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Visceral abdominal fat accumulation predicts the conversion of metabolically healthy obese subjects to an unhealthy phenotype

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Abstract

Background—A proportion of obese subjects appear metabolically healthy (MHO) but little is known about the natural history of MHO and factors predicting its future conversion to metabolically unhealthy obese (MUO).

Objectives—The aim was to determine prospectively the frequency of conversion of MHO to MUO and the clinical variables that independently predicted this conversion, with a particular focus on the role of body composition.

Methods—We identified 85 Japanese Americans with MHO (56 men, 29 women), aged 34–73 years (mean age 49.8 years) who were followed at 2.5, 5, and 10 years after enrollment with measurements of metabolic characteristics, lifestyle, and abdominal and thigh fat areas measured by computed tomography. Obesity was defined using the Asian body mass index criterion of ≥ 25 kg/m^2. Metabolically healthy was defined as the presence of ≤ 2 of 5 metabolic syndrome components proposed by the National Cholesterol Education Program Adult Treatment Panel III, while metabolically unhealthy was defined as ≥ 3 components.

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Conflict of interest

The authors declare no conflict of interest.

Results—Over 10 years of follow-up, 55 MHO individuals (64.7%) converted to MUO. Statistically significant univariate predictors of conversion included dyslipidemia, greater insulin resistance, and greater visceral abdominal (VAT) and subcutaneous abdominal fat area (SAT). In multivariate analysis, VAT (odds ratio per 1 SD increment (95% confidence interval) 2.04 (1.11 – 3.72), P=0.021), high density lipoprotein (HDL) cholesterol (0.24 (0.11 – 0.53), P<0.001), fasting plasma insulin (2.45 (1.07 – 5.62), P=0.034), and female sex (5.37 (1.14 – 25.27), P=0.033) were significantly associated with future conversion to MUO. However, SAT was not an independent predictor for future conversion to MUO.

Conclusions—In this population, MHO was a transient state, with nearly two-thirds developing MUO over 10 years, with higher conversion to MUO independently associated with VAT, female sex, higher fasting insulin level, and lower baseline HDL cholesterol level.

Keywords

metabolically healthy obese; metabolically unhealthy obese; visceral abdominal fat; subcutaneous abdominal fat; Japanese American

Introduction

In a 2010 report by the World Health Organization, non-communicable diseases including cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases, accounted for nearly two-thirds of deaths worldwide and this chronic disease burden largely results from obesity both directly and indirectly. In the United State, the proportion of the population that is obese has increased gradually over time. The age-adjusted prevalence of obesity in adults increased from 30.5% to 35.7% between 1999 and 2010 and over the same time period, the prevalence of diabetes also increased from 9.0% to 11.5%.[1]

It has been suggested that disease risk associated with obesity may not be uniform and that a subgroup of obese individuals, referred to as metabolically healthy but obese (MHO), appears resistant to metabolic and cardiovascular risk from obesity.[2–5] An important issue, however, is that all of the criteria for MHO that have been used in the reported literature do not exclude all of the variables associated with the metabolic syndrome. Thus, the prevalence of MHO has been reported to vary between 10% and 40% depending upon the definition used and is higher in the non-Hispanic white populations, younger individuals, and women.[6] However, it has also been suggested that healthy obesity is a transient state with one-third of such subjects developing metabolic abnormalities or diabetes in the future.[7] In addition, a recent meta-analysis that included prospective studies with at least 10-years of follow-up showed that MHO individuals had a 1.24-fold higher risk for all-cause mortality and/or cardiovascular events compared with metabolically healthy normal-weight individuals. Therefore, the authors concluded that greater body mass index (BMI) conveys additional health risks even in the absence of metabolic abnormalities, thereby challenging the concept of MHO.[8]

To date, however, little is known about the natural history of MHO and predictors of future conversion to metabolically unhealthy obese (MUO) phenotype. Thus, the aims of this study were to determine how frequently MHO converts to MUO, and which demographic,

lifestyle, clinical, and metabolic variables predict this conversion, with a particular focus on the roles of visceral abdominal fat (VAT) and subcutaneous abdominal fat (SAT) directly measured by computed tomography (CT).

