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Dysmetabolic Signals in "Metabolically Healthy" Obesity

Peter Manu, M.D.[1,2,3], **Constantin Ionescu-Tirgoviste, M.D., Ph.D.**[4], **James Tsang, M.A.**[5], **Barbara A. Napolitano, M.A.**[5], **Martin L. Lesser, Ph.D.**[5], and **Christoph U. Correll, M.D.**[1,2,3]

[1] Hofstra North Shore LIJ School of Medicine, Hempstead, New York

[2] Zucker Hillside Hospital, Glen Oaks New York

[3] Albert Einstein College of Medicine, Bronx, New York

[4] University of Medicine and Pharmacy "C. Davila", Bucharest

[5] Feinstein Institute for Medical Research, Manhasset, New York

Abstract

Background—Obesity is associated with decreased insulin sensitivity, atherogenic dyslipidemia and hypertension, but clinical studies have also identified a "metabolically healthy" obese phenotype.

Objective—To compare the characteristics of so-called "metabolically healthy" obese (MHO), normal weight subjects (MHNW) and obese with insulin resistance in a nationally representative sample in the United States.

Design, Setting and Participants—Insulin resistance was defined by a homeostatic model assessment (HOMA) value in the upper tertile for the entire NHANES cohort. "Metabolic health" was defined as the absence of diabetes, insulin resistance, metabolic syndrome, and lipid-lowering therapy. The study evaluated the 314 MHO, 1173 MHNW and 843 insulin-resistant obese from among the 6485 non-diabetic, nno-pregnant adults aged 20–79 years, who participated to the United States National Health and Nutrition Examination Survey, 1999–2004.

Main Outcome Measures—Demographic, metabolic, nutrition and physical activity features.

Results—MHO and MHNW groups were similar regarding age, and fasting glucose and triglyceride levels. MHO had higher insulin (P<0.0001), insulin resistance as measured with the homeostatic model (p<0.0001), non-HDL cholesterol (P=0.002 in females and P=0.049 in males) and C-reactive protein levels (P<0.0001 in females and P=0.038 in males), and lower high-density lipoprotein cholesterol (HDL) levels (P<0.002). In addition, MHO females had higher low-density lipoprotein (LDL) cholesterol levels (P=0.012) and systolic blood pressure (P=0.02), and lower

Corresponding Author: Peter Manu, MD, Medical Services, Zucker Hillside Hospital, 59-75 263rd Street, Glen Oaks, NY 11004 (pmanu@nshs.edu).

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intake of dietary fiber (P=0.0009) and levels of physical activity (p=0.002). Triglycerides levels were normal in the MHO group.

Conclusions—"Metabolically healthy" obese people have multiple dysmetabolic changes that may signal increased risk for coronary artery disease.

Obesity is present in 32.2% of adults living in the U.S. (1) and is perceived as a major public health issue primarily because it contributes to an increased incidence of type 2 diabetes and coronary heart disease (2). This reality has motivated the definition of obesity-related, high-risk clusters of abnormalities, such as atherogenic dyslipidemia and the metabolic syndrome (2). Longitudinal population surveys support the designation of metabolic syndrome and atherogenic dyslipidemia as major therapeutic targets for the prevention of coronary heart disease (2–5).

The relationship between obesity, insulin resistance and dyslipidemia is complex. Briefly, visceral adipocytes in the obese mobilize large amounts of free fatty acids and glycerol. At the hepatic level, the increased availability of this substrate stimulates triglycerides synthesis and enhances gluconeogenesis. At the skeletal muscle level, the excess of free fatty acids is responsible for insulin-resistance, which decreases the insulin-mediated glucose uptake. A vicious circle is created by the fact that the large amounts of circulating free fatty acids promote a decrease in insulin sensitivity also at the adipocyte level, where insulin normally has an inhibitor effect on lipolysis (2,6,7). Other factors involved in these processes are the decreased production of adiponectin and increased output of the pro-inflammatory cytokines, like tumor necrosis factor α and interleukin-6, which stimulate the hepatic production of the atherogenic C-reactive protein (2).

