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EDITORIAL

UPDATING THE CONCEPT OF METABOLICALLY HEALTHY OBESITY

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Abstract

Obesity is a well-recognized risk factor for type 2 diabetes, cardiovascular disease, and several types of cancer. However, a proportion of the obese individuals display a significantly lower risk for metabolic complications than expected for their degree of body mass index, and this subtype of obesity was described as "metabolically healthy obesity" (MHO). No universally accepted criteria for the diagnosis of MHO exists and the prevalence of this subtype of obesity varies largely according to criteria used. Broadly, MHO is characterized by a lower amount of visceral fat, a more favorable inflammatory profile, and less insulin resistance as compared to the metabolically unhealthy obesity. Currently, controversies exist regarding the risk of cardiovascular events and all-cause mortality associated with MHO as compared to metabolically-healthy non-obese individuals. Further research is needed in order to identify the MHO phenotype and if MHO is truly healthy for a long period of time or if it is a transient state from normal metabolic/normal weight to abnormal metabolic/obese state. This review will discuss the MHO definition criteria; the differences between MHO and metabolically unhealthy obesity; the possible underlying mechanisms and clinical implications of MHO.

Key words: metabolically healthy obesity, obesity, insulin resistance, inflammation, visceral adipose tissue.

INTRODUCTION

Obesity is increasing worldwide (1) and is a well-recognized risk factor for type 2 diabetes, cardiovascular disease, and several types of cancer (2-4). Individuals with a body mass index (BMI) ≥30 kg/m^2 also have higher all-cause mortality rates (5). These obesity consequences are generally attributed to impaired glucose tolerance or type 2 diabetes, hypertension, atherogenic dyslipidemia and systemic inflammation (6).

However, since 1982 many studies have identified a subset of obese individuals displaying a significantly lower risk of metabolic complications than expected for their degree of BMI (7-10), and this subtype of overall obesity was described as "metabolically healthy obesity" (MHO). Broadly, individuals with MHO are considered those who meet the BMI cutoff point for obesity (≥30 kg/m^2), but do not have other major cardiovascular risk factors and who are not at higher cardiovascular risk than non-obese individuals (11-13). By contrast, individuals with obesity and major cardiovascular risk factors are considered as having "metabolically unhealthy obesity" which is associated with risk of diabetes, cardiovascular diseases and malignancies.

There are no universal criteria for distinguishing metabolically healthy from metabolically unhealthy obesity. Consequently, data on MHO's epidemiology and its impact on cardiovascular risk vary largely among studies. Also, biological mechanisms underlying MHO and its implications for clinical management and public health are a matter of debate.

Definition criteria, mortality risk and prevalence of metabolically healthy obesity

In general, four categories of clinical, biochemical or functional parameters have been used in epidemiological studies to define MHO (11): absence of abdominal obesity based on waist circumference (men ≤102 cm, women ≤88 cm); absence of metabolic syndrome components (e.g. normal blood pressure, normal lipid values, normal fasting glucose concentrations, and in some studies normal C-reactive protein concentrations); absence of insulin resistance as evaluated by homeostatic model assessment of insulin resistance (HOMA-IR); high level of cardiorespiratory fitness. Within each category, the cutoff values and the combination of parameters to define MHO also varied among studies (14-21). In other studies, a combination of parameters from different categories was used to define MHO.

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Some of the criteria used to define MHO in prospective studies examining relative risk of mortality are presented in Table 1.

Several, but not all studies found that MHO was associated with lower risk of total mortality and of cardiovascular mortality (14-27). Possible explanations for the conflicting results of these studies may be the large variation among criteria used to define MHO and the variation of reference groups (14-27). Still, in few studies that applied more than one set of criteria, the outcomes converged irrespective of the criteria used. For example, in the study of Kuk *et al*. (16) metabolically healthy obese according to insulin sensitivity status had similar hazard ratios for mortality as did metabolically healthy obese with <2 metabolic syndrome criteria and both had similar risk with those with metabolically abnormal obesity. Another plausible explanation is a difference in the follow-up duration between studies (12). Most studies supporting the hypothesis that metabolically healthy obese phenotype is associated with lower risk had a relatively short follow-up period of <10 years. Data from the community-based Uppsala Longitudinal Study of Adult Men (ULSAM) with a median follow-up period of 30 years (18) showed that MHO was associated with an increased risk for CVD events as compared with normal weight individuals (with or without metabolic syndrome).