Methods

Study subjects

The study population consisted of Japanese American men and women enrolled in the Japanese American Community Diabetes Study, a cohort of second- (Nisei) and third-generation (Sansei) Japanese Americans of 100% Japanese ancestry. A detailed description of the selection and recruitment of the study subjects has been published previously.[9,10] In brief, study participants were selected as volunteers from a community-wide comprehensive mailing list and telephone directory that included nearly 95% of the Japanese-American population in King County, Washington. Among the total of 658 subjects in the original cohort, 384 non-obese subjects were excluded. Six subjects were excluded because data for defining metabolic health status were not available at baseline, leaving 271 obese subjects for analysis. Among these 271 obese subjects, 97 (35.7%) showed the MHO phenotype at baseline and over 10 years, 85 with MHO (56 men and 29 women), aged 34–73 years (mean age of 49.8 years), had sufficient follow-up data for this analysis. Subjects were followed up at 2.5 years (Nisei men only), 5 years and 10 years after a baseline examination to determine metabolic status and clinical and biochemical variables of interest.

The study received approval from the University of Washington Human Subjects Division, and written informed consent was obtained from all subjects.

Clinical and laboratory examination

All evaluations were performed at the General Clinical Research Center, University of Washington. At baseline, a complete physical examination was performed, and personal medical history and lifestyle factors were determined using a standardized questionnaire. Smoking was classified into three groups (current smoker, past smoker, and never smoker). Excessive alcohol intake was defined as more than three drinks per day (>30 g ethanol/day). Paffenbarger physical activity index questionnaire was used to determine physical activity level (usual kilocalories spent weekly)[11] and regular physical activity was defined as more than moderate intensity physical activity. The collection of dietary data followed a format adapted from the Burke diet-history method including 1) a food frequency questionnaire (FFQ), 2) background information, and 3) a 24-h recall of dietary intake.[12]

Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the level of the umbilicus. Blood pressure was measured with a mercury sphygmomanometer read to the nearest 2 mmHg with the subjects in a recumbent position. Systolic blood pressure was determined by the first perception of sound and diastolic blood pressure was determined at the disappearance of sounds (fifth-phase Korotkoff). Average blood pressure was calculated from the second and third of three consecutive measurements.

Biochemical measurements were performed as reported previously.[13] All blood samples were obtained following an overnight fast of 10 hours. Plasma glucose was measured by the hexokinase method using an autoanalyzer (University of Washington, Department of Laboratory Medicine, Seattle, WA). Plasma insulin was measured by radioimmunoassay (Immunoassay Core, Diabetes Endocrinology Research Center, University of Washington, Seattle, WA). To estimate insulin sensitivity, the homeostasis model assessment (HOMA) insulin resistance based on fasting glucose and insulin concentration was used.[14] Lipids and lipoproteins measurements were performed according to modified procedures of the Lipid Research Clinics (Northwest Lipid Research Laboratory, University of Washington, Seattle, WA). Single 10 mm slice CT scans were performed at the abdomen, and right mid-thigh to measure cross-sectional fat areas (cm^2) as described previously.[15] VAT and SAT areas were measured at the umbilicus level. Attenuation range for identification of fat was -250 to -50 Hounsfield Units.

Definition of MHO

'Metabolic health' was defined using the criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) for the diagnosis of metabolic syndrome with minor modification[16]: (1) the presence of central obesity (waist circumference ≥90 cm in men and ≥80 cm in women). This cutoff for central obesity was adopted from the International Diabetes Federation (IDF) definition for Asian populations[17]; (2) triglyceride levels ≥150 mg/dL; (3) HDL cholesterol <40 mg/dL in men and <50 mg/dL in women, (4) systolic or diastolic blood pressure ≥130/85 mmHg or use of antihypertensive medications, or (5) fasting plasma glucose ≥100 mg/dL or 2 hour glucose after oral glucose tolerance test ≥140 mg/dL or use of oral hypoglycemic agents and/or insulin. Obesity was defined as BMI of ≥25 kg/m^2 using the cut-point for Asian populations as recommended by the World Health Organization.[18] According to these criteria, and since no standard definition of MHO exists, we used one commonly used definitions of MHO, namely the presence of two or fewer of the above five metabolic syndrome components plus BMI ≥25.0 kg/m^2. MUO was defined as the presence of three or more of aforementioned metabolic syndrome components plus BMI ≥25.0 kg/m^2.

