Predicting Development of the Metabolically Healthy Obese Phenotype

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Abstract

Objective—The metabolically healthy (MHO) and unhealthy obese (MUHO) differ in terms of cardiovascular risk. However, little is known about predicting the development of these phenotypes and the future stability of the MHO phenotype. Therefore, we examined these two issues in the San Antonio Heart Study.

Design—Longitudinal, population-based study of cardiometabolic risk factors among Mexican Americans and non-Hispanic whites in San Antonio.

Subjects—The study sample included 2,368 participants with neither MUHO nor diabetes at baseline. Median follow-up was 7.8 years. MHO was defined as obesity with ≤1 metabolic abnormality; MUHO, as obesity with ≥2 abnormalities.

Results—At baseline, 1,595 and 498 individuals were non-obese with ≤1 and ≥2 metabolic abnormalities, respectively; 275 were MHO. Among non-obese individuals, independent predictors of incident MHO (OR for 1-SD change [95% CI]) included body mass index (8.12 [5.66 – 11.7]), triglycerides (0.52 [0.39 – 0.68]), and HDL-C (1.41 [1.11 – 1.81]), whereas independent predictors of incident MUHO included BMI (5.97 [4.58 – 7.77]) and triglycerides (1.26 [1.05 – 1.51]). Among participants with ≤1 metabolic abnormality, obesity was associated with greater odds of developing multiple metabolic abnormalities (OR 2.26 [1.74 – 2.95]).

Conclusions—Triglycerides and HDL-C may be useful for predicting progression to MHO. MHO may not be a stable condition, because it confers an increased risk of developing multiple metabolic abnormalities.
Introduction

Strongly associated with the development of diabetes and cardiovascular disease, obesity has reached epidemic proportions.\(^1,2\) Obesity is usually associated with other metabolic abnormalities, but not all obese individuals are affected.\(^3-5\) Specifically, the obesity phenotype contains a subtype that is characterized by the absence of multiple metabolic abnormalities, the “metabolically healthy obese” (MHO).\(^5\) Up to 30% of obese individuals are metabolically healthy.\(^5,6\) Although existing data supports the adverse effects of obesity on health,\(^2,7,8\) other evidence demonstrates that MHO individuals are not at increased short-term risk of developing cardiovascular disease.\(^5,9\) MHO individuals may also differ from the metabolically unhealthy obese (MUHO) in terms of response to a lifestyle intervention.\(^10-13\) Consequently, stratification of obese individuals as metabolically healthy and unhealthy may have important implications for preventive and treatment strategies.\(^5,10,11\)

The natural course of the MHO condition is unknown and there is no consensus on the MHO definition.\(^5,14\) MHO is often defined as absence of multiple metabolic abnormalities including high blood pressure, low HDL cholesterol (HDL-C), hypertriglyceridemia, elevated fasting glucose, insulin resistance, and inflammation.\(^15\) These conditions have been selected because they tend to be available in both the clinical and epidemiologic settings. We hypothesized that a participant’s status with regard to one or more of these metabolic abnormalities could predict maintenance of healthy metabolic state among those who subsequently develop obesity. Therefore, the aim of our study was twofold: 1) to determine the ability of demographic and metabolic variables to differentiate between non-obese individuals who will develop later MHO vs. MUHO; and 2) to examine the metabolic stability over time of MHO individuals.

Subjects and Methods

Subjects

The San Antonio Heart Study (SAHS) was designed as a population-based study of type 2 diabetes and cardiovascular disease among Mexican Americans and non-Hispanic whites in San Antonio, Texas, USA. SAHS protocols were approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio (UTHSCSA). All participants gave written informed consent. Detailed descriptions of study procedures have been published previously.\(^16,17\) Briefly, all Mexican American and non-Hispanic white, men and non-pregnant women aged 25 to 64 years, who resided within randomly selected households from low-, middle-, and high-income census tracts in San Antonio, Texas, were invited to participate. Ethnic classification (Mexican American or non-Hispanic white) was based on a previously published algorithm.\(^18\) A total of 5,158 individuals (response rate: 65.3%) were enrolled in 2 cohorts: cohort 1, from January 1979 to December 1982; cohort
from January 1984 to December 1988. Cohort 1 participants were re-examined between January 1984 and December 1988, and cohort 2 participants between October 1991 and October 1996. Among 3,864 participants who had neither diabetes nor MUHO at the baseline examination, 2,368 individuals (61.7%) returned to follow-up and comprise the sample for the present analyses. The median follow-up period was 7.8 years (range, 6.3 – 9.8 years). Compared with returning participants, those who did not return to follow-up were younger (p <0.001) and had greater adiposity (p = 0.037); insulin resistance, however, was similar in both groups (p = 0.191).

