

# 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)

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**Background:** The prevalence and correlates of obese individuals who are resistant to the development of the adiposity-associated cardiometabolic abnormalities and normal-weight individuals who display cardiometabolic risk factor clustering are not well known.

**Methods:** The prevalence and correlates of combined body mass index (normal weight, <25.0; overweight, 25.0-29.9; and obese,  $\geq 30.0$  [calculated as weight in kilograms divided by height in meters squared]) and cardiometabolic groups (metabolically healthy, 0 or 1 cardiometabolic abnormalities; and metabolically abnormal,  $\geq 2$  cardiometabolic abnormalities) were assessed in a cross-sectional sample of 5440 participants of the National Health and Nutrition Examination Surveys 1999-2004. Cardiometabolic abnormalities included elevated blood pressure; elevated levels of triglycerides, fasting plasma glucose, and C-reactive protein; elevated homeostasis model assessment of insulin resistance value; and low high-density lipoprotein cholesterol level.

**Results:** Among US adults 20 years and older, 23.5% (approximately 16.3 million adults) of normal-weight

adults were metabolically abnormal, whereas 51.3% (approximately 35.9 million adults) of overweight adults and 31.7% (approximately 19.5 million adults) of obese adults were metabolically healthy. The independent correlates of clustering of cardiometabolic abnormalities among normal-weight individuals were older age, lower physical activity levels, and larger waist circumference. The independent correlates of 0 or 1 cardiometabolic abnormalities among overweight and obese individuals were younger age, non-Hispanic black race/ethnicity, higher physical activity levels, and smaller waist circumference.

**Conclusions:** Among US adults, there is a high prevalence of clustering of cardiometabolic abnormalities among normal-weight individuals and a high prevalence of overweight and obese individuals who are metabolically healthy. Further study into the physiologic mechanisms underlying these different phenotypes and their impact on health is needed.

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**T**HE VARIATION IN METABOLIC and cardiovascular disease (CVD) risk factors observed among individuals of similar body mass index (BMI), and recent studies indicating that individuals' CVD risk may depend

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jointly on their body size and metabolic profile<sup>1-3</sup> has led to increasing recognition that the disease risks associated with obesity may not be uniform. This has resulted in the investigation of body size phenotypes. One recognized body size pheno-

type is the metabolically healthy but obese individual, sometimes referred to as "uncomplicated" obesity.<sup>4</sup> Although obese (BMI  $\geq 30$  [calculated as weight in kilograms

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divided by height in meters squared]), this subset of individuals appears to be relatively resistant to the development of the adiposity-associated cardiometabolic abnormalities that increase CVD risk.<sup>5,6</sup> A second body size phenotype includes individuals with normal weight (BMI <25), who express cardiometabolic abnormalities often associated with being overweight and obese.<sup>7</sup>

## MEASUREMENT OF DEMOGRAPHIC, HEALTH BEHAVIOR, AND PHYSICAL FACTORS

Age, sex, race/ethnicity, smoking status, physical activity, and alcohol intake were assessed by self-report. Participants who had not smoked 100 or more cigarettes in their lifetimes were considered never smokers; participants who had smoked 100 or more cigarettes in their lifetimes were considered current smokers if they answered “some days” or “every day” to the question “Do you smoke now?” and former smokers if they answered “not at all.” Moderate or vigorous leisure-time physical activity was assessed via assessment of the number of times an activity was performed per day, per week, or per month, depending on the activity, the number of minutes the activity was performed each time, and the level of exertion reported. Metabolic equivalents task (MET) scores were then assigned.<sup>8,9</sup> If moderate or vigorous physical activity was not reported, then a 0 value was assigned. Owing to a large prevalence of MET scores of 0, physical activity was categorized into a 5-level variable representing an MET score of 0 plus quartiles of METs scores for those reporting moderate or vigorous activity. Alcohol intake was split into 4 categories (nondrinkers, <1 drink per day, 1-2 drinks per day, and >2 drinks per day). Nondrinkers were classified as those who reported consuming less than 12 alcoholic drinks in their lifetime, and drinkers reported the frequency of drinking alcoholic beverages in the past 12 months and the mean number of drinks consumed on those occasions.<sup>8</sup> The use of antihypertensive, lipid-lowering, and antidiabetic medications were also assessed by self-report.

Height was measured using a fixed stadiometer with a vertical backboard and movable headboard, with participants standing on the floor. Weight was taken by asking each participant to stand on the center of the platform of a Toledo digital scale (Mettler-Toledo Inc, Columbus, Ohio) while wearing underwear, a disposable gown, and foam slippers. Based on their BMI, individuals were classified as being normal weight (BMI, 18.5-24.9), overweight (BMI, 25.0-29.9), or obese (BMI,  $\geq 30.0$ ). Waist circumference was measured to the nearest 0.1 cm at the level of the iliac crest at the end of normal respiration.<sup>8</sup>

### MEASUREMENT OF CARDIOMETABOLIC COMPONENTS

The 6 metabolic components measured include elevated blood pressure; elevated levels of triglycerides, fasting glucose, and high-sensitivity C-reactive protein; elevated homeostasis model assessment of insulin resistance value; and reduced high-density lipoprotein cholesterol (HDL-C) level. Seated systolic and diastolic blood pressures were measured using a mercury sphygmomanometer according to the American Heart Association's recommendations.<sup>10</sup> Up to 3 measurements were averaged for systolic and diastolic blood pressures. High-density lipoprotein cholesterol and triglycerides were measured enzymatically, and glucose was also measured enzymatically via a hexokinase reaction.<sup>8</sup> Insulin was measured by immunoenzymatic assay.<sup>8</sup> Homeostasis model assessment was used to evaluate insulin resistance using the following formula:

$$\text{Fasting Serum Insulin Level (Microunits per Milliliter)} \times \text{Fasting Plasma Glucose Level (Millimoles per Liter)} / 22.5.$$

High-sensitivity C-reactive protein was measured by latex-enhanced nephelometry.