Statistical analyses

Data are expressed as means ± SD for continuous measures except for skewed continuous variables, which are presented as the median (interquartile range, 25–75%) or as proportions for categorical variables. Differences between groups were tested by the student *t*-test or Mann-Whitney U test for continuous variables and the χ^2-test or Fischer's exact test for categorical variables. Multiple logistic regression analysis with backward selection was used to determine independent associations between clinical and biochemical variables and future conversion to MUO as a binary variable. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated for independent variables included in logistic models, with a 1-SD increment used for odds ratio calculations for continuous measurements. We assessed the presence of nonlinearity in the final model by inserting quadratic transformations of the three continuous variables that it contained into the model. The presence of interaction was tested in multivariate models by testing the significance of first order interaction terms. All

statistical analyses were performed using PASW version 18.0 (SPSS, Chicago, IL, USA). A *P*-value of <0.05 was considered significant.

Results

Over 10 years of follow-up, almost two-thirds of subjects with the MHO phenotype (64.7%, 55/85) developed MUO. Table 1 shows the baseline characteristics of study participants by MHO or MUO phenotype at the 10 year follow-up. There were no differences in age, sex, menopause in women, dietary intake including daily energy intake and macronutrient composition and lifestyle factors including alcohol consumption, smoking, and physical activity between the MHO and MUO subjects. In addition, no differences were noted in fasting and 2-hour plasma glucose levels and blood pressure between the two groups. However, subjects with future conversion to MUO had significantly lower HDL cholesterol and higher triglyceride levels and showed greater insulin-resistance (as reflected by fasting insulin levels and HOMA-IR) compared with subjects in whom MHO persisted throughout follow-up. In terms of body composition, baseline SAT and VAT areas were significantly and positively associated with the development of MUO over follow-up; however, no significant differences were observed in baseline BMI, waist circumference, VAT to SAT ratio, or subcutaneous thigh fat area between the two groups.

Similarly, in univariate logistic regression analysis, fasting plasma insulin, HOMA-IR, and triglyceride showed positive associations with the development of MUO while HDL cholesterol was inversely associated with this outcome. Regarding body fat compartments, SAT (OR per 1-SD increment (95% CI), 1.81 (1.08 – 3.02), *P*=0.024) and VAT (OR per 1-SD increment (95% CI), 1.99 (1.17 – 3.39), *P*=0.011) were associated with future conversion to MUO in subjects with baseline MHO; however, VAT to SAT ratio and subcutaneous thigh fat were not (Table 2).

To determine which variables independently predicted future conversion to MUO, a backwards selection logistic regression model was fit that included age and sex as well as variables found significantly related to the MUO outcome in univariate analysis from Table 2 (HDL cholesterol, triglyceride, fasting insulin, SAT, and VAT). Since fasting insulin and HOMA-IR are highly correlated, the former only was chosen for inclusion in the backwards selection model due to its smaller p-value in univariate analysis (Table 2). In the final model, HDL cholesterol (OR per 1 SD increment (95% CI), 0.24 (0.11 – 0.53), *P*<0.001), female sex (OR per 1 SD increment (95% CI), 5.37 (1.14 – 25.27), *P*=0.033), fasting plasma insulin (OR per 1 SD increment (95% CI), 2.45 (1.07 – 5.62), *P*=0.034), and VAT (OR per 1 SD increment (95% CI), 2.04 (1.11 – 3.72), *P*=0.021) were associated with the risk of future MUO. However, SAT was not independently associated with future conversion to MUO (Table 3). No significant interactions were observed between sex and each of the independent variables shown in the model in Table 3 in predicting the occurrence of MUO. Quadratic transformations of HDL cholesterol, VAT and fasting plasma insulin were inserted into the final model. None of these was statistically significant, arguing against a nonlinear association between any of these continuous predictors and risk of conversion to MUO.

