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Normal-Weight Central Obesity: Implications for Total and Cardiovascular Mortality

Karine R. Sahakyan, MD, PhD, MPH; Virend K. Somers, MD, PhD; Juan P. Rodriguez-Escudero, MD; David O. Hodge, MS; Rickey E. Carter, PhD; Ondrej Sochor, MD; Thais Coutinho, MD; Michael D. Jensen, MD; Véronique L. Roger, MD, MPH; Prachi Singh, PhD; and Francisco Lopez-Jimenez, MD, MS

Background: The relationship between central obesity and survival in community-dwelling adults with normal body mass index (BMI) is not well-known.

Objective: To examine total and cardiovascular mortality risks associated with central obesity and normal BMI.

Design: Stratified multistage probability design.

Setting: NHANES III (Third National Health and Nutrition Examination Survey).

Participants: 15 184 adults (52.3% women) aged 18 to 90 years.

Measurements: Multivariable Cox proportional hazards models were used to evaluate the relationship of obesity patterns defined by BMI and waist-to-hip ratio (WHR) and total and cardiovascular mortality risk after adjustment for confounding factors.

Results: Persons with normal-weight central obesity had the worst long-term survival. For example, a man with a normal BMI (22 kg/m^2) and central obesity had greater total mortality risk than one with similar BMI but no central obesity (hazard ratio [HR], 1.87 [95% CI, 1.53 to 2.29]), and this man had twice the mortality risk of participants who were overweight or obese according to BMI only (HR, 2.24 [CI, 1.52 to 3.32] and 2.42 [CI, 1.30 to 4.53], respectively). Women with normal-weight central obesity also had a higher mortality risk than those with similar BMI but no central obesity (HR, 1.48 [CI, 1.35 to 1.62]) and those who were obese according to BMI only (HR, 1.32 [CI, 1.15 to 1.51]). Expected survival estimates were consistently lower for those with central obesity when age and BMI were controlled for.

Limitations: Body fat distribution was assessed based on anthropometric indicators alone. Information on comorbidities was collected by self-report.

Conclusion: Normal-weight central obesity defined by WHR is associated with higher mortality than BMI-defined obesity, particularly in the absence of central fat distribution.

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For author affiliations, see end of text.
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Obesity defined by body mass index (BMI) or measures of central obesity, such as waist-to-hip ratio (WHR) and waist circumference, is associated with increased total and cardiovascular mortality (1–3). However, a recent meta-analysis (4) showed that being overweight according to BMI was actually associated with lower total mortality, challenging the paradigm that BMI is linked to increased mortality. Further, whether measures of fat distribution provide any incremental risk information beyond BMI alone has been a major source of controversy (2, 3, 5–8). Indeed, the 2013 American Heart Association/American College of Cardiology/The Obesity Society guideline for the management of obesity (9) does not recommend measuring WHR and assumes that persons with normal BMI are not exposed to any obesity-related cardiovascular risk in view of the limited available data proving otherwise.

A recent large study (6) showed that incorporating waist circumference information in prediction models did not increase the prognostic value already provided by BMI; however, for a given BMI category, subgroups of waist circumference or WHR were also associated with increased mortality risk. Other studies showed that measures of central obesity, such as WHR, waist-to-height ratio (10, 11), or waist circumference alone, may provide additional information beyond BMI on mortality risk among middle-aged adults, provided there is no adjustment for obesity-related cardiovascular risk factors (2, 3, 7). Further, a study (12) has shown that measures of central obesity are more strongly associated with total and cardiovascular disease mortality rates than BMI. Another study (13) showed that persons with normal body weight measured by BMI, but who had increased body fat measured by bioimpedance, have higher total and cardiovascular mortality rates and a higher prevalence of metabolic syndrome and its components than those with normal BMI and body fat content. In addition, a recent meta-analysis of individual-patient data in those with coronary artery disease (12) has shown that persons with normal BMI who are in the top tertile of central obesity measures had the highest total mortality rate.

These results have been attributed to several factors. First, the diagnostic accuracy of BMI for obesity is not optimal, especially in persons with greater body fat percentages and normal or intermediate BMI (14). Second, those with normal body weight and higher body

See also:

Editorial comment 880
Summary for Patients I-30

EDITORS' NOTES

Context

It is uncertain whether measures of central obesity, such as waist-to-hip ratio (WHR), provide additional information beyond body mass index (BMI) in defining mortality risks associated with obesity.

Contribution

This population-based cohort study found that normal BMI and central obesity (defined by WHR) were associated with the worst long-term survival compared with individuals with normal fat distribution regardless of BMI category.

Caution

Information on body fat distribution was based on anthropometric indicators alone.

Implication

Normal weight with central obesity may represent an important group for targeted lifestyle modifications and other preventive strategies.

fat have less muscle mass, which is a factor associated with higher mortality risk and metabolic dysregulation (15, 16). Third, animal and human studies (17) have recently shown that adipose tissue in the legs and buttocks may have a favorable effect on glucose metabolism. Finally, persons with a central distribution of fat, particularly when measured with WHR, have less adipose tissue in the lower extremities (17).

