Endocrine (2015) 49:130–138
DOI 10.1007/s12020-014-0444-2

ORIGINAL ARTICLE

Comparison of the effect of 'metabolically healthy but obese' and 'metabolically abnormal but not obese' phenotypes on development of diabetes and cardiovascular disease in Chinese

Deng Luo · Fang Liu · Xiaowen Li · Dechao Yin · Ziwei Lin · Hui Liu · Xuhong Hou · Chen Wang · Weiping Jia

Received: 11 August 2014 / Accepted: 1 October 2014 / Published online: 14 October 2014

Abstract The present study was designed to determine the prevalence of 'metabolically healthy but obese' (MHO) and 'metabolically abnormal but not obese' (MANO) phenotypes in Chinese population, and to investigate the association of these two phenotypes with the risk of diabetes and cardiovascular disease (CVD). A total of 2,764 subjects aged 30–90 were followed up over a mean period of 43.80 ± 11.25 months. The metabolic syndrome was defined according to the joint committee for developing Chinese guidelines on prevention and treatment of dyslipidemia in adults. Subjects with body fat percentage (BF %) >25 % for men or BF % >35 % for women were defined as being obese. The proportion of MHO and MANO phenotypes were 22.9, 7.6 % in men, and 26.2, 6.0 % in women, respectively. The MANO phenotype was associated with increased risk for diabetes both in men [hazard ratios (HR): 4.44 (1.21–16.26)] and women [HR: 8.68 (2.87–24.96)] after adjustment of age, serum total cholesterol (TC), triglycerides (TG), and family history of diabetes. This association held for CVD in women [HR: 2.87 (1.44–5.73)], but not in men after adjustment of age, serum TC, TG, and family history of CVD. No association was observed between the MHO phenotype and incident diabetes or CVD. MHO and MANO phenotypes are common in Chinese population. Metabolic risk factors appeared to play a more important role in the development of diabetes and CVD than body fat alone.

Keywords Obesity · Metabolic syndrome · Diabetes · CVD

Deng Luo and Fang Liu are contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s12020-014-0444-2) contains supplementary material, which is available to authorized users.

D. Luo · X. Li · D. Yin · Z. Lin · X. Hou · C. Wang (✉) · W. Jia
Shanghai Diabetes Institute, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, People's Republic of China
e-mail: wangchen@sjtu.edu.cn

D. Luo · F. Liu · X. Li · D. Yin · Z. Lin · X. Hou · C. Wang · W. Jia
Shanghai Key Laboratory of Diabetes Mellitus, 600 Yishan Road, Shanghai 200233, People's Republic of China

D. Luo · F. Liu · Z. Lin · C. Wang · W. Jia
Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, People's Republic of China

H. Liu
Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China

Introduction

The prevalence of obesity is rising dramatically worldwide in recent decades [1]. It is associated with various health conditions in humans, of which the adverse metabolic effects of obesity in part mediated by insulin resistance put obese individuals on their way to developing a variety of diseases, including hypertension, type 2 diabetes (T2D), and stroke [2, 3]. However, the typical relationship between weight status and metabolic health has not been conclusively demonstrated for some subtypes of individuals, as 'metabolically healthy but obese' (MHO) and 'metabolically abnormal but not obese' (MANO) phenotypes [4–7]. The former phenotype describes those with a normal metabolic profile who are obese and the latter

phenotype includes those who are not obese with an abnormal metabolic status.

The prevalence of MHO and MANO phenotypes was reported to be 3–28, 10–25, and 15.2 % in Europeans, North Americans, and Korean population, respectively [8–11]. Both the European Group for the Study of Insulin Resistance (EGIR) and the Bruneck Study demonstrated that in individuals with MHO, the prevalence of insulin resistance was relatively low and not all subjects with normal body weight were healthy [12, 13]. Subjects with the MANO phenotype had a higher risk for developing cardiovascular disease (CVD) [9, 14–16].

It is well accepted that the characteristics of obesity in Chinese populations are different from those in westerners even though they might have the same body weight [17, 18]. In Chinese populations, adipose tissue tends to accumulate as visceral fat leading to higher waist circumference, whereas comparatively more adipose tissue can be found in subcutaneous tissue in western populations. While the subgroup of obesity has been studied in Caucasian [19], data regarding the prevalence of MHO and MANO phenotypes and the association between the two phenotypes and the risk of T2D and CVD in Chinese population are scarce.

The aims of the current study are (1) to estimate the prevalence of MHO and MANO phenotypes in a Chinese population and (2) to assess the association of the two phenotypes with the risk of diabetes and CVD. This phenotypic classification could further increase our understanding of the relationship between weight status and metabolic health.

Materials and methods

Study population

The subjects were from a community-based prospective cohort study in Shanghai communities—Shanghai Diabetes Study (SHDS). The SHDS population has been described in detail elsewhere [20, 21]. The subjects were selected from the two urban communities starting from 1998 in the Huayang community and from 2001 in the Caoyang community. A total of 2,902 subjects aged from 30 to 95 and with complete data for identification of MetS and for body fat percentage (BF %) were included in the present cohort study, which was followed from December 2003 to November 2004 for the occurrence of CVD and diabetes. When analyzing CVD events, a total of 2,764 subjects aged from 30 to 90 were used for the present analysis, after exclusion of 123 subjects with CVD at baseline and 8 deaths with reasons unknown. When analyzing diabetes, 2,380 subjects were included from the above 2,764 subjects, after excluding 335 (152 newly diagnosed) diabetic patients during the baseline exam and 49 with missing follow-up data for diabetes. Informed consent was obtained from each participant. The protocol was in accordance with Helsinki Declaration and approved by the local ethical committee.