These mechanisms have been extensively validated, but they do not seem to affect the health of all subjects with increased adiposity. The existence of a "metabolically healthy" obese (MHO) phenotype was proposed in 2001 (8). In two small samples of North American postmenopausal obese women, those with high insulin sensitivity were found to be similar to the insulin-resistant subjects with regard to total adiposity, but they had less visceral adiposity, lower triglycerides, higher HDL levels (9) and lower levels of C-reactive protein (10). The prevalence of MHO among the 154 postmenopausal obese women entered in these two studies was 12.3%. A similar design was used in a study of 681 Italian obese subjects and yielded a prevalence of "uncomplicated obesity" of 27.5% (11). However, none of these studies had a normal weight control group and, therefore, they did not demonstrate that MHO are healthy, but only that insulin resistance and increased visceral adiposity are associated with metabolic abnormalities.

The "metabolically healthy" obese phenotype was also assessed in a cross-sectional study of participants to the United States National Health and Nutrition Examination Surveys (NHANES) from 1999–2004 (12), in which it was defined as the presence of at most 1 of 6 "cardiometabolic" abnormalities. Four of these 6 abnormalities were identical to the glucose, triglyceride, HDL- cholesterol and blood pressure criteria of the U.S. definition of metabolic syndrome (2); one was a marker of insulin resistance as measured by the homeostatic model (HOMA); and one was a marker of systemic inflammation (C-reactive protein. The differences between MHO and metabolically healthy normal weight (MHNW) subjects were not examined.

In the study presented here, we examined the NHANES cohort to determine whether MHO and MHNW are truly similar from the standpoint of metabolic health. For increased clinical relevance, we simplified the definition of metabolic health as the absence of diabetes, insulin resistance, metabolic syndrome and treatment with lipid-lowering drugs. Based on the strong association between excess weight and lipid abnormalities (2), we hypothesized that

compared with MHNW subjects, MHO would have a dysmetabolic state that might increase their risk for coronary artery disease. For clinical purposes and to expand the research comparison, we will also present and discuss the anthropometric and metabolic characteristics of obese subjects, not treated with lipid-lowering drugs, whose HOMA values were in the upper tertile of the inception cohort.

Methods

NHANES Specifics

The study sample was derived from participants to the NHANES from 1999 through 2004. The survey has a cross-sectional design for the evaluation of a group representative of 171 million United States civilian, noninstitutionalized residents aged 20 to 79 years. Participants were recruited using a multistage, stratified sampling design. The survey used validated algorithms to assign weights to all of its age, gender and racial samples. The participants received a household interview followed by physical examination and fasting laboratory testing at a mobile medical unit the following morning. A detailed description of methodology and the data files are in the public domain and are available online from the National Center for Health Statistics (http://www.cdc.gov/nchs/nhanes.htm). The Institutional Review Board of the General Clinical Research Center, Feinstein Institute for Medical Research, Manhasset, New York approved the research protocol.

We limited our study to men and nonpregnant women 20–79 years of age who attended the medical examination, had a BMI of at least 18.5, had fasted at least 8 hours prior to phlebotomy, and had complete data for the assessment of insulin resistance and metabolic syndrome. We excluded all subjects who had a fasting glucose concentration greater than 125 mg/dL or who had answered in the affirmative the question “Have you ever been told by a doctor that you had diabetes?”. The final sample consisted of 6485 subjects, of which 1500 were of normal weight (BMI 18.5–24.9) and 1513 were obese (BMI 30 or greater).

Insulin was measured by radioimmunoassay with the double antibody batch method and serum glucose was measured enzymatically with the Cobas Mira assay, a modified hexokinase reaction at the Diabetes Diagnostic laboratory, University of Missouri, Columbia, Missouri. Lipid analyses were performed at the Johns Hopkins University Hospital Lipoprotein Analytical Laboratory. Serum triglycerides were measured after hydrolysis to glycerol, and HDL-cholesterol concentrations were measured after precipitations of other lipoproteins with a heparin-manganese chloride mixture. C-reactive protein (CRP) was measured with latex-enhanced nephelometry.