To our knowledge, no studies in the general U.S. population have specifically focused on assessing the mortality risk in persons with normal BMI and central obesity compared with those who are overweight or obese according to BMI. Thus, we hypothesized that persons with normal BMI and central obesity would have greater mortality risk than those who have any other combination of BMI and central obesity. We investigated the total and cardiovascular mortality risks associated with different patterns of body adiposity in a large cohort of participants in NHANES III (Third National Health and Nutrition Examination Survey) (1988 to 1994). Because hip circumference was not measured in the most recent National Health and Nutrition Examination Surveys (conducted yearly from 1999 to 2010) and WHR data to define central obesity were crucial to our primary hypothesis, we have used data from NHANES III instead.

METHODS

Study Design and Participants

NHANES III is a cross-sectional survey that produces generalizable health estimates for the U.S. population using a stratified, multistage, probability sampling design. From a sample of 39 695 persons, 33 994 were interviewed and 30 818 were examined at mobile examination centers. The examination consisted of extensive anthropometric, physiologic, and laboratory testing. Waist and hip circumferences were measured by a trained examiner with a measuring tape positioned at the high point of the iliac crest for the waist and at the greatest circumference of the buttocks. The design and methods for the survey are available elsewhere (18).

In our study, 16 124 adults aged 18 years or older had WHRs available. Because extremely thin persons and those with a history of nonskin cancer have a higher mortality risk, we further restricted our analysis to persons with a BMI greater than 18.5 kg/m^2 and those without a history of nonskin cancer. The resulting sample was 15 184 participants (7249 men and 7935 women).

Total and Cardiovascular Mortality Assessment

Identifier data were matched to the National Death Index to determine mortality status, with mortality follow-up from the date of the NHANES survey through 31 December 2006. A complete description of the methodology to link baseline NHANES III data to the National Death Index can be found elsewhere (19). International Classification of Diseases, Ninth Revision (ICD-9), codes from 1986 to 1998 and International Classification of Diseases, 10th Revision (ICD-10), codes from 1999 to 2000 were used to ascertain the underlying cause of death. Cardiovascular deaths were defined as those with ICD-9 codes 390 to 398, 402, and 404 to 429 and ICD-10 codes I00 to I09, I11, I13, and I20 to I51 (NHANES III codes 53 to 75).

Statistical Analysis

The overarching analytic goal was to estimate the influence of various magnitudes of central obesity and BMI on total mortality. To do this, we conducted weighted survival modeling that enabled the estimation of the relative risk for mortality, quantified by the hazard ratio (HR), and the expected survival for NHANES III participants. The NHANES III survey design and sampling weights were incorporated into the statistical analysis to calculate weighted means, SEs for continuous variables, and weighted percentages for categorical variables. To determine the total mortality associated with the different patterns of adiposity, we created multivariable Cox proportional hazards models and adjusted for potential confounders previously shown to be associated with obesity and mortality (4). These variables were age at examination, sex, education level, and smoking history. Although we considered adjusting for obesity-related cardiovascular risk factors in the models, we did not adjust our final estimates for these factors. Epidemiologic obesity research has shown that it might be inappropriate to control for factors in the causal pathway between obesity and death, such as diabetes, atherogenic dyslipidemia, and hypertension.

In testing for differences in mortality risk for combinations of central obesity (defined by WHR) and BMI, we considered higher-order interactions of WHR with BMI and other covariates. The association pattern of WHR and BMI was found to be different for men versus women (that is, statistically significant higher-order in-

teraction terms), so the final modeling was conducted using sex-stratified data to more clearly present the findings. The interaction terms allowed the potential quadratic risks (U-shaped risks) of values for these variables. The estimated model contains polynomial functions of BMI and WHR (for example, BMI^2 and $BMI^2 \times WHR^2$). These terms allow for relationships that are more sensitive to change in risk for mortality based on unique combinations (profiles) of WHR and BMI. The estimated risk function, when other covariates in the model are controlled for, will resemble a saddle with high- and low-risk areas. When possible, covariates were the grand mean centered to lessen the collinearity induced from quadratic effects. Likelihood ratio tests were used to determine whether these higher-order model terms could be removed. The proportional hazards assumption for all variables was assessed and satisfied for the final models.

After these models were established, we estimated HRs with estimated model variables for different combinations of WHR and BMI stratified by sex. For these comparisons, we chose a BMI of 22 kg/m^2 to represent persons with normal BMI, 27.5 kg/m^2 to represent overweight persons, and 33 kg/m^2 to represent obese persons. For WHR, we chose 0.89 and 1.00 for men and 0.80 and 0.92 for women as a measure of central obesity. Each of these sets of values were chosen either to reflect the approximate midpoint of standard clinical interpretations—to avoid issues with values at common thresholds (for example, BMI values at 30 kg/m^2)—or to be clinical targets we sought to better understand. Wald-based (or large sample-based) HR estimates and their SEs were assessed to provide significance tests among these representative patient profiles (20).