Recently, three meta-analyses examined the relationship between MHO and total and cardiovascular mortality (28-30). One meta-analysis (28) included eight studies with 61,386 participants in which metabolic health was defined as the absence of metabolic syndrome according to Adult Treatment Panel III or International Diabetes Federation criteria. Metabolically healthy obese individuals had a relative risk [RR] for total or cardiovascular mortality of 1.24 (95% CI, 1.02 to 1.55) compared with metabolically healthy normal-weight while metabolically unhealthy obese had a RR of 2.65 (CI, 2.18 to 3.12). Another meta-analysis (29) included 14 prospective studies with a total of 299.059 participants. Metabolically healthy overweight and obese individuals showed a 47% and 100% higher risk for CVD events as compared with metabolically healthy normal weight individuals and

Table 1. Criteria used to define MHO in prospective studies

Study	Definition criteria
Criteria based on metabolic syndrome/metabolic syndrome components	
Kip *et al.*, 2004 (14) Durward *et al*, 2012 (15)	National Cholesterol Education Program Adult Treatment Panel III (without waist circumference); ≥3 components
Kuk *et al.*, 2009 (16) Choi *et al.*, 2013 (17)	Modified NCEP ATP III (without waist circumference); ≥3 components
Arnlöv *et al.*, 2010 (18) Hinnouho *et al.*, 2013 (19)	Modified NCEP ATP III (without waist circumference); ≥2 components
Ortega *et al.*, 2013 (20)	International Diabetes Federation; ≥2 components
Hamer *et al.*, 2012 (21)	≥2 components: waist circumference >88 cm in women and >102 cm in men, blood pressure >130/85 mm Hg, diagnosis of hypertension, use of antihypertensive drugs, doctor-diagnosed diabetes, low-grade inflammation (C-reactive protein ≥3 mg/l), and HDL cholesterol <1.30 mmol/L in women and <1.03 men
Criteria based on HOMA-IR	
Kuk *et al.*, 2009 (16) Calori *et al.*, 2011 (22) Bo *et al.*, 2012 (23) Durward *et al.*, 2012 (15)	HOMA-IR ≥2.5
Arnlöv *et al.*, 2010 (18)	HOMA-IR in top 25% of the distribution in participants without diabetes (>3.43)
Hinnouho *et al.*, 2013 (19)	HOMA-IR in top 25% of the distribution Matsuda index in lower 75% of the distribution
Studies using cardiorespiratory fitness	
Wei *et al.*, 1999 (24) Stevens *et al.*, 2002 (25)	Metabolic equivalents during maximum treadmill exercise test; value <age-specific cut points
Sui *et al.*, 2007 (26) Farrell *et al.*, 2010 (27)	Duration of maximum treadmill exercise test; lowest 20%
Studies using combined criteria	
Hinnouho *et al.*, 2013 (19)	≥2 components: blood pressure ≥130/85 mm Hg, triglycerides ≥1.7 mmol/L, fasting glucose ≥5.6 mmol/L, HOMA >90th percentile, C-reactive protein >90th percentile, HDL cholesterol <1.3 mmol/L;

NCEP ATP, National Cholesterol Education Program Adult Treatment Panel; HOMA-IR, homoeostatic model assessment of insulin resistance

the association appeared stronger during the long-term follow-up period of >15 years compared with shorter follow-up periods. The third meta-analysis (30) examined whether there is a suitable criterion for the identification of a subset of obese participants who are not at increased risk of CV events when compared with healthy normal-weight individuals. The conclusion was that, irrespective of the parameters used to define MHO (presence or absence of metabolic syndrome, insulin resistance, hypertension, diabetes, hyperlipidemia and any of these metabolic factors), individuals with MHO are at increased risk of cardiovascular mortality compared with healthy normal-weight participants and the risk is particularly high on long term.

