Metabolic Syndrome in Normal-Weight Americans

New definition of the metabolically obese, normal-weight individual

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OBJECTIVE — To determine the prevalence rates and likelihood of the metabolic syndrome and its individual components in normal-weight and slightly overweight individuals (BMI 18.5–26.9 kg/m^2).

RESEARCH DESIGN AND METHODS — There were a total of 7,602 adult participants of the Third National Health and Nutrition Examination Survey, a nationally representative cross-sectional survey. Prevalence and odds ratios (ORs) of the metabolic syndrome, defined according to National Cholesterol Education Program Adult Treatment Panel III criteria, were computed according to 2.0- to 2.5-unit increments in BMI.

RESULTS — Depending on ethnicity and sex, the prevalence of the metabolic syndrome increased in a graded fashion from 0.9–3.0% at BMI 18.5–20.9 kg/m^2 to 9.6–22.5% at BMI 25.0–26.9 kg/m^2. Compared with men with BMI 18.5–20.9 kg/m^2, the odds for the metabolic syndrome were 4.13 (95% CI 1.57–10.87) for men with BMI 21–22.9 kg/m^2, 5.35 (2.41–11.86) for men with BMI 23–24.9 kg/m^2, and 9.08 (4.23–19.52) for men with BMI 25–26.9 kg/m^2 after controlling for age, ethnicity, education, income, physical activity, smoking status, and alcohol and total fat, saturated fat, carbohydrate, and fiber intakes. The corresponding ORs in women were 4.34 (2.08–9.07), 7.77 (3.95–15.26), and 17.34 (9.29–32.38).

CONCLUSIONS — Individuals in the upper normal-weight and slightly overweight BMI range have a relatively high prevalence and are at increased risk of having the metabolic syndrome. Therefore, screening in individuals with normal or slightly elevated BMI is important in the prevention of diabetes and cardiovascular disease.

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The concept of the metabolically obese, normal-weight (MONW) individual was originally developed >20 years ago (1,2); however, a formal definition has not been developed. When it was originally introduced, it was suggested that MONW individuals were those whose BMI (weight in kilograms divided by the square of height in meters) was considered normal but who had any one of the following metabolic disorders that could be improved via caloric restriction: type 2 diabetes, hypertension, and hypertriglyceridemia (1).

The metabolic syndrome is a constellation of diabetes (3), hypertension, and dyslipidemia risk factors that are easily and routinely assessed by physicians. The Third Report of the National Cholesterol Education Program Expert Panel (Adult Treatment Panel III) not only draws attention to the importance of the metabolic syndrome but also provides the first practical definition of this syndrome (4). We propose that individuals whose BMI is within the normal to slightly elevated range, 18.5–26.9 kg/m^2, but who also fulfill the criteria for the metabolic syndrome be classified as MONW.

A previous study reported that ~24% of the U.S. population had the metabolic syndrome (5) but did not report the prevalence of this syndrome among individuals within the various BMI categories. Although Park et al. (6) have shown the prevalence of the metabolic syndrome across broad BMI categories, they have not examined each metabolic syndrome component individually and did not demonstrate the risk of having the metabolic syndrome across the normal-weight range.

The main objective of this trial was to examine the prevalence of the metabolic syndrome and each of its components in the U.S. population, specifically focusing on individuals who had normal BMI and those who were slightly overweight.

RESEARCH DESIGN AND METHODS

— Between 1988 and 1994, a representative sample of the U.S. population participated in the Third National Health and Nutrition Examination Survey (NHANES III). NHANES III was conducted by the National Center for Health Statistics to estimate the prevalence of major diseases, nutritional disorders, and risk factors for these diseases (7). The complex sampling plan used a stratified, multistage, probability cluster design. The total sample included 33,199 subjects. Full details of the study are available elsewhere (7). Participants gave informed consent, and the protocol was approved by the National Center for Health Statistics.

