mmHg, diastolic blood pressure (DBP) <90 mmHg, leukocyte count <8000 Gpt/l, C-reactive protein (CRP) <5.0 mg/dl, no concomitant medication except contraceptives. Insulin sensitivity was determined by glucose infusion rate (GIR) during the steady state of an euglycemic–hyperinsulinemic clamp. The dotted hyperbolic line is a regression curve of GIR over BMI based on all available subjects. Two individuals (BMI = 50.0 kg/m²; pictures of the abdominal region) are selected to represent either insulin sensitive, metabolically healthy, or insulin resistant obesity, which do not fulfill all criteria (13) to define metabolically healthy obesity. FPG, fasting plasma glucose; TG, triglycerides; BP, blood pressure.

of healthy obesity and the metabolic syndrome have been recently investigated in the BioShare-EU project (13). Among 11 465 men and 16 612 women with obesity, age-standardized prevalence of MHO was 12% across all ten cohorts, with great variation between cohorts from different regions in Europe (13). 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 (13). MHO prevalence was in general higher in women compared with men and could be identified in 28.4% in the UK NCDS, 23.1% in the Dutch LifeLines, 21.8% in the German KORA, and 21.1% in the Italian CHRIS studies (13). Lowest prevalence of MHO was identified both for men and women detected in Finnish cohorts with 2.3–3.6% for men and 7.3–12.3% for women (13). The greatest gender difference has been found in the NCDS from the UK, with a MHO prevalence of 9% in men compared with 28.4% in women, whereas MHO prevalence was similar in men (19%) and women (21.1%) in the CHRIS study from Italy. Similar prevalence differences have been found by earlier studies in Caucasian, Asian, and African American populations, which varied between ~9 and 34% (summarized in reference (11)). The frequency of MHO was estimated with 11% among 888 randomly selected individuals with an age range between 40 and 79 years in the Bruneck study (42), whereas in the Finnish type 2 diabetes survey, MHO was observed in 9.2% men and 16.4% women (28). Although it is difficult to directly compare these numbers with data from studies in Asian and African American populations due to different definitions of MHO, it is important to note that MHO can be identified independent of ethnicity and geographic regions of the world. For instance, MHO was found in a study from Taiwan (43) and in a study among African Americans (44), with a prevalence of 28.5%. In the Chennai Urban Rural Epidemiology Study, MHO prevalence was 13.3% among Asian Indians (45). Noteworthy, in contrast to Caucasian and African American populations, prevalence estimations in the Asian studies were based on an obesity WHO Asia Pacific guidelines definition using a BMI ≥25 kg/m² (43, 44, 45). Moreover, it has been recently suggested that MHO prevalence may be underestimated, when BMI as compared with body fat mass is used (46).

The age-standardized prevalence of metabolic syndrome in obese individuals also shows great variance ranging from 24% in the Italian CHRIS study to 65% in the Health2000 cohort from Finland in women and from 43% (CHRIS) to 78% (Finnish DILGOM study) in men (13). Interestingly, the prevalence of metabolic syndrome among obese was mainly driven by elevated blood pressure, whereas increased blood glucose contributed least to the diagnosis of metabolic syndrome (13).

The BioShare-EU project also demonstrated that the prevalence of MHO significantly decreases with age in both genders, independent of geographical region and the MHO criteria applied (13). The only exception was the Italian CHRIS study, in which frequency of MHO individuals was relatively constant up to an age of 60 years (13). These data are at least suggestive for the hypothesis that MHO represents a transient phenotype.
obese individuals could be found (13). In obese individuals, the MHO prevalence was particularly high (~8% of the 60 years and older) in a Dutch study (13). However, until 2013, there were only a few small and contradictory prospective studies on the natural course of MHO, and one could speculate whether MHO represents a stable phenotype or whether transitions from MHO to metabolically high-risk obese individuals occur. Recently, the prospective Pizarra study has investigated individual changes in the diagnosis of MHO over time (47). In 1051 study participants, the baseline prevalence of MHO was 3.0–16.9% depending on the applied criteria, but significantly changed in the 6 and 11 years follow-up reevaluation. Moreover, although MHO individuals had a significantly lower risk to develop type 2 diabetes, the obesity-associated diabetes risk was still significant over time (47). The authors therefore concluded that the concept of MHO as a clinically important entity is questionable (47). For individual predictions of obesity-related outcomes, it is still not clear whether MHO maintains their phenotype during the entire life span or whether MHO represents a delayed onset of obesity-related metabolic diseases (48). The latter hypothesis is supported by the notion that MHO is more frequently observed in pre-menopausal women and changes into metabolically high-risk obesity with increasing age (13, 49).