The longitudinal risk of MHO for diabetes and cardiovascular disease (CVD)/stroke mortality was examined in the North West Adelaide Health Study which included 4.056 randomly selected adults aged ≥18 years. The metabolic risk was defined as having two or more International Diabetes Federation metabolic syndrome criteria, excluding waist circumference (31). Overall, the MHO participants were more likely to develop metabolic risk and incident diabetes but not CVD/stroke during the follow-up period of 5.5-10.3 years. These risks were not observed in MHO participants maintaining metabolic health (representing 67% from initial MHO group; 33% changed from MHO to metabolically unhealthy obesity). Sustained metabolic health in obese participants was associated with age ≤40 years and lower waist circumference. Compared with the metabolically at-risk obese, MHO women had a significantly higher percentage of leg fat and lower waist circumference, with non significant differences in overall adiposity. These findings suggest that in some cases MHO can be a transient phase in the natural history of obesity and that a single evaluation is not sufficient to classify an obese individual as having no obesity-related risk for metabolic and cardiovascular consequences.

Reported prevalence of MHO in the obese population is 6-40%, largely depending on criteria and cut off values used to define it (32). In the cohort of the National Health and Nutrition Examination Survey (NHANES) III, 20% of obese participants were classified as metabolically healthy obese based on a HOMA-IR <2.5 and 44% of the obese participants were classified as metabolically healthy obese when MHO was defined as the absence of metabolic syndrome according to ATP III criteria. Only 40 of 1160 obese individuals (3.44%) were identified as metabolically healthy obese by all definitions (15).

Only several studies (15, 16, 18, 23, 33) compared different criteria for MHO in the same populations and all found a small overlap of criteria used. For example, in a cross-sectional sample of 1.008 men and 1.039 women aged 45-74 years, MHO was defined according to five criteria and the prevalence of MHO in the whole study population varied considerably between definitions, ranging from 2.2% to 11.9%. Among the obese persons, the MHO's prevalence ranged between 6.8% and 36.6%. Agreement between MHO classifications was poor, with only 20 subjects simultaneously classified as MHO according to the four definitions which led to the greatest prevalence. In the same study, physical activity (moderate and high levels) and compliance with food pyramid were found to increase the likelihood of MHO phenotype.

Despite lack of universal criteria for definition of MHO, this phenotype of obesity could be generally described as more common in younger people, occurring more often in women with gluteo-femoral type of first class obesity, starting in childhood and persisting into adulthood, more common in well fit individuals and more compliant with food pyramid. People with MHO are more resistant to adverse metabolic effects of moderate weight gain and MHO can be a transient phase with one third of individuals reclassified as metabolically unhealthy obese after 6 years of follow up (32-34).

The pathophysiology of metabolic healthy obesity

Genetic factors of BMI and fat storage

Population and twin-pairs studies demonstrated that anthropometric parameters, including body mass index (BMI) and fat tissue characteristics, are heritable traits (35). In a cross-sectional study with 325 female and 299 male like-sex healthy twin pairs (18-67 years), the heratibility for BMI was 0.58 to 0.63, for body fat percent it was 0.59 to 0.63 and for waist circumference it was 0.48 to 0.61 (35). In a very interesting study published by Stunkard *et al.* in 1990, which enrolled twins who had been reared apart or reared together, the heritability of BMI in twins reared apart was 0.7 for men and 0.66 for women (36). Another study confirmed substantial heritability for BMI and waist circumference (WC) (77% for both) and 60% of the genetic influence on WC was common to BMI, but 40% was an independent genetic effect (37). Fat mass, fat distribution and number of adipocytes are influenced by genetic (major and/or polygenic) factors which may explain 29 to 50% of the phenotypic variance (38). The

age and the gender may influence the expression of those genes.

Both Genome-Wide Association Studies (GWAS) and gene-expression studies showed that fat distribution is influenced by developmental genes. Genes Tbx15, Shox2, En1, Sfrp2, and HoxC9 are mostly expressed in subcutaneous addipose tissue and Nr2f1, Gpc4, Thbd, HoxA5, and HoxC8 are significantly more expressed in intraabdominal adipose tissue (39).

Another study showed that genes HOXA2, HOXA3, HOXA4, HOXA5, HOXA9, HOXB7, HOXB8, HOXC8, and IRX2 were down-regulated in the gluteal depot in both genders and HOXA10 was up-regulated in gluteal tissue. HOXC13 was detected exclusively in this depot. These results were independent of BMI (40). A recently published study showed that fat-depot specific expression of HOXC9 and HOXC10 may contribute to adverse fat distribution and related metabolic traits (41). mARN expression of these genes is significantly higher in subcutaneous than in omental adipose tissue and its expression correlates significantly with body fat mass, independent of age and gender. In a smaller group, the expression of these genes was associated with adipose tissue metabolism (as adipocytes size) and glucose metabolism parameters (as fasting plasma glucose or glicated hemoglobin) (41).