Acquisition of data and definition of variables and outcomes

Anthropometric measurements and smoking status were gathered by trained personnel. Systolic (SBP: Korotkoff phase 1) and diastolic (DBP: Korotkoff phase 5) blood pressures were recorded with a Random-Zero sphygmomanometer (Gelman- Hawksley, Sussex, UK) with the participant sitting. Blood pressure was reported as the mean of the second and third blood pressure readings. Blood specimens were obtained after a 12-h fast. Oral glucose tolerance tests using a 75-g oral glucose load (Orangedex; Custom Laboratories, Baltimore, MD) were performed to assess diabetes status at both baseline and follow-up examinations. Plasma glucose and serum lipids were measured with an Abbott Bichromatic Analyzer (South Pasadena, CA) in the laboratory of the Department of Medicine, Division of Clinical Epidemiology at UTHSCSA. Serum insulin was measured by a radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA), which had a high degree of cross-reactivity with proinsulin (70–100%).

We used the homeostasis model assessment to estimate insulin resistance (HOMA-IR), which was calculated using the following formula: HOMA-IR = fasting insulin (μU/ml) × fasting glucose (mmol/l) / 22.5. Diabetes was defined according to the plasma glucose cut-points of the 2003 American Diabetes Association (fasting glucose ≥ 7.0 mmol/l and/or 2-hour glucose ≥ 1.1 mmol/l).

Regardless of glucose values, participants reporting current therapy with glucose-lowering medications were considered to have diabetes. We used Framingham risk equations to estimate 10-year coronary heart disease (CHD) risk. Body mass index (BMI) and waist circumference were considered measures of overall and central adiposity respectively. Obesity was defined as BMI ≥ 30 kg/m². Metabolic abnormalities were defined as reported by Wildman et al., with the exception of elevated C-reactive protein, which was not tested in the SAHS cohort. Elevated blood pressure was defined as either SBP ≥ 130 mm Hg, DBP ≥ 85 mm Hg, or treatment with antihypertensive medications; elevated triglycerides, as fasting triglyceride concentration ≥ 1.7 mmol/l; low HDL-C, as HDL-C < 1.04 mmol/l, in men, < 1.29 mmol/l in women, or treatment with lipid-lowering medications; dysglycemia, as fasting plasma glucose 5.6 to 6.9 mmol/l; and insulin resistance, as HOMA-IR > 5.13. All individuals with ≥ 2 metabolic abnormalities were considered metabolically abnormal; among these, those with BMI > 30 kg/m² were categorized as MUHO. Individuals with BMI > 30 kg/m² but ≤ 1 metabolic abnormality were categorized as MHO. Because some authors have defined healthy metabolic state in the context of obesity as being insulin-sensitive, we used this approach to generate alternative definitions of MHO and MUHO. Using this criterion, individuals whose HOMA-
IR was in the three lower quartiles for non-diabetic participants were categorized as metabolically healthy; those in the upper quartile, as metabolically unhealthy.\textsuperscript{22,23}

**Statistical analyses**

Statistical analyses were performed using SAS statistical software (version 9.2, SAS Institute Inc. Cary, NC). Differences in participant characteristics between categories of adiposity were assessed by one-way analysis of covariance (continuous variables) or logistic regression analysis (dichotomous variables) in order to take into consideration the effect of age, sex, and ethnicity. We generated multiple logistic regression models to test our hypothesis: one or more demographic or metabolic characteristics could predict maintenance of healthy or development of unhealthy metabolic state among those who subsequently develop obesity. In these models, incident MHO (or incident MUHO) was the dependent variable and demographic and metabolic variables were the independent variables. To avoid the potential for bias due to misclassification of MHO and MUHO individuals and therefore test the robustness of our results, we produced different logistic regression models using alternative definitions\textsuperscript{23} of MHO and MUHO as the dependent variable. We used logit-transformed values of 10-year CHD risk and log-transformed values of fasting insulin, triglycerides, and HOMA-IR in all analyses to minimize the influence of extreme observations. We considered a \( p \) value <0.05 to be statistically significant.

**Results**

At baseline, the study sample included 2,368 participants who had neither MUHO nor diabetes. Of these, 2,093 were non-obese (1,595 and 498 with \( \leq 1 \) and \( \geq 2 \) metabolic abnormalities, respectively), and 275 had MHO.