Exposure to tobacco smoke was assessed with serum cotinine concentrations. Income was presented as the poverty-income ratio calculated as the family income divided by the poverty threshold defined annually by the United States Census Bureau. Energy expenditure was calculated for the type and duration of physical activity as the Metabolic Equivalent Task (MET) score, which represents the work metabolic rate divided by the resting metabolic.

Assessment of Insulin Resistance

Insulin resistance was determined with the homeostatic model assessment (HOMA), which was calculated by dividing the product of fasting insulin (microU/mL) and glucose (millimoles/L) by 22.5 (13). The entire sample including all BMI groups was split for gender and divided into insulin-resistant (upper tertile of HOMA) and insulin-sensitive (middle and lower tertile of HOMA). The sample-derived HOMA cut-off values for insulin resistance were 3.60 for males and 3.13 for females. Recent large-sample studies have used the upper tertile of steady-state plasma glucose concentrations or HOMA and published

HOMA thresholds for insulin resistance in the general population range from 2.1 to 3.8 (14–19).

Definition of Metabolic Syndrome

Metabolic syndrome was defined based on the American Heart Association/National Heart, Lung and Blood Institutes guidelines published in 2005 (2) as the presence of at least three of the following five criteria: waist circumference: men, greater than 102 cm, and women, greater than 88 cm; triglyceride level of 150 mg/dL or greater; HDL level: men, less than 40 mg/dL, and women, less than 50 mg/dL; blood pressure of 130 mm Hg or greater systolic, or 85 mmHg or greater diastolic, or taking antihypertensive medications; and fasting glucose level of 100 mg/dL or greater.

Statistical Analyses

The two-sample t-test was used to compare each continuous endpoint variable across the two groups. The chi-square test or Fisher's Exact test, where appropriate, were used to compare each categorical endpoint variable across the MHO and MHNW groups. To adjust for multiple comparisons, we specified a P value of less than 0.01 for statistical significance of differences between MHO and MHNW. P values 0.01–0.05 were considered to indicate a trend. All statistical tests were performed with SAS version 9.1 (SAS Institute, Cary, NC) separately for men and women and incorporated the differential weighting, clustering and stratification required by the NHANES complex sample design

Results

The Metabolically Healthy Samples

A state of metabolic health, defined as the absence of diabetes, insulin resistance, metabolic syndrome and history of treatment with lipid-lowering drugs was identified in 314 (120 men and 194 women) obese individuals and 1173 (594 men and 579 women) normal weight subjects. Among the obese participants found to have HOMA levels in the upper tertile, the metabolic syndrome was identified in 76.8% of the 393 males and 70.8% of the 450 females.

Demographic and Socioeconomic Characteristics

The distribution of age and availability of health insurance were similar in the MHO and MHNW groups (Table 1). Among women, the MHO phenotype comprised more non-Hispanic Blacks and fewer non-Hispanic Whites ($p<0.0001$), lower level of education ($p=0.006$), and lower household income ($p=0.001$). Obese with HOMA in the upper tertile of the NHANES cohort were significantly older than the MHO and MHNW.

Anthropometric Characteristics

Six (5%) of the 120 MHO males had extreme obesity (BMI range: 40.2–44.7), 17 (14.2%) had BMI 35.3–39.9, and 97 (80.8%) had BMI 30.1–34.8. Among MHO females, 20 (10.3%) of the 194 had extreme obesity (BMI range: 40.1–61.2), 42 (22.1%) had BMI 35.1–39.9 and 112 (57.6%) had BMI 30.1–34.9. The mean differences in waist circumference between MHO and MHNW was 25.7 cm for males and 25.0 cm for females ($p<0.0001$). Compared with MHO, the obese with insulin-resistance had larger waist circumferences 8.6 cm larger in males and 8.4 cm in females.

