Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds

ShanKuan Zhu, ZiMian Wang, Stanley Heshka, Moonseong Heo, Myles S Faith, and Steven B Heymsfield

ABSTRACT

Background: Waist circumference (WC) is strongly linked to obesity-associated risks. However, currently proposed WC risk thresholds are not based on associations with obesity-related risk factors but rather with body mass index (BMI; in kg/m²).

Objective: The objective was to determine the relations of WC to obesity-associated risk factors in a representative sample of US whites and to derive comparable risk thresholds for WC and BMI.

Design: Data on 9019 white participants of the third National Health and Nutrition Examination Survey were divided into 2 groups according to the presence of ≥1 of 4 obesity-associated risk factors: low HDL cholesterol, high LDL cholesterol, high blood pressure, and high glucose. Odds ratio (OR) equations were derived from logistic regression models for WC and BMI with the use of the 25th percentile in the study population as the reference. Receiver operating characteristic curves for identifying risk factors were computed for WC and BMI.

Results: At BMIs of 25 and 30, ORs were 1.19 (95% CI: 1.06, 1.35) and 2.37 (95% CI: 1.33, 4.22) for men and 1.56 (95% CI: 1.29, 1.91) and 3.16 (95% CI: 1.94, 5.28) for women, respectively. The corresponding ORs for WC were at 96 cm for WC and at 86 cm for WC and 25 for BMI.

Conclusion: WC is more closely linked to cardiovascular disease risk factors than is BMI. Am J Clin Nutr 2002;76:743–9.

KEY WORDS Body mass index, BMI, cardiovascular disease risk factors, obesity, waist circumference, third National Health and Nutrition Examination Survey, NHANES III

INTRODUCTION

Body mass index (BMI; in kg/m²) is widely used for the classification of overweight (BMI ≥ 25) and obesity (BMI ≥ 30) in men and women (1, 2). BMI correlates reasonably well with laboratory-based measures of adiposity for population studies (3) and is extremely practical in most clinical settings. However, BMI does not account for the wide variation in body fat distribution, the nature of obesity across different individuals and populations, and the joint relation of body composition and body size to health outcomes (2, 4). Many studies have reported that body fat distribution is a more powerful predictor than is BMI for risk factors, diseases, and mortality (5–12). Increased visceral or abdominal adipose tissue in particular have been shown to be more strongly associated with metabolic and cardiovascular disease risk and a variety of chronic diseases (9–11, 13–16). Therefore, measurements that are more sensitive to individual differences in abdominal fat might be more useful than BMI for identifying obesity-associated risk factors (2).

Waist circumference (WC) is a convenient measure of abdominal adipose tissue (17–19) and is unrelated to height (20), correlates closely with BMI (21, 22) and total body fat (23), and is associated with cardiovascular disease risk factors independent of BMI (24). Accordingly, WC may be an effective clinical tool for assessing the risk of cardiovascular diseases (25, 26). The identification of WC cutoffs to discriminate individuals at significantly elevated risk for obesity-associated risk factors would be a valuable tool for clinical care and public health research (18, 24, 27). However, because populations may differ in the level of risk associated with a particular WC, it is not advisable to identify universally applicable risk thresholds (2). For example, women have a greater relative risk of cardiovascular disease at lower WCs than do men (2). The development of sex- and ethnicity-specific cutoffs is thus warranted.

Current WC cutoffs proposed by the National Institutes of Health and the World Health Organization were not chosen on the basis of their empirical relation to risk factors. Rather, these cutoffs were derived by identifying WC values corresponding to BMI cutoffs for overweight (BMI = 25) or obesity (BMI = 30) (2, 21). If WC has an independent or a stronger association with risk factors than BMI has, then it is inappropriate to base WC thresholds on their association with BMI thresholds. Rather, thresholds for each should be based on their relation to risk factors. Hence, existing cutoff recommendations may not take full advantage of the relation between WC and obesity-related cardiovascular disease risk factors.

