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Risk of the Development of Diabetes and Cardiovascular Disease in Metabolically Healthy Obese People

The Korean Genome and Epidemiology Study

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Abstract: The reported effects of a metabolically healthy obese (MHO) phenotype on diabetes and cardiovascular disease (CVD) risk are contradictory. Within the context of a population-based cohort study, we aimed to investigate the long-term risk of an MHO status for the development of diabetes and CVD, and whether consistency of this phenotype or age affected cardiometabolic outcomes.

We recruited 7588 subjects without diabetes or CVD, aged 40 to 69 years at baseline examination, from the Korean Genome and Epidemiology Study, and followed-up these subjects for 10 years biennially. Participants were divided into 4 groups based on the body mass index and the presence of metabolic syndrome: metabolically healthy normal weight (MHNW), MHO, metabolically unhealthy normal weight (MUNW), and metabolically unhealthy obese (MUO). We defined persistent phenotypes if subjects maintained the same phenotype at every visit from baseline to their last visit. Incident diabetes and CVD morbidity or mortality were identified during 10 years of follow-up.

Compared to MHNW controls, MUNW and MUO groups had increased risk for development of diabetes (hazard ratio [HR] 3.0 [95% CI: 2.5–3.6], and 4.0 [3.4–4.7], respectively) and CVD (HR 1.6 [1.3–2.0], and 1.9 [1.5–2.4], respectively). However, the MHO group showed only a marginal increase in risk for diabetes and CVD (HR 1.2 [0.99–1.6], 1.4 [0.99–1.8], respectively). The impact of MHO on the development of diabetes was more prominent in younger individuals (HR 1.9 [1.2–3.1] vs 1.1 [0.8–1.4], <45 years vs ≥45 years at baseline). Only 15.8% of MHO subjects maintained the MHO phenotype at every visit from baseline to the 5th biennial examination (persistent MHO). In subjects with persistent MHO, the risk for diabetes and CVD was significantly higher than those with persistent MHNW (1.9 [1.2–3.1], 2.1 [1.2–3.7], respectively).

MHO phenotype, even if maintained for a long time, was associated with a significantly higher risk for the development of diabetes and CVD in Korean subjects.

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Abbreviations: 2hPG = post 2-h glucose after the 75-g OGTT, BMI = body mass index, CVD = cardiovascular disease, HbA1c = glycated hemoglobin, MHNW = metabolically healthy normal weight, MHO = metabolically healthy obese, MUNW = metabolically unhealthy normal weight, MUO = metabolically unhealthy obese, OGTT = 75-g oral glucose tolerance test.

INTRODUCTION

Obesity now represents one of the major health problems in the world. As in most developed countries, the prevalence of obesity in Korean adults is rapidly increasing; a 2011 Korean nationwide survey revealed that 34.9% of men and 30.5% of women were obese.[1] Although obesity is closely associated with complications such as type 2 diabetes and cardiovascular disease (CVD), there is a subset of individuals who appear to be resistant to the development of metabolic abnormalities despite the presence of obesity.[2] These individuals are characterized as ''metabolically healthy obese (MHO),'' and the proportion of MHO subjects differs according to ethnicity, age, and level of physical activity.[3] However, there are contradictory data on future risk for developing diabetes, CVD, or mortality in subjects with the MHO phenotype.[4–8] In the San Antonio Heart Study, MHO subjects had >2-fold increased risk of incident diabetes and CVD compared to metabolically healthy normal weight (MHNW) controls.[4] In contrast, Hosseinpanah et al reported that metabolically healthy, overweight, or obese subjects had a similar risk for future CVD as MHNW controls based on 8 years of follow-up.[5] Interestingly, Kramer et al reported that elevated risk for all-cause mortality and CVD was

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only evident for MHO subjects after long-term follow-up (≥10 years).[9] This finding implies that the duration of follow-up is an essential component that should be considered when assessing future risk of diabetes development and CVD in MHO subjects.