Once the fitted Cox model was deemed satisfactory, we sought to estimate measures of absolute risk by means-adjusted 5- and 10-year survival estimates (21). In this analysis, we replicated observations to standardize (reweight) them and ensure balance across sex, age, WHR, and BMI categories. The expected survival was computed as a weighted estimate (based on the sampling weights) of the estimated survival per participant. A 95% bootstrap CI based on the 2.5th and 97.5th percentiles of 500 replicates was calculated.

For the sensitivity analysis of the primary study, we repeated the analyses, excluding deaths that occurred within 6 months of enrollment, to account for undetected conditions that could have caused these deaths and were unrelated to BMI or central obesity status. In addition, we repeated the models and added physical activity, a candidate explanatory variable, to determine whether any association between adiposity and mortality was modified by physical activity.

Statistical significance was defined as a *P* value less than 0.05. Standard descriptive statistics and population estimates were calculated using the SURVEYMEANS and SURVEYFREQ procedures in SAS, version 9.3 (SAS Institute). This analysis accounted for the complex survey design using pseudostrata, pseudoprimary sampling units, and sampling weights provided by the National Institute for Health Statistics (18). The Taylor series linearization approach was used for variance estimation because it was recommended by the NHANES (18). The Cox models used for HR estimates were weighted similarly and calculated with the SURVEYPHREG procedure. These models were confirmed with the estimates obtained from the R survival package, version 2.38-1 (running on base R software, version 3.2.0 [R Foundation for Statistical Computing]), which was used to estimate the expected 5-year survival.

Role of the Funding Source

The funding sources had no role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication.

RESULTS

The mean age of the 15 184 survey participants in this study was 45 years, and 7935 (52.3%) were women. According to the BMI of the 15 184 participants, 6062 (39.9%) were normal (18.5 to 24.9 kg/m^2), 5249 (34.6%) were overweight (25 to 29.9 kg/m^2), and 3873 (25.1%) were obese (≥30.0 kg/m^2). In addition, 10 655 persons (70.2%) would be categorized as centrally obese using World Health Organization criteria on WHR for central obesity (WHR ≥0.85 in women and ≥0.90 in men). In contrast, only 4381 persons (28.9%) met the criteria for central obesity when we used waist circumference, sex-specific criteria defined by the World Health Organization (>88 cm in women and >102 cm in men). Of those with normal BMI, 322 men (11.0%) and 105 women (3.3%) had a large WHR (>1.0). Of those who were overweight according to BMI, 1064 men (37.0%) and 289 women (12.0%) had a large WHR. Of those who were defined as obese based on BMI, 928 men (63.0%) and 336 women (14.0%) had a large WHR (>1.0). The analysis of the association between the factors showed that waist circumference was highly correlated with BMI (correlation coefficient, 0.87); WHR was also related to BMI (correlation coefficient, 0.34) but to a lesser extent. The other baseline characteristics of participants stratified by sex are outlined in **Table 1**.

Over a mean follow-up of 14.3 years, there were 3222 deaths (1413 in women), 1404 of which were due to cardiovascular disease. The results of the multivariable Cox proportional hazards analysis showed that WHR, but not BMI, was associated with high mortality risk after including both variables in the model (**Appendix Tables 1** and **2**, available at www.annals.org). On the basis of the results from this model, we estimated HRs for total and cardiovascular deaths attributed to normal-weight central obesity compared with other groups.

Individual comparison results for different combinations of BMI, central adiposity, and total deaths are presented in **Figure 1**. Men with normal-weight central obesity (profile 2 in **Figure 1**) would have a higher total mortality risk than men with any other combination of BMI and WHR. Of note, men with normal-weight central