In addition to the genetic factors, the epigenetic ones, that are inheritable modification of gene expression, can contribute to metabolic disturbances (42). Maternal metabolic modifications during pregnancy and lactation could favour the development of metabolic syndrome in the offsprings (43).

Environmental factors

An interesting aspect of genetic influence on adiposity is that the heritability decreases with advancing age (35). The genes may turn on or off depending on age, gender and environmental factors. Gene-environment interaction models showed a down-regulation of genes associated to obesity in individuals with high physical activity, but no effect was observed for protein intake (44).

The body weight is the result of the energy balance of the human body. This process involves a communication between the adipose tissue, which is the long-term energy depot, and the brain, which coordinates the behaviour and the energy expenditure (45). An interesting study with 12 pairs of young men identical-twins, who were overfed for one hundred days, showed that the twins lost the 7-8 kg gained during the study in the first 4 months of follow-up, but after 5 years of follow-up their weight was increased by a mean of 5 kg (46). The principal mechanism which controls the energy homeostasis was established to be the leptin-melanocortin signaling pathway. This pathway is formed by neurons of hypothalamic arcuate nucleus which are stimulated by various peripheral and central factors, including leptin - released in systemic circulation by adipocytes. The neurons from the arcuate nucleus projects particularly to hypothalamic appetite-regulating nuclei and after being stimulated by leptin, they release melanocortin peptides (melanocyte stimulating hormone form α or β). The receptors type 4 of melanocortin (MC4R) are present in the appetite-regulating nuclei from the hypothalamus and are stimulated by melanocortin peptides, with an important role in regulating satiety and energy homeostasis (47). The obesity is the result in the alteration of perception of appetite and satiety, being now considered a heritable neurobehavioral disorder (45).

The body fat distribution

The white adipose tissue (WAT) is responsible for storage and release of the energy surplus and brown adipose tissue (BAT) is specialised in energy expenditure *via* beta-oxidation coupled to thermogenesis (48). The WAT depots can be divided into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT).

The total fat mass is not a sufficient criterion to evaluate the healthy status of a person. Brochu *et al*. showed that in a population of postmenopausal obese sedentary women with 50% body fat were observed cases of MHO and women with MHO had a 49% lower amount of VAT compared with MUHO (49). MHO is associated with insulin-sensitivity and is characterized by a lower VAT, less ectopic fat depot in the liver and in the skeletal muscles compared with insulin-resistant obese (50). The source and the turnover of fat present in depots is different according to the location; dietary fat is the primary source for the abdominal stores, and the lower-body adipose tissue has the ability to accommodate to fat redistribution, being able to recruit new adipocytes and has fewer signs of inflammatory activity (51).

The main factor that influences the storage of fat is the plasticity of the SAT (52). It was observed that people with lipodystrophies, characterized by a generalized or partial loss of SAT, develop ectopic fat storage and insulin-resistance, dyslipidemia and diabetes (53). An interesting study published by Alligier *et al.*

(54) demonstrated that after 56 days of overfeeding, the fat storage had a large inter-individual variation. Postprandial FFA release in circulation after a test meal was positively associated with VAT. The largest VAT was observed in men with defective expression of genes linked to the storage of fat in SAT (DGAT2, SREBP1c and CIDEA). Interestingly, a dysfunctional SAT was observed in non-obese individuals with type 2 diabetes, expressed by an adipocyte hypertrophy, which may be caused by an impaired capacity to recruit progenitor cells (55). This may also have an impact on adipose tissue inflammation, ectopic fat disposition and insulin resistance (55).

Ectopic fat tissue is accompanied by insulin resistance, type 2 diabetes, hypertension, dyslipidemia, inflammation and all these increase the cardiovascular risk (56, 57). The adipose-tissue derived TNF-α can indirectly affect both function and expandability of the adipose tissue (58).

The role of glucose metabolism

The role of adipose tissue in the up-take and the utilization of glucose is an important piece in the puzzle of metabolic abnormalities observed in obese patients. The insulin produces the postprandial disposal of glucose, increasing its up-take in adipocytes through GLUT4 mobilization, the main transporter of glucose into the adipose cell. Previous data (59) showed that the maximum insulin-stimulated glucose transport and glucose utilization in adipocytes of diabetic patients are significantly lower than those of healthy controls (by 40% and 32%, respectively) (59).

