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Metabolically healthy obesity: Is it really healthy for type 2 diabetes mellitus?

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Abstract

Metabolically healthy obese (MHO) individuals are reported to have a lower risk of developing cardiovascular diseases in comparison with individuals with metabolic syndrome. However, the association between MHO and type 2 diabetes (T2DM) is still controversial. Some studies indicated that MHO is a favorable phenotype for T2DM, but more studies showed that MHO individuals have an increased risk of developing T2DM compared with metabolically healthy normal-weight individuals, especially among those who would acquire metabolically unhealthy obesity. This has been supported by finding insulin resistance and low-grade inflammatory responses in MHO individuals with a tendency for impaired beta-cell dysfunction. Studies also showed that liver fat accumulation increased the risk of incidence of T2DM in MHO. Here, we reviewed current literature on the relationship between MHO and T2DM, discussed the determinants for the development of diabetes in MHO, and summarized the measures for the prevention of T2DM in MHO.

Key Words: Metabolically healthy obesity; Type 2 diabetes; Non-alcoholic fatty liver diseases; Insulin resistance; Low-grade inflammatory status; Beta-cell dysfunction

Core Tip: Metabolically healthy obese individuals have already developed impaired insulin sensitivity with dysfunction of insulin action on subcutaneous tissue, as well as a tendency for beta-cell dysfunction and a chronic low-grade inflammatory status compared with metabolically healthy normal-weight individuals. Thus, it is an

unfavorable phenotype for type 2 diabetes, with metabolic changes preceding the incidence of diabetes. Liver fat content might be an important contributor to the development of diabetes in metabolically healthy obesity among all risk factors. More attention should be paid to the weight management and metabolic status of these individuals.

INTRODUCTION

Obesity and diabetes have been growing public health problems for decades. The prevalence of obesity had doubled worldwide in 2015 compared with that in 1980[1]. Individuals with obesity are generally likely to develop type 2 diabetes mellitus (T2DM), since obesity is linked to increased risk of insulin resistance, beta-cell dysfunction, and imbalanced fat tissue metabolism[2]. However, there is a subset of obese individuals who are at low risk of cardiovascular disease with a relatively normal metabolic profile compared with metabolic unhealthy obesity (MUO) individuals, a condition known as metabolically healthy obesity (MHO)[3]. Some studies showed that MHO individuals were not at increased risk for diabetes compared with those who are classified as metabolically healthy normal weight (MHNW)[4,5], but others indicated that MHO was associated with an increased risk of developing T2DM over a lifetime than MHNW[6,7]. Whether MHO is a real health status, or more specifically, whether it predisposes individuals to T2DM, is still controversial.

In this review, we address the above questions by discussing controversies related to metabolically healthy obesity, including the causal relationship between MHO and T2DM and its related diseases as well as the underlying mechanisms.

PREVALENCE OF METABOLICALLY HEALTHY OBESITY

MHO was described by Sims in 2001 as obesity with the absence of metabolic syndrome and metabolic complications[8]. Most definitions of MHO are based on the criteria for metabolic syndrome based on the definition provided by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III)[9], which include: (1) The presence of central obesity, waist circumference ≥ 102 cm (90 cm for Asians) in men and ≥ 88 cm (80 cm for Asians) in women; (2) Systolic blood pressure ≥ 17.3 kPa (130 mmHg) and/or diastolic blood pressure ≥ 11.3 kPa (85 mmHg); (3) Triglycerides ≥ 1.7 mmol/L (150 mg/dL); (4) Fasting blood glucose ≥ 5.6 mmol/L (100 mg/dL); and (5) High-density lipoprotein cholesterol (HDL-C) less than 1.03 mmol/L (40 mg/dL) in men or less than 1.30 mmol/L (50 mg/dL) in women. Most definitions of MHO require fewer than two or the absence of any metabolic abnormalities except for waist circumference[7,10-13]. However, the details of the MHO definitions are slightly different. One study defined MHO as individuals who possess no more than two of four metabolic abnormalities except waist circumference[14]. Some researchers believe that those who use anti-hypertension drugs, lipid-lowering agents, or glucose-lowering medicines are also metabolically abnormal even though their metabolic levels are good[15,16]. The level of low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) were also included in the definition of MHO by Karelis *et al*[17]. Insulin resistance evaluated by the homeostasis model assessment for insulin resistance (HOMA-IR) and inflammatory status expressed by C-reactive protein (CRP) has been added to the criteria for MHO by Wildman *et al*[18]. Lwow *et al*[19] proposed using a combined lipid accumulation product with the criteria mentioned above as new criteria for MHO. Smith *et al*[20] decreased the cut point of triglyceride to a level of 95 mg/dL and includes the criteria for the evaluation of intrahepatic lipid content. MHO was also defined as the absence of metabolic diseases such as hypertension, T2DM, and dyslipidemia[15]. The detailed information of common definitions of

MHO was showed in Table 1.

