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Metabolically Healthy Obesity and Its Associates in Mongolian Chinese Adults

Mingzhi Zhang, MD, PhD,[1,2] Weijun Tong, MS,[1] Jing Chen, MD, MS,[3] Yonghong Zhang, MD, PhD,[1] and Shengxu Li, MD, PhD[2]

Abstract

Background: Not all obese individuals show cardiometabolic abnormalities. We examined metabolically healthy obesity (MHO) and its associates in 2530 Mongolian Chinese adults.
Methods: MHO was defined by waist circumference, low-density lipoprotein (LDL-C) cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), systolic blood pressure (SBP), diastolic blood pressure (DBP), and glucose.
Results: Only 3.0% of the participants had MHO, with 0.8% of men and 4.5% of women having this condition ($P < 0.001$ for sex difference). Despite striking differences in obesity measures, MHO individuals had a comparable cardiometabolic profile to that for metabolically healthy, nonobese individuals (MHNO) and an improved cardiometabolic profile, *i.e.*, lower levels of blood pressure, glucose, insulin, LDL-C, TGs, and higher levels of HDL-C compared to metabolically abnormal individuals (all $P < 0.01$, except for insulin). MHO individuals had lower levels of high-sensitivity C-reactive protein and soluble intercellular adhesion molecule-1, compared to metabolically abnormal individuals, and had comparable levels of these markers to those in MHNO individuals. Furthermore, only 5.3% of MHO individuals had a family history of hypertension, comparable to 5.0% in MHNO individuals, and much lower than 15.9% in metabolically abnormal, nonobese individuals and 12.8% in metabolically abnormal, obese individuals (overall $P < 0.001$).
Conclusions: We conclude that MHO is associated with a low inflammation state, and family history of hypertension may play a role in the MHO phenotype.

Introduction

OBESITY HAS REACHED EPIDEMIC proportions worldwide over the last few decades.[1,2] It is associated with numerous cardiometabolic abnormalities, such as insulin resistance, elevated blood pressure, dyslipidemia, and inflammation.[3,4] Consequently, obesity is a major risk factor for type 2 diabetes and cardiovascular diseases (CVD), among many other adverse conditions.[3–8] However, a growing body of evidence supports that not all obese individuals show cardiometabolic abnormalities.[9–12]

An obese but metabolically healthy phenotype has been termed ''metabolically healthy obesity'' (MHO). The prevalence of MHO varies depending on its definition and study populations.[13,14] Most definitions cover the following risk factor variables: Waist circumference (for central obesity), blood pressure, lipids, and glucose. MHO may account for as much as 20%–30% of the obese from the general population.[13,14]

Determinants of the MHO phenotype remain to be established. Dietary factors, physical activity, inflammation, and probably genetic factors may contribute to the MHO phenotype.[15–19] In this regard, limited information is available in the Chinese population, particularly in ethnic minorities. In the current study, we examined the associates of the MHO phenotype, particularly markers of inflammation and family history of hypertension, in a population-based sample ($n = 2530$) of Mongolian Chinese in Inner Mongolia, China.

Materials and Methods

Ethics statement

This study was approved by the institutional review board at the Soochow University, Jiangsu, China, Kezuohouqi Banner Center for Disease Prevention and Control Ethics

[1]Department of Epidemiology, School of Public Health, Soochow University, Suzhou, Jiangsu, China.
[2]Department of Epidemiology, Tulane University School of Public Health and Tropic Medicine, New Orleans, Louisiana.
[3]Division of Nephrology and Hypertension, Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana.

Committee, Inner Mongolia, China, and Naiman Banner Center for Disease Prevention and Control Ethics Committee, Inner Mongolia, China. Written informed consent was obtained for each study participant.

Study participants

The study sample has been described previously in detail.[20] Briefly, a population-based, cross-sectional study was conducted between 2002 and 2003 in Inner Mongolia, a Mongolian autonomous region in northern China. Participants aged 20 years or older were recruited from 32 villages in two adjacent townships located in Kezuohou Banner and Naiman Banner in Inner Mongolia, China. Participants were Mongolian Chinese and maintained a traditional diet that was high in fat and salt. A total of 2589 individuals (74.5%, 2589/3475, of those eligible) participated in the study. Among those, 2530 individuals that had all risk factor variables measured to define MHO were included in the current study. Characteristics of the study sample were presented in Table 1.

Data collection

A standard questionnaire was administered by trained staff to obtain data on demographic characteristics, lifestyle factors, family history of hypertension, and personal medical history. Three sitting blood pressure measurements were taken for each participant using a random-zero mercury sphygmomanometer according to a standard protocol after the subjects had been resting for 30 min. The mean of these three blood pressure measurements was used in the data analysis.