Experimental studies on mice showed that the mutation of GLUT4 gene decreases the expression of this transporter in adipose tissue and skeletal muscle. This decrease did not result in obesity, but led to hypertension and diabetes, thus being a good animal model for the study of diabetes without complications induced by obesity (60).

Other animal studies showed that adipose tissue selective insulin receptor knock-out protects against obesity and obesity-related glucose intolerance (61). FIRKO mice, which are mice with fat-specific knock-out of the insulin receptor gene, have low fat mass, loss of the normal relationship between plasma leptin and body weight (inappropriately elevated serum levels of leptin) and are protected against the negative effect of obesity on glucose metabolism, demonstrating that insulin signalling in adipocytes is critical for the development of obesity and its associated metabolic abnormalities (62). The same study showed that these mice display heterogeneity in adipocyte size and function. Furthermore, FIRKO mice have an increase in mean life-span of approximately 134 days (18%), compared to the controls mice (62).

The role of BAT and WAT in the storage and the utilization of energy is different. Mice with selective knock-out insulin receptor in brown adipocytes show an age-dependent loss of interscapular brown fat and develop an insulin-secretion defect resulting in a progressive glucose intolerance, but without insulin resistance. This model provides a direct evidence for the role of the insulin receptors in brown fat adipogenesis and also suggests the role of brown adipose tissue in the regulation of insulin secretion and glucose homeostasis (63).

The MHO phenotype is characterized by an improved insulin-sensitivity compared to their counterparts with metabolic unhealthy obesity (19). The accumulation of abdominal, visceral and ectopic fat will induce insulin resistance and metabolic unhealthy profile (64). A recently published study showed that individuals with either liver or muscle insulin-resistance had an abdominal visceral fat area similar to the one of the insulin-sensitive individuals; those with insulin resistance at the both levels had a significantly higher visceral fat area than those insulin-sensitive in both tissues (65).

The role of inflammation and adipokines secretion

Adipose tissue inflammation is one of the most important links between obesity and metabolic abnormalities (66). Factors secreted by the adipose tissue are collectively named adipokines (chemokines, cytokines and hormones) and to date more than 200 such molecules were identified (67, 68). SAT and VAT secrete a specific profile of adipokines (69). The MHO phenotypes may be characterized also by an adipose tissue with reduced secretion and/or low metabolic effect of the adipokines (10). The pro-inflammatory adipokines are leptin, TNF-α, interleukin (IL)-6, resistin, retinol-binding protein 4, lipocalin 2, IL-18, angiopoietin-like protein 2, CC-chemokine ligand 2, CXC-chemokine ligand 5, and nicotinamide phospho- ribosyltransferase (67). The most important anti-inflammatory adipokine is adiponectin (67), a decreased level being associated with metabolic dysfunction. Adiponectin is secreted exclusively by adipocytes and is negatively corelated with VFA (70). It has anti-inflammatory actions on macrophages, endothelial cells, cardiomyocytes and fibroblasts (71). Secreted frizzled-related protein 5 is

a new anti-inflammatory adipokine with beneficial effects on metabolic dysfunction (72). Another anti-inflammatory adipokine is IL-10 (73).

The presence of macrophages around dead adipocyte develops a characteristic aspect, called "crown-like structures" (74). The presence of "crown-like structures" in SAT is equally distributed between sexes and is correlated, independent of total fat, with higher visceral fat area and hepatic fat fraction, higher values of fasting glucose and insulin, and decreased beta-cell function (75).

The macrophages activated in the adipose tissue by free-fatty acids (FFA) through toll-like receptor-4-mediated signal secrete TNF-α, which enhances lipolysis in the surrounding adipocytes, leading to increased production of FFA. This paracrine loop between macrophages and adipocytes promotes and maintains the inflammation of the adipose tissue (58). Furthermore, the TNF-α secretion in ectopic fat depots in the close proximity of visceral tissue (as liver, skeletal muscle or pancreas) induces malfunction of these organs (58). The level of TNF-α was demonstrated to be high in the adipose tissue of diabetic mice and to play a major role in the obesity-related insulin resistance (76). Phillips *et al.* showed in a large cohort of 2,047 men that those with MHO presented lower levels of complement component C3, C-reactive protein, IL-6, TNF-α and plasminogen activator inhibitor-1, reduced white blood cells count and high levels of adiponectin (77). Another study showed that obese patients have fewer circulating natural killer cells and cytotoxic T lymphocytes than lean subjects, but MHO individuals present significantly higher levels of circulating cytotoxic T lymphocytes and natural killers, independent of age or BMI, this characteristic being a potential protective mechanism against malignancy, infection, and metabolic disease seen in obesity (78).