Data collection

Participants came to a local hospital at 6:00–7:00 AM following a 10-h overnight fast. After the fast, a venous blood sample was collected and each participant received a 75 g OGTT, except for those with a validated history of diabetes mellitus. Serum true insulin was assayed with a bio-antibody technique (Linco, St Louis, MO, USA). Plasma glucose levels were measured using the glucose oxidase method. Serum lipid profiles were measured with an automated biochemical instrument. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated based on fasting insulin (FINS) and fasting plasma glucose (FPG) according to the equation: HOMA-IR = FINS [μU/mL] × FPG [mmol/L]/22.5 [22]. Insulin resistance was determined by HOMA-IR, in which the 75th percentile value was used as the cut-off point to define insulin resistance (IR) as per SHDS background population study results [23]. Insulin sensitivity index was calculated based on the equation of Matsuda [24].

Height and weight were measured with subjects standing without shoes and in light clothing. Waist circumference was measured at the horizontal plane at the midpoint between the inferior costal margin and the iliac crest on midaxillary line with the subjects standing relaxed and in underwear. Body mass index (BMI) was calculated as weight (Kilograms) divided by height (in meters) squared. Blood pressure measurements were taken three times (with a 1-min rest interval) using a sphygmomanometer and then averaged. Total body fat was estimated from the Body Composition Analyzer (TANITA Corporation, Japan). At the same time, a standardized health questionnaire was completed by trained nurses. It covered demographics, past medical history and family history of diseases, etc.

Definition of variables and outcomes

Metabolic syndrome (MetS) was defined according to the joint committee for developing Chinese guidelines on prevention and treatment of dyslipidemia in adults (JCDCG) definition [25]. MetS was defined as the presence ≥3 of the following abnormalities: (1) waist circumference >90 cm for men and >85 cm for women; (2) serum triglycerides (TG) ≥1.70 mmol/L or specific treatment for lipid abnormality; (3) high-density cholesterol (HDL-C) <1.04 mmol/L or specific treatment for lipid abnormality; (4) blood pressure ≥130/85 mmHg or known treatment for hypertension; (5) FPG ≥6.1 mmol/L and/or 2 h plasma glucose

(2hPG) ≥7.8 mmol/L and/or diabetes mellitus having been diagnosed and currently receiving therapy. Obesity was defined based on body fat percentage (BF %). Subjects with BF % >25 % for men or BF % >35 % for women were defined as being obese. BF % ≤25 % for men or BF % ≤35 % for women was defined as being non-obese [26]. Subjects in the present study were divided into four groups: metabolically healthy and non-obese (MHNO), MHO MANO, and metabolically abnormal and obese (MAO). MHNO was defined as having no MetS and no obesity. MHO was defined as having obesity but no MetS. MANO was defined as having MetS but no obesity. MAO was defined as having MetS and obesity. Abdominal obesity was defined as waist circumference >90 cm for men and >85 cm for women [27]. The diagnosis of diabetes was based on the WHO criteria. Impaired glucose regulation (IGR), including impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) [28].

The incidence of CVD events was determined from 2 sources: hospital records and death certificates. CVD events were defined as the first occurrence of coronary heart disease (CHD) or stroke. According to the USA national institute of neurological and communicative diseases and stroke (NINCDS) diagnostic criteria [29], Stroke was defined as physician-diagnosed intracranial hemorrhage or cerebral infarction, which included venous thrombosis, embolic stroke, lacunar infarction, and hemorrhagic stroke. According to monitoring of trends and determinants in cardiovascular disease (MONICA) diagnostic criteria [30], CHD was defined as physician-diagnosed acute coronary syndrome which includes acute ST elevation myocardial infarction, non-ST segment elevation myocardial infarction, unstable agina, systolic or diastolic dysfunction, coronary artery bypass graft surgery, and congestive heart failure. All diagnoses were verified by the hospital records.

Statistical analysis

The data were expressed as mean ± SD for normal distributions and as median (interquartile range 25–75 %) for skewed variables. The statistical analysis was performed with SPSS software for Windows (Version 11.0). Skewed variables were converted into normal distributions before analysis. Differences for continuous variables were assessed by performing *t* test, or ANOVA as appropriate. Bonferroni correction was used for the post-hoc analyses. Differences in ratio variables were assessed by χ^2 test and corrected with Bonferroni correction when needed. Hazard ratios (HR) and 95 % confidence intervals (CIs) were calculated to estimate the associations of each group with diabetes and CVD events by binary logistic regression analysis. All reported *P* values were two-tailed and *P* values less than 0.05 were considered statistically significant.

Results

Baseline characteristics of subjects

The baseline characteristics of the population in each group are shown in Table 1. Of all subjects included in the present study, 51.4, 24.8, 6.7, and 17.1 % were defined as MHNO, MHO, MANO, and MAO, respectively (Table 1). No differences could be viewed in the above proportion in each group between men and women (Table 1). Due to definition, indices of obesity (including BF %, BMI, waist circumference) were higher in MHO than in MHNO groups (all $P < 0.05$). Furthermore, MHO subjects also had higher TG, total cholesterol (TC), and low-density cholesterol (LDL-C) levels than MHNO subjects (all $P < 0.05$). No difference was documented in HDL-C levels between these two groups ($P > 0.05$). Similar to the MAO group, subjects in the MANO had higher systolic blood pressure (SBP), diastolic blood pressure (DBP), FPG, 2hPG, TG, and lower HDL-C than those in the MHNO and MHO group both for men and women (all $P < 0.05$). Insulin, TC, and LDL-C levels were significantly increased across the MHNO, MANO, MHO, and MAO groups both for men and women.