### BODY SIZE PHENOTYPE DEFINITIONS

There is not yet a standardized definition of body size phenotypes. For the present analyses, 6 metabolic abnormalities were considered (elevated blood pressure; elevated triglyceride and glucose levels; insulin resistance; systemic inflammation; and decreased HDL-C level; **Figure 1A**). Body size phenotypes were

#### A Cardiometabolic abnormalities considered:

1. **Elevated blood pressure:** Systolic/diastolic blood pressure  $\geq 130/85$  mm Hg or antihypertensive medication use
2. **Elevated triglyceride level:** Fasting triglyceride level  $\geq 150$  mg/dL
3. **Decreased HDL-C level:** HDL-C level  $< 40$  mg/dL in men or  $< 50$  mg/dL in women or lipid-lowering medication use
4. **Elevated glucose level:** Fasting glucose level  $\geq 100$  mg/dL or antidiabetic medication use
5. **Insulin resistance:** HOMA-IR  $> 5.13$  (ie, the 90th percentile)
6. **Systemic inflammation:** hsCRP level  $> 0.1$  mg/L (ie, the 90th percentile)

#### B Criteria for body size phenotypes:

- Normal weight, metabolically healthy:** BMI  $< 25.0$  and  $< 2$  cardiometabolic abnormalities
- Normal weight, metabolically abnormal:** BMI  $< 25.0$  and  $\geq 2$  cardiometabolic abnormalities
- Overweight, metabolically healthy:** BMI 25.0-29.9 and  $< 2$  cardiometabolic abnormalities
- Overweight, metabolically abnormal:** BMI 25.0-29.9 and  $\geq 2$  cardiometabolic abnormalities
- Obese, metabolically healthy:** BMI  $\geq 30.0$  and  $< 2$  cardiometabolic abnormalities
- Obese, metabolically abnormal:** BMI  $\geq 30.0$  and  $\geq 2$  cardiometabolic abnormalities

**Figure 1.** Definition of body size phenotypes. A, Cardiometabolic abnormalities considered; B, criteria for body size phenotypes. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; and hsCRP, high-sensitivity C-reactive protein. To convert to millimoles per liter, multiply by 0.0259 for HDL-C, by 0.0113 for triglycerides, and by 0.0555 for glucose; to convert hsCRP to nanomoles per liter, multiply by 9.524.

Despite the potential implications of these phenotypes for disease risk, little is known regarding their prevalence and correlates. Therefore, the purpose of the present study was 3-fold: (1) to determine the prevalence of each of 6 body size phenotypes (normal weight with and without cardiometabolic abnormalities, overweight with and without cardiometabolic abnormalities, and obese with and without cardiometabolic abnormalities) among a nationally representative sample of the US adult population, (2) to examine the demographic and behavioral correlates of expressing clustered cardiometabolic abnormalities if normal weight, and (3) to examine the demographic and behavioral correlates of being metabolically healthy (no cardiometabolic risk factor clustering) if overweight or obese.

## METHODS

### STUDY PARTICIPANTS

The National Health and Nutrition Examination Surveys (NHANES) 1999-2004 included a nationally representative sample of the US noninstitutionalized, civilian population identified through a stratified, multistage probability sampling design. As described in detail on the Web site of the National Center for Health Statistics,<sup>8</sup> non-Hispanic blacks and Mexican Americans were oversampled in NHANES 1999-2004 to provide stable estimates for these groups. The present analyses are limited to individuals 20 years and older.

Of the 6036 participants of the NHANES 1999-2004 who were 20 years and older, and from whom blood samples were obtained after an overnight fast of 8 or more hours, 409 were excluded because of a positive history of self-reported CVD at baseline, and 187 were excluded for being underweight (BMI  $< 18.5$ ). Therefore, the final sample for these analyses included 5440 participants.

