Metabolic and Cardiovascular Implications of a Metabolically Healthy Obesity Phenotype

Mi Hae Seo¹, Eun-Jung Rhee²

¹Division of Endocrinology and Metabolism, Department of Internal Medicine, Soonchunhyang University College of Medicine, Gumi; ²Department of Endocrinology and Metabolism, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Metabolically healthy obesity (MHO) is a new concept in which an individual may exhibit an obese phenotype in the absence of any metabolic abnormalities. There are a number of definitions of MHO that utilize a variety of components. The findings of clinical and basic studies indicate that subjects with MHO do not exhibit an increased mortality, an increased risk of cardiovascular disease, or an increased risk of type 2 diabetes mellitus, as compared to normal-weight controls. Although these findings imply that metabolic health is a more important factor than obesity, several studies have shown that subjects with MHO have a similar risk of metabolic or cardiovascular diseases as those with metabolically unhealthy obesity. Thus, there is still debate regarding not only the implications of the MHO phenotype but its very existence. Accordingly, future studies should focus on developing a unified definition of MHO and distinguishing subjects who will be at a high risk for metabolic and cardiovascular diseases.

Key Words: Metabolically healthy obesity; Cardiovascular diseases; Diabetes

INTRODUCTION

The rise in the prevalence of obesity over the past decade has become an increasingly relevant issue because this medical condition is an important risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), which may lead to a higher incidence of all-cause mortality [1]. Approximately 30% of obese individuals do not have metabolic syndrome and are thus at a lower risk of developing T2DM and CVD [2]; these individuals are thought to exhibit metabolically healthy obesity (MHO), which is an obese phenotype free of any metabolic abnormalities [3]. Conversely, not all non-obese individuals exhibit a healthy metabolic profile [2].

The phenotypes of MHO, metabolically unhealthy obesity (MUHO), and nonobesity have been recognized since the 1980s [3] but between the years of 1980 and 2000 epidemiological research demonstrated that individuals who were overweight or obese did not always exhibit higher rates of CVD and mortality [4,5]. Subsequently, there has been an increase in the number of studies attempting to characterize the MHO phenotype [6-8], which is characterized by the absence of metabolic parameters such as dyslipidemia, insulin resistance, hypertension, and unfavorable inflammatory profiles despite the presence of an elevated body mass index (BMI) [8].

Several diverse definitions of the MHO phenotype have been proposed based on the presence of various metabolic abnormalities in a subject [9]. Accordingly, the prevalence rate of MHO in obese individuals varies from 10% to 25% based on
the criteria and populations that are used by a particular study [10,11]. Despite the enhanced interest and increasing number of studies investigating MHO, there are no unique criteria that can be used to define MHO and, as a result, the implications of the MHO phenotype and even its very existence are still under debate. Thus, the present review discusses the various definitions, pathophysiologies, and clinical implications of MHO as well as the debate regarding its existence.

**THE MHO PHENOTYPE: DEFINITION MATTERS**

Individuals with MHO display a favorable metabolic profile that is characterized by a high level of insulin sensitivity, a low incidence of hypertension, favorable lipid profiles, satisfactory fat distribution, and a low level of systemic inflammatory responses [10]. It has been suggested that the MHO phenotype exists, even though there are large variations in its prevalence rate, as a function of the criteria used to define it [12]. Several definitions are currently used to account for metabolic health (Table 1) and most authors define MHO using measures of blood pressure, lipid status (mainly high density lipoprotein cholesterol and/or triglycerides), glycemic and insulin resistance statuses (fasting blood glucose levels or homeostasis model assessment [HOMA]), and systemic inflammation (as defined by high-sensitivity C-reactive protein levels). However, it is difficult to compare the findings of various studies because there is no accepted standard definition of metabolic health and different studies use different inclusion criteria and/or cutoff points for metabolic measures.