Comparison of the risk factor in subjects from each group

Among obese subjects, 40.8 % had MetS. Among non-obese subjects, 11.5 % had. The metabolic abnormal over metabolic healthy ratio was higher in obesity than in non-obesity (Fig. 1a, $P < 0.01$). Subjects from the MAO group had the highest proportion (70.6 and 83.1 % for men and women, respectively) of abdominal obesity (Fig. 1b). Although subjects with MANO were defined with no obesity by BF %, the proportion of subjects with abdominal obesity is similar with that in MHO group both for men (37.8 vs. 32.0 %, $P > 0.05$) and women (30.5 vs. 33.8 %, $P > 0.05$), respectively (Fig. 1b). As for the IR, the proportion of subjects with IR increased across each groups from MHNO, MHO, MANO, and MAO groups both for men and women (*P* for trend < 0.01). It was significantly higher in each group than that in MHNO (Fig. 1c) with their insulin sensitivity index decreased across above groups (Fig. 1d). Of note, the proportion of subjects with IGR, a pre-diabetes status (including isolated IFG, isolated IGT, and combined IFG and IGT), was comparable between MANO (29.5 % for men 38.0 % for women, respectively) and MAO groups (31.8 % for men 32.6 % for women, respectively) ($P > 0.05$). It was significantly higher in MANO group than that in both MHO group ($P < 0.01$) and MHNO ($P < 0.01$) (Fig. 1e).

Table 1 Baseline characteristics of subjects

Variable	MHNO	MHO	MANO	MAO
Men (n = 1,186)				
N (%)	613 (51.7)	272 (22.9)	90 (7.6)	211 (17.8)
Age (year)	59.0 (43.0–71.5)	50.0 (39.0–66.0)^{a**}	70.0 (59.8–75.0)$^{a**, b**}$	62.0 (46.0–71.0)^{b**}
SBP (mm Hg)	125.9 ± 19.0	125.8 ± 18.6	140.8 ± 21.5$^{a**, b**}$	139.1 ± 18.9$^{a**, b**}$
DBP (mm Hg)	78.5 ± 9.9	81.5 ± 10.8^{a**}	85.2 ± 11.6$^{a**, b*}$	88.7 ± 10.7$^{a**, b**}$
Waist circumference (cm)	77.3 ± 7.9	87.1 ± 6.3^{a**}	85.9 ± 8.9^{a**}	93.5 ± 6.9$^{a**, b**}$
BMI (kg/m^2)	21.7 ± 2.6	25.1 ± 2.1^{a**}	24.3 ± 2.6$^{a**, b*}$	27.3 ± 2.6$^{a**, b**}$
BF (%)	19.2 (16.0–22.0)	27.7 (26.1–29.7)^{a**}	22.3 (20.2–23.7)$^{a**, b**}$	29.4 (27.3–32.8)$^{a**, b**}$
FPG (mmol/L)	4.9 (4.6–5.2)	5.0 (4.5–5.3)	5.6 (5.0–6.8)$^{a**, b**}$	5.6 (5.0–6.6)$^{a**, b**}$
2hPG (mmol/L)	5.3 (4.2–6.4)	5.5 (4.5–6.8)^{a*}	8.5 (6.0–12.1)$^{a**, b**}$	8.3 (6.2–10.8)$^{a**, b**}$
Fins (mU/L)	5.5 (3.5–8.3)	7.5 (5.3–10.1)^{a**}	7.3 (5.1–11.1)^{a**}	10.4 (7.1–14.9)$^{a**, b**}$
2hIn (mU/L)	26.0 (15.1–42.3)	40.1 (24.8–62.6)^{a**}	37.0 (17.5–62.0)^{a*}	53.0 (32.9–82.6)$^{a**, b**}$
TG (mmol/L)	1.3 (0.9–1.7)	1.6 (1.3–2.3)^{a**}	2.0 (1.7–2.7)$^{a**, b**}$	2.3 (1.9–3.1)$^{a**, b**}$
TC (mmol/L)	4.7 ± 1.0	5.0 ± 1.0^{a*}	5.1 ± 1.0^{a*}	5.2 ± 1.3^{a**}
LDL-C (mmol/L)	3.2 ± 0.9	3.5 ± 0.9^{a**}	3.6 ± 0.8^{a*}	3.7 ± 1.0^{a**}
HDL-C (mmol/L)	1.3 ± 0.2	1.3 ± 0.2	1.2 ± 0.3$^{a**, b*}$	1.2 ± 0.4$^{a**, b**}$
Family history of diabetes (%)	14.4	10.7	6.7	12.3
Family history of stroke (%)	13.4	16.1	13.3	13.3
Family history of CHD (%)	17.0	18.4	11.1	12.3
Women (n = 1,578)				
N (%)	808 (51.2)	414 (26.2)	95 (6.0)	261 (16.5)
Age (year)	46.5 (40.0–65.0)	50.0 (42.0–65.0)	67.0 (54.0–75.0)$^{a**, b**}$	66.0 (53.0–73.0)$^{a**, b**}$
SBP (mm Hg)	119.5 ± 19.5	124.4 ± 18.6^{a**}	142.3 ± 19.5$^{a**, b**}$	142.0 ± 21.4$^{a**, b**}$
DBP (mm Hg)	75.6 ± 9.5	78.8 ± 9.9^{a**}	83.0 ± 9.4$^{a**, b**}$	86.0 ± 11.0$^{a**, b**}$
Waist circumference (cm)	72.9 ± 6.8	82.9 ± 6.6^{a**}	80.0 ± 8.4$^{a**, b*}$	91.0 ± 7.7$^{a**, b**}$
BMI (kg/m^2)	21.9 ± 2.4	26.4 ± 2.2^{a**}	23.4 ± 2.5$^{a**, b**}$	28.3 ± 3.0$^{a**, b**}$
BF (%)	29.4 (26.0–32.0)	38.9 (36.7–41.5)^{a**}	31.2 (29.0–33.0)$^{a**, b**}$	41.1 (38.0–44.9)$^{a**, b**}$
FPG (mmol/L)	4.9 (4.5–5.2)	5.1 (4.7–5.4)^{a**}	5.6 (5.0–6.5)$^{a**, b**}$	5.6 (5.1–6.6)$^{a**, b**}$
2hPG (mmol/L)	5.1 (4.3–6.0)	5.8 (5.0–6.7)^{a**}	8.3 (6.3–9.4)$^{a**, b**}$	8.1 (6.4–10.5)$^{a**, b**}$
Fins (mU/L)	5.8 (3.9–8.4)	8.0 (5.8–10.8)^{a**}	8.4 (5.1–11.4)^{a**}	10.9 (7.3–15.9)$^{a**, b**}$
2hIn (mU/L)	31.6 (19.3–47.3)	44.0 (30.6–64.7)^{a**}	43.1 (17.5–74.1)^{a*}	59.8 (36.3–93.1)$^{a**, b**}$
TG (mmol/L)	1.2 (0.9–1.7)	1.5 (1.1–2.0)^{a**}	2.1 (1.8–2.9)$^{a**, b**}$	2.3 (1.9–2.8)$^{a**, b**}$
TC (mmol/L)	4.9 ± 1.2	5.1 ± 1.1^{a**}	5.5 ± 1.5^{a**}	5.5 ± 1.2$^{a**, b**}$
LDL-C (mmol/L)	3.3 ± 1.0	3.5 ± 1.0^{a**}	3.8 ± 1.2^{a*}	3.8 ± 1.0$^{a**, b**}$
HDL-C (mmol/L)	1.4 ± 0.2	1.4 ± 0.3	1.2 ± 0.4$^{a**, b**}$	1.3 ± 0.3$^{a**, b**}$
Family history of diabetes (%)	10.9	7.0	6.3	10.0
Family history of stroke (%)	12.3	12.8	21.0	12.3
Family history of CHD (%)	18.1	16.9	13.7	13.4