Table 1. Baseline Characteristics of Study Participants*

Characteristic	Men (*n* = 7249)	Women (*n* = 7935)
Mean age (range), *y*	40.71 (18.00–90.00)	42.04 (18.00–90.00)
Mean height (range), *cm*	175.50 (139.40–206.50)	161.71 (126.90–189.00)
Mean weight (range), *kg*	79.81 (40.70–241.80)	66.04 (32.50–213.50)
Mean BMI (range), kg/m^2	26.74 (18.50–70.20)	25.15 (18.50–79.60)
Mean waist circumference (range), *cm*	93.89 (62.80–174.10)	86.52 (59.40–170.40)
Mean hip circumference (range), *cm*	98.55 (69.10–179.20)	100.15 (69.90–174.70)
Mean WHR (range)	0.94 (0.51–1.56)	0.85 (0.55–2.09)
Highest education level, *n (%)*		
<12 y	3152 (27.22)	3050 (24.30)
12 y	2008 (30.72)	2693 (37.62)
≥13 y	2044 (42.06)	2156 (38.10)
Race, *n (%)*		
White	4952 (84.93)	5279 (83.95)
African American	2029 (10.54)	2408 (12.26)
Other	266 (4.53)	246 (3.79)
Below poverty level, *n (%)*	1415 (10.96)	1896 (14.42)
Smoking history, *n (%)*		
Nonsmoker	2826 (38.50)	4977 (56.10)
Former smoker	2240 (29.98)	1286 (19.38)
Current smoker	2182 (31.52)	1672 (24.55)
History of MI, *n (%)*	388 (4.21)	206 (2.17)
History of hypertension, *n (%)*	2487 (29.49)	2737 (29.17)
Mean systolic BP (range), *mm Hg*	121.06 (80.00–244.00)	114.10 (69.00–237.00)
Mean diastolic BP (range), *mm Hg*	75.44 (23.00–134.00)	70.78 (20.00–126.00)
History of diabetes mellitus, *n (%)*	769 (7.20)	919 (7.54)
Mean fasting serum insulin level (range), *pmol/L*	58.90 (12.20–16 438.00)	56.60 (12.20–6046.90)
Mean fasting plasma glucose level (range)		
mmol/L	5.26 (1.96–35.67)	5.04 (2.35–32.98)
mg/dL	94.8 (35.3–642.7)	90.8 (42.3–594.2)
Mean glycosylated hemoglobin level (range), %	5.20 (3.00–16.20)	5.10 (3.30–16.10)
History of hypercholesterolemia, *n (%)*†	1042 (34.59)	1443 (33.92)
Mean total cholesterol level (range)		
mmol/L	5.12 (1.53–18.16)	5.14 (2.09–17.48)
mg/dL	198 (59–701)	198 (81–675)
Mean serum LDL cholesterol level (range)		
mmol/L	3.27 (0.52–9.83)	3.12 (0.52–9.34)
mg/dL	126 (20–380)	120 (20–360)
Mean serum HDL cholesterol level (range)		
mmol/L	1.11 (0.21–4.16)	1.36 (0.30–5.07)
mg/dL	43 (8–161)	53 (12–196)
Mean serum triglyceride level (range)		
mmol/L	1.36 (0.25–40.84)	1.17 (0.26–25.58)
mg/dL	120 (22–3614)	104 (23–2264)
Disease history, *n (%)*		
Heart failure	256 (1.97)	218 (1.70)
Stroke	172 (1.60)	166 (1.61)
Asthma	469 (7.55)	584 (7.89)
Chronic bronchitis	284 (4.05)	522 (7.80)
Emphysema	165 (2.22)	84 (1.04)
Physical activity level, *n (%)*		
Inactive	1063 (9.7)	2008 (17.3)
Insufficiently active	2315 (31.9)	2787 (35.1)
Active	3871 (58.4)	3140 (47.6)

BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; WHR = waist-to-hip ratio.
* Numbers may not sum to totals due to missing values. Percentages may not sum to 100 due to rounding.
† Total cholesterol level >5.18 mmol/L (200 mg/dL).

obesity had an 87% higher mortality risk than a man with similar BMI but no central obesity (profile 1 in **Figure 1**; HR for profile 2 vs. profile 1, 1.87); further, these men had more than a 2-fold higher mortality risk than a man who was overweight (profile 3 in **Figure 1**) or obese (profile 5 in **Figure 1**) according to BMI but who was not centrally obese. Women with normal-weight central obesity (profile 2 in **Figure 2**) had a 48% higher total mortality risk than a woman with similar BMI but no central obesity (profile 1 in **Figure 2**); further, these women had a 40% or 32% higher total mortality risk (profiles 3 or 5, respectively, in **Figure 2**) than a woman who was overweight or obese according to BMI but did not have central obesity. In the sensitivity analyses, exclusion of early deaths in the follow-up assessment (first 6 months) from analysis did not change the results. Cardiovascular mortality showed the same relationship. A man with normal-weight central obesity had a higher

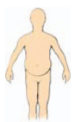
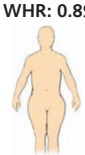
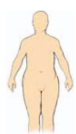
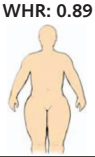
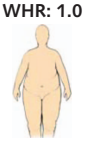
cardiovascular mortality risk than a man with similar BMI without central obesity (HR, 1.78 [95% CI, 1.23 to 2.57]). A woman with normal-weight central obesity had more than a 2-fold higher cardiovascular mortality risk than a woman with similar BMI but without central obesity (HR, 2.25 [CI, 1.66 to 3.05]).

Table 2 presents the standardized expected mortality estimates for men and women. These results have been normalized to reflect a similar composition of the risk factors adjusted in the models. For men, the effect of central obesity on 5- and 10-year survival across all age groups is pronounced. The rank-ordering pattern of expected survival, both within age groups and overall, consistently favors men with less central obesity. The same general pattern is seen in women.