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Abbreviations: MONW, metabolically obese, normal weight; NHANES III, Third National Health and Nutrition Examination Survey.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Of the total sample, we excluded those who were <20 years of age, did not have a normal weight or more than slightly overweight (BMI <18.5 and >26.9 kg/m^2), were pregnant, were missing height or weight measurements, did not fast for a minimum of 6 h before their blood samples were obtained, and were missing one or more of the metabolic syndrome components. A total of 7,602 subjects were retained for analysis in the current study.

Body composition

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using standardized equipment and procedures (7,8). Waist circumference was measured at minimal respiration to the nearest 0.1 cm at the level of the iliac crest (7).

Metabolic variables

Three blood pressure measurements were obtained with the subject in a seated position using a manual mercury sphygmomanometer (7). The average of the three readings was used. Blood samples were obtained after a minimum 6-h fast for the measurement of serum triglyceride and glucose, as described in detail elsewhere (7,9). Briefly, triglyceride levels were measured enzymatically in a series of coupled reactions hydrolyzing triglyceride to glycerol and free fatty acids. Plasma glucose was assayed using a hexokinase enzymatic method (7,10).

Confounding variables

Confounding variables were those variables that influence metabolic syndrome components and included age, ethnicity, education, and income; alcohol, carbohydrate, fat, and fiber intakes; and physical activity participation. All confounding variables were assessed by questionnaire. Age was included in the analysis as a continuous variable. Ethnicity was categorized as non-Hispanic whites, non-Hispanic blacks, Hispanics, and others. Education level was divided into <8 years, 8–12 years, and >12 years. Economic status was divided according to the participant's yearly household income: ≤$15,000, $15,001–$25,000, and >$25,000. Alcohol consumption was categorized as none, moderate (1–30 drinks/month), or heavy (>30 drinks/month). Cutoff points for carbohydrate, fiber, and fat intakes were based on current national dietary guidelines (11). Carbohydrate intakes corresponding to >60%, 40–60%, and <40% of total caloric intake were categorized as high, moderate, and low, respectively. Fiber was classified as low (<20 g/day), moderate (20–30 g/day), or high (>30 g/day). The percentage of total caloric intake from fat was categorized as high (>40%), moderate (30–40%), or low (<30%). Low, moderate, and high polyunsaturated fat intake was considered as <7%, 7–12%, and >12%, respectively. Subjects were considered current smokers if they smoked cigarettes at the time of the interview, previous smokers if they were not current smokers but had smoked 100 cigarettes in their entire life, and nonsmokers if they smoked less than this amount. Physical activity was graded as being none (<4 times/month), low (4–10 times/month), moderate (11–19 times/month), or high (>19 times/month) based on the monthly frequency of engaging in leisure time physical activities, such as walking for ≥1 mile, jogging, swimming, cycling, aerobic or other forms of dance, calisthenics, sports, gardening, and weight training.

Normal-weight individuals (BMI 18.5–24.9 kg/m^2) (12) were subdivided into three BMI groups using 1.5– to 2.4–BMI unit increments (18.5–20.9, 21.0–22.9, and 23.0–24.9 kg/m^2). In the overweight category (BMI 25.0–29.9 kg/m^2) (12), only individuals with a BMI 25.0–26.9 kg/m^2 were examined since formal or aggressive weight-loss treatments and pharmacological interventions are not usually recommended for this subgroup.

The metabolic syndrome was defined according to the Adult Treatment Panel III guidelines (4). Therefore, an individual was classified as having the metabolic syndrome if three or more of the following were present: triglycerides ≥1.7 mmol/l, HDL cholesterol <1.0 mmol/l in men or <1.3 mmol/l in women, blood pressure ≥130/85 mmHg, fasting glucose ≥6.1 mmol/l, and waist circumference >102 cm in men or >88 cm in women.