Data represent mean ± SD, median (interquartile range 25–75 %) or *n* (%). Statistical significance of differences between groups was analyzed with ANOVA followed by Dunnett as post-hot analysis for mean, Mann–Whitney test followed by Bonferroni correction for median

MHNO metabolically healthy and non-obese, *MHO* metabolically healthy and obese, *MANO* metabolically abnormal and non-obese, *MAO* metabolically abnormal and obese, *SBP* systolic blood pressure, *DBP* diastolic blood pressure *BMI* body mass index *BF* % body fat percentage, *FPG* fasting plasma glucose, *2hPG* 2 h plasma glucose, *FINS* fasting insulin, *2hIn* 2 h insulin, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density cholesterol, *HDL-C* high-density cholesterol

[a] versus MHNO

[b] versus MHO

* $P < 0.05$; ** $P < 0.01$

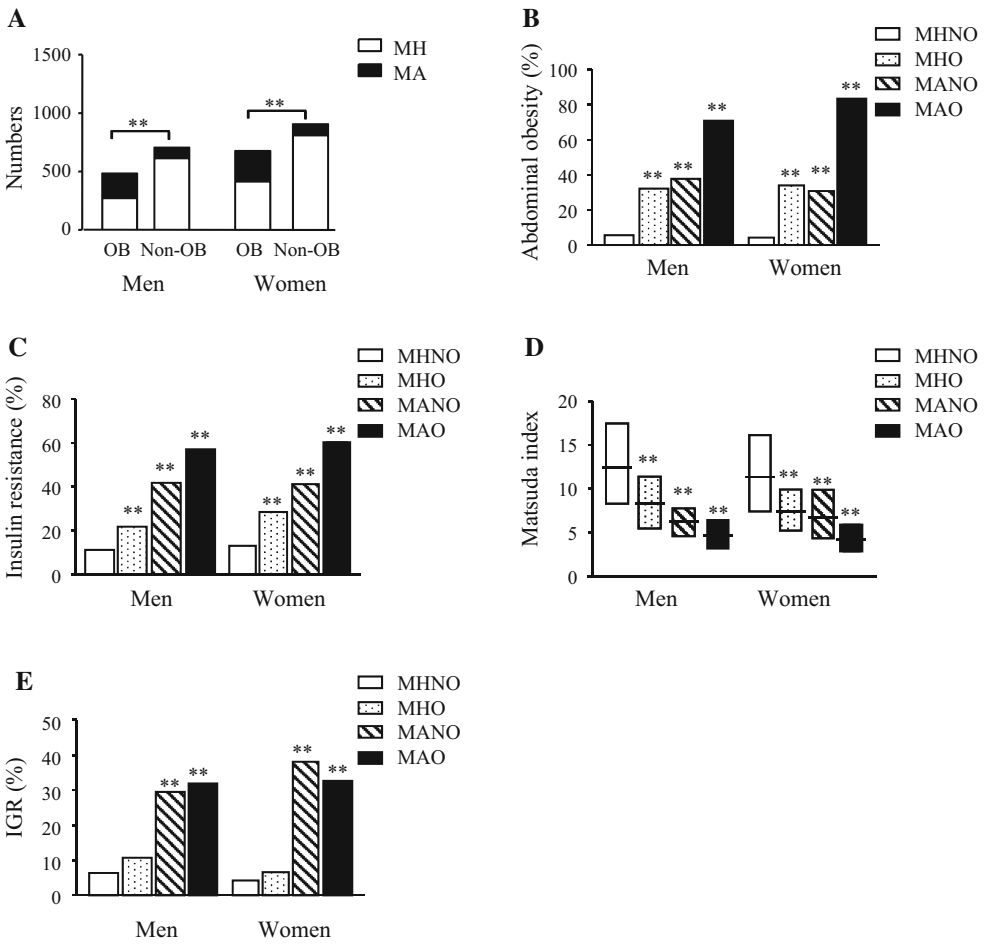

Fig. 1 Comparison of the risk factors in subjects from each group. **a** metabolic abnormal (MA) over metabolic healthy (MH) ratio; **b** proportion of abdominal obesity; **c** proportion of insulin resistance; **d** insulin sensitivity index; **e** proportion of impaired glucose regulation (IGR) status. *OB* obesity, *MHNO* metabolically healthy and non-obese, *MHO* metabolically healthy and obese, *MANO* metabolically abnormal and non-obese, *MAO* metabolically abnormal and obese. $^{**}P < 0.01$ versus indicated groups or MHNO