Height and body weight were measured by trained staff using a balance beam scale; subjects removed their shoes and were wearing light clothing. Waist circumference was measured at the level of 1 cm above the umbilicus. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2). Waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) were calculated accordingly.

Overnight fasting blood samples were drawn by venipuncture from all subjects in the morning after at least 8 hr of fasting, and fasting glucose was examined using a glucose meter (Roche, Basel, Switzerland) in the field. Serum was subsequently isolated from the whole blood, and all serum samples were frozen at −80°C. Cholesterol, insulin, high-sensitivity C-reactive protein (hsCRP), soluble intercellular adhesion molecule-1 (sICAM-1), and soluble E-selectin (sE-selectin) were measured in a certified laboratory. Concentration of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) were assessed enzymatically on a Beckman Synchrony CX5 Delta Clinical System (Beckman Coulter, Fullerton, CA) using commercial reagents. Concentration of low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald equation for participants whose TGs level was less than 400 mg/dL.[21] Serum insulin was measured using a radioimmunoassay method (Pharmacia Diagnostics, Piscataway, NJ). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as HOMA-IR = [insulin (mU/L) * glucose (mmol/L)]/22.5.[22] Concentration of hsCRP was determined by an immunoturbidimetric assay on a Beckman Synchron CX5 Delta Clinical System using commercial reagents. sE-selectin and sICAM-1 were measured by an enzyme-linked immunosorbent assay (ELISA) assay (R & D Systems, Minneapolis, MN) that employs the quantitative sandwich enzyme immunoassay technique.[23,24]

Definitions

Smoking was defined as having smoked at least one cigarette per day for 1 year or more. Alcohol consumption was defined as drinking at least 50 grams of alcohol per day

Table 1. Characteristics of the Study Participants by Sex in Inner Mongolia, China, 2002–2003

	Men (n = *1030*)	*Women* (n = *1500*)	P *Value*
Age (years)	47.47 ± 12.78	45.71 ± 11.97	< 0.001
Body mass index (kg/m^2)	21.90 ± 3.12	22.49 ± 3.61	< 0.001
Waist circumference (cm)	81.85 ± 9.17	80.04 ± 9.75	< 0.001
Hip circumference (cm)	92.98 ± 6.37	93.08 ± 6.92	0.88
WHR	0.88 ± 0.06	0.86 ± 0.07	< 0.001
WHtR	0.49 ± 0.06	0.51 ± 0.06	< 0.001
Current cigarette smoking (%)	64.2	30.6	< 0.001
Alcohol consumption (%)	64.9	11.5	< 0.001
LDL-C (mg/dL)	89.46 ± 41.26	89.44 ± 38.46	0.07
HDL-C (mg/dL)	44.69 ± 12.58	45.65 ± 12.45	< 0.001
Triglycerides (mg/dL)	133.77 ± 151.19	96.24 ± 72.63	0.02
Glucose (mg/dL)	89.66 ± 20.30	89.94 ± 22.96	0.86
Insulin (mU/L)	13.66 ± 7.72	13.42 ± 7.95	0.13
HOMA-IR	3.09 ± 2.18	3.03 ± 2.16	0.07
SBP (mmHg)	132.37 ± 23.82	127.77 ± 25.04	0.09
DBP (mmHg)	87.19 ± 12.55	82.63 ± 12.76	< 0.001
hsCRP (mg/L)	10.20 ± 9.49	8.58 ± 8.77	0.004
sE-selectin (ng/mL)	22.45 ± 13.75	20.51 ± 9.17	0.57
sICAM-1 (ng/mL)	334.67 ± 99.13	324.86 ± 96.80	0.28

Mean ± standard deviation is shown unless otherwise noted.

WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis assessment model of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1.

for 1 year or more. Obesity was defined as waist circumference ≥90 cm for men or ≥80 cm for women according to International Diabetes Federation (www.idf.org/webdata). We chose waist circumference instead of BMI to define obesity because it was more closely correlated to other risk factors than BMI in this sample. Cardiometabolic abnormality was defined as with one or more of the following: Elevated blood pressure [systolic blood pressure (SBP) ≥130 or diastolic blood pressure (DBP) ≥85 mmHg], elevated TGs (≥150 mg/dL), or LDL-C (≥130 mg/dL), low HDL-C (<40 mg/dL for men, <50 mg/dL for women), and elevated glucose (≥100 mg/dL). Participants were categorized into one of the four groups: MHO, obesity with no metabolic abnormality; metabolically healthy nonobesity (MHNO), nonobesity with no metabolic abnormality; metabolically abnormal obesity (MAO), obesity with any of the abnormalities above; and metabolically abnormal nonobesity (MANO), and nonobesity with any of the abnormalities above. Sensitivity analyses were also performed by excluding LDL-C as one of the defining variables for the MHO phenotype in the total sample.