Statistical analysis

The Intercooled Stata 7 program (Stata, College Station, TX) was used to properly weight the sample to be representative of the population and to take into account the complex sampling strategy of the NHANES III design. We compared prevalences of the metabolic syndrome and its individual components according to BMI category using χ^2 statistics. Logistic regression analysis was also used to examine the associations between BMI classification and the metabolic syndrome. Dummy variables were created to compute odds ratios (ORs) and 95% CIs for these factors. The BMI category 18.5–20.9 kg/m^2 was used as the referent group (OR 1.00). The ORs were adjusted for both nonmodifiable (age, ethnicity, education, and income) and modifiable (smoking status, dietary fat, carbohydrate and fiber intake, alcohol intake, and physical activity) risk factors. Logistic regression analyses were also performed without waist circumference as a criterion for the metabolic syndrome. *P* values associated with tests for linear trend in these ORs are provided.

RESULTS — Subject characteristics according to sex and ethnic background are shown in Table 1. By study design, these subjects are characteristic of the U.S. population with a BMI 18.5–26.9 kg/m^2. The overall prevalence of the metabolic syndrome, including all BMI categories, ranged from 17.5% in non-Hispanic black men to 30.6% in Hispanic women (Fig. 1). Within each sex and ethnic category, the prevalence of the metabolic syndrome increased in a graded fashion from 0.9–3.0% at a BMI 18.5–20.9 kg/m^2 to 9.6–22.5% at a BMI 25.0–26.9 kg/m^2 (*P* for trend <0.001).

The prevalences for each component of the metabolic syndrome are shown in Table 2. In men, the prevalence of a large waist circumference was <2% within the normal BMI range and increased to 9.7% in non-Hispanic white men with a BMI 25.0–26.9 kg/m^2. Compared with men, a greater proportion of women had a large waist circumference ($P < 0.001$), and up to 47.7% of the women with a BMI 25.0–26.9 kg/m^2 had a large waist circumference. The prevalence of high triglyceride levels increased with increasing BMI in all sex and ethnic groups ($P < 0.01$). Similarly, the prevalence of low HDL cholesterol increased with increasing BMI ($P < 0.01$). About 25–30% of normal-weight non-Hispanic white men and women and Hispanic women had low HDL cholesterol, and the prevalence rose to 41.9% in all individuals with a BMI 25.0–26.9 kg/m^2. The prevalence of high blood pressure ranged from 6.6% in Hispanic men

Table 1—*Subject characteristics*

	Men				Women			
	Black	Hispanic	White	All*	Black	Hispanic	White	All*
n	994	1,060	1,640	3,855	840	863	1,861	3,747
Age (years)	39.8 ± 15.8	34.6 ± 13.9	43.2 ± 16.9	42.1 ± 16.7	40.2 ± 16.9	36.8 ± 15.1	45.7 ± 18.2	44.5 ± 18.0
Height (cm)	176.1 ± 7.2	169.6 ± 6.6	176.4 ± 6.9	175.4 ± 7.4	163.5 ± 6.5	157.1 ± 5.9	162.6 ± 6.8	162.1 ± 6.9
Weight (kg)	72.7 ± 9.4	68.9 ± 7.9	74.4 ± 8.5	73.3 ± 8.9	62.2 ± 7.7	57.8 ± 6.8	60.3 ± 7.6	60.1 ± 7.7
BMI (kg/m^2)	23.4 ± 2.3	23.9 ± 2.0	23.9 ± 3.0	23.8 ± 2.0	23.2 ± 2.3	23.4 ± 2.2	22.8 ± 2.2	22.9 ± 2.2
Waist circumference (cm)	83.7 ± 8.3	86.2 ± 7.1	89.3 ± 7.6	88.3 ± 7.9	80.7 ± 8.3	80.9 ± 8.3	80.5 ± 8.7	80.5 ± 8.5

Data are mean ± SE. *Includes non-Hispanic black, Hispanic, non-Hispanic white, and other races.

with a BMI 18.5–20.9 kg/m^2 to 41.5% in non-Hispanic black men with a BMI <25.0–26.9 kg/m^2. Elevated plasma glucose concentrations was the least prevalent of the metabolic syndrome components among normal-weight and slightly overweight individuals, with prevalence rates <12% in all ethnic and sex subgroups.