Body size and metabolic phenotype are unstable, and transition to a different metabolic status occurs frequently over time.[10,11] Therefore, future metabolic risk relative to the baseline phenotype may be a summation of the changes in phenotypes during follow-up. To clearly determine if the MHO phenotype poses a metabolic risk, it is necessary to differentiate the risk of those subjects who experienced changes in their phenotype from those who retained the MHO phenotype for the duration of the study period. In most previous studies, however, the effects of chronological changes or duration of exposure to metabolic–BMI phenotypes on morbidity or mortality were not considered.

Recently, Appleton et al reported that MHO subjects who maintained metabolic health during follow-up showed no increase in risk for developing future diabetes or CVD.[10] In contrast, Lee et al reported a higher incidence of diabetes in persistent MHO subjects (those who maintained the MHO phenotype on 1 or 2 follow-up visits) from a rural population than subjects who did not maintain the MHO status during the study period.[12] The paucity of previous studies in persistent MHO phenotype individuals and the short follow-up periods make it hard to determine whether people who maintain the MHO phenotype for a long time have increased cardiometabolic risk.

Furthermore, the prognostic implication of obesity might differ with age. Previous epidemiological studies suggested excess mortality risk associated with obesity was weakened or inversed in elderly subjects.[13,14] However, the impact of the MHO phenotype on future metabolic risk according to age group has not previously been investigated.

Therefore, our aim in the present study was to evaluate the long-term risk for development of diabetes and CVD in MHO-phenotype individuals from a Korean population-based cohort. In particular, we wanted to determine how maintenance of the MHO phenotype over time and age affected diabetes and CVD risk.

METHODS

Study Subjects

All study subjects were derived from the Ansan (urban area) and Anseong (rural area) cohort of the Korean Genome Epidemiology Study (KoGES), an ongoing population-based cohort study that began in 2001. Details of KoGES and the sampling method have been provided in previous reports.[15,16] Briefly, the cohort consisted of 10,037 subjects aged 40 to 69 years at baseline who had undergone a comprehensive health examination, including interviews. They were followed up biennially. Of these 10,037 subjects, subjects with diabetes at baseline exam (n = 1,328), previous history of cardiovascular disease (n = 254), or missing information about diabetes or CVD (n = 73) or metabolic health status (n = 49) were excluded. Among those subjects who underwent a baseline examination, subjects who did not have at least 1 follow-up examination until 2012 (n = 857) were excluded. Finally, a total of 7588 subjects were enrolled in this study. All subjects participated in the study voluntarily, and informed consent was obtained in all cases. The study protocol was approved by the Ethics Committee of the Korean Health and Genomic Study of the Korea National Institute of Health.

Definition of Incident Diabetes and Fatal or Nonfatal CVD

All study subjects underwent a 2-h 75-g oral glucose tolerance test (OGTT) at each follow-up visit. Incident diabetes was defined as a fasting glucose concentration of ≥126 mg/dL or a post 2-h glucose after the 75-g OGTT (2hPG) of ≥200 mg/dL based on the World Health Organization criteria.[17] Regardless of glucose values, subjects who reported current therapy with antidiabetic medications were considered to have diabetes. To analyze incident diabetes, subjects were followed-up until the development of diabetes or their last examination.

To determine fatal CVD, each subject's cause of death as of 31 December 2012 was determined by linking cohort data with death certificate data from the Korean National Statistical Office. Terminology and codes from the International Classification of Disease, Tenth Revision (ICD-10), were used to classify the underlying cause of death (death due to CVD corresponds to codes I00–I79 in ICD-10). Nonfatal CVD was determined by questionnaire as newly developed CV events including myocardial infarction, coronary artery disease, congestive heart failure, and/or stroke. To evaluate CVD outcome, which comprised fatal or nonfatal CVD, subjects were followed-up until the development of CVD or their last examination.