Among the inclusion criteria used in various studies, there is a diversity of adiposity measures although they typically include waist circumference (WC), BMI, and body fat percentage (BF%) [9]. The prevalence of metabolic health was investigated in a population of Swedish subjects using six sets of criteria for obesity, which included measures such as BMI, abdominal obesity, and BF% [9]. Based on the different sets of criteria, the prevalence of MHO ranged between 3.3% and 43.1% in men and 11.4% and 57.5% in women. Similarly, the proportions of MHO individuals among obese participants were 6.8% when using the criteria of Aguilar-Salinas et al., 14.2% when using the criteria of Karelis et al., 23.7% when using the criteria of Wildman et al., 30.2% when using the criteria of Meigs et al., and 36.6% when using HOMA [13,14]. Furthermore, the agreement of MHO classifications among these studies was poor. Likewise, the proportions of MHO individuals in a Korean population...
were 24.2% when using the criteria of Meigs et al., 28.5% when using the criteria of Karelis et al., and 59.7% when using the criteria of Wildman et al. [15]. These comparative studies illustrate the considerable variability that exists in estimations of the incidence of MHO when different sets of criteria are used to define metabolic health [14]. Despite the controversy surrounding these definitions and doubts concerning the existence of the MHO phenotype, a characterization of MHO individuals represents an important tool that can be used to evaluate the contribution of various types of fat distribution to the development of metabolic diseases and CVD. Additional studies and a consensus regarding the MHO phenotype are necessary in order to determine the manner in which this tool can be used to assess the cardiometabolic status of a patient in relation to appropriate fat accumulation.

**PATHOPHYSIOLOGY OF MHO**

It is likely that the MHO phenotype is the result of several underlying mechanisms and the interaction between genetic, environmental, and behavioral factors (Fig. 1). Each of these factors affects abdominal fat distribution, visceral and ectopic fat accumulation, and insulin resistance, which are all important causative factors that contribute to the development of unhealthy obesity [10]. In some instances, the concept of the MHO phenotype is used interchangeably with the notion of insulin-sensitive obesity because MHO subjects display better insulin sensitivity than MUHO subjects [16].

The plasticity of adipose tissue, which allows for the storage of the excessive fat that is accumulated by obese individuals, may be the primary factor that discriminates healthy obesity from unhealthy obesity. The amount of visceral fat mass in insulin-resistant obese individuals is independently associated with BMI and total body fat mass [17] while an artificial increase in the subcutaneous fat mass of rodents results in positive metabolic effects [18]. In MUHO individuals, the storage capacity of adipocytes may be exceeded and lipids can accumulate ectopically in visceral fat depots, liver and muscle cells, and pancreatic β-cells whereas the subcutaneous adipose tissue of MHO individuals possesses the (intrinsic) propensity to expand which, in turn, leads to a preservation of insulin sensitivity [10]. Additionally, MHO subjects exhibit a greater proportion of subcutaneous fat compared with MUHO subjects [19]. Therefore, the plasticity of adipose tissue that allows for expansion in response to excess fat in obese individuals with proper angiogenesis is important for healthy obesity [20].

The interaction between genes and the environment will also matter in the development of MHO. Fat mass, fat distribution and the number of adipocytes are heritable traits for which genes account for between 25% and 70% of the observed variability [21]. A number of studies have attempted to determine whether there would be a common genetic influence of these two phenotypes in addition to their gene-specific effects associated with fat mass and visceral fat. Developmental genes such as *HoxA5*, *Gpc4*, and *Tbx15* exhibit changes in expression that are closely correlated with patterns of fat distribution [22], and B6J mice gain more weight, have higher levels of insulin and leptin, and show a greater degree of glucose intolerance than 129J mice on a normal diet [23]. Kulkarni et al. [24] generated mice from three genetic backgrounds (C57BL/6 [B6], 129Sv, and DBA) that were double heterozygous knockouts of the insulin receptor and insulin receptor substrate-1 and found that 90% of B6J mice developed diabetes while less than 5% of 129J mice developed diabetes. Additionally, a genome-wide scan of an intercross between these strains indicated that at least four loci on three different chromosomes are involved in