**Table 1. Demographic and Metabolic Characteristics of the Study Population by Body Size Phenotype<sup>a</sup>**

Demographic and Behavioral Characteristic	Overall	Metabolically Healthy			Metabolically Abnormal		
		Normal Weight	Overweight	Obese	Normal Weight	Overweight	Obese
Prevalence, % (population frequency)	100 (200 690 825)	26.4 (52 982 378)	17.9 (35 923 658)	9.7 (19 467 010)	8.1 (16 255 957)	17.0 (34 117 440)	20.9 (41 944 382)
Age, y	45.0 (0.4)	39.7 (0.6)	42.0 (0.6) <sup>c</sup>	40.1 (0.8)	54.7 (1.0)	50.8 (0.6) <sup>c</sup>	48.2 (0.6) <sup>c</sup>
Men, %	47.9 (0.6)	40.3 (1.4)	54.4 (2.2) <sup>c</sup>	39.2 (2.5)	49.8 (3.1)	59.8 (2.1) <sup>d</sup>	45.8 (1.4)
Race/ethnicity, %							
Non-Hispanic white	71.3 (1.9)	74.9 (1.8)	69.3 (2.4)	61.4 (3.1)	74.2 (3.6)	71.3 (3.2)	71.9 (2.2)
Non-Hispanic black	10.8 (1.1)	9.9 (1.2)	11.5 (1.5)	19.7 (2.3)	6.1 (1.2)	6.5 (1.0)	12.6 (1.5)
Mexican American	7.7 (0.9)	6.0 (0.7)	8.8 (1.3)	10.3 (1.8)	4.9 (0.9)	9.1 (1.5)	7.7 (1.0)
Other	10.2 (1.4)	9.2 (1.3)	10.4 (2.0) <sup>d</sup>	8.7 (2.1) <sup>c</sup>	14.8 (3.5)	13.2 (2.5) <sup>e</sup>	7.7 (1.7) <sup>c</sup>
Smoking, %							
Never	50.9 (1.2)	53.5 (1.8)	53.5 (2.2)	55.4 (3.3)	42.2 (3.7)	45.1 (2.3)	51.3 (1.8)
Former	25.5 (1.0)	19.5 (1.4)	25.1 (2.0)	22.3 (2.6)	27.5 (2.8)	32.0 (2.0)	28.7 (1.6)
Current	23.7 (1.0)	27.1 (1.9)	21.4 (1.8) <sup>e</sup>	22.3 (2.4)	30.3 (2.7)	23.0 (1.7) <sup>d</sup>	20.0 (1.6) <sup>c</sup>
Alcohol intake, %							
Nondrinkers	47.2 (1.6)	37.7 (1.9)	43.2 (2.3)	53.4 (3.4)	49.6 (3.5)	49.2 (2.6)	57.4 (2.4)
< 1 drink per day	39.4 (1.3)	48.6 (1.6)	41.9 (2.5)	35.3 (2.7)	35.3 (2.8)	34.7 (2.2)	32.9 (2.0)
1-2 drink per day	7.7 (0.5)	8.9 (1.0)	9.4 (1.2)	7.0 (1.3)	7.2 (1.8)	7.7 (1.0)	5.1 (0.8)
> 2 drink per day	5.7 (0.5)	4.7 (0.7)	5.5 (0.9)	4.3 (1.1) <sup>c</sup>	7.9 (1.2)	8.4 (1.3)	4.6 (0.7)
Leisure time physical activity, %							
0 METs/d	36.3 (1.2)	30.3 (2.1)	30.1 (1.8)	36.1 (2.8)	46.6 (3.3)	40.7 (2.0)	41.5 (1.8)
1.0-49.9 METs/d	15.8 (0.8)	14.4 (1.6)	15.6 (1.2)	16.6 (1.7)	10.6 (2.0)	15.5 (1.3)	19.7 (1.8)
50.0-131.9 METs/d	16.0 (0.8)	17.4 (1.4)	18.0 (1.4)	16.5 (2.2)	13.1 (1.7)	13.8 (1.6)	15.3 (1.3)
132.0-279.9 METs/d	15.9 (0.8)	18.5 (1.6)	16.1 (1.6)	16.1 (2.3)	17.0 (2.8)	14.8 (1.3)	13.0 (1.3)
≥ 280.0 METs/d	16.0 (0.8)	19.3 (1.3)	20.3 (1.8)	14.7 (1.9)	12.7 (2.1)	15.2 (1.3)	10.6 (1.0) <sup>e</sup>
SBP, mm Hg	122.4 (0.4)	114.7 (0.6)	117.2 (0.7) <sup>e</sup>	119.2 (0.7) <sup>c</sup>	131.3 (1.4)	128.9 (0.7)	129.3 (0.6)
DBP, mm Hg	72.0 (0.3)	69.4 (0.4)	70.7 (0.5) <sup>d</sup>	72.3 (0.6) <sup>c</sup>	70.7 (0.9)	73.7 (0.4) <sup>c</sup>	75.4 (0.5) <sup>c</sup>
Elevated blood pressure (SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg and/or medication use), %	39.1 (1.0)	14.6 (1.0)	18.8 (1.7) <sup>d</sup>	21.6 (2.4) <sup>e</sup>	65.2 (3.7)	61.0 (1.8)	66.9 (1.8)
HDL-C, mg/dL	52.0 (0.4)	60.5 (0.6)	54.1 (0.5) <sup>c</sup>	53.4 (0.6) <sup>c</sup>	50.2 (1.2)	46.0 (0.5) <sup>c</sup>	44.2 (0.5) <sup>c</sup>
HDL-C < 40 mg/dL for men or < 50 mg/dL for women, %	33.5 (0.9)	12.0 (1.6)	16.7 (1.5) <sup>d</sup>	18.8 (1.7) <sup>e</sup>	46.3 (2.8)	53.0 (2.2)	60.7 (1.9) <sup>c</sup>
Triglycerides, mg/dL <sup>b</sup>	121.1 (1.5)	84.7 (1.3)	95.3 (1.6) <sup>c</sup>	100.0 (2.3) <sup>c</sup>	158.2 (6.7)	176.8 (3.6) <sup>d</sup>	168.3 (3.8)
Triglycerides ≥ 150 mg/dL, %	33.0 (0.8)	6.3 (0.8)	10.2 (1.3) <sup>d</sup>	10.1 (1.5) <sup>d</sup>	59.4 (2.8)	66.5 (1.8) <sup>d</sup>	59.0 (1.9)
Glucose, mg/dL <sup>b</sup>	98.1 (0.4)	90.4 (0.3)	92.0 (0.4) <sup>c</sup>	93.0 (0.5) <sup>c</sup>	103.7 (1.2)	106.9 (0.9) <sup>d</sup>	107.8 (0.9) <sup>e</sup>
Glucose ≥ 100 mg/dL and/or antidiabetic medication use, %	34.1 (1.1)	8.7 (1.0)	10.6 (1.4)	11.2 (1.4)	54.9 (3.0)	66.3 (1.7) <sup>c</sup>	62.4 (1.6) <sup>d</sup>
Insulin, μU/mL <sup>b</sup>	9.2 (0.1)	5.6 (0.1)	7.5 (0.2) <sup>c</sup>	11.1 (0.3) <sup>c</sup>	7.7 (0.3)	11.0 (0.3) <sup>c</sup>	17.0 (0.4) <sup>c</sup>
HOMA-IR <sup>b</sup>	1.8 (0.04)	0.9 (0.02)	1.4 (0.03) <sup>c</sup>	2.2 (0.06) <sup>c</sup>	1.6 (0.07)	2.5 (0.07) <sup>c</sup>	4.1 (0.1) <sup>c</sup>
HOMA-IR > 5.13, %	10.2 (0.7)	0	0.1 (0.1)	1.7 (0.7)	6.2 (1.6)	13.3 (1.4) <sup>e</sup>	34.4 (2.0) <sup>c</sup>
BMI	28.2 (0.1)	22.4 (0.05)	27.3 (0.06) <sup>c</sup>	34.2 (0.18) <sup>c</sup>	22.9 (0.08)	27.6 (0.06) <sup>c</sup>	36.2 (0.26) <sup>c</sup>
Waist circumference, cm	96.4 (0.3)	81.2 (0.2)	94.2 (0.3) <sup>c</sup>	107.9 (0.6) <sup>c</sup>	86.8 (0.5)	98.1 (0.3) <sup>c</sup>	115.0 (0.6) <sup>c</sup>
hsCRP, mg/L <sup>b</sup>	0.02 (<0.001)	0.009 (<0.001)	0.016 (0.001) <sup>c</sup>	0.026 (0.001) <sup>c</sup>	0.023 (0.002)	0.025 (0.001)	0.045 (0.001) <sup>c</sup>
hsCRP > 0.1 mg/L, %	9.7 (0.5)	1.6 (0.4)	1.9 (0.4)	5.2 (1.2) <sup>d</sup>	16.2 (2.0)	11.4 (1.5)	25.0 (1.4) <sup>e</sup>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; METs, metabolic equivalent tasks; SBP, systolic blood pressure.