Discussion

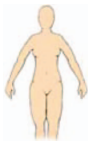
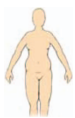
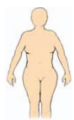
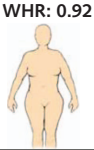
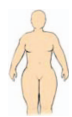
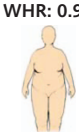
Our analyses of data from a large cohort of NHANES III participants show that normal-weight U.S. adults with central obesity have the worst long-term survival compared with participants with normal fat distribution, regardless of BMI category, even after adjustment for potential mediators. These results confirm and expand the findings of other population-based studies in adults aged 18 years or older by addressing the value of combining measures of central obesity and overall adiposity for predicting mortality risk (2, 3, 7). Prior studies showed that, even in persons with normal weight according to BMI, measures of central obesity were independently related to an increased risk for mortality in the general population.

Figure 1. HRs and 95% CIs for total mortality for men.

1. BMI: 22 kg/m² WHR: 0.89 	**2 vs. 1 1.87 (1.53–2.29)**	**3 vs. 1 0.84 (0.64–1.09)**	**4 vs. 1 1.53 (1.27–1.86)**	**5 vs. 1 0.77 (0.46–1.30)**	**6 vs. 1 1.38 (1.07–178)**
1 vs. 2 0.53 (0.44–0.65)	**2. BMI: 22 kg/m² WHR: 1.0** 	**3 vs. 2 0.45 (0.30–0.66)**	**4 vs. 2 0.82 (0.69–0.97)**	**5 vs. 2 0.41 (0.22–0.77)**	**6 vs. 2 0.74 (0.55–0.99)**
1 vs. 3 1.20 (0.91–1.57)	**2 vs. 3 2.24 (1.52–3.32)**	**3. BMI: 27.5 kg/m² WHR: 0.89** 	**4 vs. 3 1.84 (1.39–2.42)**	**5 vs. 3 0.93 (0.72–1.20)**	**6 vs. 3 1.65 (1.34–2.04)**
1 vs. 4 0.65 (0.54–0.79)	**2 vs. 4 1.22 (1.03–1.45)**	**3 vs. 4 0.54 (0.41–0.72)**	**4. BMI: 27.5 kg/m² WHR: 1.0** 	**5 vs. 4 0.50 (0.30–0.84)**	**6 vs. 4 0.90 (0.79–1.03)**
1 vs. 5 1.29 (0.77–2.18)	**2 vs. 5 2.42 (1.30–4.53)**	**3 vs. 5 1.08 (0.84–1.40)**	**4 vs. 5 1.98 (1.20–3.29)**	**5. BMI: 33 kg/m² WHR: 0.89** 	**6 vs. 5 1.79 (1.18–2.70)**
1 vs. 6 0.72 (0.56–0.94)	**2 vs. 6 1.36 (1.01–1.82)**	**3 vs. 6 0.60 (0.49–0.75)**	**4 vs. 6 1.11 (0.97–1.26)**	**5 vs. 6 0.56 (0.37–0.85)**	**5. BMI: 33 kg/m² WHR: 1.0** 

The group of interest versus the referent are shown in the cells above. For example, to compare a normal-weight centrally obese man (profile 2: BMI = 22 kg/m^2; WHR = 1.0) with an overweight but not centrally obese person (profile 4: BMI = 27.5 kg/m^2; WHR = 1.0), the cell in row 4, column 2 would be referenced (denoted as 2 vs. 4: HR = 1.22 [95% CI, 1.03 to 1.45]). To interpret the HRs, select an intersection of 2 anthropometric profiles of interest. The HRs and 95% CIs were estimated by statistical models presented in **Appendix Tables 1** and **2** (available at www.annals.org). Courtesy of the Mayo Clinic. BMI = body mass index; HR = hazard ratio; WHR = waist-to-hip ratio.

Figure 2. HRs and 95% CIs for total mortality for women.

1. BMI: 22 kg/m^2 WHR: 0.80 	2 vs. 1 1.48 (1.35–1.62)	3 vs. 1 1.06 (0.99–1. 13)	4 vs. 1 1.56 (1.38–1.77)	5 vs. 1 1.12 (0.99–1.27)	6 vs. 1 1.65 (1.39–1.97)
1 vs. 2 0.68 (0.62–0.74)	2. BMI: 22 kg/m^2 WHR: 0.92 	3 vs. 2 0.72 (0.65–0.79)	4 vs. 2 1.06 (0.99–1.13)	5 vs. 2 0.76 (0.66–0.87)	6 vs. 2 1.12 (0.99–1.27)
1 vs. 3 0.95 (0.89–1.01)	2 vs. 3 1.40 (1.27–1.54)	3. BMI: 27.5 kg/m^2 WHR: 0.80 	4 vs. 3 1.48 (1.35–1.62)	5 vs. 3 1.06 (0.99–1.13)	6 vs. 3 1.56 (1.38–1.77)
1 vs. 4 0.64 (0.56–0.72)	2 vs. 4 0.95 (0.89–1.01)	3 vs. 4 0.68 (0.62–0.74)	4. BMI: 27.5 kg/m^2 WHR: 0.92 	5 vs. 4 0.72 (0.65–0.79)	6 vs. 4 1.06 (0.99–1.13)
1 vs. 5 0.89 (0.79–1.01)	2 vs. 5 1.32 (1.15–1.51)	3 vs. 5 0.95 (0.89–1.01)	4 vs. 5 1.40 (1.27–1.54)	5. BMI: 33 kg/m^2 WHR: 0.80 	6 vs. 5 1.48 (1.35–1.62)
1 vs. 6 0.60 (0.51–0.72)	2 vs. 6 0.89 (0.79–1.01)	3 vs. 6 0.64 (0.56–0.72)	4 vs. 6 0.95 (0.89–1.01)	5 vs. 6 0.68 (0.62–0.74)	6. BMI: 33 kg/m^2 WHR: 0.92 