---

**Fig. 1.** Possible pathophysologies of metabolically healthy obesity and metabolically unhealthy obesity. The gene-environment interactions may play dual roles as both causative factors for the development of obesity and for the dissociation of obesity into subphenotypes of physiological (predominantly subcutaneous, insulin sensitive, and healthy) or pathological (visceral, ectopic, and unhealthy) fat accumulation. Adapted from Bluher, Curr Opin Lipidol 2010;21:38-43, with permission from Wolters Kluwer Health [10].
this process [25]. In a study of obesity-discordant monozygotic twins (age range, 22.8 to 35.8 years), the metabolic responses to obesity differed greatly. Approximately half of the obese co-twins exhibited a typical response to obesity that was characterized by marked insulin resistance, dyslipidemia, and fatty liver tissue whereas the other half of the obese co-twins were as metabolically healthy as their lean co-twins [16]. In the same study, the MHO group exhibited a very low percentage of liver fat and the maintenance of mitochondrial function in conjunction with the absence of inflammation in subcutaneous adipose tissue.

The MHO phenotype may also be characterized by the presence of adipose tissue with reduced secretory capabilities or diminished responsiveness to the effects of adipokines [26]. It has been shown that fat distribution and differences in the adipocytokine secretory properties of fat depots are likely play an important role in the outcomes associated with the MHO phenotype [27]. Furthermore, changes during the adipose expansion process can influence the secretion of good adipokines, such as adiponectin [28], which promotes insulin sensitivity, decreases inflammation, and enhances cell survival [29]. In fact, obese co-twins who are as metabolically healthy as their lean co-twins exhibit a disproportionate increase in circulating leptin levels and a lower expression level of adiponectin in adipose tissue [16].

Low systemic inflammation may be another key feature of the obesity status of an individual. For example, of 44 obese (BMI >30 kg/m²) patients who underwent laparoscopic bariatric surgery, the MUHO patients had a less favorable inflammatory profile in their visceral adipose tissue that resulted from the infiltration of proinflammatory macrophages, which exhibited increased nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 inflammmasome activity and interleukin-1 β production [30]. Adipose tissue also acquires immunological properties via the infiltration of activated macrophages, neutrophils, and T- and B-cells [31] and these immunometabolic interactions lead to low-grade inflammation. In fact, the involvement of the immune system in obesity-related metabolic diseases in humans leads to a specific T-cell signature in adipose tissue [32]. There are additional mechanisms and various differences that distinguish the MHO and MUHO phenotypes, such as improved mitochondrial function, increased aerobic fitness, and a greater degree of insulin sensitivity (Fig. 2), but the precise mechanisms supporting the MHO concept remain to be elucidated.

CLINICAL IMPLICATIONS OF MHO: MORTALITY AND CARDIOVASCULAR DISEASE

A number of studies have reported that the MHO phenotype is associated with increases in mortality, CVD, T2DM, and non-alcoholic fatty liver disease. In a prospective cohort study of 22,654 individuals between the ages of 20 and 59 years (average duration, 13.4 years; EPIC-MORGEN), the mortality risk of metabolically healthy abdominal obese (MHAO) subjects was investigated using the criteria of the Adult Treatment Panel III report of the National Cholesterol Education Program criteria and a definition of obesity based on WC [33]. These authors found that the mortality risk of MHAO individuals was approximately 40% higher than that of metabolically healthy non-abdominal obese individuals [33]. However, regardless of the definition, MHO and metabolically abnormal obese individuals have been found to have an increased risk of mortality relative to metabolically healthy normal-weight individuals [12]. A 30-year follow-up cohort study of obese men with and without metabolic syndrome identified a 2.4- and 1.7-fold higher risk of mortality, respectively, compared to normal-weight subjects without metabolic syndrome [2]. These studies suggest that the MHO phenotype may not accurately predict increased mortality.