Metabolic Characteristics

Fasting insulin and HOMA were higher and HDL-cholesterol levels were significantly lower in the MHO group. Non-HDL cholesterol and C-reactive protein levels were higher in the

MHO group, a difference with statistical significance in females and a statistical trend in males. MHO females also showed a trend toward higher LDL-cholesterol levels and systolic blood pressure (Tables 2 and 3). The triglycerides levels were significantly greater and HDL-cholesterol significantly lower in the insulin-resistant obese as compared with MHO.

Nutrition, Physical Activity, Alcohol Use and Exposure to Tobacco Smoke

MHO and MHNW males had similar energy intake, diet composition, alcohol consumption, duration of physical activities and intensity of effort during physical activities, but MHO had less exposure to tobacco smoke. MHO females consumed less fiber and were not as physically active as their MHNW counterparts (Tables 4 and 5). The total energy intake of MHO subjects was similar to that reported by the obese with HOMA in the upper tertile of the NHANES cohort.

Discussion

For both males and females, mortality is lowest for individuals with body mass index (BMI) of 22.5–25 kg/square meter (20). Above BMI 25, each 5 kg/square meter change is associated with a 30% excess in overall mortality, which is mainly due to increased risk of cardiovascular death for which excess weight is considered “probably largely causal’ (20). These findings have been confirmed in North American, European and East Asian populations (21)

The “metabolically healthy” obese (MHO) phenotype has a prevalence of 4.8% among adults in the United States and of 20.8% in the obese if defined as the absence of diabetes, insulin-resistance, metabolic syndrome and exposure to lipid-lowering drugs. MHO and MHNW groups were similar only with regard to age, fasting glucose and triglyceride levels. MHO had higher insulin ($P<0.0001$), non-HDL cholesterol ($P=0.002$ in females and $P=0.049$ in males) and C-reactive protein levels ($P<0.0001$ in females and $P=0.038$ in males), and lower high-density lipoprotein cholesterol (HDL) levels ($P<0.002$). In addition, MHO females had higher low-density lipoprotein (LDL) cholesterol levels ($P=0.012$) and higher systolic blood pressure ($P=0.02$), lower intake of dietary fiber ($P=0.0009$) and lower levels of physical activity ($p=0.002$), and included a higher proportion of non-Hispanic Blacks ($P<0.0001$).

The clearest dysmetabolic signal in this national sample of “metabolically healthy” obese is a lower plasma level of HDL-cholesterol than in normal weight subjects. Low HDL-cholesterol levels are a major risk factor for coronary artery disease (22). The effect is evident across the full range of HDL-cholesterol levels after adjustments for age, sex, smoking, waist circumference and physical activity; each standard deviation increased HDL-cholesterol (18 mg/dL) being associated with a hazard ratio of incident coronary artery disease events of 0.70, i.e., a 30% reduction (23). Furthermore, at least in women, the HDL-cholesterol is the only component of the metabolic syndrome that predicts the 9-year risk of vascular events (24). The differences observed with regard to the concentration of non-HDL cholesterol are also meaningful, because non-HDL cholesterol appears to be superior to direct measurements of LDL-cholesterol in terms of concordance with the risk of cardiovascular disease in subjects with triglycerides of less than 200 mg/dL (25). The strength of the correlation is due to the fact that non-HDL cholesterol approximates better than LDL-cholesterol the plasma levels of apolipoprotein B, which reflect the number of total atherogenic particles (26) and explain the stronger association between increased non-HDL cholesterol and increased arterial stiffness parameters, intima-media thickness and number of subclinical plaques (27). The relative lack of fiber in the diet of many “metabolically healthy” obese may also influence the importance of the non-HDL-cholesterol dysmetabolic signal, given data showing that a doubling of dietary fiber (to 18.6

g/day) produces a significant reduction of apolipoprotein B concentration in normocholesterolemic subjects (28). On the other hand, the contribution of the higher level of the proinflammatory C-reactive protein in the “metabolically healthy” obese is unlikely to markedly change the magnitude of the atherogenic risk already suggested by the dysmetabolic lipid levels (29). Low HDL-cholesterol with normal triglyceride levels is a common lipid pattern in African-Americans, as well as in West Africans, the ancestral population of African Americans, which is consistent with the high prevalence of non-Hispanic Blacks among “metabolically healthy” obese females in the NHANES cohort (30).