**Incidence of MUHO and MHO among baseline non-obese**

Table 1 presents baseline characteristics grouped by categories of adiposity and metabolic status at baseline (non-obese and MHO) and follow-up visits (non-obese, MHO, and MUHO). Among the 2,093 non-diabetic individuals who were non-obese at baseline, 111 (5.3\%) and 226 (10.8\%) developed MHO and MUHO, respectively, during the follow-up period. Non-obese individuals who later developed MHO were younger and had higher adiposity and lower triglycerides than those who remained non-obese. Other characteristics were similar including smoking, blood pressure, cholesterol and glucose levels, and insulin resistance. In contrast, participants who later developed MUHO had, in addition to adiposity, more dyslipidemia, dysglycemia, and insulin resistance, and higher blood pressure and 10-year CHD risk than those who remained non-obese. Individuals who developed MHO did not differ from those who developed MUHO in terms of smoking, adiposity (overall and central adiposity), blood pressure, or dysglycemia; those who developed MUHO, however, had more dyslipidemia and insulin resistance, and higher 10-year CHD risk.

We used multiple logistic regression to assess the relationship of baseline demographic variables, BMI, SBP, HOMA-IR, fasting glucose, triglycerides, and HDL-C to incident MHO and MUHO among baseline non-obese (Table 2). Younger age was associated with
increased incidence of obesity, for both phenotypes. Men were less likely to acquire multiple metabolic abnormalities with developing obesity than women. Independent predictors of progression to MHO (OR for 1 SD [95% CI]) included BMI (OR 8.12 [5.66 – 11.7]), triglycerides (OR 0.52 [0.39 – 0.68]), and HDL-C (OR 1.41 [1.11 – 1.81]). Higher triglycerides were associated with decreased likelihood of progression to MHO, while higher HDL-C was associated with greater likelihood of progression to MHO. Both BMI (OR 5.97 [4.58 – 7.77]) and triglycerides (OR 1.26 [1.05 – 1.51]) independently predicted increased likelihood of progression to MUHO. The relationship of BMI and triglyceride concentration to incident MHO and MUHO is shown by age, sex, and ethnicity in Table 3. For incident MUHO, no significant interactions were observed between any of these variables and either BMI or triglycerides. For MHO, there were only two interactions: BMI was a better predictor of MHO in older, compared with younger, participants, and in men compared with women.

Compared with those who remained non-obese, individuals who developed MHO had larger increases in BMI, waist circumference, and insulin resistance, but similar changes in the remaining variables: blood pressure, lipid levels, fasting glucose, and 10-year CHD risk (Table 4). Individuals who developed MHO and MUHO exhibited similar increases in BMI and waist circumference during follow-up. By contrast, those who developed MUHO exhibited greater increases in triglycerides and fasting glucose, compared with individuals who developed MHO.

**Conversion from MHO to MUHO**

Of those with MHO at baseline, almost half (47.6%) progressed to MUHO within the 7.8-year follow-up period (Table 1). MHO individuals who developed MUHO were older and had more adiposity, higher 10-year CHD risk, and lower HDL cholesterol than those who remained as MHO or become non-obese.

Progression to MUHO was associated with greater interim declines in HDL-C and greater increases in BMI, waist circumference, HOMA-IR, fasting glucose, fasting insulin, triglycerides, and 10-year CHD risk (Table 4).

**Obesity and risk of developing the unhealthy metabolic phenotype**

We also assessed the impact of obesity on the risk of developing multiple metabolic abnormalities by the end of the 7-8 year follow-up period among all 1,870 participants (both non-obese and obese) with ≤1 metabolic abnormality at baseline. The odds of developing multiple metabolic abnormalities by follow-up were 2.26 (1.74 – 2.95) times greater in obese participants, compared with non-obese participants.

**MHO and MUHO definitions based on insulin resistance**

To avoid the potential for bias due to misclassification of MHO and MUHO individuals, we generated alternative definitions of MHO and MUHO. MHO was defined as obesity without insulin resistance (HOMA-IR in the three lower quartiles), and MUHO, as obesity with insulin resistance (HOMA-IR in the upper quartile). At baseline, 44.1% of obese participants were insulin-sensitive, and thus met the alternative definition of MHO. Triglyceride
concentration was able to discriminate between individuals who developed incident MHO and those who developed incident MUHO in this model as well: the higher the triglycerides, the lower the odds of developing obesity without insulin resistance (Table 5).