Measurement of Anthropometric and Biochemical Parameters

Height, body weight, and waist circumference were measured using standard methods in light clothes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Smoking status was divided into 3 categories: current smokers, ex-smokers, and never smokers. Alcohol intake was categorized as no or current (alcohol consumption of ≥15 g per day for the previous 12 months) drinker. Exercise status was categorized as no exercise, light exercise (<3 times/week), or regular exercise (≥3 times/week, ≥30 minutes per session) during the previous month.

After fasting overnight for 12 hours, plasma concentrations of glucose, total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were measured enzymatically using a 747 Chemistry Analyzer (Hitachi, Tokyo, Japan). Plasma glucose was measured 2 hours after a 75-g oral glucose loading test. Fasting plasma insulin concentrations were determined by a radioimmunoassay kit (Linco Research, St. Charles, MO). Glycated hemoglobin (HbA1c) level was measured by high-performance liquid chromatography (VARIANT II; Bio-Rad Laboratories, Hercules, CA).

Classification of Metabolic Phenotype

Study subjects were classified according to BMI (obese: ≥25 kg/m^2, nonobese: <25 kg/m^2) and metabolic health status determined by the presence/absence of ≥ 2 components of metabolic syndrome using the modified National Cholesterol Education Project Adult Treatment Panel (NCEP ATP III) criteria, except abdominal obesity. The components of metabolic syndrome used for classification were (1) high blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or medication for hypertension); (2) hyperglycemia (fasting plasma glucose ≥100 mg/dL or

2hPG ≥140 mg/dL or medication for diabetes); (3) hypertriglyceridemia (fasting plasma triglycerides ≥150 mg/dL); and (4) low HDL cholesterol (fasting HDL cholesterol <40 mg/dL in men, <50 mg/dL in women). By combining the BMI and metabolic health status data, we categorized study subjects into 4 groups: metabolically healthy normal weight (MHNW), metabolically healthy obese (MHO), metabolically unhealthy normal weight (MUNW), and metabolically unhealthy obese (MUO). To investigate the effect of a consistent metabolic phenotype over time on future diabetes and cardiovascular risk, we assigned subjects who maintained the baseline phenotype at every visit until their last follow-up examination to persistent groups (persistent MHNW, persistent MHO, persistent MUNW, and persistent MUO).

Comparison of Metabolic Phenotypes at Baseline and the Fifth Examinations

To investigate if there was a transition in metabolic phenotype between baseline and the 5th biennial examination, a total of 4811 subjects who participated in both examinations were selected. We compared the prevalence of the 4 metabolic phenotypes and changes in these phenotypes between these 2 visits, regardless of the interim examination results.

Statistical Analysis

The demographic characteristics of the study subjects were expressed as means ± SD, or numbers and percentages, or median and interquartile ranges if the distributions were skewed. For continuous variables, 1-way analysis of covariance (ANOVA) was used to assess differences in means according to metabolic phenotype. A chi-square test was used for categorical variables. Risk for incident diabetes or CVD was compared among the 4 metabolic phenotype groups using Cox-proportional hazard models after adjusting for age, sex, study site (Ansan vs Anseong), exercise status, smoking status, and alcohol intake. Similarly, the impact of persistent phenotype on future development of diabetes or CVD was also examined. We compared diabetic risk between MHNW and MHO phenotypes in 2 age group (<45 years vs ≥45 years at baseline) separately to evaluate if there was an age interaction. The time to development of diabetes was estimated by the Kaplan–Meier method, and statistical differences between MHNW and MHO according to age group were compared by the log-rank test. Assumptions of proportionality were tested using log follow-up time interaction terms for each baseline variable. Statistical analyses were conducted using SAS version 9.1 for Windows (SAS Institute Inc, Cary, NC). All reported P values were 2-tailed. P values of <0.05 were considered statistically significant.

RESULTS

The anthropometric and biochemical characteristics of study subjects in the 4 metabolic phenotype groups are shown in Table 1. Of the 7588 participants, 4025 study participants (53.0%) were metabolically healthy. The proportion of MHO subjects in the obese group was 37.7%. Metabolically healthy subjects, that is, MHNW and MHO subjects, were younger than metabolically unhealthy subjects. During 7.7 ± 2.9 years of follow-up, 1268 incident cases of diabetes (16.7% of study subjects) developed, and during 8.2 ± 2.7 years of follow-up, 508 CV events (6.7%, 119 fatal and 389 nonfatal events) occurred between 2002 and 2012.