The transitory nature of MHO over time can be demonstrated using patients’ case examples: from our own experience, we found metabolic improvements toward MHO in a 53-year-old initially extremely obese man (BMI: 53.4 kg/m²), who underwent a Roux-en-Y gastric bypass surgery (Fig. 2). This patient initially presented with type 2 diabetes, hypertension, and dyslipidemia, but upon weight loss, he ‘gradually’ developed MHO defined by different criteria (13). As early as 6 months after surgery, the patient could be categorized as MHO using previously reported less strict criteria, and 12 months after surgery the patient fulfilled the even more strict criteria for MHO (13) (Table 1). This case demonstrates the transitory nature of MHO over time, and there are many more examples that over time the MHO phenotype may change into a metabolically high-risk individual. Supporting the concept that MHO represents an intermediate rather than a permanent

Figure 2
The obesity phenotype changes upon weight loss after Roux-en-Y gastric bypass surgery. Example of a patient initially presented with type 2 diabetes, hypertension, and dyslipidemia who underwent bariatric surgery and gradually developed metabolically healthy obesity defined by different criteria as previously described (13). Six months after surgery, the patient could have been diagnosed as metabolically healthy obese (MHO) using previously reported less strict criteria; 12 months after surgery, the patient fulfilled even the strict criteria for MHO (13). The case demonstrates the transitory nature of metabolically healthy obesity over time. FPG, fasting plasma glucose; TG, triglycerides; BP, blood pressure.
obesity subphenotype, individuals who have been classified as MHO at baseline of the West Adelaide Health Study (50), \(\sim 30\%\) changed during the study course to an obesity phenotype with high metabolic risk. Interestingly, in this study only those individuals who maintained MHO had a significantly lower risk to develop type 2 diabetes and cardiovascular disease (50). Taken together, the diagnosis of MHO at one time point does not (always) translate into a life-long reduced cardio-metabolic risk, although maintained MHO is clearly beneficial for reduced cardiovascular risk (21, 24).

Mechanisms underlying the metabolically healthy phenotype

The MHO phenotype may be caused by several mechanisms, which have been identified both in human and animal studies (reviewed in reference (14)), and include preserved insulin sensitivity, specific fat distribution with low visceral and ectopic fat accumulation (including low liver and skeletal muscle fat storage) compared with subcutaneous fat depots, normal adipose tissue function defined by lower adipose tissue infiltration of immune cells, and normal adipokine secretion pattern as well as high physical activity and fitness (11, 14).

Physical activity and preserved cardio-respiratory fitness

The individuals' obesity-associated risk to develop type 2 diabetes and cardiovascular diseases can be reduced by a higher fitness level (51). A high fitness level despite being obese – a phenotype frequently referred to as ‘fit and fat’ – is associated with less visceral and intrahepatic fat accumulation, which could mediate the beneficial effects of physical activity (11, 52). Among children, moderate-to-vigorous physical activity has been identified as the strongest predictor of MHO (41). Indeed, in a recent study, MHO participants have been shown to have a better fitness than metabolically abnormal obese participants (53). However, physical activity as a single factor may not explain the MHO phenotype entirely, especially because MHO individuals had a lower risk of all-cause mortality, non-fatal and fatal cardiovascular disease, and cancer mortality compared with metabolically high risk obese patients even after adjusting for better fitness and other confounders (53). High fitness level in MHO may therefore only be an indicator for a specific (healthier) lifestyle of this obesity subphenotype and does not necessarily represent the major mechanism defining MHO (14).