The prevalence of MHO differs from 2.2% to 11.9% in the general population according to the different definitions of MHO[21]. The prevalence of MHO in Americans from the National Health and Nutrition Examination Survey was 19.9% when metabolic health was defined as the absence of components of NCEP ATP-III; the prevalence decreased to 16.0% when the threshold of glucose was reduced to 100 mg/dL, and it decreased to 14.8% when HbA1c was included in the definition of MHO. The prevalence further decreased to 12.2% when the cut-off point of blood pressure was reduced from 17.3/11.3 kPa (130/85 mmHg) to 16.0/10.6 kPa (120/80 mmHg)[22]. Using the criteria of less than three components of NCEP ATP-III, the prevalence of MHO was 8.6% in Spanish[23] and 10.3% in China[24]. There was an age-related reduction in the proportion of MHO regardless of different definitions[24]. Besides, obese patients with higher body mass index (BMI) levels had a lower proportion of MHO, which accounted for 53.7% of participants with BMI at 30-34.9 kg/m^2 and 4.9% of participants with BMI at 35-39.9 kg/m^2[25]. When a more stringent criterion of having no components of NECP ATP-III was applied to the definition of MHO, there was no metabolic healthy individual with BMI ≥ 35 kg/m^2[23]. It means that there might be a cut-off point in individuals with MHO, beyond which their metabolic status would no longer be healthy.

Metabolically healthy individuals will develop metabolic disorders over time. Feng *et al*[7] discovered that only 42.84% of individuals in a group of MHO remained metabolic healthy after a 4-year follow-up. Gilardini *et al*[26] reported that 44% of MHO became metabolically unhealthy after 6-year follow-up, and the proportion increased to 62% after 12-year follow-up. The proportion of transition from MHO to MUO might differ because of different definitions of MHO and various lengths of follow-up[27]. Generally speaking, MHO is not a health status according to the current definitions of having one or two abnormal conditions but rather a transient state that can transition to an unhealthy state over time. Thus, it is fundamentally inaccurate to define those groups of people as "healthy" and worthwhile to investigate the relationship between MHO and T2DM.

RISK OF T2DM IN MHO SUBJECTS

The association between T2DM and MHO has been studied with diverse results, as shown in Table 2. Although MHO is believed to be a healthier phenotype for T2DM when compared with metabolically unhealthy normal weight and MUO individuals, most of the current studies supported that MHO phenotype relates to an increased incidence of T2DM in cohort studies compared to MHNW individuals, independent of the length of follow-up[7,16,28-31]. Wei *et al*[30] examined 17801 individuals in the Dongfeng-Tongji cohort study and showed that the hazard ratio [95% confidence interval (CI)] of diabetes for MHO was 1.74 (1.16-2.59). The multivariate-adjusted hazard ratio (95%CI) of diabetes for MHO without non-alcoholic fatty liver diseases (NAFLD) was 1.57 (1.14-2.16) after an average 4.1-year follow-up in The Kangbuk Samsung Health Study[16]. However, studies have also found that different subgroups of MHO individuals have different risks of developing diabetes at follow-up [14,30,32,33]. For example, Wang *et al*[33] found that an MHO phenotype that is stable over time is not significantly related to an increased risk of incident diabetes in a 6-year follow-up cohort study when compared with the MHNW phenotype, while the majority of MHO participants had an increased risk of developing diabetes over their lifetimes. Consistently, our human data from Shanghai Changfeng Study showed a similar result that MHO individuals who transition into MUO had a higher risk of developing T2DM while there was no significant association between MHO and incidence of diabetes in the whole population (unpublished data). Thus, it will be of great importance to investigate the determinants related to incident diabetes in MHO individuals.

Several factors might contribute to the development of T2DM in the MHO participants. Baseline body weight is an important factor associated with the high risk of incidence of diabetes. It is universally known that obesity can increase the risk of T2DM. One study found that obese individuals (BMI ≥ 30 kg/m^2) with a healthy metabolic status were at greater risk of developing diabetes than either overweight or normal-weight subjects, and the risk was in proportion to the degree of obesity[14,34]. The previous study has also shown that all metabolically unhealthy individuals, regardless of their body weight, have a higher risk of diabetes[14]. Unstable MHO individuals who progress into unhealthy metabolic statuses also have an elevated risk