There is also conflicting evidence regarding the association of the MHO phenotype with subclinical markers of atherosclerosis. Compared to MHO subjects, MUHO subjects exhibit a
significant increase in the odds ratio (OR) for subclinical atherosclerosis as assessed by coronary artery calcium (CAC) scores [34,35]. In a similar population, MHO subjects exhibited a significantly increased OR for CAC scores, which were attenuated when metabolic risk factors were adjusted for [36]. These findings suggest that the definition of the MHO phenotype should include the absence of any metabolic components. However, when MHO individuals were followed up during longitudinal studies investigating increases in the risks of CVD and all-cause mortality, there were conflicting findings. A 7-year study found that MHO subjects were not at an increased risk of CVD or all-cause mortality compared with healthy non-obese individuals [37] while another study identified a higher prevalence and a greater severity of angiographic coronary artery disease among MUHO and normal-weight subjects, as compared to MHO and normal-weight subjects [38]. An extended follow-up period (>15 years) revealed that obese participants without metabolic syndrome at baseline had an increased risk of major CVD events compared with non-obese subjects who were healthy at baseline [39]. In a Norwegian cohort of more than 60,000 people who were free of CVD, the findings of a 12-year follow-up period revealed that there was an increased risk of acute myocardial infarction among MUHO individuals and that obesity was more important than metabolic factors in the development of heart failure [40].

**CLINICAL IMPLICATIONS: T2DM**

A majority of the studies investigating the relationship between the MHO phenotype and the risk of T2DM are longitudinal. During a 20-year follow-up period conducted by the Uppsala Longitudinal Study of Adult Men (ULSAM) study, the risk of diabetes was significantly increased in normal-weight individuals with metabolic syndrome (OR, 3.28), overweight subjects without metabolic syndrome (OR, 3.49), overweight subjects with metabolic syndrome (OR, 7.77), obese subjects without metabolic syndrome (OR, 11.72), and obese subjects with metabolic syndrome (OR, 10.06), as compared to normal-weight subjects without metabolic syndrome [2]. Similarly, another study found that MHO individuals were at a threefold increased risk of developing diabetes but only if they progressed to an unhealthy phenotype during the follow-up period (5.5 to 10.3 years) [41]. In a study of Mexican-Americans and non-Hispanic whites (San Antonio Heart Study) [42], both metabolically unhealthy normal-weight and MHO individuals had a 2.5-fold increased risk of developing diabetes. Likewise, middle-aged Asian MHO individuals had a higher risk of developing T2DM than their non-obese counterparts during a 5.4-year study [43]. However, in a study of 6,748 Koreans with a 4-year follow-up period, MHO subjects did not have an increased risk of T2DM compared with metabolically healthy non-obese subjects, which suggests that metabolic health is a more important determinant of the development of diabetes than obesity [44].

**MYTH OF MHO**

As mentioned above, a number of studies have provided strong evidence supporting the existence of the MHO phenotype. However, debate remains whether MHO individuals are truly healthy, especially because no consensus has been reached regarding an accepted definition of MHO or the influence of this phenotype on morbidity and mortality [39,40,45]. Nonetheless, the MHO-like phenotype does not appear to be associated with a significant increase in the risk for CVD [46] especially because, as in the ULSAM study, an increased risk for CVD was observed in normal-weight subjects with metabolic syndrome, obese subjects without metabolic syndrome, and obese subjects with metabolic syndrome when compared to normal-weight individuals without metabolic syndrome [39]. However, that study did not support the existence of an MHO phenotype when defining this concept based on the absence of metabolic syndrome.

Very recently, a systematic review of eight studies (n=61,836 subjects) investigated the associations of BMI and metabolic status with total mortality and cardiovascular events [47] and found that MHO individuals have an increased risk of cardiovascular events, as compared to metabolically healthy normal-weight individuals. This study also revealed that all metabolically unhealthy subjects, including normal-weight, overweight, and obese individuals, had a similarly elevated risk of cardiovascular events. The researchers concluded that obese individuals are at increased risk for adverse long-term outcomes, even in the absence of metabolic abnormalities, compared with metabolically healthy normal-weight individuals and emphasized that there is no healthy pattern of increased weight.