Preserved insulin sensitivity

Insulin sensitivity defined by euglycemic–hyperinsulinemic clamps, HOMA-IR, the Matsuda-index, or other parameters has been frequently used in human studies to distinguish MHO from metabolically unhealthy obesity (11, 14). However, the association between MHO and reduced cardiovascular risk (21) could not be related to differences in insulin sensitivity. We recently compared individuals MHO with either insulin sensitivity or insulin resistance defined by the glucose infusion rate during the steady state of an euglycemic–hyperinsulinemic clamp (cut-off \(<60\) or \(>70\) \(\mu\)mol/kg per min) (38). Confirming other studies (15, 18, 54), we found that independent of BMI and total body fat mass, individuals with insulin sensitive MHO had significantly lower visceral and liver but unchanged subcutaneous fat accumulation (38). In addition, parameters of adipose tissue function were significantly different between the two MHO subphenotypes. The human insulin sensitive MHO phenotype closely reflects the healthy obese phenotype of \(ob/ob\) mice with an experimental over-expression of adiponectin (55). A preserved expandability of subcutaneous adipose tissue may cause lower visceral and ectopic fat stores and may underlie the MHO phenotype (55). In another mouse model with an overexpression of the mitochondrial membrane protein mitoNEET, with an \(ob/ob\) background, the subcutaneous adipose tissue expandability theory has been supported by the observation that these mice are normal insulin sensitive despite large subcutaneous adipose tissue accumulation (56). These animal data are further supported by studies employing pharmacological activation of PPAR\(\gamma\) by thiazolidinediones. In patients with type 2 diabetes, thiazolidinedione treatment causes redistribution of the drug from visceral to subcutaneous adipose tissue depots, increased adiponectin serum concentrations, decreased liver fat content, and improved whole-body insulin sensitivity (57).

Normal adipose tissue function

In addition to adipose tissue distribution, preserved adipose tissue function determined by parameters such as lower adipocyte size, less macrophage infiltration into adipose tissue, and normal adipokine secretion patterns have been identified as contributing factors underlying insulin sensitivity in MHO (Fig. 3) (38, 55). Changes in the adipose tissue biology of insulin-resistant MHO individuals were accompanied by alterations in adiponectin,
progranulin, chemerin, RBP4, fetuin-A, and DPP4 serum concentrations (38). Interestingly, the adipose tissue-related mechanisms which may underlie the MHO phenotype are consistent across animal and human studies (38, 58).

Importantly, we and others (59) have identified inflammation of visceral adipose tissue as the strongest predictor of insulin-sensitive MHO (38). Increased immune cell infiltration of visceral adipose tissue may reflect additional mechanisms contributing to MHO, which have not been recognized previously. Such mechanisms may include accumulation of lipophilic food contaminants and endocrine disruptors (60) in visceral depots and could reflect a specific nutritional behavior, but could also be the result of a specific microbiome environment in individuals with MHO (61). Further studies are necessary to test these hypotheses.

Low visceral and ectopic fat accumulation

Individuals with MHO are characterized by a distinct fat distribution with lower visceral fat mass, lower liver fat and skeletal muscle fat content compared with obese individuals with higher metabolic risk (12, 14, 15, 38). In particular, increased liver fat content has been shown to be independent of obesity and predict the risk of coronary artery disease (62) and type 2 diabetes (63). The adverse effects of hepatic steatosis may be mediated by increased production of molecules including fetuin-A (64) or retinol-binding protein (RBP)-4 (65, 66).

Clinical relevance of MHO

In the future, the diagnosis of MHO may be facilitated by recently standardized definitions of this phenotype (13). It has been shown that MHO individuals do not significantly improve the risk for cardiovascular and metabolic diseases upon weight loss interventions (17, 18, 19). With limited healthcare resources, and not always successful anti-obesity interventions, it remains an important challenge in clinical practice to determine which obese patient will benefit the most from different interventions. The concept of MHO became more clinically relevant with recent data showing that individuals with MHO are not at increased risk for cardiovascular diseases compared with healthy normal-weight controls (21). It is therefore surprising that current guidelines for obesity treatment are mainly based on BMI and measures of body fat distribution including waist circumference, and still do not distinguish between MHO and metabolically unhealthy obese individuals and recommend lifestyle intervention for all obese individuals (10, 11). In clinical practice, additional stratification of obese individuals according to their metabolic and cardiovascular comorbidities (10, 13) would provide a better guidance for individual decision making (10). In post hoc analyses of the Swedish Obese Subjects study, BMI at baseline was not sufficient to predict the effectiveness of bariatric surgery on mortality, cardiovascular disease, type 2 diabetes, or cancer (65, 66, 67). However, inclusion of baseline fasting insulin concentrations – a surrogate parameter for insulin resistance – suggested that those individuals with higher baseline values benefit more from the intervention with respect to reduced mortality and incidence of type 2 diabetes (67).