Table 1 Definitions of metabolic health in previous publications

Ref.	BP, kPa (mmHg)	Plasma glucose, mmol/L	TG, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	TC, mmol/L	WC, cm	Insulin sensitivity	CRP, mg/L	Intrahepatic lipid content	Others	Metabolic health
NECP ATP III [9]	SBP ≥ 17.3 (130) and/or DBP ≥ 11.3 (85) and/or treatment	FPG ≥ 5.60	≥ 1.70	< 1.29 in women, < 1.03 in men	-	-	> 88 in women, >102 in men	-	-	-	-	< 3 of above
Karelis *et al*[17]	-	-	≤ 1.70	≥ 1.30 and no treatment	≤ 2.60 and no treatment	≤ 5.20	-	HOMA-IR ≤ 1.95	-	-	-	> 3 of above
Meigs *et al*[4]	SBP ≥ 17.3 (130) or DBP ≥ 11.3(85) or treatment	5.6 < FPG ≤ 6.9	≥ 1.70	< 1.30 in women, < 1.00 in men	-	-	> 88 in women, > 102 in men	-	-	-	-	< 2 of above
Meigs *et al*[4]	-	-	-	-	-	-	-	HOMA-IR ≥ 75th percentile	-	-	-	None of above
Aguilar-Salinas *et al*[89]	SBP > 18.6 (140) and/or DBP > 12.0 (90) and/or treatment	FPG ≥ 7.0, or 2-h OGTT ≥ 11.1, or RBG ≥ 11.11 or treatment	-	< 1.04	-	-	-	-	-	-	-	None of above
Wildman *et al* [18]	SBP ≥ 17.3 (130) or DBP ≥ 11.3 (85) or treatment	FPG ≥ 5.56 or treatment	≥ 1.70	< 1.30 in women, < 1.04 in men or treatment	-	-	-	HOMA-IR > 90th percentile	> 90th percentile	-	-	< 2 of above
van Vliet-Ostaptchouk *et al*[90]	SBP ≥ 17.3 (130) or DBP ≥ 11.3 (85) or treatment	FPG ≥ 6.10 or treatment or history/diagnosis of type 2 diabetes	≥ 1.70 or treatment	< 1.03 in men or < 1.30 in women or treatment	-	-	-	-	-	-	-	<2 of above
Jana V van Vliet-Ostaptchouk *et al*[90]	SBP ≥ 18.6 (140) or DBP ≥ 12.0(90) or treatment	FPG ≥ 7.0 or treatment or history/diagnosis of type 2 diabetes	≥ 1.70 or treatment	< 1.03 in men or < 1.30 in women or treatment	-	-	-	-	-	-	-	< 2 of above
Smith *et al*[20]	SBP < 17.3 (130) and/or DBP < 11.3 (85)	FPG < 5.60, or 2-h OGTT glucose < 7.80	< 1.07	≥ 1.29 in women, ≥ 1.04 in men	-	-	-	GIR > 8 mg/kg FFM/min during an HECP (insulin infusion rate: 40 mU/m^2/min)	-	< 5% of liver volume by imaging or < 5% of hepatocytes with intracellular TG by histology	Basic criteria: Absence of diagnosis or therapy of cardiometabolic diseases	all of above

BP: Blood pressure; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; OGTT: Oral glucose tolerance test; RBG: Random blood glucose; HbA1c: Glycosylated hemoglobin A1c; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; WC: Waist circumference; HOMA-IR: Homeostasis model assessment of insulin resistance; GIR: Glucose infusion rate; HECP: Hyperinsulinemic-euglycemic clamp procedure; hs-CRP: High-sensitivity C-reactive protein.

Table 2 Cohort studies of the association of metabolically healthy obesity and type 2 diabetes in the last 5 years