However, the findings of the present meta-analysis should be interpreted with caution as there are several limitations inherent in this study. The majority of studies included in this review provided relatively inadequate information regarding the health behaviors of the participants, they did not present data concerning weight gain in the subjects, they tended to fo-
cus only on total mortality and cardiovascular events, and they did not include older participants. According to a very recent editorial by Hill and Wyatt [48], along with the urgent focus to treat obesity regardless of the presence or absence of metabolic risk factors, it is important to reduce the long-term risk of death and cardiovascular events, as with any other chronic disease. However, the findings of the present meta-analysis indicate that any interventions or attempts to treat obesity should target not only the reduction of weight but also the type and proportion of fat that should be reduced. Additionally, the manner in which this is achieved is important because the treatment of obesity without any consideration of the metabolic risk factors is not likely to improve the lives of patients.

CONCLUSIONS

The implications and very existence of the MHO phenotype are still associated with controversy due to the discrepancies among studies regarding the criteria used to define obesity, the experimental designs of these studies, and the ethnicity of the subjects included in these studies. Although the clinical implications of MHO, such as cardiovascular mortality, CVD, and the development of diabetes, cannot be conclusively determined, the concept of a MHO phenotype is important as a tool for the stratification of patients at a high risk for metabolic and CVDs. However, a more unified set of criteria that can be used to define metabolic health needs to be established and clinical efforts aiming to treat obese patients should target reductions in body weight as well as improvements in metabolic risks. If this goal cannot be accomplished, it would be like running from Athens to Marathon without carrying the message box.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Seidell JC. Obesity, insulin resistance and diabetes: a worldwide epidemic. Br J Nutr 2000;83 Suppl 1:S5-8.
2. Arnlöv J, Sundstrom J, Ingelsson E, Lind L. Impact of BMI and the metabolic syndrome on the risk of diabetes in middle-aged men. Diabetes Care 2011;34:61-5.
3. Ruderman NB, Schneider SH, Berchtold P. The “metabolically-obese,” normal-weight individual. Am J Clin Nutr 1981;34:1617-21.
4. Andres R. Effect of obesity on total mortality. Int J Obes 1980;4:381-6.
5. Sims EA. Are there persons who are obese, but metabolically healthy? Metabolism 2001;50:1499-504.
6. Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V, Sladek R, Rabasa-Lhoret R. Characterizing the profile of obese patients who are metabolically healthy. Int J Obes (Lond) 2011;35:971-81.
7. Samocha-Bonet D, Chisholm DJ, Tonks K, Campbell LV, Greenfield JR. Insulin-sensitive obesity in humans: a ‘favorable fat’ phenotype? Trends Endocrinol Metab 2012;23:116-24.
8. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol 2013;1:152-62.
9. Velho S, Paccaud F, Waebber G, Vollenweider P, Marques-Vidal P. Metabolically healthy obesity: different prevalences using different criteria. Eur J Clin Nutr 2010;64:1043-51.
10. Bluher M. The distinction of metabolically ‘healthy’ from ‘unhealthy’ obese individuals. Curr Opin Lipidol 2010;21:38-43.
11. Karelis AD. To be obese: does it matter if you are metabolically healthy? Nat Rev Endocrinol 2011;7:699-700.
12. Himmouho GM, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? Diabetes Care 2013;36:2294-300.
13. Phillips CM, Dillon C, Harrington JM, McCarthy VJ, Kearney PM, Fitzgerald AP, Perry IJ. Defining metabolically healthy obesity: role of dietary and lifestyle factors. PLoS One 2013;8:e76188.
14. Phillips CM. Metabolically healthy obesity: definitions, determinants and clinical implications. Rev Endocr Metab Disord 2013;14:219-27.
15. Yoo HK, Choi EY, Park EW, Cheong YS, Bae RA. Comparison of metabolic characteristics of metabolically healthy but obese (MHO) middle-aged men according to different criteria. Korean J Fam Med 2013;34:19-26.
16. Naukkarinen J, Heinonen S, Hakkarainen A, Lundbom J, Vuolteenaho K, Saarinen L, Hautaniami S, Rodriguez A, Frühbeck G, Pajunen P, Hytöläinen T, Oresic M, Moilanen E, Suomalainen A, Lundbom N, Kaprio J, Rissanen A, Pietiläinen KH. Characterising metabolically healthy obesity in weight-discordant monozygotic twins. Diabetologia