The normal triglyceride levels found in this MHO cohort do not have a clear-cut explanation. It is possible that this phenotype includes a free fatty acid-stimulated overexpression of the peroxisome proliferators-activator receptor (PPAR) α, because the lipid profile of the MHO phenotype appears similar to that of patients treated with synthetic ligands PPAR α as fibrates. Experimental data suggest that young animals are protected from insulin resistance during periods of high-fat feeding by activation of the PPAR α in the skeletal muscles (31.32). The activation of PPAR α leads to increased channeling of fatty acids to mitochondrial oxidation instead of triglyceride synthesis in the liver and, to a lesser extent, in the skeletal muscle (31). At the same time, PPAR α activation has a glucose sparing effect (31), which may explain the greater insulin concentrations required to maintain normal fasting glycemia observed by us in the MHO phenotype.

The implications of the higher insulin levels and HOMA observed in the “metabolically healthy” obese group are more are likely a direct reflection of abdominal adiposity in the NHANES sample (31) and their specific impact on future morbidity is less clear than that of the pattern observed for HDL- and non-HDL cholesterol. In a 12-year follow up study of nondiabetics who participated to NHANES from 1988–1994, HOMA was significantly associated with all-cause mortality (adjusted hazard ratio: 1.16) only among persons with normal BMI (32). Similarly, in the Australian Diabetes, Obesity and Lifestyle Study, HOMA was not associated with all-cause mortality and its modest correlation with the cardiovascular disease events was explained by its covariance with HDL-cholesterol (33). The findings are supported by the recently published results of the large Multi-Ethnic Study of Atherosclerosis (34), a population with a median HOMA of 1.2, in which the correlation between the 2nd–4th quartiles of HOMA and the incidence and progression of coronary artery calcification was not predictive after adjustment for components of metabolic syndrome. In this context, we note also that the association between lower HDL-cholesterol and insulin resistance was associated with a 14-year hazard ratio for coronary events of 2.38 among the Framingham Study participants without diabetes or history of coronary heart disease (35). Surrogate measures of insulin resistance, such as HOMA, have had modest performance for the prediction of incident diabetes mellitus, with no threshold effects, in population-based samples from the United States (36) and Germany (37).

The findings of our study have to be interpreted within its limitations. These include the cross-sectional assessment, limited number of cardiovascular risk proxy measures and inability to determine the stability of MHO status, which could be a transient state on the path to insulin resistance or metabolic syndrome. The value of our observation is also closely tied with the way in which one defines metabolic health. From this vantage point, our study has used a conservative method for assessing the presence of insulin resistance, by selecting a HOMA threshold at the 67th percentile. Other work on the characteristics of metabolically healthy obesity in the NHANES cohort has defined insulin resistance at the 90th percentile, corresponding to a HOMA greater than 5.13 (12). Nonetheless, we acknowledge the fact that current definitions of metabolic health in obese individuals (12) may create controversy, because they allow the inclusion of subjects who are only one criterion short of metabolic syndrome. It is also important to note that the obese group may

have significantly underreported their caloric intake, a fact amply demonstrated in studies using bomb calorimetry of composite daily diet (38) and doubly labeled water (39). Under reporting of energy intake is not random, but greater among people who are overweight or obese, adults compared with teenagers and women compared with men (40), and in Hispanics who identify with the dominant Anglo culture (41). With these caveats, our findings do not support the characterization of MHO as truly healthy (12), as the NHANES data indicate statistically and clinically significant differences between "metabolically healthy" obese and normal weight subjects. Reasonable differences of opinion are understandable, but rather than relying on artificial thresholds to determine "health", it is probably better to consider a continuum of risk (42) and conduct longitudinal studies to define with precision the predictive value of the dysmetabolic signals in the absence of diabetes, insulin resistance, and metabolic syndrome identified in the MHO phenotype.