**Discussion**

It is not surprising that the risk of developing obesity is predicted by baseline BMI, the criterion measurement used in defining obesity. Indeed, baseline BMI is the strongest predictor of both MHO and MUHO. Nonetheless, neither the amount (i.e., BMI) nor the distribution of adiposity (i.e., waist circumference) at baseline, nor the degree of weight gain during follow-up, distinguished those who progressed to MHO from those who progressed to MUHO in our study. By contrast, lipid profiles appear to be useful for predicting the type of metabolic state that is likely to develop with weight gain: individuals with elevated triglyceride levels were significantly less likely to avoid developing multiple metabolic abnormalities, while the opposite was true for individuals with elevated HDL-C. Our results also suggest that MHO is not a stable condition, because it confers increased risk of developing multiple metabolic abnormalities over time (i.e., within a 7-8 year period).

The relationship of adiposity to insulin sensitivity and other metabolic traits is a continuum, with MHO individuals at the lower-risk end. Insulin sensitivity tends to be lower and have a narrower range of values within higher levels of adiposity. Nevertheless, a significant proportion of individuals with obesity are insulin-sensitive. Despite differences in measures of adiposity, the metabolic profile of individuals who are going to develop MHO is similar to that of individuals who remain non-obese. Our data suggest that the MHO phenotype is often acquired by individuals who are overweight is not surprising. But individuals who progress to MHO cannot be distinguished from those who progress to MUHO by overall or central adiposity, blood pressure, or fasting glucose concentration. The key to differentiating between at-risk individuals for these two obesity phenotypes is that a benign lipid profile and low insulin resistance precede the development of MHO, rather than MUHO.

Compared with individuals who remain non-obese, those who progress to MHO exhibit similar changes in lipid and glucose levels, blood pressure, and estimated 10-year CHD risk. By contrast, among individuals who progress to either MHO or MUHO, the onset of obesity is accompanied by similar increased in both overall and central adiposity, as well as in insulin concentration and worsening insulin resistance.

Wildman et al. have reported that, with greater waist circumference, obese individuals are less likely to express the MHO phenotype. Our data suggests that neither overall nor central adiposity can be used to differentiate between at-risk individuals who will develop multiple metabolic abnormalities, from those who will not. Individuals with MHO have a favorable lipid profile and this characteristic predicts the development of both MHO and MUHO in our study. Individuals with low triglycerides and high HDL-C are likely to develop the MHO phenotype with weight gain, whereas those with high triglycerides are likely to develop MUHO. This holds true for both definitions of the metabolically healthy...
state, based either on the absence of multiple metabolic abnormalities and on the presence of insulin sensitivity.

The MHO and MUHO phenotypes appear to be associated with certain demographic characteristics as well. Older obese individuals are less likely to express the MHO phenotype than are younger individuals. The odds of developing obesity measured by BMI are greater in young adults than in older middle-aged adults. This may reflect the epidemiology of weight change in the US adult population. Weight gain is more likely in persons younger than 55 years and weight loss in those 55 years and older. In our study, similar proportions of men and women develop MHO vs. MUHO. In logistic regression analysis, male gender is associated with decreased risk of developing MUHO, probably because men tend to have more unfavorable triglyceride and HDL-C levels. In addition, risk of developing incident MHO and MUHO was also similar in smokers and non-smokers.

Cardiovascular risk, in the short term, may not be increased in MHO individuals, although there is a controversy regarding whether MHO individuals are at increased risk later in life. Individuals with MHO appear to differ from those with MUHO in the response to short-term lifestyle interventions. These types of interventions improve the level of insulin resistance only in individuals with MUHO. In addition, it is unknown whether MHO individuals benefit from preventive strategies. Despite the relatively low short-term cardiovascular risk associated with MHO, our results indicate that this is not a stable condition, and that individuals with this phenotype are at increased risk of progressing to a higher-risk metabolic profile. Supporting the notion of a complex interrelationship between adiposity and metabolic traits, worsening of metabolic profile in individuals with MHO is linked to subsequent weight gain.

The mechanistic background of our findings is unclear based on our data. The MHO phenotype may not be a stable condition. Our results agree with those reported by Soriguer et al. In this study, 37% of MHO individuals lost their metabolically healthy status after a 6-year follow-up. Thus, the MHO and MUHO phenotypes may only represent opposite ends of the obesity spectrum. Further studies are needed to analyze the impact that the duration of obesity has on the metabolic state of the MHO individual. Conversely, our data suggest that dyslipidemia and insulin resistance rather than adiposity (whether overall or central adiposity) are differentiating characteristics between the MHO and MUHO phenotypes.