The association of MHO and MANO to the incident diabetes and CVD

During a 43.80 ± 11.25 month-period, 100 subjects developed diabetes and 212 subjects developed CVD (128 events for stroke and 84 events for CHD) (Table 2). The overall cumulative incidences of diabetes and CVD were 4.2 and 7.7 %, respectively (Table 2). The cumulative incidences of diabetes and CVD were higher in the MANO (16.4 % for diabetes and 18.9 % for CVD, respectively) and MAO groups (12.6 % for diabetes and 13.4 % for CVD, respectively) than those in the MHNO group (3.6 % for diabetes and 6.7 % for CVD) in women. In men, the cumulative incidence of diabetes was only higher in the MAO group (14.6 %), and the cumulative incidence of CVD was only higher in MANO subjects (17.8 %). No significant differences could be viewed in the cumulative incidence of diabetes and CVD between the MHO group and the MHNO group both in men and in women.

The HRs for incident diabetes and CVD are shown in Table 3. Similar to MAO, subjects with MANO had a higher risk for incident diabetes compared with subjects in MHNO group in both men and women after adjustment of age, serum TC, TG, and family history of diabetes (Table 3). This phenomenon kept the same in women for future CVD after adjustment of age, serum TC, TG, and family history of CVD, but not for men (Table 3). Within CVD, women with MANO or MAO had higher risk for future stroke, but not future CHD, compared with those in MHNO group. No difference in the incidence of diabetes and CVD could be viewed between the MHO group and the MHNO group in both genders.

Discussion

In this study, we demonstrated that certain subtypes of obesity exist in the Chinese population. The prevalence of the MHO subjects was 23 % in men and 26 % in women, and that of the MANO group was 7 % in men and 6 % in women in community population in Shanghai. Moreover, after a median follow-up period of 43.80 months, subjects from the MANO group had a higher risk for developing diabetes both for men and women. This situation holds for

Table 2 Incident rate of diabetes and cardiovascular disease in men and women at the end of follow up

Group	*N*	Diabetes		*N*	CVD		Stroke		CHD	
		n	Rate (%)		*n*	Rate (%)	*n*	Rate (%)	*n*	Rate (%)
Men										
Total	995	50	5.0	1,186	107	9.0	69	5.8	38	3.2
MHNO	565	15	2.7	613	51	8.3	33	5.4	18	2.9
MHO	255	12	4.7	272	17	6.3	13	4.8	4	1.5
MANO	45	4	8.9	90	16	17.8*	12	13.3*	4	4.4
MAO	130	19	14.6**	211	23	10.9	11	5.2	12	5.7
Women										
Total	1,385	50	3.6	1,578	105	6.7	59	3.7	46	2.9
MHNO	781	13	1.7	808	32	4.0	12	1.5	20	2.5
MHO	390	8	2.1	414	20	4.8	14	3.4	6	1.4
MANO	55	9	16.4**	95	18	18.9***	10	10.5***	8	8.4**
MAO	159	20	12.6**	261	35	13.4***	23	8.8***	12	4.6

Statistical significance of differences was analyzed with χ^2 test followed by Bonferroni correction

MHNO metabolically healthy and non-obese, *MHO* metabolically healthy and obese, *MANO* metabolically abnormal and non-obese, *MAO* metabolically abnormal and obese, *N* numbers of subjects in different groups, *n* numbers of subjects with the occurrence of diseases in different groups, *CVD* cardiovascular disease, *CHD* coronary heart disease

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, versus MHNO

Table 3 Adjusted hazard ratio of diabetes and cardiovascular disease in subjects

Group	Hazard ratio (95 % CI)			
	Diabetes	CVD	Stroke	CHD
Men				
MHNO	1	1	1	1
MHO	2.55 (0.97–6.69)	0.98 (0.51–1.89)	1.27 (0.62–2.61)	0.43 (0.10–1.93)
MANO	4.44 (1.21–16.26)^{a*}	1.31 (0.65–2.64)	1.35 (0.60–3.00)	1.19 (0.36–3.97)
MAO	8.31 (2.81–24.60)^{a**}	1.21 (0.66–2.20)	0.77 (0.35–1.67)	2.26 (0.94–5.47)
Women				
MHNO	1	1	1	1
MHO	1.08 (0.36–3.30)	1.10 (0.59–2.05)	2.21 (0.94–5.17)	0.53 (0.19–1.44)
MANO	8.68 (2.87–24.96)^{a***}	2.87 (1.44–5.73)^{b**}	2.97 (1.15–7.69)^{b*}	2.97 (1.12–7.73)^{b*}
MAO	5.12 (1.60–16.40)^{a**}	1.87 (1.04–3.35)^{b*}	2.43 (1.08–5.49)^{b*}	1.63 (0.67–2.91)

Hazard ratio and confidence interval (CI) was determined by binary logistic regression

[a] adjusted for age, total cholesterol (TC), triglyceride (TG) and family history of diabetes, [b] adjusted for age, TC, TG and family history of cardiovascular disease (CVD)

MHNO metabolically healthy and non-obese, *MHO* metabolically healthy and obese, *MANO* metabolically abnormal and non-obese, *MAO* metabolically abnormal and obese, *CHD* coronary heart disease

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus MHNO

MANO to CVD in women, but not in men. No differences could be documented for subjects with MHO. To the best of our knowledge, this is the first study to identify MHO and MANO individuals, and associate MANO with diabetes and CVD in Chinese adults with an observational population cohort study.