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Table 1

Demographic and Socioeconomic Characteristics

Characteristic	OBIR Males N=393	MHO Males N=120	MHNW Males (N=594)	P	OBIR Females N=450	MHO Females N=194	MHNW Females N=579	P
Age (mean, 95% CI)	45.7 (44.0–47.3)	38.3 (35.6–41.6)	38.4 (37.0–39.8)	0.96	46.7 (44.6–48.8)	41.2 (38.4–44.0)	40.0 (38.6–41.4)	0.38
Race (%)				0.09				<0.0001
Non-Hispanic White	73.5	67.5	67.8		65.1	60.8	81.6	
Non-Hispanic Black	10.2	12.7	12.7		19.1	21.7	6.3	
Mexican American	8.6	14.3	7.7		8.6	7.9	4.3	
Other Hispanic	2.8	4.6	4.5		5.5	7.6	3.4	
Other	5	0.9	7.3		1.7	1.9	4.3	
Education (%)				0.57				0.006
Less Than High School	19.8	17.3	20.9		22.7	21.1	11.1	
High School	29.7	28.4	24.1		26.6	26.8	22.4	
More Than High School	50.5	54.3	55.0		50.6	52.1	66.5	
Income								
Poverty-Income Ratio	3.2	3.1	3.0	0.41	2.8	2.7	3.2	0.001
Household Authorized for Food Stamps (%)	8.4	4.3	5.4	0.37	22.8	25.5	11.1	0.008
Health Insurance								
Covered by Any Type of Insurance (%)	83.8	93.3	89.2	0.20	80.5	85.7	91.5	0.04
Covered by Medicare (%)	13.4	8.2	8.4	0.97	19	8.7	8.1	0.79
Covered by Medicaid (%)	4.3	5.4	3.2	0.40	7.4	7.2	3.9	0.11

HOMA=Homeostatic Model Assessment; OBIR= obese subjects with HOMA in upper tertile for the NHANES cohort; MHO= metabolically healthy obese (see text); MHNW= metabolically healthy normal weight subjects (see text); P= values for the univariate comparisons of MHO and MHNW groups

Table 2

Anthropometric, Metabolic and Inflammatory Characteristics in Males

Characteristic	OBIR Mean N=393	OBIR 95% CI	MHO Mean N=120	MHO 95% CI	MHNW Mean N=594	MHNW 95% CI	P
Body Mass Index	35.8	34.8–36.7	32.8	32.3–33.3	22.5	22.4–22.7	<0.0001
Waist Circumference (cm)	118.9	116.8–120.9	110.2	108.3–112.1	84.5	83.8–85.2	<0.0001
Fasting Glucose (mg/dl)	108.1	105.0–111.1	95.4	93.7–97.2	93.8	93.0–94.7	0.09
Fasting Insulin (microU/mL)	26.7	23.0–30.4	9.5	8.8–10.2	6.5	6.2–6.7	<0.0001
HOMA	7.2	6.2–8.2	2.2	2.1–2.4	1.5	1.4–1.6	<0.0001
Triglycerides (mg/dl)	222.9	188.2–257.6	112.8	102.8–122.7	107.1	99.8–114.3	0.34
HDL-Cholesterol (mg/dl)	40.5	39.2–41.7	47.7	45.4–49.9	52.0	50.5–53.4	0.0016
Total Cholesterol (mg/dl)	208.4	202.0–214.7	194.4	185.9–203.0	189.7	185.3–194.0	0.29
LDL-Cholesterol (mg/dl)	127.6	123.3–131.9	124.3	117.3–131.3	116.9	113.0–120.9	0.07
Non-HDL Cholesterol (mg/dL)	167.9	161.5–174.4	146.8	138.7–154.9	137.7	133.1–142.3	0.049
C-reactive Protein (mg/dL)	0.49	0.41–0.56	0.33	0.23–0.43	0.22	0.18–0.26	0.038