Other studies have described distinctive characteristics of the MHO phenotype. Short-term lifestyle interventions improve insulin sensitivity not in MHO but in MUHO individuals. The MHO phenotype has been linked to smaller fat cells and a more favorable inflammatory profile. Among severely obese individuals, inflammatory gene expression is decreased, and mitochondrial gene expression increased, in individuals who are insulin-sensitive relative to those who are insulin-resistant. In experimental models of obesity, there is down-regulation of 5' adenosine monophosphate-activated protein (AMP) kinase activity. Acting as a sensor of cellular metabolism, this enzyme is involved in the regulation of glucose and lipid homeostasis and insulin sensitivity. AMP kinase activity is down-
regulated, and oxidative stress increased, in morbidly obese individuals who are insulin resistant as compared with those who are insulin sensitive.\textsuperscript{38}

Our study has several limitations. First, the SAHS lacks information on C-reactive protein. The inclusion of inflammation as a criterion may modify the identification of MHO and MUHO individuals. However, our results are similar using alternative definitions of the healthy metabolic phenotype. Second, follow-up information is not available for 38.3\% of the eligible baseline participants. There were small but significant differences in age and adiposity between individuals who returned to follow-up and those who did not, although insulin resistance was similar in both groups. Therefore, it is unlikely that different results would have been obtained if we had a better response rate. Third, there are limited data on physical activity at baseline. Therefore, other studies need to analyze the role of physical activity in the development of the MHO phenotype. Our study also has significant strengths. The SAHS is a large and well-characterized epidemiological study designed to investigate diabetes and cardiovascular disease in two different ethnic populations, Mexican Americans and non-Hispanic whites. We analyzed longitudinal data and results were consistent in younger and older middle-aged participants, men and women, and both ethnic groups.

In summary, triglycerides and HDL-C may be useful markers for predicting which individuals will develop MHO, and which will go on to develop MUHO. MHO may not be a stable condition, because it confers dramatically increased risk of developing multiple metabolic abnormalities in the future.

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Table 1

Baseline characteristics by categories of adiposity and metabolic status at baseline and follow-up among the 2,368 participants without either diabetes or MUHO at baseline