Different definitions of obesity and metabolic status were applied in individuals with MANO and MAO in different ethnic groups in previous studies [4, 8, 31–33]. So far, no uniform criteria have been established to define MANO and MHO phenotypes [4, 16, 34]. Different definitions allowed only indirect comparisons of the prevalence of MHO and MANO phenotypes in different populations which have demonstrated highly variable prevalence among different studies [4, 10]. Some studies suggested that the MANO phenotype was reasonably

common, with a prevalence of 3–28 % according to the specific definition of MetS and the population source [4, 35, 36]. MHO phenotype also appeared to be common in other studies, with a prevalence of 11–28 % [6, 37]. The metabolic healthy status was defined as having less than 3 components of the metabolic syndrome in the present study, which is different from some of the previous studies, in which metabolic healthy status was defined as having less than 2 components of the metabolic syndrome or no IR [4]. We showed, however, that in a Chinese community population, the prevalence of MHO was about one-fourth of the population and that of MANO phenotype was less than 10 %, which was in agreement with the reports from Hamer et al. [38].

In the present study, we use BF % to define obesity, while most of studies defined obesity by BMI $\geq$30 kg/m^2 or BMI $\geq$25 kg/m^2. The reasons for using BF % to define obesity are as follows. Firstly, BF % was correlated with BMI [21], and both of them were associated with high risk for T2D [21]. Secondly, with similar BF %, Chinese people normally have lower BMI compared with people in western countries [17, 18, 39], and in our previous study we found that BMI had limitations in the interpretation of subjects with BMI between 24 and 27.9 kg/m^2 [21]. Diagnose of MetS in the present study was based on the JCDCG definition, a criteria been included in the guideline for MetS in Chinese. We reported in the previous study that the association of overall morbidity and mortality of CVD with MetS defined by the JCDCG was significantly strong in women, but not in men [25].

Similar to MAO, subjects from the MANO, but not MHO group had a higher risk for incident diabetes. Same is true for the development of CVD in women, however, not in men. These suggested that metabolic risk factors, compared with obesity, appeared to play a more important role in the development of diabetes and CVD. Our finding in the MANO was in consistent with the previous studies, as from Greece and the United States [9, 14, 15, 40]. However, the reported association of MHO with increased risk for diabetes or CVD seems controversial [11, 31, 41, 42]. We found in the present study that the risk for developing diabetes and CVD in MHO subjects is similar with that in MHNO subjects, which is in agreement with the study of Meigs et al. in a Caucasian population [11, 38, 41] but not with the study reported by Soriguer et al. from Spain and Appleton et al. from Australia [31, 42], in which the risk for diabetic in MHO subjects was significant. They claimed that subjects in the MHO group were younger than those in MAO, and as age increases, they may transition from being obese and healthy to be obese with a cluster of risk factors [42].

Compared with MAO phenotype, subjects, in the present study, with MHO phenotype presented with lower IR determined by HOMA-IR levels, and had a lower proportion of visceral obesity, and pre-diabetes. Most strikingly, the number of subjects with pre-diabetes in MHO is much lower than that in MANO, which might be one of the reasons for the higher risk of new-onset diabetes in MANO groups in the present study. However, the reasons for the differences between MHO and MANO for CVD are not clear. Abdominal obesity was reported to be one of risk facts for IR and MetS, and was associated with CVD [43–45]. However, the proportion of subjects with abdominal obesity in MHO group is similar with that in the MANO group. Of note, by definition, subjects with the latter phenotype were defined with no obesity by BF %. Liver fat content was found to be associated with the metabolic risk [46] and that altered release of hepatokines from fatty liver may play a role in mediating the metabolic risk in the MANO group [47]. Further studies are needed to confirm the possibility.

In addition, the associations of MANO and MAO phenotypes with CVD differ in gender. MANO and MAO phenotype are only associated with an increased risk of CVD in women, but not in men. Gender differences regarding risk for CVD have been reported previously. Some have shown that MetS is only associated with an increased risk of CVD in women [48], whereas others have reported that MetS has conferred more risk of CVD in men [49]. The exact mechanisms behind the lower risk for diabetes and CVD in MHO subjects, and the gender differences in MANO with CVD need to be explored in future studies.

A number of limitations have to be taken into consideration in the present study. No precise information about lifestyle parameters, in particular smoking, was available in the present analysis. So far most of the studies used BMI cut-offs to define obesity. To better compare the present data with other studies, the data based on the BMI value ($\geq$ 25 kg/m^2) were also analyzed (Supplementary Table 1 and Table 2). Similar trends could be viewed for risk of diabetes and CVD in both MHO and MANO subjects with BMI cut-offs (Supplementary Table 1 and Table 2).

In conclusion, MHO and MANO phenotypes are common in a Chinese population. MANO phenotype confers a high risk for the development of diabetes and CVD, whereas MHO phenotype does not after years of follow-up. Distinguishing MHO and MANO from other phenotypes is of importance for guiding the treatment strategies for patients with different metabolic phenotypes. However, the exact mechanisms behind the lower risk for diabetes and CVD in MHO subjects are not clear.

Acknowledgments This work was supported by Drug Innovation Program of National Science and Technology Project (No. 2011ZX09307-001-02) and the Public Health Key Disciplines of Shanghai (No. 12GWZX0104).

Conflict of interest None.