Independent of sex, the likelihood of having the metabolic syndrome increased with increasing BMI within our study range (*P* for trend <0.001) (Fig. 2). Compared with men with BMI 18.5–20.9 kg/m^2, the odds of the metabolic syndrome were 2.97 (95% CI 1.24–7.15) for men with BMI 21–22.9 kg/m^2, 4.95 (2.13–11.54) for men with BMI 23–24.9 kg/m^2, and 9.88 (4.29–22.75) for men with BMI 25–26.9 kg/m^2 after controlling for age, ethnicity, education, income, physical ac-

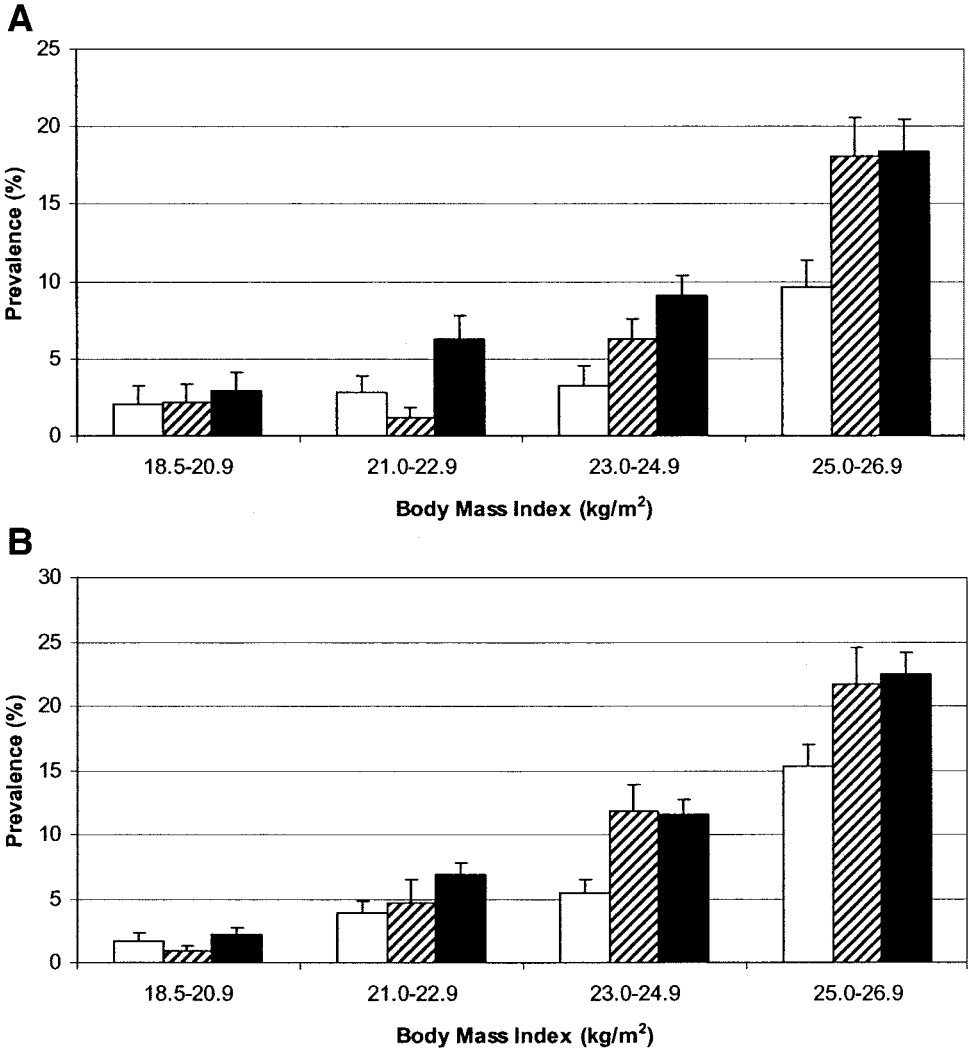

Figure 1— *Overall prevalence (SE) of the metabolic syndrome within each ethnicity, sex, and BMI category. Prevalence rates in men* (A) *and women* (B). □*, blacks;* ▨*, Hispanics;* ■*, whites.*