Ref.	Definition of "metabolic health"	MHO, *n*	Main findings
Wei *et al*[30], 2020	Having < 2 of the following criteria: (1) TG ≥ 1.7 mmol/L or lipid-lowering drugs; (2) SBP ≥ 17.3 kPa (130 mmHg) or DBP ≥ 11.3 kPa (85 mmHg) or anti-hypertensive drugs; (3) FPG ≥ 5.6 mmol/L; and (4) HDL-C < 1.04 mmol/L for men and < 1.29 mmol/L for women.	693	MHO was associated with an increased incidence of diabetes, and the association did not differ by the presence or absence of NAFLD.
Feng *et al*[7], 2020	Having < 2 of the following criteria: (1) Hyperglycemia, defined as FPG ≥ 5.6 mmol/L (100 mg/dL); (2) Elevated blood pressure, defined as SBP ≥ 17.3 kPa (130 mmHg) and/or DBP ≥11.3 kPa (85 mmHg) or antihypertensive drug treatment; (3) Hypertriglyceridemia, defined as TG ≥ 1.7 mmol/L (150 mg/dL); and (4) Reduced HDL-C levels, defined as drug treatment to increase HDL-C levels.	3728	The MHO phenotype was associated with an increased incidence of diabetes in older adults. The presence of metabolic disorders in the group with MHO was associated with increased diabetes risk and was predicted by the waist circumference at baseline.
Kim *et al*[32], 2019	Having two or fewer metabolic abnormalities as follows: (1) WC ≥ 90 cm in men and ≥ 85 cm in women; (2) SBP ≥ 17.3 kPa (130 mmHg) or DBP ≥ 11.3 kPa (85 mmHg) or medication use; (3) FPG ≥ 5.6 mmol/L (100 mg/dL) or claim for T2DM or on anti-diabetic medications; (4) Hypertriglyceridemia ≥ 1.7 mmol/L (150 mg/dL) or on lipid medications; and (5) HDL-C < 1.04 mmol/L (40 mg/dL) in men and < 1.29 mmol/L (50 mg/dL) in women, or medication use.	796371	MHO and MHNW phenotypes were transient phenotypes, and their change into metabolic unhealthy status was an important risk factor for the development of T2DM both in obese and normal-weight subjects. Transition into a metabolically unhealthy phenotype was a more significant risk factor of developing T2DM than obesity itself.
Wang *et al*[33], 2018	Having < 2 of the following criteria: (1) SBP ≥ 17.3 kPa (130 mmHg) or DBP ≥ 11.3 kPa (85 mmHg) or current treatment for hypertension; (2) Fasting TG level ≥ 1.7 mmol/L; (3) HDL-C level < 1.03 mmol/l for males or < 1.29 mmol/L for females; and (4) FPG ≥ 5.60 mmol/L.	2153	Stable metabolically healthy overweight/obesity Individuals and those who transitioned to the metabolically healthy status from MUNW did not have an increased risk of incident T2DM. Participants who transitioned from the metabolically healthy overweight/obesity to metabolically unhealthy overweight/obesity phenotype and stable MUNW phenotype showed an increased risk of incident T2DM.
Fingeret *et al* [31], 2018	Having two or fewer metabolic abnormalities as follows: (1) FPG ≥ 5.6 mmol/L or drug treatment; (2) Fasting TG ≥ 1.7 mmol/L or drug treatment; (3) Fasting HDL-C < 1.30 mmol/L in women and < 1.00 mmol/L in men or drug treatment; (4) SBP ≥ 17.3 kPa (130 mmHg), DBP ≥ 11.3 kPa (85 mmHg), or drug treatment; and (5) WC ≥ 102 cm for men and ≥ 88 cm for women.	170	MHO leads to a higher risk of developing cardiovascular risk factors such as hypertension, diabetes, dyslipidemia as compared with MHNW. MHO is transient and should be regarded by clinicians as a warning sign.
Liu *et al*[91], 2018	Having < 2 of metabolic abnormalities as follows: (1) TG ≥ 1.7 mmol/L; (2) HDL-C < 1.0 mmol/L; (3) SBP ≥ 17.3 kPa (130 mmHg) and/or DBP ≥ 11.3 kPa (85 mmHg); and (4) FPG ≥ 5.6 mmol/ L (≥ 100 mg/dL).	1184	MHO and MUNW phenotypes had an increased risk for diabetes. Both baseline metabolic status and follow-up changes played more important roles than obesity for diabetes incidence after adjusted for potential confounding factors. MHO is a transient condition.
Janghorbani *et al*[29], 2017	Having none of metabolic abnormalities as follows: (1) TG ≥ 1.7 mmol/L (150 mg/dL); (2) HDL < 1.04 mmol/L(40 mg/dL) in men and < 1.29 mmol/L(50 mg/dL) in women; (3)BP ≥ 17.3/11.3 kPa (130/85 mmHg) or on antihypertensive medication; and (4) FPG ≥ 5.6 mmol/L (100 mg/dL).	75	Metabolic abnormalities increased risk for incident T2D at any BMI status. Also, obesity is a risk factor for the incidence of T2DM, even in the absence of any metabolic abnormalities.
Latifi *et al*[25], 2017	Having none of metabolic abnormalities as follows: (1) WC ≥ 102 cm in men and ≥ 88 cm in women; (2) TG ≥ 1.7 mmol/L (150 mg/dL) or drug use; (3) HDL < 1.04 mmol/L (40 mg/dL) in men and 1.29 mmol/L (50 mg/dL) in women or drug consumption for hyperlipidemia; (4) BP ≥ 17.3/10.6 kPa (130/80 mmHg) or a history of anti-hypertensive drug consumption; and (5) FPG ≥ 5.6 mmol/L (100 mg/dL), or a history of diabetes mellitus or consumption of anti-diabetes drugs.	NA	There was a specific higher risk of developing metabolic syndrome and diabetes in MHO.
Navarro-Gonzalez *et al* [14], 2016	Having < 3 of the following criteria: (1) TG ≥ 1.7 mmol/L (150 mg/dL); (2) HDL-C > 1.04 mmol/L (40 mg/dL) for men and > 1.29 mmol/L (50 mg/dL) for women; (3) BP ≥ 17.3/11.3 kPa (130/85 mmHg); or (4) FPG ≥ 5.6 mmol/L (100 mg/dL). All individuals currently taking a pharmacological treatment for hypertension were assumed to have raised BP.	389	MHO individuals had an increased risk of incident type 2 diabetes but mainly among those who progressed MUO. MHO individuals who remained with one or no metabolic health risk factors or lost weight overtime did not have a significant risk of diabetes. Metabolically unhealthy individuals had a greater risk of diabetes compared with subjects with MHO.
Guo *et al*[3], 2016	Having all three components as follows: (1) Untreated SBP < 17.3 kPa (130 mmHg) and DBP < 11.3 kPa (85 mmHg); (2) Untreated FPG < 5.6 mmol/L (100 mg/dl) or HbA1c < 5.7%; and (3) Untreated TC < 6.2 mmol/L (240 mg/dL) and HDL ≥ 1.04 mmol/L (40 mg/dL) in men and ≥ 1.29 mmol/L (50 mg/dL) in women.	260	People with healthy obesity have lower risks for diabetes, coronary heart disease, stroke, and mortality compared with unhealthy subjects regardless of their BMI status. Obesity did not affect the risks of coronary heart disease, stroke, and mortality, but did increase diabetes risk.