Discussion

In the current prospective study of Japanese American men and women with BMI of ≥25 kg/m^2, approximately one-third (35.7%, 97/271) showed the MHO phenotype at baseline. However, almost two-thirds of the subjects with MHO (64.7%, 55/85) deteriorated to the MUO phenotype during 10 years of follow-up. In particular, greater VAT at baseline was independently associated with future metabolic deterioration to MUO in subjects with MHO; however, other measurements of body fat such as baseline BMI and waist circumference in univariate analysis, and SAT in a multivariate model did not confer any significant alteration in risk for future conversion to MUO.

There has been much debate about whether MHO is a totally benign condition or is associated with future disease burden. In the Framingham Offspring Study in the U.S., obese individuals with metabolic syndrome or insulin resistance showed greater risk for diabetes and cardiovascular disease compared with obese subjects without metabolic syndrome or insulin resistance. In addition, MHO subjects had lower risk for cardiovascular disease similar to normal weight subjects without insulin resistance.[19] Another community-based prospective observational study in Scotland and England also suggested that MHO subjects had similar risk for future cardiovascular and all-cause mortality compared to metabolically healthy nonobese subjects over 7 years. Moreover, the same result was observed even when lean subjects (BMI <25 kg/m^2) without any metabolic risk factors were used as the reference group. Metabolically unhealthy nonobese subjects showed a higher cardiovascular and all-cause mortality compared with metabolically healthy nonobese subjects. Thus, the authors suggested that metabolic risk factors are more important for future disease burden than adiposity itself.[20] However, accumulating evidence does not support the concept that MHO is a sustained benign condition.[7,21–24] In a meta-analysis of eight prospective cohort studies, although MHO subjects had lower risk for incident type 2 diabetes compared with MUO subjects, this subgroup showed over four times greater risk compared with healthy normal weight adults.[25] Another meta-analysis of eight prospective observational studies showed that MHO subjects have a higher risk for all-cause mortality and cardiovascular events than metabolically healthy normal weight individuals, and that all subjects with unhealthy metabolic phenotype have a higher risk regardless of BMI. Therefore, the authors concluded that comprehensive evaluation of both adiposity and metabolic factors are necessary to predict future morbidity and mortality.[8]

In support of the finding that MHO is not a benign condition, recent studies suggested that MHO is transient and may change into an unhealthy phenotype over time.[7,23] In the prospective Pizarra study in Spain, more than 30% of MHO subjects at baseline became metabolically unhealthy by the 6-year follow-up and were at a significantly higher risk for the development of diabetes over time.[23] In addition, the North West Adelaide Health Study in Australia showed that approximately one-third of MHO subjects at baseline converted into the metabolically unhealthy phenotype during 5.5–10.3 years of follow-up, with lower risk for incident type 2 diabetes evident only in subjects with sustained MHO.[7] In partial agreement with these studies, MHO subjects in our study converted to an unhealthy phenotype over time; however, our results showed a higher conversion rate (64.7%) to MUO phenotype than in previous studies. We speculate that our longer follow up period (10 years)

than the aforementioned two studies may explain these differences. The proportion of our subjects who converted to MUO was somewhat lower at 5 year (43.5%, 37/85) than 10 year follow-up. In addition, several different criteria have been used to define MHO in the reported studies as well as ethnic differences in study subjects may explain these different results. Several definitions are currently used to describe metabolic health and there is no unifying established MHO definition. In addition, different inclusion criteria and/or cut-offs have been used to discriminate metabolically healthy from metabolically unhealthy subjects. For example, not all metabolic health definitions include insulin resistance (defined by HOMA-IR), blood pressure or fasting plasma glucose concentrations, while others consider inflammatory markers.[5]