SI conversion factors: To convert to millimoles per liter, multiply by 0.0259 for HDL-C, by 0.0113 for triglycerides, and by 0.0555 for glucose; to convert insulin to picomoles per liter, multiply by 6.945; and hsCRP to nanomoles per liter, multiply by 9.524.

<sup>a</sup>Data are given as mean (SE) value or percentage (SE) of participants unless otherwise specified.

<sup>b</sup>Geometric mean (SE of the geometric mean).

<sup>c</sup>*P* < .001 vs normal weight within metabolic subgroup.

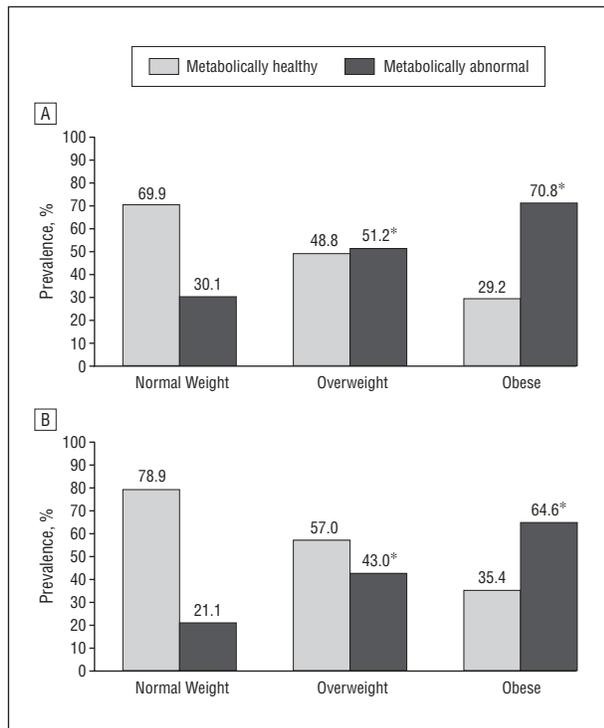
<sup>d</sup>*P* < .05 vs normal weight within metabolic subgroup.

<sup>e</sup>*P* < .01 vs normal weight within metabolic subgroup.

defined based on the combined consideration of BMI category (normal weight, overweight, and obesity) and having 0 to 1 (metabolically healthy) or 2 or more (metabolically abnormal) cardiometabolic abnormalities (Figure 1B). Sensitivity analyses were performed using definitions with more stringent (metabolically healthy, 0 cardiometabolic abnormalities; metabolically abnormal, ≥1 metabolic abnormalities) and less stringent criteria for definition of the “metabolically healthy” phenotype (using Adult Treatment Panel III [ATP-III] criteria for metabolic syndrome,<sup>11</sup> with metabolically healthy classified as ≤2 metabolic abnormalities and metabolically abnormal as ≥3 metabolic abnormalities).

## STATISTICAL ANALYSIS

Participant characteristics were calculated as means, geometric means, and percentages, overall and by body size phenotype. Differences in these characteristics across BMI category, for metabolically healthy and metabolically abnormal individuals separately, were tested using linear orthogonal contrasts and adjusted Wald  $\chi^2$  tests. The age-standardized prevalence of having 0 to 1 and 2 or more metabolic abnormalities was calculated by body size phenotype and sex using direct standardization, with the age distribution of the US population as the standard. Also, the age- and sex-standardized prevalence of hav-