2014;57:167-76.
17. Kloting N, Fasshauer M, Dietrich A, Kovacs P, Schon MR, Kern M, Stumvoll M, Bluher M. Insulin-sensitive obesity. Am J Physiol Endocrinol Metab 2010;299:E506-15.
18. Tran TT, Yamamoto Y, Gesta S, Kahn CR. Beneficial effects of subcutaneous fat transplantation on metabolism. Cell Metab 2008;7:410-20.
19. Koster A, Stenholt S, Alley DE, Kim LJ, Simonsick EM, Kanaya AM, Visser M, Houston DK, Nicklas BJ, Tylavsky FA, Satterfield S, Goodpaster BH, Ferrucci L, Harris TB; Health ABC Study. Body fat distribution and inflammation among obese older adults with and without metabolic syndrome. Obesity (Silver Spring) 2010;18:2354-61.
20. Samocha-Bonet D, Dixit VD, Kahn CR, Leibel RL, Lin X, Nieuwdorp M, Pietilainen KH, Pietilainen JP, Rabasa-Lhoret R, Roden M, Scherer PE, Klein S, Ravussin E. Metabolically healthy and unhealthy obese: the 2013 Stock Conference report. Obesity (Silver Spring) 2014;22:557-64.
21. Almind K, Kahn CR. Genetic determinants of energy expenditure and insulin resistance in diet-induced obesity in mice. Diabetes 2004;53:3274-85.
22. Kulkarni RN, Almind K, Goren HJ, Winnay JN, Ueki K, Okada T, Kahn CR. Impact of genetic background on development of hyperinsulinemia and diabetes in insulin receptor/insulin receptor substrate-1 double heterozygous mice. Diabetes 2003;52:1528-34.
23. Almind K, Kulkarni RN, Lannon SM, Kahn CR. Identification of interactive loci linked to insulin and leptin in mice with genetic insulin resistance. Diabetes 2003;52:1535-43.
24. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, Sowers MR. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med 2008;168:1617-24.
25. Amer P. Regional differences in protein production by human adipose tissue. Biochem Soc Trans 2001;29(Pt 2):72-5.
26. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes 2006;55:1537-45.
27. Kim JY, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, Schraw T, Durand JL, Li H, Li G, Jelicks LA, Mehler MF, Hui DY, Deshaies Y, Shulman GI, Schwartz GJ, Scherer PE. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest 2007;117:2621-37.
28. Esser N, L’Homme L, De Roover A, Kohen L, Scheen AJ, Moutschen M, Piette J, Legrand-Poels S, Paquot N. Obesity phenotype is related to NLRP3 inflammasome activity and immunological profile of visceral adipose tissue. Diabetologia 2013;56:2487-97.
29. Almind K, Kahn CR. Genetic determinants of energy expenditure and insulin resistance in diet-induced obesity in mice. Diabetes 2004;53:3274-85.
30. Kulkarni RN, Almind K, Goren HJ, Winnay JN, Ueki K, Okada T, Kahn CR. Impact of genetic background on development of hyperinsulinemia and diabetes in insulin receptor/insulin receptor substrate-1 double heterozygous mice. Diabetes 2003;52:1528-34.
31. Almind K, Kulkarni RN, Lannon SM, Kahn CR. Identification of interactive loci linked to insulin and leptin in mice with genetic insulin resistance. Diabetes 2003;52:1535-43.
32. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, Sowers MR. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med 2008;168:1617-24.
33. Amer P. Regional differences in protein production by human adipose tissue. Biochem Soc Trans 2001;29(Pt 2):72-5.
28. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes 2006;55:1537-45.
29. Kim JY, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, Schraw T, Durand JL, Li H, Li G, Jelicks LA, Mehler MF, Hui DY, Deshaies Y, Shulman GI, Schwartz GJ, Scherer PE. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest 2007;117:2621-37.
30. Esser N, L’Homme L, De Roover A, Kohen L, Scheen AJ, Moutschen M, Piette J, Legrand-Poels S, Paquot N. Obesity phenotype is related to NLRP3 inflammasome activity and immunological profile of visceral adipose tissue. Diabetologia 2013;56:2487-97.
31. Almind K, Kahn CR. Genetic determinants of energy expenditure and insulin resistance in diet-induced obesity in mice. Diabetes 2004;53:3274-85.
32. Kulkarni RN, Almind K, Goren HJ, Winnay JN, Ueki K, Okada T, Kahn CR. Impact of genetic background on development of hyperinsulinemia and diabetes in insulin receptor/insulin receptor substrate-1 double heterozygous mice. Diabetes 2003;52:1528-34.
33. Almind K, Kulkarni RN, Lannon SM, Kahn CR. Identification of interactive loci linked to insulin and leptin in mice with genetic insulin resistance. Diabetes 2003;52:1535-43.
34. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, Sowers MR. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med 2008;168:1617-24.
ed with both the prevalence and severity of angiographic coronary artery disease. Metabolism 2013;62:952-60.