Jung *et al*[40], 2016	Having < 2 of the following criteria: (1) SBP ≥ 17.3 kPa (130 mmHg) and/or a DBP ≥ 11.3 kPa (85 mmHg), or on antihypertensive treatment; (2) TG ≥ 1.7 mmol/L; (3) FPG ≥ 5.6 mmol/L (impaired fasting glucose, IFG); (4) HDL-C < 1.0 mmol/L in men and < 1.3 mmol/L in women; (5) HOMA-IR ≥ 90th percentile (≥ 2.91); and (6) Hs-CRP ≥ 90th percentile (≥ 2.0 mg/L).	4635	MHO subjects have a substantially increased risk of incident type 2 diabetes compared with MHNO subjects in an Asian population. The presence of FLD assessed by FLI partially explains this increased risk.
Chang *et al*[16], 2016	Having none of the following criteria: (1) BP ≥ 17.3/11.3 kPa (130/85 mmHg) or current use of blood pressure-lowering agents; (2) FPG ≥ 5.6 mmol/L (100 mg/dL) or current use of blood glucose-lowering agents; (3) TG ≥ 1.7 mmol/L (150 mg/dL) or current use of lipid-lowering agents (15); (4) HDL-C < 1.04 mmol/L (40 mg/dL) in men or < 1.29 mmol/L (50 mg/dL) in women; or (5) Insulin resistance, defined as HOMA-IR score ≥ 2.5.	8140	Metabolically healthy overweight and obese individuals were both associated with an increased incidence of diabetes, even in the absence of NAFLD. Obese phenotype itself can drive the development of diabetes, even in the absence of metabolic abnormalities and NAFLD.
Ryoo *et al*[34], 2015	Having < 2 of the following criteria: (1) SBP ≥ 17.3 kPa (130 mmHg) and/or DBP ≥ 11.3 kPa (85 mmHg); (2) TG ≥ 1.7 mmol/L; (3) FPG ≥ 5.6 mmol/L; (4) HDL-C < 1.0 mmol/L; and (5) HOMA-IR ≥ 90th percentile.	240	The risk for diabetes was in proportion to both metabolic health status and degree of obesity in Korean men. Additionally, metabolically healthy status was a more significant determinant for the development of diabetes than obesity itself.

TG: Triglycerides; BP: Blood pressure; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; HOMA-IR: Homeostatic model assessment of insulin resistance; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; hs-CRP: High sensitivity C reactive protein; WC: Waist circumference; T2DM: Type 2 diabetes mellitus; MHO: Metabolically healthy obesity; MUO: Metabolically unhealthy obesity; MHNW: Metabolically healthy normal weight; MUNW: Metabolically unhealthy normal weight; NAFLD: Non-alcoholic fatty liver disease; FLI: Fatty liver index.

of developing diabetes. Weight gain was a risk factor for the progression from a healthy condition to an unhealthy one, which further develops into T2DM. In one study, MHO individuals who developed cardiometabolic risk complications gained 6% ± 14% of their body weight (4.9 ± 11.8 kg) compared to 5% ± 14% (3.9 ± 11.3 kg) for those that retained a healthy status[35]. Besides, MHO participants with larger waist circumference at baseline are more likely to transition into an unhealthy phenotype[7]. This has been supported by studies showing that visceral abdominal fat accumulation and fatty liver in MHO contribute to this transition[12,36,37]. Thus, MHO individuals with high liver fat content or large waist circumference are possibly associated with a high risk of diabetes as they have a trend to transferring into MUO phenotype. Our previous study found that visceral adipose area measured by visceral adiposity index in Chinese adults has a more favorable function to predict the development of diabetes than BMI and waist circumference in MHO individuals[38]. Some researchers found that MHO individuals with a high fatty liver index[39] have an increased risk of incident T2DM[40].

LIVER FAT ACCUMULATION IS CRUCIAL FOR DETERMINING THE DEVELOPMENT OF T2DM IN MHO

NAFLD is believed to be significantly associated with the long-term risk of T2DM, and increased liver fat can predict the incidence of T2DM independent of obesity[41,42]. Bian *et al*[43] found that elevated liver fat content (LFC) showed a positive association with insulin resistance and a higher level of nocturnal mean blood concentration before the onset of diabetes. The presence of NAFLD will promote the transition from MHO to a metabolic unhealthy state, and further increases the long-term risk of

incidence of T2DM and even aggravates the deterioration of liver diseases in MHO. Hwang *et al*[12] found that the presence of NAFLD in MHO could predict the conversion from a metabolic health status into a metabolic unhealthy status independent of age, sex, BMI, lifestyle factors, components of metabolic syndrome, and insulin resistance evaluated by HOMA-IR. This result was supported by Hashimoto *et al*[37] with findings that fatty liver index was a predictor for the transition from MHO to MUO phenotype even adjusted for body weight change. However, Hwang *et al*[12] also found that the association between the NAFLD and future transition of MHO into MUO weakened as BMI increased, and the relationship was more prominent in lower BMI individuals. Studies also found that the risk of NAFLD, non-alcoholic steatohepatitis, and liver fibrosis increased as BMI elevated in MHO[16,44]. The unstable MHO status predicted by NAFLD would increase the risk for the development of T2DM, as mentioned above, and therefore the presence of NAFLD in MHO might increase the risk of incident T2DM. Chang *et al*[16] supported this with the result that the risk of incidence of T2DM in MHO subjects with NAFLD increased compared to those free of NAFLD. Ampuero *et al*[45] also found that MHO individuals with biopsy-proven NAFLD or with an intermediate-to-high risk of significant fibrosis evaluated by Hepanet Fibrosis Score (> 0.12) were at risk of developing T2DM.

However, despite the presence of elevated LFC in MHO increasing the risk for the transition of MHO and the incidence of T2DM, few studies regarded intrahepatic lipids content as one of the criteria for the definition of metabolic health. Our previous study found that LFC was positively associated with metabolic disorders independent of related anthropometric and metabolic parameters, and the risk for metabolic diseases increased in an LFC-dependent manner when LFC ≥ 5%[46]. Besides, part of normal individuals without metabolic disorders had a higher LFC[46]. Hence, we agree with Smith *et al*[20] that the evaluation of LFC should be regarded as another crucial criterion for defining "metabolic health".