Table 2—*Prevalence of each metabolic syndrome risk factor within each race, sex, and BMI category

	Men			Women			
BMI (kg/m^2)	Black	Hispanic	White	Black	Hispanic	White	All
High waist circumference (>102 cm men, >88 cm women)							
18.5–20.9	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.4 ± 0.4	0.5 ± 0.4	0.1 ± 0.1	0.2 ± 0.1
21.0–22.9	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1	3.1 ± 0.9	8.3 ± 2.3	4.0 ± 0.7	3.6 ± 0.5
23.0–24.9	0.0 ± 0.0	1.0 ± 0.6	1.9 ± 0.5	7.3 ± 1.3	19.6 ± 2.7	12.5 ± 1.1	11.6 ± 1.1
25.0–26.9	4.0 ± 1.3	1.7 ± 0.5	9.7 ± 1.2	22.6 ± 2.0	47.7 ± 3.7	27.1 ± 1.6	25.8 ± 1.2
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
High triglycerides (>150 mg/dl)							
18.5–20.9	14.2 ± 2.8	10.5 ± 3.3	15.4 ± 3.3	11.5 ± 1.8	8.9 ± 2.6	8.9 ± 1.3	9.7 ± 1.2
21.0–22.9	12.7 ± 2.2	19.7 ± 3.1	19.0 ± 2.6	10.8 ± 1.5	17.1 ± 3.1	18.4 ± 1.6	18.7 ± 1.2
23.0–24.9	18.7 ± 2.5	29.8 ± 2.9	27.5 ± 2.4	16.1 ± 1.8	24.4 ± 3.0	26.1 ± 1.6	25.1 ± 1.5
25.0–26.9	24.6 ± 3.1	46.9 ± 3.1	44.3 ± 2.8	21.9 ± 2.1	36.5 ± 3.5	39.9 ± 2.0	38.6 ± 1.8
P for trend	0.008	<0.001	<0.001	0.005	<0.001	<0.001	<0.001
Low HDL cholesterol (<40 mg/dl men, <50 mg/dl women)							
18.5–20.9	11.8 ± 2.7	8.9 ± 2.7	23.3 ± 4.2	14.6 ± 2.0	30.4 ± 4.3	26.2 ± 2.1	24.4 ± 2.0
21.0–22.9	11.5 ± 3.0	18.3 ± 2.9	20.6 ± 2.6	18.9 ± 2.3	34.9 ± 4.1	26.9 ± 1.8	26.9 ± 2.0
23.0–24.9	12.0 ± 2.1	28.2 ± 3.1	29.7 ± 2.5	18.6 ± 1.9	44.2 ± 3.6	30.7 ± 1.8	30.3 ± 1.6
25.0–26.9	27.2 ± 3.1	40.3 ± 3.1	42.0 ± 2.7	31.9 ± 2.4	47.5 ± 3.7	42.5 ± 2.0	41.9 ± 1.7
P for trend	<0.001	<0.001	<0.001	0.005	<0.001	<0.001	<0.001
High blood pressure (systolic >130 mmHg or diastolic >85 mmHg)							
18.5–20.9	26.2 ± 3.3	6.6 ± 2.0	17.7 ± 3.1	21.9 ± 2.3	8.3 ± 2.8	15.8 ± 1.5	15.7 ± 1.6
21.0–22.9	36.2 ± 3.5	17.3 ± 2.9	27.4 ± 2.8	31.1 ± 2.4	13.5 ± 2.5	23.8 ± 1.6	23.7 ± 1.4
23.0–24.9	32.8 ± 2.9	18.5 ± 2.2	28.9 ± 2.4	29.8 ± 2.2	16.7 ± 2.5	29.0 ± 1.7	28.4 ± 1.6
25.0–26.9	41.5 ± 3.2	34.5 ± 2.9	40.2 ± 2.7	41.0 ± 2.4	21.7 ± 2.7	39.7 ± 1.9	38.0 ± 1.7
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
High glucose (>110 mg/dl)							
18.5–20.9	4.9 ± 1.6	5.1 ± 2.3	3.6 ± 1.2	3.9 ± 1.0	1.0 ± 0.9	2.6 ± 0.6	3.0 ± 0.5
21.0–22.9	5.2 ± 1.3	6.0 ± 1.5	6.2 ± 1.3	6.1 ± 1.1	3.9 ± 1.3	5.0 ± 0.8	5.3 ± 0.6
23.0–24.9	6.0 ± 1.3	6.5 ± 1.5	5.8 ± 1.0	5.5 ± 1.0	6.4 ± 1.6	5.5 ± 0.7	6.2 ± 0.7
25.0–26.9	9.1 ± 1.6	11.5 ± 1.8	7.8 ± 1.1	11.5 ± 1.5	8.5 ± 1.6	7.5 ± 0.8	7.9 ± 0.5
P for trend	0.039	0.003	0.049	0.002	<0.001	0.001	<0.001