| Status at the follow-up visit | Non-obese at baseline | MHO at baseline | p value | p value |
|------------------------------|------------------------|----------------|---------|---------|
|                              | [1] Non-obese [2] MHO [3] MUHO [1] vs [2] | [1] vs [3] | [4] MHO or non-obese [5] MUHO [4] vs [5] |
| n                            | 1756 111 226                | 144 131          |         |         |
| Age (years) 
*                      | 43.8 ± 0.3 40.0 ± 1.0 41.8 ± 0.7 <0.001 0.010 0.153 | 41.0 ± 0.9 43.8 ± 0.9 0.031 |
| Female (%) 
*                      | 57.5 (55.1 – 59.8) 63.1 (53.7 – 71.5) 56.2 (49.7 – 62.5) 0.247 0.717 0.230 | 61.1 (52.9 – 68.7) 68.7 (60.3 – 76.1) 0.189 |
| Mexican Americans (%)  
*                      | 57.9 (55.5 – 60.1) 64.0 (54.6 – 72.3) 71.2 (65.0 – 76.8) 0.207 <0.001 0.230 | 71.5 (63.6 – 78.3) 75.6 (67.5 – 82.2) 0.448 |
| Smoking (%)  
*                      | 26.7 (24.7 – 28.8) 34.3 (17.2 – 33.2) 25.2 (20.0 – 31.3) 0.581 0.634 0.858 | 26.4 (19.8 – 34.2) 22.9 (16.5 – 30.9) 0.503 |
| BMI (kg/m²)                  | 24.3 ± 0.1 27.8 ± 0.2 27.7 ± 0.2 <0.001 <0.001 0.737 | 33.2 ± 0.2 33.9 ± 0.2 0.019 |
| Waist circumference (cm)     | 82.5 ± 0.3 89.8 ± 0.9 90.4 ± 0.6 <0.001 <0.001 0.627 | 100.0 ± 0.9 102.6 ± 0.9 0.031 |
| SBP (mm Hg)                  | 112.5 ± 0.3 114.1 ± 1.2 115.8 ± 0.9 0.195 <0.001 0.270 | 117.0 ± 1.1 117.7 ± 1.1 0.699 |
| DBP (mm Hg)                  | 70.1 ± 0.2 71.5 ± 0.8 72.6 ± 0.6 0.095 <0.001 0.252 | 73.7 ± 0.7 73.0 ± 0.7 0.517 |
| Total cholesterol (mmol/l)   | 5.19 ± 0.02 5.08 ± 0.09 5.42 ± 0.06 0.257 <0.001 0.002 | 5.08 ± 0.08 5.10 ± 0.08 0.857 |
| LDL cholesterol (mmol/l)     | 3.16 ± 0.02 3.09 ± 0.09 3.37 ± 0.06 0.386 <0.001 0.005 | 3.11 ± 0.08 3.19 ± 0.08 0.417 |
| HDL cholesterol (mmol/l)     | 1.41 ± 0.01 1.44 ± 0.03 1.27 ± 0.02 0.368 <0.001 <0.001 | 1.39 ± 0.03 1.29 ± 0.03 0.026 |
| Triglycerides (mmol/l) †      | 1.21 ± 0.01 1.08 ± 0.06 1.55 ± 0.05 0.026 <0.001 <0.001 | 1.16 ± 0.05 1.23 ± 0.05 0.281 |
| Fasting glucose (mmol/l)      | 4.81 ± 0.01 4.81 ± 0.05 4.90 ± 0.03 0.937 0.011 0.138 | 4.84 ± 0.04 4.92 ± 0.01 0.200 |
| Fasting insulin (pmol/l) †    | 46.8 ± 1.2 50.4 ± 3.6 66.0 ± 3.6 0.217 <0.001 0.001 | 71.4 ± 4.2 68.4 ± 4.2 0.584 |
| HOMA-IR †                    | 1.65 ± 0.03 1.80 ± 0.13 2.36 ± 0.12 0.227 <0.001 0.001 | 2.56 ± 0.16 2.48 ± 0.15 0.745 |
| Framingham risk (%) †        | 2.46 ± 0.02 2.30 ± 0.14 3.14 ± 0.12 0.224 <0.001 <0.001 | 2.48 ± 0.12 2.93 ± 0.15 0.018 |

Data are n, mean ± SE, or percentage plus 95% confidence intervals

* non-adjusted values;
† log-transformed variable then back-transformed;
‡ Logit transformation then back transformed;

Non-obese indicates BMI < 30 kg/m²; MHO, obesity with ≤1 metabolic abnormality; MUHO, obesity with ≥2 metabolic abnormalities
Table 2

Demographic and metabolic variables as predictors of incident MHO or incident MUHO among the 2,093 non-obese participants at baseline.

| Independent variables                  | Model 1 Incident MHO as the dependent variable | OR (95% CI) | Model 2 Incident MUHO as the dependent variable | OR (95% CI) |
|----------------------------------------|-----------------------------------------------|-------------|-----------------------------------------------|-------------|
| Age                                    | 0.96 (0.93 – 0.98)                            |             | 0.96 (0.95 – 0.98)                            |             |
| Men vs. women                          | 0.66 (0.41 – 1.06)                            |             | 0.52 (0.37 – 0.73)                            |             |
| Mexican Americans vs. non-Hispanic whites | 0.77 (0.49 – 1.22)                         |             | 0.92 (0.65 – 1.30)                            |             |
| Smokers vs. non-smokers                | 1.31 (0.80 – 2.15)                            |             | 1.15 (0.80 – 1.64)                            |             |
| BMI                                    | 8.23 (5.72 – 11.8)                            | 5.99 (4.60 – 7.81) |                                             |
| Log triglycerides                      | 0.51 (0.38 – 0.67)                            | 1.25 (1.04 – 1.50) |                                             |
| HDL cholesterol                        | 1.41 (1.10 – 1.80)                            | 0.91 (0.75 – 1.11) |                                             |
| SBP                                    | 0.86 (0.66 – 1.12)                            | 0.95 (0.79 – 1.14) |                                             |
| Fasting glucose                        | 0.86 (0.67 – 1.11)                            | 0.92 (0.77 – 1.09) |                                             |
| Log HOMA IR                            | 0.86 (0.67 – 1.10)                            | 1.13 (0.93 – 1.37) |                                             |

All independent variables were included in each of the two models.