Other factors

The gut microbiota, formed mostly of Bacteroidetes and Firmicutes, has emerged as an important factor which modulates the host metabolism (i.e. bile acid transformation, absorption of nutrients) or its immune response (i.e. cytokines production). Gut microbiota induces acute inflammation which activates the signal transducers and is involved in the control of the obesity development, adipose tissue inflammation and insulin resistance (79).

The malfunction of the liver induces muscle insulinresistance, being suggested an endocrine axis between these two organs, with molecules originated from the liver, modulating insulin sensitivity of the skeletal muscle. A study including low-birth weight subjects showed that insulin-resistance developed in the liver and in skeletal muscle can be independent of lipid depot in these organs thus supporting the above mentioned hypothesis (80).

Recently, a new concept named chrononutrition, is linking the biological clock to nutrition. The food ingestion and absorption of nutrients is correlated with the endogenous clock - with circadian secretion of hormones and different metabolic processes during daylight and night time. This new concept supports the role of the circadian clock in the development of metabolic diseases (81).

Clinical implications and interventions in metabolically healthy obesity

The lack of a standard definition of MHO makes it difficult to give clear recommendations for the clinical management of MHO. Any obese individual should be carefully assessed for metabolic status. Few steps are recommended (11): measurement of the waist circumference, to provide an assessment of the body fat distribution beyond overall adiposity, measurement of other parameters included in the metabolic syndrome and assessment of insulin resistance by HOMA-IR. Because the methods used for insulin measurement are not standardized, at present a cut-off for insulin resistance cannot be defined. MHO could be considered in the absence of any of the above factors.

In general, obesity treatment recommended by the guidelines includes lifestyle interventions (nutrition and physical exercise), cognitive behavioural therapy, pharmacological interventions and bariatric and metabolic surgery (82). No specific recommendations are given for MHO. However, pharmacological interventions and bariatric surgery are only recommended in individuals with certain degrees of obesity and comorbidities.

Very few studies specifically examined interventions in MHO. In a study (83) including 267 post-menopausal overweight/obese women with a moderately elevated systolic blood pressure who underwent a 6 month exercise intervention program, exercise training significantly increased cardio-respiratory fitness but no significant changes were observed in their cardio-metabolic risk profile. In another study on MHO men and women (84), exercise- or diet-induced weight loss improved only insulin sensitivity and fasting insulin as cardio-metabolic factors. In a similar study (85), no improvement of

insulin sensitivity was seen in MHO subjects, whilst in metabolically unhealthy obese subjects such an improvement occurred. In a 12-week energy restricted diet intervention it was demonstrated that significant improvements in insulin, hepatic enzymes, fatty liver and leptin levels were obtained both in metabolically healthy and unhealthy obese premenopausal women (86). Most recently, a 2-months well-balanced diet in 103 MHO persons resulted in significant improvements in fatty acid profile, desaturase activity, BMI and android fat mass, lipid profile, adipokines, insulin resistance, and C-reactive protein (87).

Controversies

The definition of MHO is an important aspect of controversies. First of all, a unified criterion of definition of MHO must be adopted. From our point of view, the correct and complete definition of MHO should include: non-risk waist circumference; non-risk level of LDL cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides, Apolipoprotein B, Apolipoprotein A, Lipoprotein(a); normal glycemia and non-insulin resistance state; non-inflammatory state; non-oxidative state; non-prothrombotic state and normal blood pressure. Second, further research is needed in order to identify the MHO phenotype and if MHO is truly healthy for a long period of time or if it is a transient state from normal metabolic/normal weight to abnormal metabolic/obese state. Finally, it is important to determine which is the MHO's prediction power for cardiovascular risk, type 2 diabetes risk and total mortality risk.

In conclusion, MHO represents a subset of individuals with obesity having a significantly lower risk of metabolic complications than expected for their degree of BMI. No universally accepted criteria for diagnosis of MHO exist and the prevalence of this subtype of obesity varies largely according to criteria used. The clinical implications and interventions in MHO are still to be established.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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