References

1. S. Frood, L.M. Johnston, C.L. Matteson, D.T. Finegood, Obesity, Complexity, and the Role of the Health System. Curr. Obes. Rep. **2**, 320–326 (2013)
2. G. Reaven, F. Abbasi, T. McLaughlin, Obesity, insulin resistance, and cardiovascular disease. Recent Prog. Horm. Res. **59**, 207–223 (2004)
3. E. Bonora, The metabolic syndrome and cardiovascular disease. Ann. Med. **38**, 64–80 (2006)
4. N. Stefan, H.U. Haring, F.B. Hu, M.B. Schulze, Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol. **1**, 152–162 (2013)
5. F. Conus, R. Rabasa-Lhoret, F. Peronnet, Characteristics of metabolically obese normal-weight (MONW) subjects. Appl. Physiol. Nutr. Metab. **32**, 4–12 (2007)
6. A.D. Karelis, M. Brochu, R. Rabasa-Lhoret, Can we identify metabolically healthy but obese individuals (MHO)? Diabetes Metab. **30**, 569–572 (2004)
7. G.V. Denis, M.S. Obin, 'Metabolically healthy obesity': origins and implications. Mol. Aspects Med. **34**, 59–70 (2013)
8. M. Bluher, The distinction of metabolically 'healthy' from 'unhealthy' obese individuals. Curr. Opin. Lipidol. **21**, 38–43 (2010)
9. C. Voulgari, N. Tentolouris, P. Dilaveris, D. Tousoulis, N. Katsilambros, C. Stefanadis, Increased heart failure risk in normal-weight people with metabolic syndrome compared with metabolically healthy obese individuals. J. Am. Coll. Cardiol. **58**, 1343–1350 (2011)
10. S.H. Lee, H.S. Ha, Y.J. Park, J.H. Lee, H.W. Yim, K.H. Yoon, M.I. Kang, W.C. Lee, H.Y. Son, Y.M. Park, H.S. Kwon, Identifying metabolically obese but normal-weight (MONW) individuals in a nondiabetic Korean population: the Chungju Metabolic disease Cohort (CMC) study. Clin. Endocrinol. (Oxf) **75**, 475–481 (2011)
11. J.B. Meigs, P.W. Wilson, C.S. Fox, R.S. Vasan, D.M. Nathan, L.M. Sullivan, R.B. D'Agostino, Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J. Clin. Endocrinol. Metab. **91**, 2906–2912 (2006)
12. S. Camastra, E. Bonora, S. Del Prato, K. Rett, M. Weck, E. Ferrannini, Effect of obesity and insulin resistance on resting and glucose-induced thermogenesis in man. EGIR (European Group for the Study of Insulin Resistance). Int. J. Obes. Relat. Metab. Disord. **23**, 1307–1313 (1999)
13. E. Bonora, S. Kiechl, J. Willeit, F. Oberhollenzer, G. Egger, G. Targher, M. Alberiche, R.C. Bonadonna, M. Muggeo, Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. Diabetes **47**, 1643–1649 (1998)
14. N. Ruderman, D. Chisholm, X. Pi-Sunyer, S. Schneider, The metabolically obese, normal-weight individual revisited. Diabetes **47**, 699–713 (1998)
15. R.V. Dvorak, W.F. DeNino, P.A. Ades, E.T. Poehlman, Phenotypic characteristics associated with insulin resistance in metabolically obese but normal-weight young women. Diabetes **48**, 2210–2214 (1999)
16. F. Conus, D.B. Allison, R. Rabasa-Lhoret, M. St-Onge, D.H. St-Pierre, A. Tremblay-Lebeau, E.T. Poehlman, Metabolic and behavioral characteristics of metabolically obese but normal-weight women. J. Clin. Endocrinol. Metab. **89**, 5013–5020 (2004)
17. W.H.O. Expert, Consultation, Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet **363**, 157–163 (2004)
18. R.C. Ma, J.C. Chan, Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann. N. Y. Acad. Sci. **1281**, 64–91 (2013)
19. L.L. Roberson, E.C. Aneni, W. Maziak, A. Agatston, T. Feldman, M. Rouseff, T. Tran, M.J. Blaha, R.D. Santos, A. Sposito, M.H. Al-Mallah, R. Blankstein, M.J. Budoff, K. Nasir, Beyond BMI: The "Metabolically healthy obese" phenotype and its association with clinical/subclinical cardiovascular disease and all-cause mortality – a systematic review. BMC Public Health **14**, 14 (2014)
20. W.P. Jia, C. Pang, L. Chen, Y.Q. Bao, J.X. Lu, H.J. Lu, J.L. Tang, Y.M. Wu, Y.H. Zuo, S.Y. Jiang, K.S. Xiang, Epidemiological characteristics of diabetes mellitus and impaired glucose regulation in a Chinese adult population: the Shanghai Diabetes Studies, a cross-sectional 3-year follow-up study in Shanghai urban communities. Diabetologia **50**, 286–292 (2007)
21. C. Wang, X.H. Hou, M.L. Zhang, Y.Q. Bao, Y.H. Zou, W.H. Zhong, K.S. Xiang, W.P. Jia, Comparison of body mass index with body fat percentage in the evaluation of obesity in Chinese. Biomed. Environ. Sci. **23**, 173–179 (2010)
22. D.R. Matthews, J.P. Hosker, A.S. Rudenski, B.A. Naylor, D.F. Treacher, R.C. Turner, Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia **28**, 412–419 (1985)
23. W. Jia, H. Wu, Y. Bao, C. Wang, J. Lu, J. Zhu, K. Xiang, Association of serum retinol-binding protein 4 and visceral adiposity in Chinese subjects with and without type 2 diabetes. J. Clin. Endocrinol. Metab. **92**, 3224–3229 (2007)
24. M. Matsuda, R.A. DeFronzo, Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care **22**, 1462–1470 (1999)
25. C. Wang, X. Hou, Y. Bao, J. Pan, Y. Zuo, W. Zhong, W. Jia, K. Xiang, The metabolic syndrome increased risk of cardiovascular events in Chinese–a community based study. Int. J. Cardiol. **139**, 159–165 (2010)
26. L. Li, C. Wang, Y. Bao, L. Peng, H. Gu, W. Jia, Optimal body fat percentage cut-offs for obesity in Chinese adults. Clin. Exp. Pharmacol. Physiol. **39**, 393–398 (2013)
27. Y. Bao, J. Lu, C. Wang, M. Yang, H. Li, X. Zhang, J. Zhu, H. Lu, W. Jia, K. Xiang, Optimal waist circumference cutoffs for abdominal obesity in Chinese. Atherosclerosis **201**, 378–384 (2008)
28. K.G. Alberti, P.Z. Zimmet, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet. Med. **15**, 539–553 (1998)
29. M.A. Foulkes, P.A. Wolf, T.R. Price, J.P. Mohr, D.B. Hier, The Stroke Data Bank: design, methods, and baseline characteristics. Stroke **19**, 547–554 (1988)
30. H. Tunstall-Pedoe, K. Kuulasmaa, P. Amouyel, D. Arveiler, A.M. Rajakangas, A. Pajak, Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation **90**, 583–612 (1994)
31. F. Soriguer, C. Gutierrez-Repiso, E. Rubio-Martin, E. Garcia-Fuentes, M.C. Almaraz, N. Colomo, I. Esteva de Antonio, M.S. de Adana, F.J. Chaves, S. Morcillo, S. Valdés, G. Rojo-Martínez, Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. J. Clin. Endocrinol. Metab. **98**, 2318–2325 (2013)
32. Z. Pataky, E. Bobbioni-Harsch, A. Golay, Open questions about metabolically normal obesity. Int. J. Obes. (Lond) **34**(Suppl 2), S18–23 (2010)
33. B.J. Kwon, D.W. Kim, S.H. Her, D.B. Kim, S.W. Jang, E.J. Cho, S.H. Ihm, H.Y. Kim, H.J. Youn, K.B. Seung, J.H. Kim, T.H. Rho, Metabolically obese status with normal weight is associated with both the prevalence and severity of angiographic coronary artery disease. Metabolism **62**, 952–960 (2013)