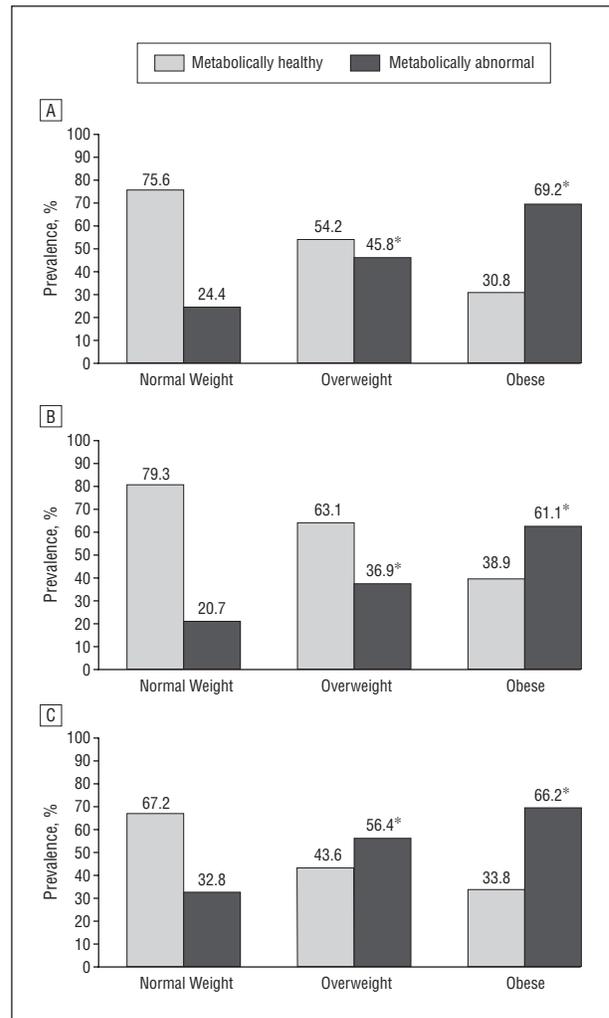
**Figure 2.** Age-standardized prevalence of cardiometabolic abnormalities by body size and sex (A, men; B, women). \* $P < .001$  for proportion metabolically abnormal vs normal weight.

ing 0 to 1 and 2 or more metabolic abnormalities by body size phenotype was calculated by race/ethnicity using direction standardization, with the joint age and sex distribution of the US population as the standard. Among normal-weight individuals, prevalence ratios of expressing 2 or more metabolic abnormalities associated with demographic and behavioral characteristics were calculated, while among overweight or obese individuals, prevalence ratios of expressing 0 to 1 metabolic abnormality associated with demographic and behavioral characteristics were calculated. Unadjusted prevalence ratios were calculated initially, followed by multivariate-adjusted models including all demographic and behavioral factors simultaneously. Finally, prevalence ratios were calculated after further adjustment for waist circumference. All analyses were conducted using SUDAAN 9.0 (Research Triangle Institute, Research Triangle Park, North Carolina) statistical software and used techniques appropriate to the complex survey design of NHANES 1999-2004.

## RESULTS

### PREVALENCE OF BODY SIZE PHENOTYPES

Among the overall US population 20 years and older, 17.9% (approximately 35.9 million adults) were overweight yet metabolically healthy (0 or 1 metabolic abnormalities) and 9.7% (approximately 19.5 million adults) were obese yet metabolically healthy, whereas 8.1% (approximately 16.3 million adults) were normal weight but metabolically abnormal ( $\geq 2$  metabolic abnormalities) (**Table 1**). As a percentage of each BMI group, 51.3% of overweight individuals were metabolically healthy, 31.7% of obese individuals were metabolically healthy, and 23.5% of normal-weight individuals were metabolically abnormal.



**Figure 3.** Age- and sex-standardized prevalence of cardiometabolic abnormalities by body size and race/ethnicity. A, Non-Hispanic whites; B, non-Hispanic blacks; and C, Mexican Americans. \* $P < .001$  for proportion metabolically abnormal vs normal weight.

Compared with normal-weight men and women, the age-standardized prevalence of the metabolically abnormal phenotype was significantly higher among overweight and obese men and women (**Figure 2**). Despite this, 30.1% of normal-weight men and 21.1% of normal-weight women were metabolically abnormal, whereas 29.2% of obese men and 35.4% of obese women were metabolically healthy. Similar patterns were seen when prevalence estimates were stratified by race/ethnicity (**Figure 3**).

The prevalence of the metabolically abnormal phenotype among normal-weight individuals was 10.3% among those aged between 20 and 34 years, 16.9% among those aged between 35 and 49 years, 41.7% among those aged between 50 and 64 years, 54.7% among those aged between 65 and 79 years, and 56.2% among those 80 years and older. The prevalence of the metabolically healthy phenotype among obese individuals was 47.7% among those aged between 20 and 34 years, 31.1% among those aged between 35 and 49 years, 20.4% among those aged between 50 and 64 years, 14.3% among those aged between 65 and 79 years, and 22.1% among those 80 years and older.

**Table 2. Unadjusted and Multivariate-Adjusted Prevalence Ratios of the Metabolically Abnormal Phenotype ( $\geq 2$  Cardiometabolic Abnormalities) Associated With Demographic and Behavioral Characteristics Among Normal-Weight Individuals**