In the present study we identified the odds ratios (ORs) for cardiovascular disease and diabetes risk factors that correspond to...
BMIs of 25 and 30 for men and women, respectively, in the white subsample of the third National Health and Nutrition Examination Survey (NHANES III). We then identified the WCs that have the same ORs for these risk factors as do the BMI thresholds and compared the WC- and BMI-based cutoffs for identifying obesity-associated risks.

SUBJECTS AND METHODS

Study population

NHANES III was conducted by the National Center for Health Statistics to assess the health and nutritional status of the noninstitutionalized US population from 1988 to 1994. The study used stratified, multistage probability cluster sampling. Weights indicating the probability of being sampled were assigned to each respondent, enabling results to represent the entire US population. Detailed information on NHANES III is presented elsewhere (28).

The NHANES III staff conducted surveys in households, administering questionnaires to families, adults, and children. The household surveys included questions about demographics, socioeconomic status, diets, and health histories. Standardized medical examinations were completed at 89 mobile centers. The medical examinations included a blood chemistry panel and measurements of blood pressure, plasma lipid and glucose concentrations, and WC. The following categories of data were included in the analyses: 1) anthropometric and demographic information (including age, height, weight, BMI, WC, smoking and drinking status, physical activity, economic status, education level, and menopausal status) and 2) medical examination data (including systolic and diastolic blood pressure, total cholesterol, HDL, triacylglycerol, glucose, and medication use for diabetes, hypertension, or hypercholesterolemia at baseline). The measurements for anthropometric and laboratory tests are described elsewhere (29, 30).

Our study restricted the analyses to whites aged 20–90 y at the time of the NHANES III evaluation for whom anthropometric variables (ie, weight, height, and WC), blood pressure, and blood variables (ie, glucose, total cholesterol, HDL cholesterol, and triacylglycerol) had been measured. We excluded 1038 of the 10218 subjects because they had consumed food or beverages other than water within 6 h before the venipuncture. We also excluded 161 women who were pregnant or lactating at baseline. Of the remaining 9019 subjects, there were 4388 white men and 4631 white women. A total of 3755 whites aged ≥20 y in NHANES III were not included because of missing anthropometric or blood measurements or because they had not fasted before venipuncture. These 3755 subjects had a mean age that was not significantly different from that of the 9019 subjects who met the inclusion criteria: 43.6 compared with 44.5 y for the men and 46.9 compared with 47.0 y for the women, respectively.

Definition of obesity-associated risk factors

LDL cholesterol was calculated as total cholesterol − HDL cholesterol − triacylglycerol/5 and converted to mmol/L (31). According to The Practical Guide—Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, released by the National Institutes of Health in 2000 (24), we defined obesity-associated risk factors as follows: 1) high LDL cholesterol as a concentration ≥4.14 mmol/L (160 mg/dL), 2) low HDL cholesterol as a concentration <0.91 mmol/L (35 mg/dL) for men and <1.17 mmol/L (45 mg/dL) for women, 3) high blood pressure as a systolic blood pressure ≥90 mm Hg or a diastolic blood pressure ≥140 mm Hg, and 4) high glucose as a plasma glucose concentration >6.94 mmol/L (125 mg/dL). Subjects with one or more of these conditions or taking medication for diabetes, hypertension, or hypercholesterolemia were classified as having obesity-associated risk factors. We did not include in the analysis those subjects who received a diagnosis of hypertension, diabetes, or hypercholesterolemia by a physician but were not taking medication at baseline.