The group of interest versus the referent are shown in the cells above. To interpret the HRs, select an intersection of 2 anthropometric profiles of interest. The HRs and 95% CIs were estimated by statistical models presented in **Appendix Tables 1** and **2** (available at www.annals.org). Courtesy of the Mayo Clinic. BMI = body mass index; HR = hazard ratio; WHR = waist-to-hip ratio.

Our study not only specifically addressed the mortality risk associated with central obesity in persons with normal weight but also compared absolute mortality risk in this group with BMI-defined overweight and obese persons with or without central obesity. We also tested the independence of the association by adjusting for obesity-related cardiovascular risk factors and found that the association between normal-weight central obesity and increased mortality cannot be solely attributed to those risk factors. To our knowledge, our study is the first to show that normal-weight central obesity, measured by WHR, is associated with an increased risk for cardiovascular mortality. Our findings may have significant clinical implications because persons with normal BMI and central obesity were not considered a priority population for prevention programs by guideline developers. Indeed, the 2013 American Heart Association/American College of Cardiology/The Obesity Society guideline on obesity management (9) recommends measuring waist circumference only in persons with elevated BMI and does not recommend calculating WHR at all, thereby implying that persons with normal BMI are free of any particular adiposity-related risk.

Although our study and others have shown that WHR and waist circumference are superior to BMI in the prediction of total and cardiovascular mortality rates (2, 12, 22), other studies show different results (6). Data from Wormser and colleagues (6) showed that WHR, waist circumference, and BMI had similar strengths of association with cardiovascular disease risk only after they accounted for intermediate cardiovascular risk factors between obesity and mortality, such as blood pressure, history of diabetes, and cholesterol values, and analyzed the variables assuming linearity of any association (6). In their secondary analyses, the au-

thors reported that for any given tertile of BMI, measures of central obesity were still related to mortality, even in persons with a BMI of 20 to 24.5 kg/m^2 (6). Our study is based on simultaneous assessment of the influence of individual combinations of BMI and WHR on survival to capture any effect modification that WHR could have at different BMIs. In addition, our study reinforces independent prognostic information about central obesity beyond obesity-related cardiovascular risk factors in persons with normal weight according to BMI.

Our findings have several possible explanations. First, central obesity measured by WHR is associated with visceral fat accumulation and an adverse metabolic profile compared with BMI, which is a measure of both lean and fat mass (23, 24). Indeed, our analysis showed that BMI was only weakly correlated with WHR, which proves that WHR and BMI provide different information. Second, excessive visceral fat is associated with insulin resistance, hypertriglyceridemia, dyslipidemia, and inflammation (25, 26). A higher WHR is associated with decreased muscle mass in the legs (known as sarcopenic adiposity), higher glucose levels, and increased cardiovascular risk (14, 22). Finally, persons who are overweight or obese based on BMI may have larger amounts of subcutaneous fat in the hips and legs—fat linked to healthier metabolic profiles (17). This may explain the unexpected better survival in overweight or obese persons, even among those who were centrally obese.

Our study has various strengths. We used standardized data from a large cohort of participants in a nationally representative sample of the U.S. population, which increased the external validity of our results. Further, WHR is a simple and reliable measure for visceral obesity (22) and was measured simultaneously with BMI in this study population. Nevertheless, several limitations should be recognized, including some that are intrinsic to the NHANES. Information on comorbidities, such as hypertension, diabetes, and dyslipidemia, was