Despite accumulating evidence suggesting that MHO is not a static condition, little attention has been given regarding the variables that predict metabolic deterioration to MUO in MHO subjects. To our knowledge only cross-sectional analyses have been published that compare baseline characteristics between subjects with MHO and MUO. Previous studies have suggested that MHO subjects were more likely to be younger, female, and of non-Hispanic white ethnicity than subjects with MUO.[6] In addition, MHO subjects showed greater insulin sensitivity and higher adiponectin level than MUO subjects.[2] In terms of body composition, most studies have shown that MHO subjects have smaller VAT than MUO subjects; however, no difference was previously observed in SAT between the two groups.[26,27] In contrast, our analysis demonstrated that although baseline BMI and waist circumference were similar between the two groups, both SAT and VAT were greater in subjects with future conversion to MUO. In addition, although it was suggested that a greater amount of subcutaneous thigh fat is associated with favorable metabolic phenotype,[26,28] our results did not show any protective effect of subcutaneous thigh fat against future conversion to MUO. The discrepancies in body composition and conversion to MUO between previous studies and our results appear to be mainly from the longitudinal nature of our research and different criteria used to define MHO. In addition to the 10 year result, we determined which variables independently predict future conversion to MUO in subjects with MHO at an earlier 5 year time point. In this analysis, HDL cholesterol (OR per 1 SD increment (95% CI), 0.37 (0.19 – 0.71), P=0.003) was inversely associated and SAT (OR per 1 SD increment (95% CI), 2.39 (1.33 – 4.31), P=0.004) and VAT (OR per 1 SD increment (95% CI), 2.07 (1.19 – 3.58), P=0.010) were positively associated with the risk of future MUO (data not shown). Therefore, the 5 year and 10 year results suggest that although the association between SAT and the conversion of MHO to MUO is seen in the short term, SAT is not a sustainable long-term predictor for this conversion whereas VAT is consistently associated with the conversion to MUO in subjects with MHO at both 5 and 10 years of follow-up.

In the current study, we compared daily energy intake and composition of macronutrients between subjects who remained in MHO and subjects with converted to MUO. However, there were no differences in daily energy intake and percentage of calories from each macronutrient between the two groups. In addition, no difference was noted in physical activity between the two groups. Therefore, it appears that energy intake and expenditure were not major determinants for conversion to a metabolically unhealthy phenotype in subjects with MHO in our study cohort.

It is still uncertain whether MHO is related to sex. Some studies demonstrated that MHO was more common in women[24,29] while others showed no difference by sex.[2,27] In contrast, our result indicated that female sex independently predicts future conversion to MUO in subjects with MHO. Although the proportion of MHO among obese subjects is higher in women in some studies but not all, our study found that female sex predicts progression to a MUO phenotype among MHO subjects. In our study, we defined MHO based on the NCEP-ATP III criteria for metabolic syndrome and it has been well-documented that the prevalence of the metabolic syndrome by this definition is higher in men than women at younger ages, but becomes similar or even higher in women over 50 years of age.[30] Of note, the mean age was 61.9 years in our female subjects at the follow-up examination.

This study has some limitations. First, the small sample size may have limited our ability to detect weaker associations and prevented us from performing sub-group analyses, e.g., by gender. However, no significant interactions were observed between sex and other variables that remained in the multivariate model. Thus, our results appear to be applicable to both men and women. Second, it was reported that Asians have a relatively larger amount of abdominal fat, and that this difference was more evident in VAT compared with Caucasians.[31] Therefore, our findings may not be generalizable to other ethnic groups if the association between VAT and other body fat depots and future conversion to MUO varies with ethnicity. Third, recent studies have suggested that SAT is further separable into two distinct subdepots: the superficial SAT and the deep SAT and that they have distinct histological and physiological features and furthermore display different associations with cardiometabolic variables.[32] However, we did not measure regional SAT in this study. Fourth, we did not account for hard endpoints arising from metabolically healthy or unhealthy status such as cardiovascular disease or mortality.

Despite these limitations, this study found that MHO is a transient state and that a high proportion of this unique subgroup deteriorates metabolically over time. In addition, we believe that we have prospectively examined for the first time the roles of different body fat compartments with the development of future MUO phenotype among persons with MHO and showed VAT is the main body fat depot in predicting conversion to MUO in subjects with MHO. These results argue that clinical providers should not view MHO as a benign form of obesity and be complacent regarding their patients who have excess body weight but few metabolic abnormalities. In addition, because baseline BMI and waist circumference have limited value in predicting the conversion from MHO to MUO, the measurement of VAT may be a potential option to predict future metabolic deterioration in subjects with MHO.