Data are mean ± SE. *SE exceeding 30% of the prevalence do not meet the standard of statistical reliability and precision.

tivity, smoking, and alcohol and total fat, polyunsaturated fat, fiber, and carbohydrate intakes. Using the same regression model and BMI categories in women, the ORs were 3.68 (1.89–7.19), 7.51 (3.90–14.46), and 18.58 (10.10–34.17), respectively. Running the statistical analysis for the total population after excluding the "other" race subjects had no impact on any of the statistical results presented.

Since the definition of the metabolic syndrome includes waist circumference, and since waist circumference is highly correlated with BMI, the logistic regression were also run after removing waist circumference from the metabolic syndrome criteria. That is, subjects were required to have three or four of the remaining four metabolic syndrome components (high blood pressure, high triglycerides, low HDL cholesterol, and high glucose) to be considered positive for the metabolic syndrome. These ORs were adjusted for all of the confounding variables. Without exception, the significance of the OR did not change when this modified definition of the metabolic syndrome (no waist component) was used. However, the magnitude of the ORs was attenuated, particularly for women with BMI 23–24.9 or 25–26.9 kg/m^2 and for men with BMI 25–26.9 kg/m^2 (Fig. 2).

CONCLUSIONS — In this report, we advance the notion that MONW individuals are those with a normal or slightly elevated BMI who fulfill the criteria for the metabolic syndrome as defined by the ATP III guidelines. We observed that men and women in the upper end and just above the normal BMI range are more likely to have the metabolic syndrome compared with those with BMI 18.5–20.9 kg/m^2. These results are in accordance with a report noting that the incidence of diabetes, hypertension, and coronary heart disease increases well below the normal BMI cutoff of 25.0 kg/m^2 (13).

The high prevalence of abnormal metabolic risk factors among individuals with normal to slightly elevated BMI in the U.S. population suggests that current recommendations for weight loss may need to be modified and that weight loss in individuals with BMI <25.0 kg/m^2 should be considered if they also have the metabolic syndrome. As early as 1981, Ruderman, Schneider, and Berchtold (1) suggested that the prevailing notion of what constituted obesity at that time (body weight >15% above ideal body weight for age, height, and body build) and that the need for weight management needed to be revised. The results of our analyses suggest that this is still the case