Changes in Metabolic Phenotype During Follow-up

We compared subjects' metabolic phenotypes between their baseline and fifth follow-up visits, regardless of phenotypic changes during the other visits (n = 4811) (Table 2). About 60% of MHNW, MUNW, and MUO individuals were in the same group at baseline and the fifth visit. However, in the MHO group, only 36.2% of subjects maintained the MHO phenotype on the fifth examination. The status of about half of the MHO group members changes to metabolically unhealthy, and only 12.4% of MHO individuals achieved the MHNW phenotype. In contrast, when the phenotypes of every visit were taken into consideration, only 15.8% (n = 132) of individuals with a baseline MHO phenotype maintained the same phenotype at every visit (persistent MHO phenotype individuals).

Risk for Diabetes and CVD According to Baseline Metabolic Phenotype

We examined the risk for development of diabetes and CVD in the 4 groups using a Cox proportional hazards model (Table 3). Compared to MHNW controls, subjects in the MUNW and MUO groups had increased risk for incident diabetes and CV events in a model adjusted for age, sex, study site (Ansan vs Anseong), exercise habits, smoking status, and alcohol intake. However, the MHO group showed a marginal increase in risk for diabetes and CVD (HR [95% CI]: 1.2 [0.99–1.6], 1.4 [0.99–1.8], respectively). There was a significant age interaction between metabolic phenotype and risk of incident diabetes (Figure 1). Younger MHO subjects (<45 years at baseline) had a higher risk for diabetes than MHNW controls (HR: 1.9 [1.2–3.1]), but older MHO subjects (≥45 years at baseline) did not (HR: 1.1 [0.8–1.4]). There was no age interaction between metabolic phenotype and CVD outcome in MHO subjects (data not shown).

Risk for Diabetes and CVD According to Persistent Metabolic Phenotype

To investigate the effect of phenotype changes on the risk of incident diabetes or CVD, we performed an analysis in subjects with persistent phenotypes. The characteristics of subjects with persistent phenotypes were not different from those of subjects categorized by baseline phenotypes (Table 1 and Supplemental Table 1, http://links.lww.com/MD/A903). Compared to persistent MHNW controls, persistent MHO individuals had about a 2-fold increased risk for both diabetes and CVD (Table 4).

DISCUSSION

In this population-based cohort study of subjects that were followed-up for 10 years, we showed that the status of MHO was labile; >50% of MHO subjects progressed to the metabolically unhealthy phenotype. Although a subset of MHO subjects retained the same healthy phenotype over time, they showed a modestly increased risk for development of diabetes and cardiovascular events in long-term follow-up. The impact of MHO on the development of diabetes was more evident in younger than older individuals.

Several studies, including a recent meta-analysis, reported that MHO individuals had increased risk for incident diabetes than healthy nonobese controls.[4,7,18,19] Nevertheless, few longitudinal prospective studies have evaluated long-term outcomes.

TABLE 1. Baseline Characteristics of Study Subjects by Metabolic Phenotype According to Body Mass Index and ≥2 Metabolic Syndrome Components