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References

1. Bauer UE, Briss PA, Goodman RA, Bowman BA. Prevention of chronic disease in the 21st century: elimination of the leading preventable causes of premature death and disability in the USA. Lancet. 2014; 384:45–52. [PubMed: 24996589]
2. Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, et al. Identification and characterization of metabolically benign obesity in humans. Arch Intern Med. 2008; 168:1609–1616. [PubMed: 18695074]
3. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: Prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). Arch Intern Med. 2008; 168:1617–1624. [PubMed: 18695075]
4. Blüher M. Are there still healthy obese patients? Curr Opin Endocrinol Diabetes Obes. 2012; 19:341–346. [PubMed: 22895358]
5. Phillips CM. Metabolically healthy obesity: definitions, determinants and clinical implications. Rev Endocr Metab Disord. 2013; 14:219–227. [PubMed: 23928851]
6. Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V, et al. Characterizing the profile of obese patients who are metabolically healthy. Int J Obes (Lond). 2011; 35:971–981. [PubMed: 20975726]
7. Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, et al. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care. 2013; 36:2388–2394. [PubMed: 23491523]
8. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. Ann Intern Med. 2013; 159:758–769. [PubMed: 24297192]
9. Fujimoto WY, Leonetti DL, Kinyoun JL, Shuman WP, Stolov WC, Wahl PW. Prevalence of complications among second-generation Japanese-American men with diabetes, impaired glucose tolerance, or normal glucose tolerance. Diabetes. 1987; 36:730–739. [PubMed: 3569672]
10. Fujimoto WY, Bergstrom RW, Leonetti DL, Newell-Morris LL, Shuman WP, Wahl PW. Metabolic and adipose risk factors for NIDDM and coronary disease in third-generation Japanese-American men and women with impaired glucose tolerance. Diabetologia. 1994; 37:524–532. [PubMed: 8056192]
11. Paffenbarger RS, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. Am J Epidemiol. 1978; 108:161–175. [PubMed: 707484]
12. Tsunehara CH, Leonetti DL, Fujimoto WY. Diet of second-generation Japanese-American men with and without non-insulin-dependent diabetes. Am J Clin Nutr. 1990; 52:731–738. [PubMed: 2403066]
13. Bergstrom RW, Leonetti DL, Newell-Morris LL, Shuman WP, Wahl PW, Fujimoto WY. Association of plasma triglyceride and C-peptide with coronary heart disease in Japanese-American men with a high prevalence of glucose intolerance. Diabetologia. 1990; 33:489–496. [PubMed: 2210122]
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28:412–419. [PubMed: 3899825]
15. Shuman WP, Morris LL, Leonetti DL, Wahl PW, Moceri WM, Moss AA, et al. Abnormal body fat distribution detected by computed tomography in diabetic men. Invest Radiol. 1986; 21:483–487. [PubMed: 3721806]
16. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004; 109:433–438. [PubMed: 14744958]
17. Alberti KG, Zimmet P, Shaw J. IDF Epidemiology Task Force Consensus Group: The metabolic syndrome – a new worldwide definition. Lancet. 2005; 366:1059–1062. [PubMed: 16182882]