Table 2. Expected Mortality in Men and Women

BMI, *kg/m^2*	Men			Women		
	WHR	5-y Mortality (95% CI), %*	10-y Mortality (95% CI), %*	WHR	5-y Mortality (95% CI), %*	10-y Mortality (95% CI), %*
Age 40 y						
22.0	0.89	1.1 (0.8–1.4)	2.8 (2.1–3.4)	0.80	0.5 (0.4–0.6)	1.5 (1.2–1.8)
	1.00	2.1 (1.6–2.7)	5.1 (4.1–6.6)	0.92	0.7 (0.5–0.9)	2.2 (1.7–2.7)
27.5	0.89	0.9 (0.7–1.2)	2.3 (1.7–2.9)	0.80	0.5 (0.4–0.6)	1.6 (1.3–1.9)
	1.00	1.7 (1.4–2.1)	4.2 (3.4–4.9)	0.92	0.7 (0.6–0.9)	2.3 (1.9–2.8)
33.0	0.89	0.9 (0.5–1.3)	2.2 (1.3–3.2)	0.80	0.5 (0.4–0.7)	1.6 (1.3–2.0)
	1.00	1.6 (1.2–1.9)	3.8 (3.0–4.6)	0.92	0.8 (0.6–1.0)	2.4 (2.0–3.0)
37.0	0.89	0.9 (0.5–1.5)	2.2 (1.2–3.6)	0.80	0.5 (0.4–0.7)	1.7 (1.3–2.1)
	1.00	1.5 (1.2–2.0)	3.8 (2.9–4.9)	0.92	0.8 (0.6–1.0)	2.5 (2.0–3.2)
Age 50 y						
22.0	0.89	2.3 (1.8–2.9)	5.7 (4.5–6.7)	0.80	1.1 (0.8–1.3)	3.3 (2.7–3.9)
	1.00	4.3 (3.5–5.3)	10.3 (8.7–12.5)	0.92	1.6 (1.3–1.9)	4.8 (4.1–5.7)
27.5	0.89	1.9 (1.4–2.5)	4.8 (3.6–5.9)	0.80	1.1 (0.9–1.4)	3.5 (2.9–4.1)
	1.00	3.5 (3.0–4.1)	8.5 (7.4–9.5)	0.92	1.7 (1.4–2.0)	5.1 (4.4–5.9)
33.0	0.89	1.8 (1.2–2.6)	4.4 (2.7–6.3)	0.80	1.2 (0.9–1.5)	3.7 (3.0–4.4)
	1.00	3.2 (2.6–3.8)	7.7 (6.4–9.1)	0.92	1.7 (1.4–2.1)	5.4 (4.6–6.3)
37.0	0.89	1.8 (1.0–3.0)	4.4 (2.4–7.2)	0.80	1.2 (1.0–1.6)	3.8 (3.1–4.7)
	1.00	3.1 (2.5–4.0)	7.6 (6.0–9.6)	0.92	1.8 (1.4–2.3)	5.6 (4.7–6.7)
Age 60 y						
22.0	0.89	4.7 (3.8–5.8)	11.3 (9.3–13.2)	0.80	2.4 (1.9–2.9)	7.3 (6.2–8.3)
	1.00	8.7 (7.2–10.2)	20.1 (17.7–23.6)	0.92	3.5 (3.0–4.1)	10.6 (9.3–11.9)
27.5	0.89	4.0 (2.9–5.0)	9.6 (7.3–11.8)	0.80	2.5 (2.1–3.0)	7.7 (6.7–8.8)
	1.00	7.2 (6.2–8.0)	16.8 (15.0–18.3)	0.92	3.7 (3.2–4.3)	11.2 (10.1–12.3)
33.0	0.89	3.7 (2.4–5.4)	8.9 (5.7–12.7)	0.80	2.7 (2.2–3.2)	8.1 (6.9–9.5)
	1.00	6.5 (5.4–7.7)	15.3 (12.9–17.5)	0.92	3.9 (3.3–4.6)	11.8 (10.4–13.2)
37.0	0.89	3.7 (2.1–6.2)	9.0 (4.9–14.3)	0.80	2.8 (2.2–3.5)	8.5 (6.9–10.1)
	1.00	6.4 (5.1–8.3)	15.0 (12.2–18.3)	0.92	4.1 (3.3–5.0)	12.2 (10.5–14.1)
Age 70 y						
22.0	0.89	9.6 (7.7–11.7)	21.9 (18.2–25.7)	0.80	5.3 (4.3–6.3)	15.7 (13.5–17.8)
	1.00	17.1 (14.4–20.0)	36.6 (32.8–41.3)	0.92	7.7 (6.7–9.0)	22.2 (20.0–24.3)
27.5	0.89	8.1 (5.9–10.2)	18.7 (14.3–22.9)	0.80	5.6 (4.6–6.6)	16.5 (14.2–18.5)
	1.00	14.2 (12.4–16.0)	31.3 (28.4–33.9)	0.92	8.2 (7.1–9.4)	23.3 (21.5–25.0)
33.0	0.89	7.5 (4.9–10.8)	17.5 (11.4–24.9)	0.80	5.9 (4.7–7.2)	17.3 (14.6–19.9)
	1.00	12.9 (10.7–15.4)	28.7 (24.6–32.7)	0.92	8.6 (7.4–10.0)	24.4 (22.0–26.8)
37.0	0.89	7.5 (4.4–12.5)	17.6 (9.8–27.5)	0.80	6.2 (4.8–7.8)	18.0 (14.6–21.2)
	1.00	12.7 (10.2–16.4)	28.4 (23.3–34.4)	0.92	8.9 (7.4–10.8)	25.2 (22.0–28.5)

BMI = body mass index; WHR = waist-to-hip ratio.
* CI estimated using bootstrap methods.

self-reported by participants, which can potentially lead to error. Waist circumference was measured using a technique different from the one suggested by the World Health Organization or scientific societies. Thus, our results may not apply to studies that assessed WHR using other techniques. We cannot exclude misclassification bias related to changes in weight and WHR during follow-up. However, it is a widely accepted strategy in epidemiologic studies to use baseline measures, including exposure and confounding variables. In addition, information on body fat distribution was based on anthropometric indicators alone, such as WHR. Imaging data of adipose tissue would provide additional information but were not collected in NHANES III. Finally, we cannot exclude misclassification related to measurement errors in our exposure variables, such as WHR and BMI.