34. C.M. Phillips, C. Dillon, J.M. Harrington, V.J. McCarthy, P.M. Kearney, A.P. Fitzgerald, I.J. Perry, Defining metabolically healthy obesity: role of dietary and lifestyle factors. PLoS ONE **8**, e76188 (2013)
35. A.D. Karelis, D.H. St-Pierre, F. Conus, R. Rabasa-Lhoret, E.T. Poehlman, Metabolic and body composition factors in subgroups of obesity: what do we know? J. Clin. Endocrinol. Metab. **89**, 2569–2575 (2004)
36. M.P. St-Onge, I. Janssen, S.B. Heymsfield, Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. Diabetes Care **27**, 2222–2228 (2004)
37. G. Iacobellis, M.C. Ribaudo, A. Zappaterreno, C.V. Iannucci, F. Leonetti, Prevalence of uncomplicated obesity in an Italian obese population. Obes. Res. **13**, 1116–1122 (2005)
38. M. Hamer, E. Stamatakis, Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. J. Clin. Endocrinol. Metab. **97**, 2482–2488 (2012)
39. W.P. Jia, C. Wang, S. Jiang, J.M. Pan, Characteristics of obesity and its related disorders in China. Biomed. Environ. Sci. **23**, 4–11 (2010)
40. K.M. Choi, H.J. Cho, H.Y. Choi, S.J. Yang, H.J. Yoo, J.A. Seo, S.G. Kim, S.H. Baik, D.S. Choi, N.H. Kim, Higher mortality in metabolically obese normal-weight people than in metabolically healthy obese subjects in elderly Koreans. Clin. Endocrinol. (Oxf) **79**, 364–370 (2013)
41. A.D. Karelis, M. Faraj, J.P. Bastard, D.H. St-Pierre, M. Brochu, D. Prud'homme, R. Rabasa-Lhoret, The metabolically healthy but obese individual presents a favorable inflammation profile. J. Clin. Endocrinol. Metab. **90**, 4145–4150 (2005)
42. S.L. Appleton, C.J. Seaborn, R. Visvanathan, C.L. Hill, T.K. Gill, A.W. Taylor, R.J. Adams, North West Adelaide Health Study, Team, Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care **36**, 2388–2394 (2013)
43. T. McLaughlin, G. Allison, F. Abbasi, C. Lamendola, G. Reaven, Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals. Metabolism **53**, 495–499 (2004)
44. Y. Shimamoto, M. Mizukoshi, A. Kuroi, T. Imanishi, T. Takeshita, M. Terada, T. Akasaka, Is visceral fat really a coronary risk factor? A multi-detector computed tomography study. Int. Heart J. **54**, 273–278 (2013)
45. Y. Wang, E.B. Rimm, M.J. Stampfer, W.C. Willett, F.B. Hu, Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am. J. Clin. Nutr. **81**, 555–563 (2005)
46. N. Stefan, K. Kantartzis, J. Machann, F. Schick, C. Thamer, K. Rittig, B. Balletshofer, F. Machicao, A. Fritsche, H.U. Haring, Identification and characterization of metabolically benign obesity in humans. Arch. Intern. Med. **168**, 1609–1616 (2008)
47. N. Stefan, H.U. Haring, The role of hepatokines in metabolism. Nat. Rev. Endocrinol. **9**, 144–152 (2013)
48. K.J. Hunt, R.G. Resendez, K. Williams, S.M. Haffner, M.P. Stern, San Antonio Heart Study, National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. Circulation **110**, 1251–1257 (2004)
49. G.N. Thomas, C.M. Schooling, S.M. McGhee, S.Y. Ho, B.M. Cheung, N.M. Wat, E.D. Janus, K.S. Lam, T.H. Lam, Hong Kong Cardiovascular Risk Factor Prevalence Study Steering Committee, Metabolic syndrome increases all-cause and vascular mortality: the Hong Kong Cardiovascular Risk Factor Study. Clin. Endocrinol. (Oxf) **66**, 666–671 (2007)