ASSOCIATION BETWEEN MHO AND METABOLIC DISEASES RELATED TO T2DM

Cardiovascular disease

Studies have found that subjects with MHO have a lower risk of cardiovascular disease (CVD) than MUO individuals over their lifetimes but still have a higher risk than MHNW subjects[47-50]. The transition to an unhealthier metabolic status and the longer duration of unhealthy metabolic conditions contribute to the increased risk of developing CVD among MHO subjects[50-52]. Furthermore, the risk of developing CVD for MHO subjects who initially develop diabetes, hypertension, or hypercholesterolemia tends to be higher than in MHNW subjects[53]. Obesity might increase the risk of CVD independently. A meta-analysis concluded that CVD risk is increased in metabolically healthy overweight or obese participants than in MHNW individuals even when there are no metabolic risk factors[54]. Similarly, obese individuals have been reported to be at higher risk of coronary heart disease irrespective of metabolic health, which challenges the concept of "metabolically healthy obesity"[55].

Chronic kidney disease

Previous studies have shown an increased risk of developing chronic kidney disease (CKD), defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 in metabolically healthy overweight/obese subjects compared to MHNW individuals at follow-up, with metabolic health judged as having less than two metabolic abnormalities[56]. Another study showed a similar result in which MHO individuals with no metabolic abnormalities had a higher risk of developing CKD, and this risk was greater in those 40 years or older than in the young[57]. Systemic inflammation measured by high sensitivity-CRP (hs-CRP) might partially contribute to the association between MHO and CKD[11]. Furthermore, individuals who progress to MUO at follow-up show a higher risk of CKD compared with remaining MHO subjects[58,59]. However, Chen *et al*[60] found that the risk difference was not significant in MHO subjects compared to MHNW individuals in the early stage of CKD. This discrepancy might come from the different definitions of CKD, as Chen *et al* [60] combined proteinuria and structural changes in the kidney as indicators.

POSSIBLE MECHANISMS OF THE FUTURE INCIDENCE OF T2DM IN MHO

The possible mechanisms underlying the pathophysiology of incident T2DM in MHO include beta-cell dysfunction, insulin resistance, leptin and adiponectin imbalance, as well as a chronic low-grade inflammatory status (Figure 1). The presence of NAFLD in MHO is also an important factor for the development of T2DM.

Impaired insulin action and insulin resistance

Mature insulin and C-peptide are produced from the precursor proinsulin, and increased proinsulin is observed in insulin-resistant and/or glucose-intolerant individuals[61]. Significantly increased levels of plasma proinsulin, split proinsulin, and C-peptide are observed in MHO subjects compared to MHNW subjects[62]. A similar result has been found in a Chinese population, in which the serum insulin of MHO subjects is significantly elevated[63]. Studies have confirmed the above results showing that HOMA-IR evaluations are significantly different between MHO and MHNW subjects, with a higher value of HOMA-IR in MHO individuals[62,63].

The action of insulin on subcutaneous adipocytes is impaired as well. Rydén *et al*[10] compared the inhibitory action on lipolysis and the stimulatory effect on lipogenesis of insulin in metabolically healthy subjects who were lean, overweight, or obese and found that insulin resistance was already observed in metabolically healthy overweight and obese subjects. In the classical agonist-receptor interaction model, the half-maximum effects for insulin to inhibit adipocyte lipolysis and lipogenesis in overweight/obese people were 10 times and 100 times higher than that in lean people, respectively. The above model suggested that alterations in intracellular events downstream of the insulin receptor and their initial signaling steps have already happened in those individuals. The decreased expression of the insulin signaling mediator *AKT2* might partially explain the increased maximum concentration of insulin hormones needed for an antilipolytic effect and lipogenesis, as AKT2 is an early signaling factor common to the two pathways[64]. Furthermore, the impaired lipogenic function might in part result from a decrease in *SLC2A4* (glucose transporter type 4) mRNA expression, which is essential for insulin-induced glucose uptake by fat cells and stimulating lipogenesis[64]. When testing the maximum insulin action on subcutaneous adipocytes, Rydén *et al*[10] found that the lipogenic effect of insulin hormone was reduced by more than 50% in healthy overweight/obese subjects comparing to lean individuals, and the effect was further impaired in the unhealthy obese groups. Thus, there are reasons to believe that insulin resistance is already present in MHO individuals.

Beta-cell dysfunction

There is no apparent evidence that beta cells in MHO subjects are severely impaired, but they may be partially impaired according to previous studies. Hjelmgren *et al*[62] found that MHO individuals are at increased risk for having β-cell dysfunction, as evaluated by proinsulin levels > 11 pmol/L compared to MHNW subjects, with a relative risk of 18.2 (95%CI: 2.1-159.3). However, Zhao *et al*[63] failed to find a significant difference in HOMA-β between MHNW and obese subjects, though the value of HOMA-β in MHO tended to be higher than that in MHNW individuals among middle-aged subjects. The discrepancy between the two studies might come from their different definitions of metabolic health, differences in race and age, and the relatively small sample size in Zhao's study for evaluating statistical differences. Overall, studies on beta-cell dysfunction are too few to confirm their impaired function in MHO individuals.