Odds ratios expressed for binary traits or per 1 standard deviation (SD) unit increase for continuous traits

MHO and MUHO were defined according to Wildman et al. definitions:\(^\text{15}\): MHO, obesity with ≤1 metabolic abnormality; MUHO, obesity with ≥2 metabolic abnormalities

Age, sex, ethnicity, smoking, BMI, SBP, HOMA-IR, fasting glucose, triglycerides, and HDL cholesterol were all included in both models as independent variables
## Table 3

Risk of developing MHO or MUHO associated with BMI and triglyceride concentration by categories of age, sex, and ethnicity.

### Incident MHO as the dependent variable

| Categories | BMI | Log triglycerides |
|------------|-----|-------------------|
|            | OR (95% CI) | p for interaction | OR (95% CI) | p for interaction |
| Age *      | 25 - 45 years | 5.35 (3.71 – 7.27) | 0.002 | 0.44 (0.32 – 0.60) | 0.959 |
|           | 46 - 65 years | 26.3 (9.59 – 72.3) | 0.44 (0.27 – 0.70) | 0.44 (0.27 – 0.70) | 0.959 |
| Sex †      | Men | 12.6 (6.02 – 26.5) | 0.021 | 0.47 (0.32 – 0.69) | 0.765 |
|           | Women | 5.86 (3.98 – 8.63) | 0.42 (0.29 – 0.59) | 0.42 (0.29 – 0.59) | 0.765 |
| Ethnicity ‡ | Mexican Americans | 6.68 (4.29 – 10.4) | 0.811 | 0.43 (0.31 – 0.60) | 0.742 |
|           | Non-Hispanic whites | 7.37 (4.28 – 12.7) | 0.44 (0.29 – 0.67) | 0.44 (0.29 – 0.67) | 0.742 |

### Incident MUHO as the dependent variable

| Categories | BMI | Log triglycerides |
|------------|-----|-------------------|
|            | OR (95% CI) | p for interaction | OR (95% CI) | p for interaction |
| Age *      | 25 - 45 years | 5.65 (4.15 – 7.70) | 0.166 | 1.29 (1.04 – 1.60) | 0.426 |
|           | 46 - 65 years | 7.19 (4.53 – 11.4) | 1.31 (1.02 – 1.71) | 1.31 (1.02 – 1.71) | 0.426 |
| Sex †      | Men | 6.33 (4.12 – 9.74) | 0.242 | 1.32 (1.05 – 1.67) | 0.863 |
|           | Women | 5.94 (4.31 – 8.19) | 1.29 (1.01 – 1.63) | 1.29 (1.01 – 1.63) | 0.863 |
| Ethnicity ‡ | Mexican Americans | 6.24 (4.53 – 8.59) | 0.927 | 1.30 (1.06 – 1.59) | 0.572 |
|           | Non-Hispanic whites | 5.77 (3.75 – 8.87) | 1.31 (0.98 – 1.76) | 1.31 (0.98 – 1.76) | 0.572 |

BMI and log triglycerides were included simultaneously in each of the models

* Results adjusted for age, sex, and ethnicity

† Results adjusted for age and ethnicity

‡ Results adjusted for age and sex

OR and 95% CI expressed per 1 SD unit increase

MHO and MUHO were defined according to Wildman et al. definitions. 15
Table 4

Change in metabolic variables during the follow-up period by categories of adiposity and metabolic abnormality at baseline and follow-up