Definition of covariates

Smoking was categorized as current, past, and never. Past smokers were those who reported that they had smoked ≥100 cigarettes during their lifetime but did not currently smoke cigarettes. Drinking was categorized as heavy, moderate, never, and unknown. Heavy drinkers were defined as those who ever drank ≥5 alcoholic beverages/d or drank beer, wine, or hard liquor one time per day during the past month. Moderate drinkers were those who drank an alcoholic beverage (ie, beer, wine, or hard liquor) less than one time per day during the past month. Never drinkers were those who drank no beer, wine, or hard liquor during the past month. Physically active and inactive categories were defined on the basis of the subjects’ physical activity density rating scores obtained from participation in one of the following activities during the previous month: walking, jogging or running, bicycle riding, swimming, aerobic exercise or aerobic dancing, other dancing, calisthenics, garden or yard work, weightlifting, or other activities. The physically inactive category included subjects with a total density rating score <3.5. The point at which the total density rating score equals 3.5 corresponds to approximately the 15th and 25th percentiles in the male and female study populations, respectively. Education level was divided into 3 categories: <8 y, 8–12 y, and >12 y of education. Economic status was divided into 3 categories according to household income during the previous year: ≤$15 000, $15 001–$25 000, and >$25 000. Menopausal status was determined from the response to an interview question about when the cessation of menses was complete.

Data analyses

Subject characteristics and the percentage of risk factors were compared between men and women by using the adjusted Wald test. Pearson’s correlation coefficients were used to characterize the associations between WC and BMI with LDL, HDL, diastolic and systolic blood pressure, and glucose. Correlation coefficients were compared by using z tests (32).

Using logistic regression models, we estimated β coefficients for having one or more risk factors compared with no risk factors as a function of WC or BMI, adjusted for age, the interaction of age with WC or BMI, smoking status, alcohol consumption, physical activity, education level, economic status, and menopausal status. Specifically, the ORs were calculated by comparing the odds at one cutoff of WC or BMI for having one or more obesity-associated risk factors with the odds at a reference point.

\[
\text{OR}_i = \text{Exp} \left[ \beta (X_i - X_{\text{ref}}) \right]
\]

where Exp is exponent, \(X_i\) is a specific BMI or WC cutoff, \(X_{\text{ref}}\) is the reference point, and \(\beta\) is the coefficient of BMI or WC derived from logistic regression models. The reference point was set at the 25th percentile for BMI or WC in the male and female study population: a WC of 87.6 cm and a BMI of 23.7 in men and a WC of
TABLE 1
Subject characteristics and the prevalence of obesity-associated risk factors

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 4388)</th>
<th>Women (n = 4631)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>44.5 (43.4, 45.5)</td>
<td>47.0 (45.4, 48.5)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.8 (175.4, 176.2)</td>
<td>161.9 (161.6, 162.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.8 (81.9, 83.7)</td>
<td>68.8 (68.4, 69.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 (26.5, 26.9)</td>
<td>26.2 (26.5, 26.9)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>96.4 (95.7, 97.0)</td>
<td>88.2 (87.5, 89.0)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.30 (3.25, 3.36)</td>
<td>3.26 (3.21, 3.32)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.17 (1.15, 1.18)</td>
<td>1.43 (1.42, 1.45)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>76.6 (76.2, 77.0)</td>
<td>71.7 (71.7, 72.5)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>124.7 (124.1, 125.3)</td>
<td>120.7 (119.6, 121.8)</td>
</tr>
<tr>
<td>Systolic</td>
<td>5.51 (5.46, 5.55)</td>
<td>5.27 (5.23, 5.31)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>1.17 (1.15, 1.18)</td>
<td>1.43 (1.42, 1.45)</td>
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Medications (%)

<table>
<thead>
<tr>
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<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>Diabetes</td>
<td>2.4 (1.7, 3.1)</td>
<td>1.8 (1.3, 2.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.5 (8.8, 12.2)</td>
<td>14.0 (12.4, 15.7)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>2.9 (2.1, 3.8)</td>
<td>3.6 (2.8, 4.3)</td>
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</table>