Immune and inflammatory responses

Obesity has always been believed to be a chronic low-grade inflammatory status[65], referred to as meta-inflammation. This chronic low-grade inflammation is believed to be a central link between obesity and T2DM[66,67]. A previous study showed that meta-inflammation is presented in MHO subjects as well[68].

Macrophage infiltration in adipose tissue causes increased proinflammatory cytokines and contributes to the development of insulin resistance and T2DM[69]. Christou *et al*[70] found that circulating inflammatory intermediate monocytes [Mon2 (CD14^{++}CD16^{+})] are upregulated in MHO individuals, and nonclassical monocytes [Mon3 (CD14^{+}CD16^{++})] tended to be higher in comparison to metabolically healthy lean individuals when metabolic health was defined as fewer than two metabolic disabilities. The absolute counts of nonclassical Mon3 showed a positive association with HOMA-IR in that study. However, that result differed from previous studies, as
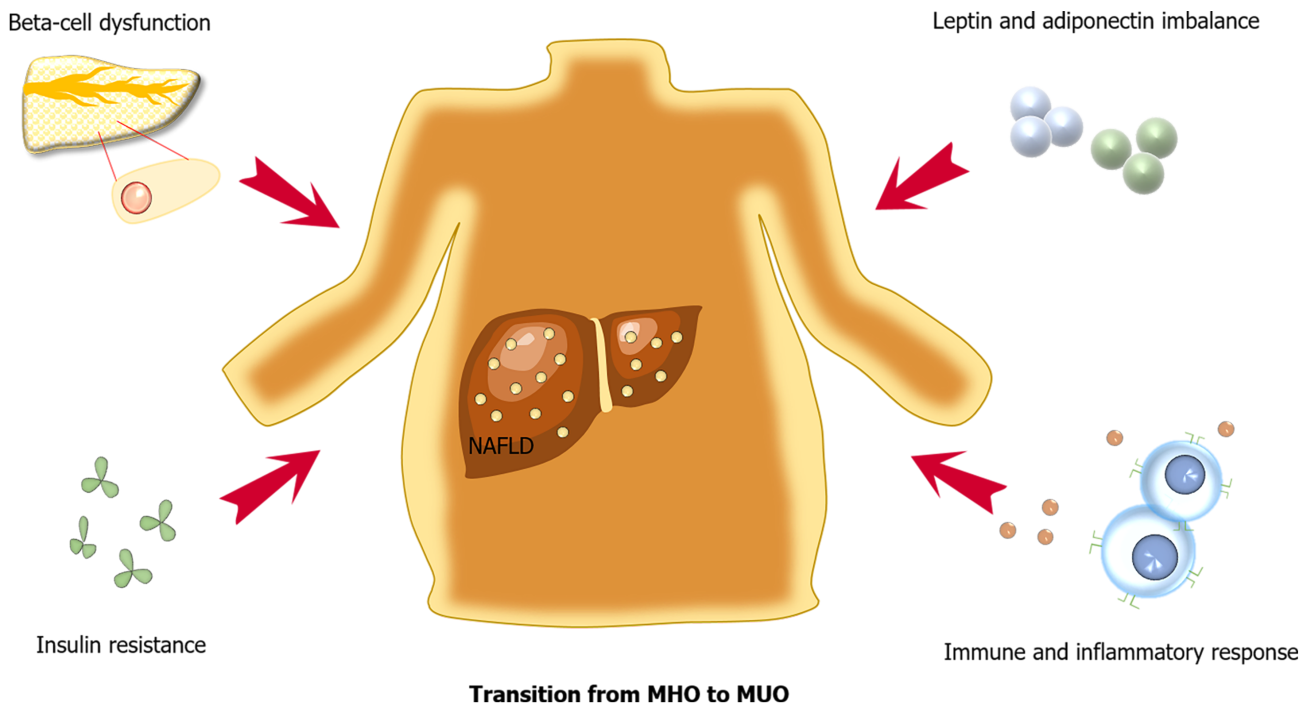
Figure 1 Possible mechanisms that contribute to the future incidence of type 2 diabetes mellitus in the transition from metabolically healthy obesity to metabolically unhealthy obesity. The presence of non-alcoholic fatty liver disease in metabolically healthy obesity is crucial to the incidence of type 2 diabetes mellitus. The possible mechanisms underlying the future development of type 2 diabetes mellitus in metabolically healthy obesity include beta-cell dysfunction, insulin resistance with impaired insulin action, adiponectin concentration reduction, as well as a chronic low-grade inflammatory status. MHO: Metabolically healthy obesity; MUO: Metabolically unhealthy obesity; NAFLD: Non-alcoholic fatty liver disease.

the participants they recruited were taking antidiabetic medications, which might have disturbed the relationship between Mon3 and the level of insulin resistance[71,72].