18. World Health Organization. The Asia-Pacific perspective: redefining obesity and its treatment. Geneva: WHO; 2000.
19. Meigs JB, Wilson PW, Fox CS, Vasan RS, Nathan DM, Sullivan LM, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab. 2006; 91:2906–2912. [PubMed: 16735483]
20. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. J Clin Endocrinol Metab. 2012; 97:2482–2488. [PubMed: 22508708]
21. Arnlov J, Ingelsson E, Sundstrom J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation. 2010; 121:230–236. [PubMed: 20038741]
22. Kuk JL, Ardern CI. Are metabolically normal but obese individuals at lower risk for all-cause mortality? Diabetes Care. 2009; 32:2297–2299. [PubMed: 19729521]
23. Soriguer F, Gutiérrez-Repiso C, Rubio-Martín E, García-Fuentes E, Almaraz MC, Colomo N, et al. Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. J Clin Endocrinol Metab. 2013; 98:2318–2325. [PubMed: 23559087]
24. van der ADL, Nooyens AC, van Duijnhoven FJ, Verschuren MM, Boer JM. All-cause mortality risk of metabolically healthy abdominal obese individuals: the EPIC-MORGEN study. Obesity (Silver Spring). 2014; 22:557–564. [PubMed: 23595997]
25. Bell JA, Kivimaki M, Hamer M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. Obes Rev. 2014; 15:504–515. [PubMed: 24661566]
26. Koster A, Stenholm S, Alley DE, Kim LJ, Simonsick EM, Kanaya AM, et al. Body fat distribution and inflammation among obese older adults with and without metabolic syndrome. Obesity (Silver Spring). 2010; 18:2354–2361. [PubMed: 20395951]
27. Kim TN, Park MS, Yang SJ, Yoo HJ, Kang HJ, Song W, et al. Body size phenotypes and low muscle mass: the Korean sarcopenic obesity study (KSOS). J Clin Endocrinol Metab. 2013; 98:811–817. [PubMed: 23293328]
28. Snijder MB, Visser M, Dekker JM, Goodpaster BH, Harris TB, Kritchevsky SB, et al. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. Diabetologia. 2005; 48:301–308. [PubMed: 15660262]
29. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007; 116:39–48. [PubMed: 17576866]
30. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 2002; 287:356–359. [PubMed: 11790215]
31. Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). Am J Clin Nutr. 2007; 86:353–359. [PubMed: 17684205]
32. Golan R, Shelef I, Rudich A, Gepner Y, Shemesh E, Chassidim Y, et al. Abdominal superficial subcutaneous fat: a putative distinct protective fat subdepot in type 2 diabetes. Diabetes Care. 2012; 35:640–647. [PubMed: 22344612]

Table 1

Baseline characteristics according to metabolic status after 10 years

	Total (n=85)	MHO at follow-up (n=30)	MUO at follow-up (n=55)	*P*
Age (years)	49.8 (12.0)	48.9 (11.0)	50.2 (12.6)	0.63
Female sex (%)	29 (34.1)	7 (23.3)	22 (40.0)	0.12
Menopause in women (%)	16 (55.2)	4 (57.1)	12 (54.5)	1.00
Body mass index (kg/m^2)	27.0 (1.8)	26.6 (1.7)	27.2 (1.8)	0.12
Waist circumference (cm)	88.9 (6.4)	87.8 (5.0)	89.5 (7.0)	0.20
Alcohol consumption (%)	5 (5.9)	3 (10.0)	2 (3.6)	0.34
Current smoking (%)	10 (11.8)	1 (3.3)	9 (16.4)	0.09
Regular physical activity (%)	23 (27.1)	11 (36.7)	12 (21.8)	0.12
Daily energy intake (kcal/day)	1901.2 (627.5)	1976.4 (733.4)	1860.1 (564.6)	0.42
Calories from carbohydrate (%)	47.3 (7.4)	46.7 (7.1)	47.6 (7.6)	0.58
Calories from fat (%)	32.4 (5.5)	31.8 (6.2)	32.7 (5.1)	0.44
Calories from protein (%)	18.5 (3.7)	18.9 (3.2)	18.3 (4.0)	0.50
Systolic blood pressure (mmHg)	125.5 (12.7)	124.5 (13.6)	126.1 (12.3)	0.59
Diastolic blood pressure (mmHg)	75.4 (7.5)	76.0 (8.8)	75.1 (6.8)	0.59
Fasting plasma glucose (mmol/L)	5.33 (0.96)	5.22 (0.82)	5.39 (1.02)	0.44
2 hour plasma glucose (mmol/L)	7.66 (2.83)	7.18 (2.61)	7.92 (2.94)	0.25
Fasting plasma insulin (pmol/L)	83.3 (69.5 – 125.0)	79.9 (61.1 – 92.4)	97.2 (76.4 – 142.4)	0.001
HOMA-IR	2.92 (2.25 – 4.35)	2.45 (1.86 – 3.11)	3.36 (2.52 – 4.86)	0.002
Total cholesterol (mmol/L)	5.79 (1.04)	5.74 (1.02)	5.82 (1.06)	0.73
HDL cholesterol (mmol/L)	1.42 (0.30)	1.56 (0.31)	1.34 (0.26)	0.001
Triglycerides (mmol/L)	1.30 (0.99 – 1.48)	1.16 (0.72 – 1.45)	1.38 (1.12 – 1.63)	0.014
LDL cholesterol (mmol/L)	3.78 (0.93)	3.69 (0.90)	3.83 (0.95)	0.50
Subcutaneous abdominal fat (cm^2)	185.9 (136.1 – 243.0)	157.9 (128.3 – 206.4)	210.1 (143.5 – 263.2)	0.012
Visceral abdominal fat (cm^2)	89.5 (68.8 – 121.9)	76.3 (45.6 – 98.8)	101.1 (78.3 – 138.5)	0.005
Visceral to subcutaneous abdominal fat ratio	0.46 (0.32 – 0.64)	0.45 (0.30 – 0.66)	0.49 (0.33 – 0.63)	0.49
Subcutaneous thigh fat (cm^2)	62.6 (43.0 – 91.9)	61.5 (43.8 – 90.3)	64.6 (42.4 – 92.2)	0.95