	MHNW	MHO	MUNW	MUO	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	*P* Value
N (% of total)	2848 (37.5)	1177 (15.5)	1622 (21.4)	1941 (25.6)	
Ansan (n [%])	1376 (48.3)	596 (50.6)	799 (49.3)	1019 (52.5)	0.03
Men (n [%])	1405 (49.3)	492 (41.8)	786 (48.5)	864 (44.5)	<0.001
Age (year)	50.6 ± 8.8	49.9 ± 7.9	53.8 ± 9.2	52.2 ± 7.9	<0.001
Body mass index (kg/m^2)	22.2 ± 1.9	27.1 ± 1.9	22.9 ± 1.7	27.5 ± 1.9	<0.001
Waist circumference (cm)	76.6 ± 6.8	86.9 ± 7.1	79.9 ± 6.7	89.3 ± 7.1	<0.001
Fasting glucose (mg/dL)	83.4 ± 7.7	84.9 ± 7.7	86.5 ± 9.8	87.8 ± 7.7	<0.001
2h-post OGTT glucose (mg/dL)	106.4 ± 26.3	110.7 ± 23.6	127.6 ± 32.6	130.8 ± 23.6	<0.001
Fasting insulin (IU/L)	6.1 (4.7–7.9)	7.5 (5.5–10)	6.8 (5.1–9.1)	8.4 (6.1–11)	<0.001
HbA1c (%)	5.5 ± 0.3	5.5 ± 0.4	5.6 ± 0.4	5.7 ± 0.4	<0.001
Systolic BP (mm Hg)	113.4 ± 15.2	116.6 ± 15.4	126.2 ± 18.8	128.1 ± 15.4	<0.001
Diastolic BP (mm Hg)	75.2 ± 9.7	78.3 ± 10.0	83.0 ± 11.5	85.2 ± 10.0	<0.001
HDL-cholesterol (mg/dL)	52.5 ± 11.1	50.2 ± 10.1	44.1 ± 10.7	41.7 ± 10.1	<0.001
Triglycerides (mg/dL)	98 (77–123)	107 (83–132)	169 (124–220)	182 (142–246)	<0.001
Total cholesterol (mg/dL)	187.2 ± 32.4	195.9 ± 34.1	193.2 ± 36.0	201.8 ± 34.1	<0.001
Exercise (n [%])					
No	1973 (69.3)	721 (61.3)	1150 (70.9)	1259 (64.9)	<0.001
Light	494 (17.3)	254 (21.6)	268 (16.5)	373 (19.2)	
Regular	381 (13.4)	202 (17.2)	204 (12.6)	309 (15.9)	
Smoking (n [%])					
Never	1614 (56.7)	768 (65.3)	923 (56.9)	1167 (60.1)	<0.001
Ex	408 (14.3)	170 (14.4)	248 (15.3)	308 (15.9)	
Current	786 (27.6)	226 (19.2)	426 (26.3)	430 (22.2)	
Alcohol intake (n [%])					
No	1426 (50.6)	578 (49.5)	937 (55.0)	1064 (55.6)	<0.001
Current	1392 (49.4)	590 (50.5)	766 (45.0)	851 (44.4)	
Hypertension (n [%])	323 (11.3)	214 (18.2)	676 (41.7)	984 (50.7)	<0.001

HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; MHNW = metabolically healthy normal weight; MHO = metabolically healthy obese; MUNW = metabolically unhealthy normal weight; MUO = metabolically unhealthy obese; OGTT = 75g-oral glucose tolerance test.

Two recent Korean studies reported a higher incidence of diabetes in MHO subjects than normal controls. However, they enrolled subjects from a health screening program of 1 hospital, not from a community, and included only men,[18] whereas the second study was performed in a rural population with only 2 follow-up visits.[12] The present study is the first Korean community-based longitudinal cohort study to evaluate the incidence of diabetes and CVD according to MHO phenotype, and individuals from both rural and urban populations were included. We enrolled 7588 people without diabetes or CVD at baseline who were thoroughly examined biennially, including administration of an oral glucose tolerance test, for up to 10 years. There have been a few studies that have investigated the stability of MHO status and the risk for incident diabetes in individuals who sustain the MHO phenotype.[10–12] In those studies, a metabolically healthy overweight or obese phenotype was maintained in 46% to 57% of individuals after 6 to 8 years of follow-up. When we compared phenotypes between the first

TABLE 2. Prevalence of Metabolic Phenotype at Baseline and 5th Follow-Up Study (n [%])