Patients with metabolically unhealthy obesity clearly benefit from lifestyle interventions (17, 18, 19), but
whether similar effectiveness of non-surgical anti-obesity treatment strategies can be expected for MHO individuals is controversial (10, 11). In a previous study, MHO individuals did not significantly benefit from a structured 9-month lifestyle intervention program with regard to improvements in cardiometabolic risk parameters (16). In contrast, other interventions including lifestyle modifications (20) and bariatric surgery (68) led to improved cardio-metabolic risk factors in MHO. In another lifestyle intervention, only metabolically high risk but not MHO participants significantly improved insulin sensitivity upon weight loss (16). These data highlight the importance of stratification systems taking MHO into account. A simple clinical and functional staging system, the so-called Edmonton obesity staging system (EOSS), that allows clinicians to describe the morbidity and functional limitations associated with excess weight has been previously proposed (10, 69, 70). The EOSS staging system independently predicted increased mortality even after adjustment for contemporary methods of classifying obesity (70). The clinical use of more sophisticated obesity stratification systems seems to be particularly important in the decision making for bariatric surgery (71). The risk:benefit ratio of bariatric surgery in MHO individuals has so far not been systematically determined.

**Are metabolically healthy obese really ‘healthy’?**

BMI alone or any anthropometric marker of adiposity do not provide measurements of functionality, quality of life, or other prognostic contextual factors that may further characterize clinical risk and guide clinical management (10, 71). ‘Health’ is defined by the WHO as ‘... a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity’ (WHO, Constitution of WHO: http://www.who.int/about/definition/en/print.html). The presented transient MHO case (Fig. 2) may therefore serve as an example that ‘metabolically healthy’ does not necessarily mean ‘healthy’ obese. Although during the course of weight loss this patient fulfilled the criteria of MHO, chronic pain due to osteoarthritis in both knees remained a significant impairment of his well-being. Quality of life of obese individuals, including those fulfilling the criteria of MHO, is impaired by a number of psychological and social factors, osteoarthritis, chronic pain, pulmonary disease, cancer, and other conditions (7). Moreover, it is questionable whether MHO individuals stay healthy (48, 50). In this context, it has been shown that individuals with MHO have an increased risk for the development of heart failure despite significantly lower risk of cardiovascular disease (21). This suggests that obesity itself may be more important than metabolic alterations for the development of heart failure (21). However, to more precisely answer the question whether MHO individuals are really healthy, systematic studies on co-morbidities of obesity other than metabolic and cardiovascular disorders are necessary.

**Conclusions**

The concept of MHO has recently gained much clinical relevance with novel prospective study data that individuals with MHO are not at increased risk of acute myocardial infarction compared with metabolically healthy normal-weight individuals (21). Importantly, individuals with MHO may not improve their obesity-related metabolic and cardiovascular risks by lifestyle changes, pharmacological, or bariatric surgery-induced weight loss (14). Previous criteria to define MHO were not standardized, but with a recent large-scale harmonization effort, definition and diagnosis of MHO may be easier in future clinical practice (13). There is a need for personalized anti-obesity intervention strategies, which should consider metabolically high-risk obese patients who may benefit more from earlier interventions than MHO individuals. As MHO seems to be a transient subphenotype, anti-obesity treatment strategies even leading to an only moderate weight loss may reverse metabolically unhealthy into healthy obesity. Until now, guidelines for obesity treatment should consider distinct obesity subphenotypes such as the distinction between MHO and metabolically high-risk obesity for a stratification of therapeutic strategies.

**Declaration of interest**

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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