HOMA=Homeostatic Model Assessment; OBIR= obese subjects with HOMA in upper tertile for the NHANES cohort; MHO= metabolically healthy obese (see text); MHNW= metabolically healthy normal weight subjects (see text); P= values for the univariate comparisons of MHO and MHNW groups

Table 3

Anthropometric, Metabolic and Inflammatory Characteristics in Females

Characteristic	OBIR Mean N=450	OBIR 95% CI	MHO Mean N=194	MHO 95% CI	MHNW Mean N=579	MHNW 95% CI	P
Body Mass Index	37.2	36.6–37.8	34.4	33.6–35.1	22.2	22.1–22.4	<0.0001
Waist Circumference (cm)	112.0	110.9–113.2	103.6	101.9–105.3	78.6	78.0–79.3	<0.0001
Fasting Glucose (mg/dl)	103.9	102.1–105.7	89.7	88.3–91.0	89.1	88.4–89.9	0.42
Fasting Insulin (microU/mL)	21.5	20.6–22.4	9.2	8.9–9.6	6.0	5.7–6.3	<0.0001
HOMA	5.5	5.3–5.8	2.0	1.9–2.1	1.3	1.2–1.4	<0.0001
Triglycerides (mg/dl)	167.3	154.5–180.1	100.3	91.1–109.5	91.8	84.1–99.6	0.15
HDL-Cholesterol (mg/dl)	48.0	46.7–49.4	55.8	53.9–57.8	64.3	62.8–65.8	<0.0001
Total Cholesterol (mg/dl)	205.9	200.5–211.4	193.0	186.7–199.3	191.8	188.1–195.5	0.71
LDL-Cholesterol (mg/dl)	125.5	119.6–131.3	117.3	111.8–122.8	109.4	106.1–112.7	0.012
Non-HDL Cholesterol (mg/dL)	157.9	152.1–163.7	137.1	131.7–142.5	127.5	123.7–131.2	0.002
C-Reactive Protein (mg/dL)	0.89	0.71–1.07	0.62	0.48–0.75	0.27	0.18–0.26	<0.0001

HOMA=Homeostatic Model Assessment; OBIR= obese subjects with HOMA in upper tertile for the NHANES cohort; MHO= metabolically healthy obese (see text); MHNW= metabolically healthy normal weight subjects (see text); P=values for the univariate comparisons of MHO and MHNW groups

Table 4

Dietary Characteristics, Alcohol Use and Tobacco Exposure, and Physical Activity in Males

Characteristic	OBIR Mean N=393	OBIR 95% CI	MHO Mean N=120	MHO 95% CI	MHNW Mean N=594	MHNW 95% CI	P
Diet							
Energy (Kcal/day)	2744	2608–2880	2822.9	2567.4–3078.5	2727.6	2635.6–2819.5	0.44
Protein (gm/day)	105.1	99.2–111.0	108.2	100.8–115.5	98.2	93.2–103.2	0.02
Total Carbohydrates (gm/day)	321.5	302.9–340.0	318.7	284.7–352.6	334.8	322.7–345.0	0.35
Total Fat (gm/day)	109.4	102.6–116.2	106.3	97.4–115.1	99.1	94.3–103.9	0.14
Saturated (gm/day)	36.1	33.5–38.7	33.9	30.4–37.4	32.2	30.7–33.7	0.36
Monounsaturated (gm/day)	41.8	38.8–44.7	40.2	36.7–43.6	37.3	35.5–39.2	0.12
Polyunsaturated (gm/day)	21.7	20.3–23.2	23.0	20.4–25.5	20.6	19.3–21.8	0.07
Cholesterol (mg/day)	411.7	373.8–449.7	358.6	319.8–397.5	344.1	319.7–368.5	0.48
Fiber (gm/day)	16.9	15.9–18.0	17.3	14.0–20.6	17.5	16.4–18.6	0.88
Tobacco Exposure							
Cotinine level (ng/mL)	59	44.7–73.3	66.5	48.6–84.5	106.7	88.2–125.2	0.0013
Alcohol Consumption							
Average number of drinks/day past 30 days	3.4	2.9–3.9	4.3	3.4–5.1	2.5	3.1–3.9	0.09
Physical Activity							
Number of times physically active past 30 days	25.3	20.1–30.5	27.6	20.6–34.5	27.8	24.1–31.5	0.96
Average duration of physical activity (minutes per activity)	157.3	130.3–184.2	185.4	141.5–229.2	198.2	176.8–219.6	0.61
Effort (MET score per activity)	11.3	9.7–12.9	16.3	12.4–20.3	17.0	14.8–19.2	0.77