	5th Follow Up				
Baseline	MHNW	MHO	MUNW	MUO	Total Baseline
MHNW	1158 (59.8)	80 (4.1)	587 (30.3)	113 (5.8)	1938 (40.3)
MHO	103 (12.4)	302 (36.2)	55 (6.6)	374 (44.8)	834 (17.3)
MUNW	251 (26.1)	17 (1.8)	596 (62.0)	97 (10.1)	961 (20.0)
MUO	63 (5.8)	137 (12.7)	161 (14.9)	717 (66.5)	1078 (22.4)
Total 5th follow-up	1575 (32.7)	536 (11.1)	1399 (29.1)	1301 (27.0)	4811

MHNW = metabolically healthy normal weight; MHO = metabolically healthy obese; MUNW = metabolically unhealthy normal weight; MUO = metabolically unhealthy obese.

TABLE 3. Incident Diabetes and Incident Cardiovascular Disease by Baseline Metabolic Phenotype

	No. with Incident Diabetes or CVD	No. at Risk	Rate, %	HR (95% CI) Model 1	HR (95% CI) Model 2
Incident diabetes					
MHNW	218	2848	7.7	*Reference*	*Reference*
MHO	115	1177	9.8	1.3 (1.0–1.6)	1.2 (0.99–1.6)
MUNW	379	1622	23.4	3.1 (2.6–3.7)	3.0 (2.5–3.6)
MUO	556	1941	28.7	4.1 (3.5–4.8)	4.0 (3.4–4.7)
Incident CVD					
MHNW	132	2848	4.6	*Reference*	*Reference*
MHO	63	1177	5.4	1.3 (0.9–1.7)	1.4 (0.99–1.8)
MUNW	141	1622	8.7	1.6 (1.3–2.0)	1.6 (1.3–2.0)
MUO	170	1941	8.8	1.8 (1.5–2.3)	1.9 (1.5–2.4)

Model 1: adjusted for age, sex, study site at baseline.
Model 2: adjusted for age, sex, study site, exercise habits, smoking status, and alcohol intake.
CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; MHNW = metabolically healthy normal weight; MHO = metabolically healthy obese; MUNW = metabolically unhealthy normal weight; MUO = metabolically unhealthy obese.

and fifth biennial examinations, 36.2% of baseline MHO subjects had the same MHO phenotype on the fifth follow-up visit. However, when we considered metabolic phenotype at every visit, only 15.8% of baseline MHO subjects had a persistent MHO phenotype, which suggests that the MHO phenotype is extremely unstable. Our cohort was followed biennially and any subject who experienced phenotype changes during any visit was excluded from the persistent phenotype analysis. Therefore, in terms of future diabetes risk, MHO status *per se* is not a benign condition.

We found a significant age interaction; the incidence of diabetes in younger MHO individuals was elevated relative to the MHNW controls, but this was not the case for the older MHO group. Previous studies reported that the MHO phenotype was more prevalent and persistent in younger individuals.[3,10]

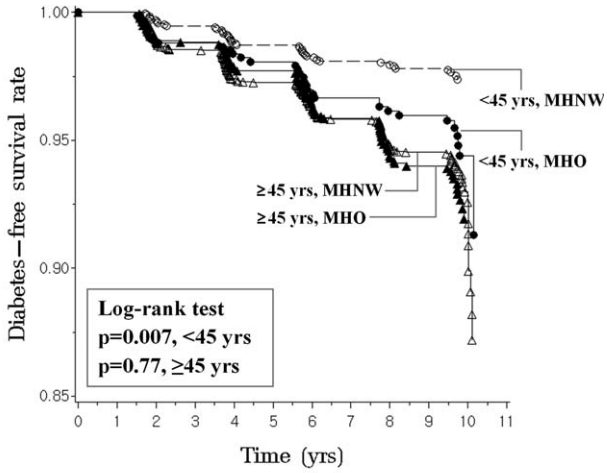

FIGURE 1. Diabetes-free survival by Kaplan–Meier analysis (log-rank test, for comparisons between MHNW and MHO at baseline according to age; <45 years, *P = 0.007*; ≥45 years, *P = 0.77*). o: <45 years, metabolically healthy normal weight (MHNW); •: <45 years, metabolically healthy obese (MHO); Δ: ≥45 years, MHNW; ≥45 years, MHO.