Statistical analysis

The chi-squared test or Fisher exact test was used to examine differences in categorical variables in different groups. A general linear model was used to examine differences in continuous variables in different groups, adjusted for age, sex, current cigarette smoking, alcohol consumption (and waist circumference) where appropriate. TGs, insulin, hsCRP, and sE-slectin were log-transformed to increase normality when comparisons were made among groups. All *P* values were two-tailed, and statistical significance was defined as $P<0.05$. Statistical analysis was conducted using SAS 9.2 (SAS Institute Inc, Cary, NC).

Results

In the total sample, 85.9% (2173/2530) of the participants (81.2% of men, 836/1030, and 89.1% of women, 1337/1500) had at least one risk factor for metabolic syndrome. In total, 36.0% (911/2530) had central obesity according to the definition by the International Federation of Diabetes (waist circumference ≥90 cm for men and ≥80 cm for women), with 18.5% (191/1030) of men and 48.0% of women (720/1500) being centrally obese ($P\le0.001$ for sex difference). Among those with central obesity, 4.2% of men (8/191) and 9.3% of women (67/720) had MHO (Fisher exact test $P=0.025$ for sex difference). Overall, only 3.0% (75/2530) of the participants had MHO, with 0.8% of men (8/1030) and 4.5% of women (67/1,500) having this condition ($P<0.001$ for sex difference). After excluding LDL-C as one of the defining variables for MHO, 3.5% (89/2530) had MHO, with 1.0% of men (10/1030) and 5.3% of women (79/1500) having MHO.

MHO individuals were older than MHNO ones ($P<0.001$; Table 2). A smaller proportion of alcohol consumption in MHO individuals was observed compared to individuals in other groups ($P<0.001$; Table 2). Overall, BMI, waist circumference, hip circumference, and WHtR were smaller in MHO individuals than in MAO individuals and greater than in MHNO or MANO individuals ($P<0.01$) (Table 2).

Despite striking differences in obesity measures between MHO and MHNO individuals, individuals in the two groups had comparable levels of risk factor variables (Table 3). MHO individuals had a favorable cardiometabolic profile compared to MANO individuals, although the difference in obesity measures between the two groups was also striking (Table 3). Compared to the MAO group, the MHO group overall had a much more favorable cardiometabolic profile (Table 3). MHO individuals had lower levels of hsCRP and sICAM-1 than individuals in the MAO or MANO groups (all $P\le0.01$; Table 3); levels in the two markers were comparable between MHO and MHNO groups.

Only 5.3% of MHO individuals reported to have a family history of hypertension, comparable to 5.0% in the MHNO group, and much lower than 15.9% in the MANO group and 12.8% in the MAO group ($P<0.001$).

Table 2. Anthropometric Variables and Lifestyle Factors by Metabolic Status in the Study Participants in Inner Mongolia, China, 2002–2003

	Healthy obesity status						
	MHNO (n=*357*)		*MANO* (n=*1262*)		*MAO* (n=*836*)		*MHO* (n=*75*)
Variable	*Mean ± SD* [a]	P [b]	*Mean ± SD*	P [b]	*Mean ± SD*	P [b]	*Mean ± SD*
Men/women ratio (*n*/*n*)	1.19 (194/163)	<0.001	1.04 (645/617)	<0.001	0.28 (183/653)	0.02	0.12 (8/67)
Age (years)	41.83 ± 10.47	<0.001	46.15 ± 13.07	0.50	48.86 ± 11.46	0.07	45.89 ± 10.54
Body mass index (kg/m^2)	20.23 ± 1.98	<0.001	20.63 ± 2.22	<0.001	25.41 ± 3.18	<0.001	23.88 ± 2.27
Waist circumference (cm)	74.78 ± 5.41	<0.001	75.84 ± 5.96	<0.001	90.27 ± 7.88	<0.001	86.66 ± 5.67
Hip circumference (cm)	89.43 ± 4.28	<0.001	90.16 ± 4.69	<0.001	98.62 ± 6.51	0.004	96.34 ± 5.16
WHR	0.84 ± 0.05	<0.001	0.84 ± 0.05	<0.001	0.92 ± 0.06	0.24	0.90 ± 0.05
WHtR	0.46 ± 0.03	<0.001	0.47 ± 0.03	<0.001	0.57 ± 0.05	<0.001	0.54 ± 0.04
Current cigarette smoking (%)	48.2	0.08	50.8	0.01	33.5	0.66	36.0
Alcohol consumption (%)	37.8	<0.001	38.1	<0.001	25.4	0.12	17.3