A previous study found that an imbalance of T cell subsets is responsible for the pathogenesis of obesity and T2DM[68]. Th22 subsets might play a role in obesity and T2DM progression, with MHO and T2DM individuals having significantly elevated peripheral blood Th22 frequencies[73]. This might partially result from the significantly increased transcription of aryl hydrocarbon receptor (AHR), a transcription factor responsible for the differentiation of Th22, on peripheral blood mononuclear cells in both obese and T2DM individuals compared with metabolically healthy normal BMI subjects. AHR is significantly positively associated with elevated hs-CRP and HOMA-IR levels in MHO individuals. Although it was tested in peripheral blood mononuclear cells and not T cells in that study, AHR expression in peripheral blood mononuclear cells is more likely to be a causative factor in Th polarization with a currently unknown mechanism[63].

Leptin and adiponectin
Adipose tissue is not only an energy storage depot, it also has endocrine functions and produces some cytokines that influence metabolism throughout the human body. White fat tissue can participate in regulating insulin sensitivity, lipid metabolism, and low-grade inflammation[74,75]. Leptin and adiponectin are important factors in these conditions. Leptin is responsible for food intake and metabolism regulation, while adiponectin release contributes to energy metabolism, insulin action, lipid metabolism regulation, and oxidative stress. Increased adiponectin is associated with better insulin sensitivity in the human body[76]. A previous study found that adiponectin is significantly decreased in MHO Han Chinese adolescents compared with a normal-weight control group, and a similar result was also found in middle-aged Norwegians [77,78]. Thus, insulin sensitivity might be disturbed in MHO individuals with elevated adiponectin. However, Carvalho *et al*[79] found an inconsistent result that the serum adiponectin concentration in MHO subjects had no significant difference with MHNW individuals. The small sample size of the latter study might have contributed to the inability to find statistically significant differences in adiponectin. Taken together, most studies indicated an increased leptin/adiponectin ratio in MHO compared to MHNW individuals[77-79], which was already regarded as a sensitive indicator of metabolic syndrome and insulin sensitivity[80]. Thus, no matter whether adiponectin

is decreased in MHO individuals, it can be deduced that insulin sensitivity has been already impaired in MHO subjects with an elevated leptin/adiponectin ratio.

WEIGHT CONTROL MIGHT IMPROVE T2DM RISK IN MHO

There are few clinical procedures for MHO individuals to prevent the high risk of incidence of T2DM, but studies have shown evidence of benefits of weight loss for MHO with the improvement of metabolic parameters and inflammatory biomarkers.

A cohort study has found that bariatric surgery could significantly achieve a great deal of total weight loss in MHO patients at follow-up[81]. Some studies have shown that MHO could achieve more weight loss than that in MUO participants after bariatric surgery[82-84], suggesting that the MHO phenotype is an independent predictor for greater body weight loss and more effective bariatric surgery in obese individuals before metabolic abnormalities appear[83]. Furthermore, cardiovascular risk factors such as blood pressure, lipid levels, and plasma glucose are improved after bariatric surgery, even when some of these levels are "normal" preoperatively[81]. Otherwise, these indexes show more improvement in metabolically unhealthy individuals[81,84]. However, Pelascini *et al*[82] failed to find significant improvements in HDL-C and plasma glucose in MHO participants, which might have resulted from their relatively small sample size and strict definition of "metabolic health" plus HOMA-IR and hs-CRP. In summary, the benefits of bariatric surgery for the MHO phenotype are considerable, potentially comparable in benefit to the unhealthier phenotype with much better weight loss[84]. However, this has only been tested and observed in MHO subjects whose BMI was ≥ 40 kg/m^2. For the majority of MHO individuals, the application of bariatric surgery is not recommended in the current clinical environment with no more solid testimonies.

For the majority of those individuals with MHO, cultivating a favorable lifestyle might be a more feasible method to achieve weight loss. Studies have demonstrated that a healthier diet with a higher proportion of fruit, vegetables, and fish and longer mealtimes (more than 10 min) in women and higher degrees of physical activity is associated with the MHO phenotype compared with the MUO phenotype[85,86]. Gomez-Huelgas *et al*[87] found that intensive lifestyle modification could induce clinically significant weight loss in MHO phenotype women, leading to the reduction of serum adipokines and inflammatory biomarkers such as hs-CRP, interleukin-6, and tumor necrosis factor-α, which play important roles in the pathological mechanism of obesity and insulin resistance.

In a prospective cohort study of the MHO population, it was found that air pollution had a significantly positive correlation with adiponectin and hs-CRP, which suggests that air pollution plays an important role in the occurrence and development of diabetes in MHO individuals[88]. It will be interesting to compare the risk of the incident in MHO with and without exposure to polluted air.

CONCLUSION

Current MHO diagnostic criteria are insufficient to exclude all obese people with the potential to develop future metabolic disorders. How to define MHO is an issue worth discussing. MHO is not absolutely "metabolically healthy" compared to MHNW with potential risks for T2DM and its related metabolic disorders. This might be explained by mechanisms such as the expansion and hypoxia of adipose tissue, increased inflammation, and decreased adiponectin concentrations in the MHO population. Liver fat accumulation is also a crucial risk factor for the incidence of T2DM in MHO. Thus, we recommend adding the intrahepatic fat content into the criteria for "metabolic health". Weight control might effectively protect the MHO individuals from the development of diabetes and its related metabolic diseases. In addition, MHO is a transitional phenotype between MHNW and MUO. It will be worthwhile to investigate the crucial factors that are responsible for the transition from MHO to MUO. The advance of multi-omics technology might help us to identify better MHO with a higher risk of developing diabetes and multiple metabolic disorders.

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