Demographic and Behavioral Characteristic	Prevalence Ratio (95% CI)		
	Unadjusted	Multivariate Adjusted <sup>a</sup>	Multivariate-Adjusted + Waist Circumference <sup>b</sup>
Age group, y			
20-34	1 [Reference]	1 [Reference]	1 [Reference]
35-49	1.58 (1.00-2.48)	1.57 (1.00-2.47)	1.44 (0.91-2.26)
50-64	4.01 (2.81-5.72)	3.80 (2.57-5.60)	3.01 (2.03-4.47)
65-79	5.49 (3.82-7.90)	5.11 (3.54-7.37)	3.86 (2.66-5.60)
$\geq 80$	5.95 (4.14-8.54)	5.90 (4.01-8.67)	4.16 (2.69-6.43)
Sex			
Women	1 [Reference]	1 [Reference]	1 [Reference]
Men	1.34 (1.08-1.66)	1.37 (1.10-1.71)	1.04 (0.84-1.28)
Race/ethnicity			
Non-Hispanic white	1 [Reference]	1 [Reference]	1 [Reference]
Non-Hispanic black	0.68 (0.49-0.95)	0.74 (0.52-1.05)	0.84 (0.59-1.19)
Mexican American	0.86 (0.61-1.21)	1.14 (0.83-1.57)	1.20 (0.86-1.67)
Smoking			
Never	1 [Reference]	1 [Reference]	1 [Reference]
Former	1.55 (1.17-2.07)	1.11 (0.85-1.43)	1.10 (0.87-1.40)
Current	1.31 (0.98-1.76)	1.31 (0.94-1.83)	1.31 (0.96-1.79)
Alcohol intake, drinks/d			
Nondrinkers	1 [Reference]	1 [Reference]	1 [Reference]
<1	0.63 (0.51-0.79)	0.83 (0.69-1.00)	0.84 (0.71-1.01)
1-2	0.69 (0.42-1.13)	0.84 (0.50-1.40)	0.85 (0.52-1.40)
>2	1.17 (0.83-1.66)	1.08 (0.73-1.58)	0.97 (0.67-1.41)
Log leisure time physical activity, METs/d			
0	1 [Reference]	1 [Reference]	1 [Reference]
1.0-49.9	0.57 (0.39-0.85)	0.70 (0.51-0.96)	0.71 (0.51-0.98)
50.0-131.9	0.59 (0.45-0.77)	0.71 (0.54-0.93)	0.71 (0.54-0.93)
132.0-279.9	0.69 (0.46-1.03)	0.82 (0.56-1.20)	0.86 (0.61-1.22)
$\geq 280.0$	0.52 (0.38-0.72)	0.73 (0.52-1.02)	0.78 (0.56-1.10)
Waist circumference, per 5 cm	1.42 (1.33-1.52)	...	1.23 (1.15-1.32)

Abbreviations: CI, confidence interval; METs, metabolic equivalent tasks.

<sup>a</sup>Each factor in the table is adjusted for every other factor in the table, except waist circumference.

<sup>b</sup>Each factor in the table is adjusted for every other factor in the table, including waist circumference.

Among those with 2 or more metabolic abnormalities, the 2 most common cardiometabolic risk factor combinations within all body size groupings were high triglyceride level/low HDL-C level and high blood pressure/high glucose level.

#### CORRELATES OF THE METABOLICALLY ABNORMAL PHENOTYPE IF NORMAL WEIGHT

Among normal-weight individuals, the prevalence of cardiometabolic risk factor clustering was higher in older age groups, men, former and current smokers, and those with larger waist circumference and was lower in non-Hispanic blacks and in moderate alcohol drinkers (<1 drink per day) (**Table 2**). In a multivariate adjustment regression model of normal-weight individuals, older age, male sex, and moderate physical activity remained

**Table 3. Unadjusted and Multivariate-Adjusted Prevalence Ratios of the Metabolically Healthy Phenotype (0-1 Cardiometabolic Abnormalities) Associated With Demographic and Behavioral Characteristics Among Overweight and Obese Individuals**

Demographic and Behavioral Characteristic	Prevalence Ratio (95% CI)		
	Unadjusted	Multivariate Adjusted <sup>a</sup>	Multivariate-Adjusted + Waist Circumference <sup>b</sup>
Age group, y			
20-34	1 [Reference]	1 [Reference]	1 [Reference]
35-49	0.75 (0.65-0.87)	0.76 (0.65-0.87)	0.80 (0.70-0.93)
50-64	0.53 (0.46-0.62)	0.55 (0.47-0.64)	0.61 (0.54-0.70)
65-79	0.38 (0.31-0.47)	0.38 (0.31-0.48)	0.44 (0.35-0.54)
$\geq 80$	0.49 (0.37-0.64)	0.50 (0.39-0.65)	0.53 (0.40-0.69)
Sex			
Women	1 [Reference]	1 [Reference]	1 [Reference]
Men	0.93 (0.84-1.04)	0.85 (0.76-0.97)	1.00 (0.89-1.11)
Race/ethnicity			
Non-Hispanic white	1 [Reference]	1 [Reference]	1 [Reference]
Non-Hispanic black	1.28 (1.16-1.40)	1.17 (1.06-1.29)	1.18 (1.08-1.29)
Mexican American	1.11 (0.99-1.24)	0.97 (0.87-1.08)	0.90 (0.80-1.00)
Smoking			
Never	1 [Reference]	1 [Reference]	1 [Reference]
Former	0.82 (0.72-0.93)	0.98 (0.87-1.12)	1.01 (0.89-1.15)
Current	0.95 (0.83-1.08)	0.92 (0.81-1.04)	0.91 (0.80-1.04)
Alcohol intake, drinks/d			
Nondrinkers	1 [Reference]	1 [Reference]	1 [Reference]
<1	1.19 (1.05-1.34)	1.11 (0.97-1.28)	1.05 (0.92-1.19)
1-2	1.28 (1.04-1.57)	1.29 (1.04-1.59)	1.17 (0.94-1.45)
>2	0.96 (0.79-1.16)	1.02 (0.82-1.28)	0.96 (0.78-1.19)
Log leisure time physical activity, METs/d			
0	1 [Reference]	1 [Reference]	1 [Reference]
1.0-49.9	1.09 (0.92-1.29)	1.03 (0.87-1.20)	1.06 (0.90-1.24)
50.0-131.9	1.28 (1.14-1.45)	1.23 (1.08-1.40)	1.16 (1.02-1.33)
132.0-279.9	1.26 (1.07-1.49)	1.25 (1.06-1.48)	1.16 (0.97-1.38)
$\geq 280$	1.41 (1.23-1.62)	1.29 (1.12-1.49)	1.13 (0.98-1.30)
Waist circumference, per 5 cm	0.84 (0.82-0.86)	...	0.85 (0.83-0.88)

Abbreviations: CI, confidence interval; METs, metabolic equivalent tasks.