Similarly, a slightly greater proportion of younger MHO subjects maintained the baseline MHO phenotype on the fifth biennial follow-up than older MHO subjects (41.0% of MHO subjects <45 years vs 34.2% of MHO subjects ≥45 years at baseline, data not shown). The labile nature of the MHO phenotype and the increase in prevalence of diabetes with aging might confound the association between MHO phenotype and risk of incident diabetes in older individuals. In addition, a recent study showed that in younger subjects, adiposity had a larger effect on metabolic risk markers such as inflammation, lipid levels, and blood pressure than in older subjects.[20] They suggested that long-term metabolic outcomes induced by obesity can be more remarkable in younger subjects than in older subjects.

Previous reports on the risks of CVD morbidity and mortality in individuals with the MHO phenotype are contradictory.[4,7,21–23] In the present study, we found a modest increase in CVD risk for MHO subjects categorized by baseline phenotype, which might be accentuated by a longer follow-up time, as in other publications.[9,24] There is little data on the impact of a consistent MHO phenotype on CVD risk. However, the elevated incidence of CVD events in subjects with persistent MHO who maintained metabolic health over time suggests that MHO increases risk for CVD and that there is no such thing as healthy obesity.

The strengths of this study are that it was a long-term population-based cohort study of a large number of subjects from a single ethnic group. We evaluated the effect of MHO status on both diabetes and CVD risk by evaluating long-term outcomes. In addition, the incidence of diabetes was identified by oral glucose tolerance tests, unlike most previous studies. Notably, we assessed the risk for diabetes and CVD by evaluating metabolic changes in MHO individuals over time. This allowed us to demonstrate an effect of MHO status on diabetes and CVD without the potentially confounding effects of phenotype changes, which distinguishes this study from previous studies. However, this study also had several limitations. We did not consider fat distribution to define obesity, even though fat distribution is closely associated with metabolic abnormalities, and the development of nonfatal CVD was based on questionnaire answers, not medical records.

TABLE 4. Incident Diabetes and Incident Cardiovascular Disease by Persistent Metabolic Phenotype

	No. with Incident Diabetes or CVD	No. at Risk	Rate, %	HR (95% CI)	
				Model 1	Model 2
Incident diabetes					
Persistent MHNW	58	1026	5.7	*Reference*	*Reference*
Persistent MHO	22	216	10.2	1.9 (1.2–3.1)	1.9 (1.2–3.1)
Persistent MUNW	134	436	30.7	5.6 (4.1–7.7)	5.3 (3.9–7.3)
Persistent MUO	249	708	35.2	7.1 (5.3–9.4)	7.0 (5.2–9.3)
Incident CVD					
Persistent MHNW	46	1012	4.6	*Reference*	*Reference*
Persistent MHO	17	211	8.1	2.2 (1.2–3.8)	2.1 (1.2–3.7)
Persistent MUNW	57	471	12.1	1.8 (1.2–2.7)	1.7 (1.1–2.6)
Persistent MUO	85	770	11.0	2.2 (1.5–3.2)	2.2 (1.5–3.1)

Model 1: adjusted for age, sex, study site at baseline.
Model 2: adjusted for age, sex, study site, exercise habits, smoking status, and alcohol intake.
CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; MHNW = metabolically healthy normal weight; MHO = metabolically healthy obese; MUNW = metabolically unhealthy normal weight; MUO = metabolically unhealthy obese.

In conclusion, MHO subjects are at increased risk for the development of diabetes and CVD even if they maintain the same phenotype over a long period of time. MHO status is unstable over time; a substantial proportion of subjects with an MHO phenotype develop a metabolically unhealthy phenotype during follow-up. Considering that MHO *per se* is a risk factor for diabetes and CVD and that progression from MHO to MUO status can boost the risk of incident diabetes, appropriate guidelines for the care of MHO individuals should be established and applied.

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