Mean ± standard deviation is shown unless otherwise noted.
[a]Except men/women ratio.
[b]Compared to MHO group, adjusted for co-variates where appropriate.
MHNO, metabolically healthy nonobesity; MANO, metabolically abnormal nonobesity; MAO, metabolically abnormal obesity; MHO, metabolically healthy obesity; SD, standard deviation; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

Table 3. Levels of Traditional Risk Factor Variables and Inflammation Markers by Metabolic Status in the Study Participants in Inner Mongolia, China, 2002–2003

	Healthy obesity status						
	MHNO (n = *357*)		*MANO* (n = *1262*)		*MAO* (n = *836*)		*MHO* (n = *75*)
Variable	*Mean ± SD*	P [a]	*Mean ± SD*	P [a]	*Mean ± SD*	P [a]	*Mean ± SD*
LDL-C (mmol/L)	74.71 ± 23.86	0.29	86.58 ± 40.91	0.003	100.75 ± 41.01	0.001	81.96 ± 26.42
HDL-C (mmol/L)	54.71 ± 9.14	0.04	43.44 ± 12.47	< 0.001	42.83 ± 11.51	< 0.001	57.94 ± 9.34
Triglycerides (mmol/L)	68.37 ± 28.49	0.10	107.25 ± 93.25	0.004	140.16 ± 152.72	< 0.001	69.49 ± 26.61
Glucose (mmol/L)	77.24 ± 10.96	0.11	90.67 ± 19.65	< 0.001	94.83 ± 26.57	< 0.001	79.66 ± 11.30
Insulin (mU/L)	12.53 ± 7.75	0.86	13.13 ± 7.28	0.21	14.62 ± 8.73	0.13	12.56 ± 5.70
HOMA-IR	2.40 ± 1.52	0.53	2.98 ± 2.00	< 0.001	3.50 ± 2.58	< 0.001	2.51 ± 1.27
SBP (mmHg)	111.62 ± 9.16	0.10	131.32 ± 24.72	< 0.001	136.25 ± 25.79	< 0.001	113.65 ± 8.80
DBP (mmHg)	74.91 ± 6.35	0.53	85.21 ± 12.69	< 0.001	88.25 ± 13.34	< 0.001	75.95 ± 5.31
hsCRP (mg/L)	5.60 ± 4.11	0.20	8.93 ± 8.68	< 0.001	11.50 ± 10.56	< 0.001	6.66 ± 8.91
sE-selectin (ng/mL)	21.10 ± 16.53	0.84	20.88 ± 10.47	0.42	22.02 ± 9.64	0.65	20.67 ± 7.90
sICAM-1(ng/mL)	298.04 ± 91.62	0.58	333.07 ± 95.46	0.002	338.18 ± 102.03	0.01	303.40 ± 87.06

[a]Compared to the MHO group, adjusted for age, sex, alcohol consumption, cigarette smoking, and waist circumference.

MHNO, metabolically healthy non-obesity; MANO, metabolically abnormal non-obesity; MAO, metabolically abnormal obesity; MHO, metabolically healthy obesity; SD, standard deviation; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis assessment model of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1.

Discussion

In this community-based study, 4.5% of women and 0.8% of men had the MHO phenotype. We found that MHO individuals, in addition to having favorable levels of traditional risk factor variables, had lower levels of hsCRP and sICAM-1 than MAO individuals, suggesting MHO individuals had lower inflammation. Importantly, findings that MHO individuals were less likely to have a family history of hypertension suggest that genetic factors may play a role in MHO.

A much smaller proportion of the study participants had MHO than that in other samples from previous studies.[14] A few factors may have contributed to the low prevalence of MHO. We used a more comprehensive definition of MHO in our study by including LDL-C, the single most important risk factor variable for atherosclerotic disease,[25] to define MHO. However, even after excluding LDL-C as one of the defining variables for MHO, the prevalence was still low. In addition, most (64.0%) of male participants were cigarette smokers, which would have adversely influenced metabolic risk factor variables. A diet high in fat and salt also likely contributed to the low prevalence of MHO in the study sample.[26] It should be noted that a very high proportion of participants had at least one risk factor for metabolic syndrome regardless of obesity status (91.8% in those with central obesity and 77.9% in those without).