<sup>a</sup>Each factor in the table is adjusted for every other factor in the table, except waist circumference.

<sup>b</sup>Each factor in the table is adjusted for every other factor in the table, including waist circumference.

independently associated with the metabolically abnormal phenotype. After further adjustment for waist circumference, male sex was no longer statistically significantly associated with the metabolically abnormal phenotype, but the associations with older age and physical activity remained.

#### CORRELATES OF THE METABOLICALLY HEALTHY PHENOTYPE IF OVERWEIGHT OR OBESE

Among overweight and obese individuals, older adults, former smokers, and those with greater waist circumferences were less likely to express the metabolically healthy phenotype (**Table 3**). In contrast, non-Hispanic blacks, moderate alcohol drinkers, and those with greater levels of physical activity were more likely to express the

metabolically healthy phenotype. In a multivariate adjustment regression model restricted to overweight and obese individuals, age, non-Hispanic black race/ethnicity, moderate alcohol intake, and higher leisure-time physical activity remained independently associated with expressing the metabolically healthy phenotype. After further adjustment for waist circumference, moderate alcohol intake was no longer significantly associated with the metabolically healthy phenotype, but age, non-Hispanic black race/ethnicity, and moderate leisure-time physical activity level remained independently associated with the metabolically healthy phenotype.

### SENSITIVITY ANALYSES

Overall, 16.6% of obese men and women had 0 cardiometabolic abnormalities. Correlates of possessing 0 cardiometabolic abnormalities among overweight and obese individuals were similar to those for possessing 0 or 1, with the following exceptions: race/ethnicity was not significantly associated with possessing 0 cardiometabolic abnormalities after multivariate adjustment, and moderate alcohol intake was associated with an approximate 60% increased prevalence of possessing 0 cardiometabolic abnormalities.

When abdominal obesity (>102 cm in men and >88 cm in women) was used in lieu of BMI categories, 28.3% of individuals without abdominal obesity expressed the metabolically abnormal phenotype ( $\geq 2$  metabolic abnormalities), whereas 36.4% of individuals with abdominal obesity expressed the metabolically healthy phenotype (0 or 1 metabolic abnormalities).

As expected, when the ATP-III metabolic syndrome definition was used ( $\geq 3$  of the following 5 abnormalities: elevated blood pressure, triglyceride level, glucose level, and waist circumference or decreased HDL-C level), the prevalence of normal-weight individuals with cardiometabolic clustering was lower, whereas the prevalences of overweight and obese individuals without cardiometabolic clustering were higher. When the ATP-III metabolic syndrome definition was used, 8.6% of normal-weight individuals were metabolically abnormal, whereas 65.8% of overweight individuals and 39.1% of obese individuals were metabolically healthy.

### COMMENT

These data show that a considerable proportion of overweight and obese US adults are metabolically healthy, whereas a considerable proportion of normal-weight adults express a clustering of cardiometabolic abnormalities. Among US adults, 29.2% of obese men and 35.4% of obese women (a total of approximately 19.5 million adults) possess a healthy profile in terms of the standard cardiometabolic risk factors. In contrast, 30.1% of normal-weight men and 21.1% of normal-weight women (a total of approximately 16.3 million adults) exhibit clustering of cardiometabolic abnormalities (ie,  $\geq 2$  cardiometabolic abnormalities). High proportions of normal-weight adults with cardiometabolic clustering and overweight and obese adults who were metabolically healthy were documented when

more conservative and less conservative definitions of the metabolically abnormal phenotype were used. This study also found that older age, smoking, and larger waist circumference were associated with the metabolically abnormal phenotype, while moderate alcohol intake and leisure-time physical activity were associated with the metabolically healthy phenotype.

The prevalence of body size phenotypes has been investigated in a limited number of studies.<sup>4,12,13</sup> Despite differences in the definitions of “metabolically healthy” that were used, the prevalence of metabolically healthy obese individuals is similar between the present and previous studies. Among a white, Italian, clinic-based population (n=681), 27.5% of obese patients were without cardiometabolic abnormalities (normal blood pressure, lipid parameters, and electrocardiograms and low white blood cell counts and plasma fibrinogen levels),<sup>4</sup> while among a sample of 43 obese postmenopausal women, 39.5% were without cardiometabolic abnormalities (glucose disposal rate >8.0 mg/min/kg of lean body mass).<sup>12</sup>

The prevalence of individuals who are normal weight yet have metabolic abnormalities has been far less studied. Among 96 normal-weight women aged between 18 and 35 years recruited in Montreal, Quebec, Canada, who were free of acute illness, diabetes, hypertension, and dyslipidemia, only 12 (12.5%) were metabolically abnormal, defined as possessing a homeostasis model assessment of insulin resistance value higher than 1.69.<sup>13</sup> In contrast, approximately 21% of normal-weight women in the present study had clustering of cardiometabolic abnormalities. The lower prevalence in the Montreal study is likely owing to the exclusion of women with diabetes, hypertension, and dyslipidemia.