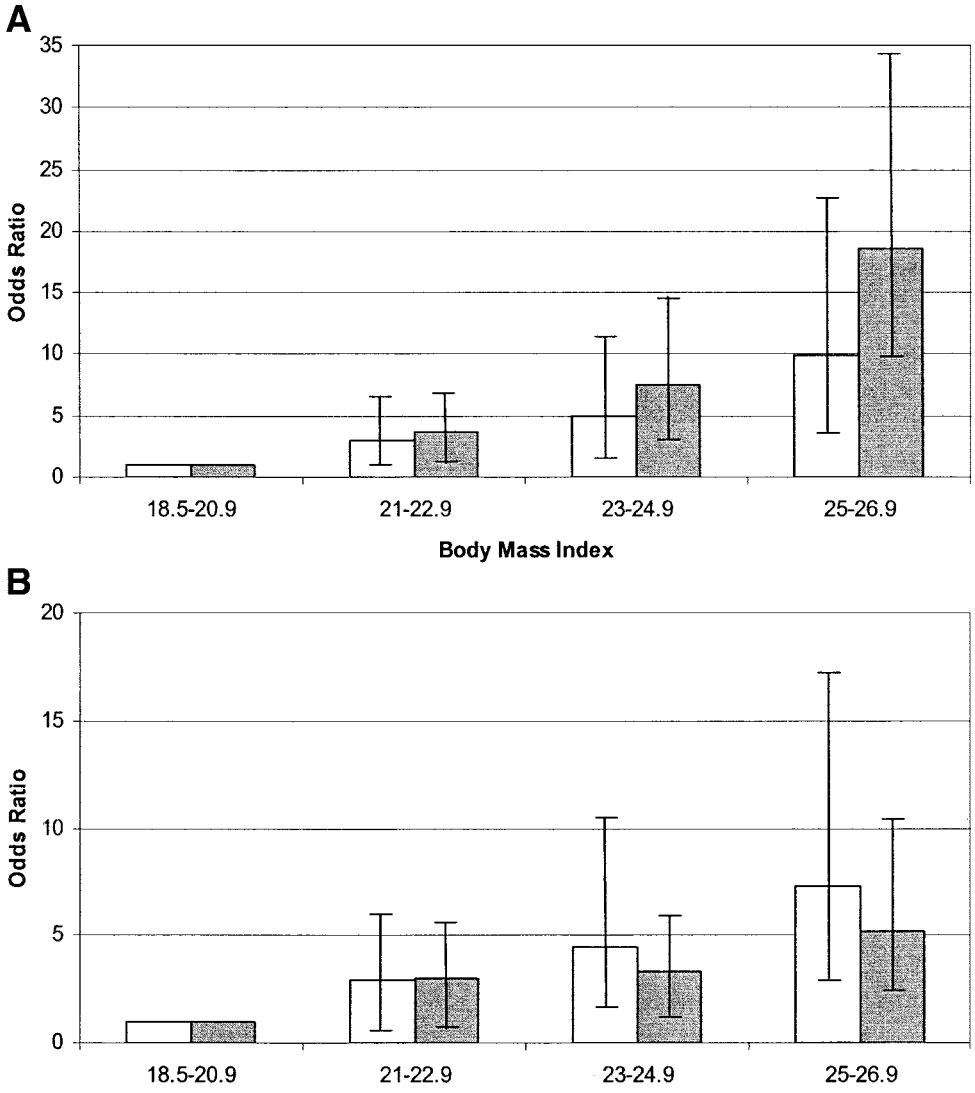

Figure 2— *OR of the metabolic syndrome in men (□) and women (▨) according to BMI category. ORs are adjusted for age, ethnicity, education, income, and physical activity levels; smoking; alcohol consumption; and total fat, polyunsaturated fat, carbohydrate, and total fiber intakes. The 18.5- to 20.9-kg/m^2 category was used as the referent group (OR 1.00), and the error bars for the remaining groups represent the 95% CIs.* A*: ORs of the metabolic syndrome using ATP III criteria.* B*: ORs of the metabolic syndrome excluding the waist circumference criterion of the ATP III criteria. For both sexes, the likelihood of the metabolic syndrome increased significantly (P <0.001) with an increasing BMI category, with and without waist circumference in the metabolic syndrome definition.*

today. Current weight-loss recommendations do not advise patients with BMI <25.0 kg/m^2 to lose weight, and it is not recommended for patients with BMI <27.0 kg/m^2 to use pharmaceutical agents as adjuncts to weight-loss regimens (14). Nevertheless, the 11.1–21.3% of individuals with BMI 23.0–26.9 kg/m^2 who have the metabolic syndrome would likely benefit from weight loss, improved dietary intakes, and physical activity programs.