Obesity-associated risk factor (%)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>High LDL</td>
<td>18.3 (16.5, 20.2)</td>
<td>17.4 (15.7, 19.1)</td>
</tr>
<tr>
<td>Low HDL</td>
<td>18.1 (17.1, 20.5)</td>
<td>25.0 (23.3, 26.6)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>19.2 (17.9, 20.4)</td>
<td>17.4 (15.6, 19.2)</td>
</tr>
<tr>
<td>High glucose</td>
<td>4.6 (3.8, 5.4)</td>
<td>3.5 (2.8, 4.2)</td>
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Subjects with one or more of the above conditions (%)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td>WC — 0.891</td>
<td>80.2</td>
<td>80.2</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.132</td>
<td>0.221</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.284</td>
<td>0.269</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>0.312</td>
<td>0.308</td>
</tr>
<tr>
<td>Systolic</td>
<td>0.273</td>
<td>0.319</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.208</td>
<td>0.259</td>
</tr>
</tbody>
</table>

RESULTS

Descriptive statistics

The baseline characteristics of and the percentage of obesity-associated risk factors in the men and women are shown in Table 1. Mean BMIs were 26.7 for men and 26.2 for women (P < 0.001), and mean WC’s were 96.4 cm for men and 88.2 cm for women (P < 0.001). Age and HDL were significantly greater for women than for men, whereas height, weight, blood pressure, and glucose were significantly greater for men than for women (all P < 0.001). None of the other differences were significant.

The percentages of subjects taking medication for diabetes and hypercholesterolemia were 2.4% and 2.9% for men and 1.8% and 3.6% for women, respectively. These differences were not significant; however, the percentage of subjects taking medication for hypertension was significantly greater for women than for men (14.0% compared with 10.5%, P < 0.001). The percentage of subjects with low HDL was significantly greater for women (25.7%) than for men (19.3%). However, the percentage of subjects with high glucose was significantly greater for men (4.6%) than for women (3.5%). The percentage of subjects with high LDL and high blood pressure was not significantly different between the men and women. The percentage of subjects with one or more of the risk factors was 48.5% for men and 50.2% for women (NS).

The correlations among BMI, WC, LDL, HDL, blood pressure, and glucose are shown in Table 2. Except for HDL, all of these variables were significantly greater than the corresponding correlations between BMI and these risk factors.

Logistic regression analyses

BMI and WC were tested separately in logistic regression models as main predictor variables. These 2 regression models were adjusted for age, the interaction of age with BMI or WC, smoking and drinking status, physical activity, economic and education levels, and menopausal status for women. In men, the β coefficients for BMI and WC were 0.1369 and 0.0669, with SEs of 0.0459 and 0.0144, respectively. In women, the β coefficients for BMI and WC were 0.1418 and 0.0689, with SEs of 0.0305 and 0.0133, respectively. All of the coefficients were significant in the regression

TABLE 2
Correlation of waist circumference (WC) or BMI with lipid profiles, blood pressure, and glucose

<table>
<thead>
<tr>
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<th>Men (n = 4388)</th>
<th>Women (n = 4631)</th>
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<tbody>
<tr>
<td>WC CM (cm) BMI (kg/m²)</td>
<td>0.132</td>
<td>0.221</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.284</td>
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<td>0.259</td>
</tr>
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</table>

1 Unweighted data. P < 0.001 for all Pearson correlation coefficients.
2 Comparisons of 2 dependent correlation coefficients between correlations of risk factors with WC or BMI by z test: 2 P < 0.001, 3 P < 0.01.
models ($P < 0.0001$). The $\beta$ coefficients for the other covariates are not presented.

For BMI and WC, the OR equations for having one or more obesity-associated risk factor are shown below for men:

\[
\text{OR}_{\text{BMI}} = \text{Exp} \left[ 0.1369 \times (\text{BMI} - 23.7) \right]
\]

(2)

\[
\text{OR}_{\text{WC}} = \text{Exp} \left[ 0.0669 \times (\text{WC} - 86.7) \right]
\]

(3)

and for women:

\[
\text{OR}_{\text{BMI}} = \text{Exp} \left[ 0.1418 \times (\text{BMI} - 21.8) \right]
\]

(4)

\[
\text{OR}_{\text{WC}} = \text{Exp} \left[ 0.0689 \times (\text{WC} - 76.5) \right]
\]

(5)

In men, the ORs were 1.19 and 2.37 at BMIs of 25 and 30, respectively. The 2 cutoffs of WC that corresponded to similar ORs for BMI at 25 and 30 were 90 and 100 cm, respectively. In women, at BMIs of 25 and 30, the ORs were 1.56 and 3.16, respectively. The 2 cutoffs that corresponded to similar ORs for WC were 83 and 93 cm, respectively. The exponential curves fitted to the ORs for WC and BMI are shown in Figures 1 and 2, respectively.