Data are expressed as mean (SD), median (inter-quartile range), or frequency (%). MHO, metabolically heathy obese; MUO, metabolically unhealthy obese

Table 2

Univariate logistic regression analysis for the metabolic abnormalities after 10 years

	OR (95% CI)*	*P*
Age	1.12 (0.72 – 1.75)	0.63
Female sex	2.19 (0.80 – 5.98)	0.13
Body mass index	1.50 (0.90 – 2.49)	0.12
Waist circumference	1.31 (0.83 – 2.07)	0.24
Alcohol consumption	0.34 (0.05 – 2.16)	0.25
Current smoking	5.67 (0.68 – 47.16)	0.11
Regular physical activity	0.54 (0.20 – 1.41)	0.21
Systolic blood pressure	1.13 (0.72 – 1.78)	0.59
Diastolic blood pressure	0.88 (0.55 – 1.40)	0.59
Fasting plasma glucose	1.23 (0.73 – 2.09)	0.44
2 hour plasma glucose	1.37 (0.80 – 2.33)	0.25
Fasting plasma insulin	3.21 (1.51 – 6.82)	0.002
HOMA-IR	3.02 (1.38 – 6.59)	0.006
Total cholesterol	1.09 (0.69 – 1.71)	0.73
HDL cholesterol	0.42 (0.24 – 0.74)	0.002
Triglycerides	2.01 (1.13 – 3.59)	0.018
LDL cholesterol	1.17 (0.74 – 1.85)	0.49
Subcutaneous abdominal fat	1.81 (1.08 – 3.02)	0.024
Visceral abdominal fat	1.99 (1.17 – 3.39)	0.011
Visceral to subcutaneous abdominal fat ratio	1.27 (0.73 – 2.22)	0.39
Subcutaneous thigh fat	1.12 (0.71 – 1.77)	0.63

*Odds ratios for continuous variables are shown for a 1-SD increment.

Table 3

Multivariate logistic regression analysis with backward selection for the development of metabolic abnormalities after 10 years

	OR (95% CI)*	*P*
Female sex	5.37 (1.14 – 25.27)	0.033
HDL cholesterol	0.24 (0.11 – 0.53)	<0.001
Fasting plasma insulin	2.45 (1.07 – 5.62)	0.034
Visceral abdominal fat	2.04 (1.11 – 3.72)	0.021

Age, sex, HDL cholesterol, triglyceride, fasting plasma insulin, subcutaneous abdominal fat, and visceral abdominal fat were initially included in this model. A backwards elimination algorithm led to the final model shown.

*Odds ratios for continuous variables are shown for a 1-SD increment.