It remains largely unknown what are the determinants of the MHO phenotype. In our study, more women (4.5%) than men (0.8%) had the MHO phenotype. A smaller proportion of alcohol consumption in the MHO group than in other groups was also observed, suggesting involvement of lifestyle factors in the MHO phenotype. The high prevalence of cigarette smoking (50.8%) and alcohol drinking (38.1%) in the MANO group provides supporting evidence for lifestyle factors' involvement in cardiometabolic health. MHO individuals also had low central obesity measures compared to MAO individuals, which is consistent with previous findings that central fat deposition is an important factor in determining obesity health consequences.[27,28] Furthermore, our study also supports that inflammation is involved in the metabolic consequences of obesity, as previously shown by Karelis et al.[16] and Shin et al.[29] Among inflammation markers, CRP is widely used. The results for sICAM-1 add new evidence that inflammation contributes to the MHO phenotype. It is known that inflammation is linked to hypertension[20] and insulin resistance[30,31] and plays an important role in the development of CVD.[32,33] Thus, a low inflammation state may partly explain the reduced risk of CVD or type 2 diabetes in MHO individuals, as observed recently.[34,35]

Family history of hypertension is an important risk factor for hypertension-related CVD.[36,37] It is likely that family history of hypertension reflects the contribution of genetic factors, although shared environmental factors are also involved in family history of hypertension. A genetic contribution to the MHO phenotype is also supported by a recent report that variants near the insulin receptor substrate 1 gene (*IRS-1*) are associated with reduced adiposity and an impaired metabolic profile.[19] Future genetic studies are needed to examine the genetic contribution to the MHO phenotype.

Our study supports previous observations that health consequences of obesity are heterogeneous, *i.e.*, obesity does not necessarily cause adverse metabolic consequences.[38] Consequently, MHO individuals may not have increased risk for developing CVD or type 2 diabetes,[34] or for mortality,[35] compared to their nonobese counterparts; on the other hand, MHO individuals have a lower risk for mortality compared to metabolically abnormal, obese individuals.[35] Heterogeneity in the health consequences of obesity has implications for intervention recommendations because MHO people may respond differently to physical activity or diet intervention.[10,29]

Lack of a consensus definition of MHO adds difficulties to studying determinants of the MHO phenotype. For example, should inflammation be included for defining MHO?

Wildman et al. included CRP in their definition of MHO[39] and many others did not.[9,34,40] In our study, we included LDL-C in the definition of MHO because LDL-C is the single most important risk factor variable for atherosclerotic diseases.[25] The lack of a consensus definition of MHO adds difficulties to identifying characteristics of the MHO phenotype. This lack also prohibits comparison of results across studies and hinders evidence synthesis in this topic. We strongly agree that a consensus definition of MHO is desperately needed to enhance future research on the MHO phenotype.[41]

Strengths and limitations of our study should be noted. Our study was community based and the participation rate was high. The study participants were ethnically homogeneous and had similar dietary habits. In addition, we adopted a rigorous quality control protocol. On the other hand, we acknowledge that our study was cross-sectional in nature, as a result of which causality could not be determined for the observed associations of MHO with measures of fat distribution and inflammation markers. Longitudinal studies are needed to help establish such causality. In addition, our study participants were ethnic Mongolian Chinese, which may limit the generalizability of our findings to other Chinese populations. Our study only included family history of hypertension, which may reflect influences of both genetic and shared environmental factors. Future studies should address specifically the contribution of genetic factors to the MHO phenotype. Finally, we recognize that the results of our study should be interpreted with caution because only 8 and 67 individuals had MHO in our study.

In conclusion, the MHO phenotype is relatively rare in the ethnic Mongolian Chinese population and is associated with reduced central obesity and a reduced inflammation status. Importantly, family history of hypertension, which reflects contributions from both genetic and shared environmental factors, may play a role in the MHO phenotype. Future studies are needed to determine the causality of the observed associations and to dissect the genetic basis of the MHO phenotype. In addition, the long-term effect of weight loss on the metabolic profiles and CVD outcomes in individuals with MHO need to be further investigated.

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Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Shengxu Li, MD, PhD
1440 Canal Street, Suite 2000
New Orleans, LA 70112

E-mail: sli10@tulane.edu or

Yonghong Zhang, MD, PhD
199 Renai Road
Industrial Park District
Suzhou 215123, Jiangsu
China

E-mail: yhzhang@suda.edu.cn