**FIGURE 1.** Odds ratios for the presence of one or more obesity-associated risk factors derived from a logistic regression model for BMI in men (—) and women (- - -).

**FIGURE 2.** Odds ratios for the presence of one or more obesity-associated risk factors derived from a logistic regression model for waist circumference in men (—) and women (- - -).

**DISCUSSION**

The present study shows the potential value of assessing WC as an indicator of obesity-associated health risk in men and women. Shown in Tables 3 and 4 is the relation of obesity-associated risk factors with BMI and WC, particularly the cutoffs at which the risk associated with a given WC corresponded to the cutoffs for BMI at 25 and 30. These correspondence cutoffs suggest that a WC of 90 cm for men and of 83 cm for women, equivalent in risk to a BMI of 25, may represent an action level for limiting future weight gain, whereas a WC of 100 cm for men and of 93 cm for women, equivalent in risk to a BMI of 30, may suggest the need for risk reduction and weight loss. In addition, WC was found to correlate better than BMI in both men and women with 4 of the 5 obesity-associated risk factors examined.

These results extend and improve on earlier results linking WC with BMI thresholds for overweight and obesity. Lean et al (21) suggest that a WC of 94 cm for men and of 80 cm for women should be considered the cutoffs for limiting weight gain, whereas a WC of 102 cm for men and of 88 cm for women should be considered the cutoffs for reducing weight. The sample of Lean et al consisted of 904 men and 1014 women from North Glasgow and the cutoffs were chosen by directly relating WC to BMI cutoffs supplemented by the use of a waist-to-hip ratio. However, this approach does not take advantage of the independent relation of WC with cardiovascular disease or obesity-associated risk factors (ie, conditioned on BMI, WC has an independent association with the risk factors) (21, 35). Similarly, Okosun et al (26) used a linear regression model to determine sex- and ethnic-specific WC values corresponding to BMIs of 25 and 30 in young, middle-aged, and elderly groups. In addition, they also plotted ROC curves using the established BMI cutoffs to compute the corresponding cutoffs for WC. The WC cutoffs for non-Hispanic whites were, on average, 5–7 cm greater for men and 3–4 cm greater for women compared with our results. In addition, their findings indicate that the cutoffs varied among the 3 different age groups. However, in our logistic regression analysis of obesity-associated risk factors, the interaction term between age and WC or BMI was not significant. The rationale used in Okosun et al’s study is similar to that in used in Lean et al’s study, linking WC directly to BMI cutoffs.

Many studies have reported that obesity, as defined on the basis of BMI, is consistently related to increased blood pressure and
unfavorable lipid profiles and glucose metabolism (36, 37). WC, however, may be a stronger predictor than BMI for the identification of metabolic and cardiovascular disease–associated risk factors (13, 16, 38). Our results show that not only are correlation coefficients of WC with most individual risk factors significantly higher than those of BMI, but the optimal distance in ROC curves corresponding to WC cutoffs is shorter than for BMI in the identification of risk factors for the same percentile level of the population.

### TABLE 3
Sensitivity and specificity corresponding to different waist circumference (WC) and BMI cutoffs in men

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>WC</th>
<th>BMI</th>
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<tbody>
<tr>
<td>cm</td>
<td>%</td>
<td>%</td>
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<tr>
<td>cm</td>
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<td>kg/m²</td>
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<td>cm</td>
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</tbody>
</table>

1 Boldface numbers represent WC or BMI cutoffs and their corresponding results. ROC, receiver operating characteristic; PV+, positive predictive value; PV−, negative predictive value.