In the present study, several demographic and behavioral characteristics were associated with being normal weight but metabolically abnormal. Although normal-weight men were 34% more likely than normal-weight women to have 2 or more metabolic abnormalities, this was not independent of waist circumference values, suggesting that sex differences in waist circumference was driving the higher prevalence of cardiometabolic clustering in men. Data were available in the present study to determine the prevalence of normal-weight, metabolically abnormal individuals and overweight or obese, metabolically healthy individuals across the adult age span. Although the prevalence of metabolic abnormalities increased with age among all body size groups, a substantial proportion of elderly obese individuals were metabolically healthy, whereas a substantial proportion of normal-weight young adults had at least 2 cardiometabolic abnormalities. Specifically, 22.1% of obese individuals 80 years and older did not express cardiometabolic clustering and 10.3% of normal-weight individuals aged between 20 and 34 years had 2 or more cardiometabolic abnormalities. In the present analyses, among normal-weight individuals there were no statistically significant race/ethnicity differences in the prevalence of clustered cardiometabolic abnormalities. However, among overweight or obese individuals, non-Hispanic blacks were 18% more likely to be metabolically healthy compared with non-Hispanic whites. Non-Hispanic blacks have generally been found to have greater hypertension prevalence compared with non-Hispanic

whites, but have a similar or lower prevalence of hypercholesterolemia,<sup>14-16</sup> which may underlie differences in the likelihood of obesity-associated cardiometabolic abnormalities demonstrated herein.

In addition to demographic factors, the present analyses also identified a number of behavioral factors associated with the normal-weight, metabolically abnormal phenotype and the overweight or obese, metabolically healthy phenotype. Cigarette smoking was associated with cardiometabolic abnormalities in each of these phenotypes, while leisure-time physical activity and alcohol intake were associated with being metabolically healthy. The beneficial effect of leisure-time physical activity was statistically significant in both normal-weight and overweight and obese individuals and was only somewhat attenuated by adjustment for waist circumference. After multivariate adjustment, current smoking was not independently associated with cardiometabolic abnormalities in either normal-weight or overweight or obese individuals, primarily due to adjustment for physical activity levels. Moderate alcohol intake, compared with non-drinking, was associated with a lower prevalence of having clustered metabolic abnormalities in the present analyses, though adjustment for age reduced this association to nonsignificance in both normal-weight and overweight or obese individuals. Since benefits of moderate alcohol intake on lipid and glucose metabolism have been identified previously,<sup>17-20</sup> it is possible that the wide age range represented in the present study explained so much of the variance as to dwarf any possible beneficial effect of moderate alcohol intake in multivariate regression analyses. Further research into the potential of moderate alcohol intake to assist obese individuals in maintaining a healthy cardiometabolic profile is needed.

The role of excess adiposity in CVD risk is unclear. Recent studies have shown that obesity was not associated with an increased risk of future cardiovascular events among individuals without the metabolic syndrome, but that among individuals with the metabolic syndrome, obesity was associated with an increased CVD risk.<sup>1-3</sup> Among the studies that stratified by combined body size and metabolic syndrome phenotypes, obese individuals without cardiometabolic abnormalities or clustering of cardiometabolic abnormalities appeared not to have increased CVD risk.<sup>1,2</sup> Adipose tissue is now recognized as an endocrine organ secreting a variety of hormones and cytokines. The presence of obese individuals, including older adults, who maintain cardiometabolic factors within the normal range suggests that certain obese individuals are either less responsive to the endocrine secretions of excess adipose tissue or that their adipose tissue does not possess the same endocrine secretory properties of those obese individuals who develop metabolic derangements. This underscores the need for future research into the physiologic mechanisms underlying these body size phenotypes.

The interpretation of these data needs to be assessed within the context of the limitations of the present study. Body size phenotype definitions have not been standardized, and as demonstrated by our sensitivity analyses, prevalence estimates are subject to alteration depending on the number of metabolic abnormalities considered and the specific cut points of those abnormalities.

In addition, BMI as a measure of obesity has limitations because it cannot distinguish between fat tissue and lean tissue. This limitation is especially pertinent for Asian populations, who have been shown to have a greater percentage of body fat per given BMI value compared with Western populations, and elderly individuals, who have a greater percentage of body fat per given BMI value compared with younger individuals.<sup>21,22</sup> Sarcopenic obesity is a condition of aging and is characterized by high body fat in the presence of reduced lean body mass.<sup>23</sup> Because of the simultaneous decrease in lean tissue that accompanies the increase in body fat, the BMI of sarcopenic individuals may underestimate their level of obesity to an even greater extent than the standard age-related underestimation associated with BMI. A similar limitation exists for waist circumference, whereby certain individuals may possess relatively more abdominal visceral fat than others with the same waist circumference, especially among older populations.<sup>24,25</sup> However, few simple, inexpensive alternatives to anthropometric indexes exist for the clinical evaluation of obesity. Bioimpedance analysis is relatively inexpensive and simple to perform, but it remains unclear whether bioimpedance analysis is significantly better at predicting cardiovascular events than BMI or waist circumference. Further research examining the effects of different definitions of body size phenotypes on the risk of CVD is needed. The NHANES 1999-2004 data set does not include information on the amount of visceral and subcutaneous adipose tissue or work-related physical activity, which may be relevant to defining and evaluating body size phenotypes.

Despite these limitations, our study had a number of strengths. This study included nationally representative data on 5440 adults, and women and non-Hispanic black and Mexican Americans were well represented. In addition, the majority of previous studies have defined obesity phenotypes based on either solely an insulin resistance cut point or the metabolic syndrome definition. The present study included not only the components of the metabolic syndrome, but also insulin resistance and inflammation criteria, thereby capturing a wider breadth of metabolic abnormalities.

In conclusion, the present data suggest a high prevalence of cardiometabolic abnormality clustering among normal-weight individuals, as well as a high prevalence of obese individuals who are metabolically healthy, irrespective of the definition used to define these phenotypes. Further studies into the behavioral, hormonal or biochemical, and genetic mechanisms underlying these differential metabolic responses to body size are needed and will likely further the identification of possible obesity intervention targets and improve CVD screening tools.

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