MET= Metabolic Equivalent Task; HOMA=Homeostatic Model Assessment; IRO= obese subjects with HOMA in upper tertile for the NHANES cohort; MHO= metabolically healthy obese (see text); MHNW= metabolically healthy normal weight subjects (see text); P=values for the univariate comparisons of MHO and MHNW groups

Table 5

Dietary Characteristics, Alcohol Use and Tobacco Exposure, and Physical Activity in Females

Characteristic	OBIR Mean N=450	OBIR 95% CI	MHO Mean N=194	MHO 95% CI	MHNW Mean N=579	MHNW 95% CI	P
Diet							
Energy (Kcal/day)	1929	1847–2010	1864.5	1757.9–1971.1	1999.2	1916.1–2082.2	0.08
Protein (gm/day)	72.8	68.8–76.9	66.9	61.5–72.3	71.9	68.6–75.3	0.16
Total Carbohydrates (gm/day)	238.7	228.0–249.4	233.8	218.8–248.9	246.8	235.7–257.9	0.18
Total Fats (gm/day)	76	71..6–80.4	73.8	68.2–79.4	775.8	71.8–79.9	0.59
Saturated (gm/day)	25.1	23.6–26.6	24.1	22.2–26.0	24.8	23.1–26.4	0.62
Monounsaturated (gm/day)	28.5	26.8–30.1	27.7	25.7–29.8	28.0	26.3–29.6	0.87
Polyunsaturated (gm/day)	15.8	14.5–17.2	15.7	13.7–17.6	16.3	15.3–17.3	0.57
Cholesterol (mg/day)	273	248.1–297.9	240.8	203.7–277.8	244.8	222.4–267.2	0.85
Fiber (gm/day)	13.4	12.3–14.4	12.7	11.5–13.9	14.7	13.9–15.5	0.0009
Tobacco Exposure							
Cotinine level (ng/mL)	31.4	22.7–40.2	44.0	26.1–61.9	51.4	39.5–63.2	0.53
Alcohol Consumption							
Average number of drinks/day past 30 days	2.3	1.9–2.3	2.5	2.1–3.0	2.0	1.9–2.1	0.02
Physical Activity							
Number of times physically active past 30 days	21.8	18.2–25.5	21.6	16.4–26.7	30.6	27.4–33.8	0.002
Average duration of physical activity (minutes per activity)	98.2	80.2–116.3	115.1	77.7–152.5	150.1	133.7–166.5	0.06
Effort (MET score per activity)	10.4	9.0–11.8	10.7	8.9–12.5	15.6	13.9–17.4	0.003

MET= Metabolic Equivalent Task; HOMA=Homeostatic Model Assessment; IRO= obese subjects with HOMA in upper tertile for the NHANES cohort; MHO= metabolically healthy obese (see text); MHNW= metabolically healthy normal weight subjects (see text)

* P values for the univariate comparisons of MHO and MHNW groups