Our findings suggest a high prevalence of large waist circumference (>88 cm) in nonobese women. Using the same cutoff point, Ascaso et al. (15) found that waist circumference was a good indicator of risk for insulin resistance and the metabolic syndrome, especially for nonobese individuals. An earlier report based on the Nurses' Health Study showed that waist circumference was strongly associated with increased coronary heart disease risk among women with BMI <25.0 kg/m^2 (16). In fact, women with a waist circumference >76.2 cm were 1.8–2.3 times more likely to develop coronary heart disease than women with a waist circumference <71.1 cm (16). Our study used a more conservative waist circumference value of 88 cm, which was based on the National Institutes of Health (12) and National Cholesterol Education Program (4) guidelines. Had we used the lower cutoff of 76.2 cm in the present analyses, considerably more women than estimated here would be at increased risk of developing diabetes and coronary heart disease.

There are limitations to the present study that warrant mentioning. First, the cross-sectional nature of the study prevents causal inferences to be made about the relationship between BMI and the metabolic syndrome. In addition, although we controlled for physical activity level, there are individual differences in cardiorespiratory fitness levels for a given amount of physical activity participation. The inverse gradient between cardiorespiratory fitness and health outcomes is generally steeper and more consistent across studies than that between physical activity and health outcomes (17). In addition, the definition of large waist circumference was determined using data from studies that measured waist circumference midway between the iliac crest and the lowest rib (12), while in the NHANES III survey waist circumference was measured at the iliac crest. In women, but not in men, there can be a difference of up to 2 cm between a waist measure-

ment taken immediately above the iliac crest and a measurement taken midway between the iliac crest and the lowest rib (18). Nonetheless, the high prevalences of low HDL cholesterol, high triglycerides, and high blood pressure indicate that the high prevalence of the metabolic syndrome in women with a normal to slightly overweight BMI is not entirely driven by waist circumference. Moreover, HDL cholesterol and triglyceride levels may be modulated by *trans* fatty acid (19) and carbohydrate (20) intakes. These variables are not available in the NHANES database and therefore could not be controlled for in the current analyses.

Despite these limitations, the data collected in this survey allowed us to control for socioeconomic status, dietary intake, and other lifestyle variables such as physical activity and smoking status. It is therefore likely that among normal-weight individuals, the increased risk of the metabolic syndrome may be genetic in origin or consequent to body composition abnormalities. In a recent study examining phenotypic differences between MONW women and women with a normal weight and metabolic profile, Dvorak et al. (21) noted greater total, abdominal subcutaneous, and visceral fat and lower physical activity energy expenditure in MONW women despite similar age, BMI, and fat-free mass. Alternatively, it has been proposed that increased adiposity later in life relative to an individual's adiposity level at a younger age may lead to increased risk of comorbidities (1,22–24). In fact, data from the Nurses' Health Study showed that a weight gain of ≥10 kg since age 18 years predicted increased mortality due to cardiovascular disease, cancer, and all causes (25). These data are provocative since an average-height man or woman with a BMI 22.0 kg/m^2 at age 18 years could gain 10 kg in body weight and still be considered normal weight. However, such individuals would be at increased risk of morbidity and mortality (25). Maintenance of a high degree of physical activity can be beneficial in slowing the increase in fat mass associated with aging (26), and it is plausible that becoming physically active in adulthood may produce similar effects.

Finally, the high prevalence of metabolic syndrome in normal-weight and slightly overweight individuals warrants investigation of the impact of weight loss and physical activity in this population group. Physicians should also screen for metabolic abnormalities in persons with a BMI at the upper end of the normal-weight and lower end of the overweight spectrum since the early detection of MONW individuals may be beneficial in the prevention of diabetes and cardiovascular disease.

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