2 Distance in ROC curve = √[(1 − sensitivity)² + (1 − specificity)²].

3 Shortest distance of √[(1 − sensitivity)^2 + (1 − specificity)^2] in ROC curve.

4 The point at which PV+ exceeds PV−.

### TABLE 4
Sensitivity and specificity corresponding to different waist circumference (WC) and BMI cutoffs in women

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>WC</th>
<th>BMI</th>
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<tbody>
<tr>
<td>cm</td>
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1 Boldface numbers represent WC or BMI cutoffs and their corresponding results. ROC, receiver operating characteristic; PV+, positive predictive value; PV−, negative predictive value.

2 Distance in ROC curve = √[(1 − sensitivity)^2 + (1 − specificity)^2].

3 The point at which PV+ exceeds PV−.

4 Shortest distance of √[(1 − sensitivity)^2 + (1 − specificity)^2] in ROC curve.
Lack of exercise, smoking, alcohol abuse, low economic and education levels, and postmenopausal status were all associated with a significantly increased risk of diabetes and other chronic diseases, even after adjustment for BMI (37, 39, 40). We controlled for any potentially confounding effects of these lifestyle or socioeconomic factors and for interactions with age in our logistic regression analyses. No significant interaction terms were observed, suggesting that the models did not vary substantially as a function of age and that the results can be generalized to US whites between the ages of 20 and 90 y.

At WC cutoffs of 90 and 100 cm for men and of 83 and 93 cm for women and at BMI cutoffs of 25 and 30 for both sexes, sensitivities corresponding to these cutoffs were higher for WC than for BMI, whereas specificities were higher for BMI than for WC. That is, some people in need of weight management would be missed if these BMI cutoffs rather than WC were adopted as screening tests. In contrast, fewer people would be recommended for weight management unnecessarily. However, except for the WC cutoff at 90 cm, the optimal distances in ROC curves were shorter for WC than for BMI in both men and women. Of course the therapeutic benefits and cost-effectiveness of different WC cutoffs should also be taken into consideration when WC or BMI cutoffs are used for the purpose of screening tests (41).

The principal limitation of this study was the use of cross-sectional data to identify predictors of the development of obesity-associated risks. Future studies using longitudinal data will provide stronger evidence on the relative predictive value of WC and BMI. In addition, studies of other race or ethnic groups are needed as are studies of the therapeutic benefits and cost-effectiveness of different WC risk thresholds as a basis for intervention recommendations. A second limitation to be borne in mind is that the obesity-related risk factors for which we computed ORs were primarily cardiovascular disease--and diabetes-related. Consequently, other risks of obesity, such as cancer or cholelithiasis, which may have different relations to WC and BMI than do cardiovascular disease and diabetes, were not included herein. However, because cardiovascular disease and diabetes are by far the most prevalent obesity-related diseases, we believe this is a minor limitation.

The strengths of this study are several. Using a population-representative sample of whites, we described the cross-sectional relation of WC and BMI with cardiovascular disease and diabetes risks in the US population. The high-quality standardization of the anthropometric measurements in NHANES III reduced measurement error and potential biases. The use of ORs derived from logistic regression models allowed us to compare WC risk thresholds in relation to BMI risk thresholds. Simultaneous adjustment for age, the interaction of age with WC or BMI, smoking and drinking status, education and income levels, and menopausal status in the regression models allowed for the potential assessment of each effect independent of the others.

In conclusion, WC in white subjects provides important health-related information as does BMI in the evaluation of overweight and obese US adults. WC thresholds are presented that correspond to established BMI thresholds in terms of the increment in health risk incurred. Additional analyses are needed to establish health-related WC cutoffs in other race groups.

SZ, SH, and ZW designed the study; SZ and SH analyzed the data; SZ, SH, and SBH wrote the manuscript; SBH, SH, ZW, MH, and MSF provided advice or consultation; and SBH and SH provided administrative support and supervision. Each author declares that he or she has no conflict of financial or personal interest in any company or organization sponsoring this study.

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