| Status at follow-up | Non-obese at baseline | MHO at baseline |
|---------------------|-----------------------|-----------------|
|                     | [1] Non-obese | [2] MHO | [3] MUHO | [1] vs. [2] | [1] vs. [3] | [2] vs. [3] | [4] MHO | [5] MUHO | [4] vs. [5] |
| n                   | 1756            | 111     | 226     |            |            |            | 144     | 131     |            |
| p value             |               |         |         |            |            |            |         |         |            |
| BMI (kg/m^2)        | 1.0 ± 0.1      | 4.2 ± 0.2| 4.2 ± 0.1| <0.001     | <0.001     | 0.921     | 0.3 ± 0.2| 2.5 ± 0.2| <0.001     |
| Waist (cm)          | 5.5 ± 0.3      | 12.9 ± 0.9| 13.3 ± 0.6| <0.001     | <0.001     | 0.686     | 7.6 ± 0.8| 12.4 ± 0.9| <0.001     |
| SBP (mm Hg)         | 7.9 ± 0.3      | 9.6 ± 1.3| 12.7 ± 0.9| 0.224      | <0.001     | 0.053     | 7.0 ± 1.2| 10.2 ± 1.2| 0.054      |
| DBP (mm Hg)         | 1.7 ± 0.2      | 3.0 ± 0.9| 4.1 ± 0.6| 0.154      | <0.001     | 0.347     | 0.4 ± 0.2| 2.0 ± 0.8| 0.168      |
| Total cholesterol (mmol/l) | 0.28 ± 0.02 | 0.35 ± 0.09| 0.29 ± 0.06| 0.455     | 0.872     | 0.593     | 0.37 ± 0.08| 0.37 ± 0.09| 0.894      |
| LDL cholesterol (mmol/l) | 0.30 ± 0.03 | 0.36 ± 0.14| 0.17 ± 0.10| 0.667     | 0.223     | 0.267     | 0.07 ± 0.12| 0.12 ± 0.13| 0.776      |
| HDL cholesterol (mmol/l) | -0.20 ± 0.01 | -0.21 ± 0.03| -0.27 ± 0.02| 0.669     | 0.002     | 0.118     | -0.12 ± 0.03| -0.21 ± 0.03| 0.013      |
| Log Triglycerides (mmol/l) | 0.14 ± 0.01 | 0.15 ± 0.04| 0.35 ± 0.03| 0.842     | <0.001    | <0.001    | 0.06 ± 0.04| 0.35 ± 0.04| <0.001      |
| Fasting glucose (mmol/l) | 0.19 ± 0.02 | 0.09 ± 0.09| 0.47 ± 0.06| 0.268     | <0.001    | <0.001    | 0.14 ± 0.08| 0.68 ± 0.08| <0.001      |
| Log fasting insulin (pmol/l) | 0.07 ± 0.02 | 0.25 ± 0.08| 0.35 ± 0.05| 0.023     | <0.001    | 0.280     | -0.14 ± 0.07| 0.39 ± 0.07| <0.001      |
| Log HOMA-IR          | 0.10 ± 0.02    | 0.26 ± 0.08| 0.44 ± 0.06| 0.043     | <0.001    | 0.080     | -0.12 ± 0.07| 0.51 ± 0.07| <0.001      |
| Logit Framingham risk | 0.91 ± 0.01    | 0.96 ± 0.05| 1.06 ± 0.04| 0.313     | <0.001    | 0.128     | 0.88 ± 0.05| 1.06 ± 0.05| 0.011      |

Data are n, mean ± SE, or percentage plus 95% confidence intervals

Non-obese indicates BMI < 30 kg/m^2; MHO, obesity with ≤1 metabolic abnormality; MHO, obesity with ≥2 metabolic abnormalities
Table 5

Metabolic variables as predictors of incident MHO or MUHO using alternative definitions *

| Independent variables                          | Model 1 Incident MHO as the dependent variable | OR (95% CI) | Model 2 Incident MUHO as the dependent variable | OR (95% CI) |
|------------------------------------------------|-----------------------------------------------|-------------|-----------------------------------------------|-------------|
| Age                                            |                                               | 0.96 (0.94 – 0.97) |                                               | 0.97 (0.95 – 0.99) |
| Men vs. Women                                  |                                               | 0.55 (0.39 – 0.79) |                                               | 0.66 (0.39 – 0.91) |
| Mexican Americans vs. non-Hispanic whites      |                                               | 0.73 (0.51 – 1.04) |                                               | 1.05 (0.68 – 1.63) |
| BMI                                            |                                               | 8.44 (6.32 – 11.3) |                                               | 4.37 (3.20 – 5.95) |
| Log HOMA-IR                                    |                                               | 0.74 (0.61 – 0.90) |                                               | 1.60 (1.26 – 2.03) |
| Log triglycerides                              |                                               | 0.76 (0.63 – 0.93) |                                               | 1.26 (1.01 – 1.57) |
| HDL cholesterol                                |                                               | 1.11 (0.91 – 1.35) |                                               | 1.03 (0.82 – 1.31) |
| SBP                                            |                                               | 1.00 (0.83 – 1.21) |                                               | 0.83 (0.65 – 1.04) |
| Fasting glucose                                |                                               | 0.97 (0.81 – 1.17) |                                               | 0.83 (0.67 – 1.03) |

All independent variables were included in each of the two models.

Odds ratios expressed for binary traits or per 1 SD unit increase for continuous traits

* MHO was defined as obesity plus HOMA-IR in the three lower quartiles of the non-diabetic population;

MUHO, as obesity plus HOMA-IR in the upper quartile of the non-diabetic population