39. Arnlov J, Ingelsson E, Sundstrom J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation 2010;121:230-6.

40. Morkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trondelag Health Study), Norway. J Am Coll Cardiol 2014;63:1071-8.

41. Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, Adams RJ; North West Adelaide Health Study Team. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care 2013;36:2388-94.

42. Aung K, Lorenzo C, Hinojosa MA, Haffner SM. Risk of developing diabetes and cardiovascular disease in metabolically unhealthy normal-weight and metabolically healthy obese individuals. J Clin Endocrinol Metab 2014;99:462-8.

43. Hwang LC, Bai CH, Sun CA, Chen CJ. Prevalence of metabolically healthy obesity and its impacts on incidences of hypertension, diabetes and the metabolic syndrome in Taiwan. Asia Pac J Clin Nutr 2012;21:227-33.

44. Rhee EJ, Lee MK, Kim JD, Jeon WS, Bae JC, Park SE, Park CY, Oh KW, Park SW, Lee WY. Metabolic health is a more important determinant for diabetes development than simple obesity: a 4-year retrospective longitudinal study. PLoS One 2014;9:e98369.

45. Voulgaris C, Tentolouris N, Dilaveris P, Tousoulis D, Katsilambros N, Stefanadis C. Increased heart failure risk in normal-weight people with metabolic syndrome compared with metabolically healthy obese individuals. J Am Coll Cardiol 2011;58:1343-50.

46. Meigs JB, Wilson PW, Fox CS, Vasan RS, Nathan DM, Sullivan LM, D’Agostino RB. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab 2006;91:2906-12.

47. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. Ann Intern Med 2013;159:758-69.

48. Hill JO, Wyatt HR. The myth of healthy obesity. Ann Intern Med 2013;159:789-90.

49. Aguilar-Salinas CA, Garcia EG, Robles L, Riano D, Ruiz-Gomez DG, Garcia-Ulloon AC, Melgarejo MA, Zamora M, Guillen-Pineda LE, Mehta R, Canizales-Quinteros S, Tusie Luna MT, Gomez-Perez FJ. High adiponectin concentrations are associated with the metabolically healthy obese phenotype. J Clin Endocrinol Metab 2008;93:4075-9.

50. Karelis AD, Brochu M, Rabasa-Lhoret R. Can we identify metabolically healthy but obese individuals (MHO)? Diabetes Metab 2004;30:569-72.

51. Lynch LA, O’Connell JM, Kwasnik AK, Cawood TJ, O’Farrelly C, O’Shea DB. Are natural killer cells protecting the metabolically healthy obese patient? Obesity (Silver Spring) 2009;17:601-5.