Our findings suggest that persons with normal-weight central obesity may represent an important target population for lifestyle modification and other preventive strategies. Future studies should focus on identifying factors associated with the development of normal-weight central obesity and better understanding the effect of normal-weight central obesity on health outcomes. Until such data are available, the use of BMI with measures of central obesity may provide better adiposity-related risk factor stratification in clinical practice than either method alone.

From the Mayo Clinic, Rochester, Minnesota; St. Anne's University Hospital Brno, Brno, Czech Republic; and University of Ottawa Heart Institute, Ottawa, Ontario, Canada.

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Requests for Single Reprints: Francisco Lopez-Jimenez, MD, MS, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905; e-mail, lopez@mayo.edu.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Sahakyan, Somers, Rodriguez-Escudero, Sochor, Roger, Singh, and Lopez-Jimenez: Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905.
Mr. Hodge and Dr. Carter: Division of Biomedical Statistics and Informatics, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905.
Dr. Coutinho: University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario K1Y 4W7, Canada.
Dr. Jensen: Division of Endocrinology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905.

Author Contributions: Conception and design: K.R. Sahakyan, J.P. Rodriguez-Escudero, R.E. Carter, T. Coutinho, F. Lopez-Jimenez.
Analysis and interpretation of the data: K.R. Sahakyan, V.K. Somers, D.O. Hodge, R.E. Carter, O. Sochor, T. Coutinho, M.D. Jensen, V.L. Roger, P. Singh, F. Lopez-Jimenez.
Drafting of the article: K.R. Sahakyan, V.K. Somers, J.P. Rodriguez-Escudero, R.E. Carter, P. Singh, F. Lopez-Jimenez.
Critical revision of the article for important intellectual content: K.R. Sahakyan, V.K. Somers, J.P. Rodriguez-Escudero, D.O. Hodge, R.E. Carter, O. Sochor, T. Coutinho, M.D. Jensen, V.L. Roger, P. Singh, F. Lopez-Jimenez.
Final approval of the article: K.R. Sahakyan, V.K. Somers, J.P. Rodriguez-Escudero, R.E. Carter, T. Coutinho, M.D. Jensen, P. Singh, F. Lopez-Jimenez.
Provision of study materials or patients: F. Lopez-Jimenez.
Statistical expertise: D.O. Hodge, R.E. Carter, F. Lopez-Jimenez.
Obtaining of funding: V.L. Roger.
Administrative, technical, or logistic support: V.K. Somers, P. Singh, F. Lopez-Jimenez.
Collection and assembly of data: R.E. Carter.

Appendix Table 1. Final Cox Proportional Hazards Models: Total Mortality Predictors

Predictor	Men			Women		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age	1.08	1.07–1.08	<0.001	1.09	1.08–1.09	<0.001
Smoking history*	1.36	1.18–1.58	<0.001	1.45	1.29–1.63	<0.001
White race†	1.43	0.75–2.73	0.27	1.41	0.85–2.35	0.18
African American race†	2.04	1.05–3.98	0.04	1.52	0.89–2.56	0.12
<12 y of school completed‡	1.56	1.26–1.94	0.001	1.58	1.30–1.93	<0.001
12 y of school completed‡	1.39	1.19–1.63	<0.001	1.16	0.98–1.39	0.10
BMI§	0.97	0.94–1.01	0.20	1.01	1.00–1.02	0.08
WHR‖ (0.1 change)	1.70	1.35–2.14	<0.001	1.38	1.28–1.50	<0.001
BMI × WHR¶ interaction	0.96	0.73–1.27	0.96	–	–	–
BMI^2	1.002	1.000–1.003	0.02	–	–	–
WHR^2 (0.01 change)	0.92	0.88–0.97	0.002	–	–	–
$BMI^2 \times WHR^2$¶ interaction	1.03	1.00–1.06	0.03	–	–	–

BMI = body mass index; HR = hazard ratio; WHR = waist-to-hip ratio.
* Smoking variable was treated in the model as continuous, using 0 as never smoked, 1 as former smoker, and 2 as current smoker.
† Other race was used as the reference value.
‡ Education reference value was >12 y of school completed.
§ Centered at 27 kg/m^2.
‖ Centered at 0.92.
¶ Interaction terms allow for relationships sensitive to change in risk based on combinations of WHR and BMI.

Appendix Table 2. Final Cox Proportional Hazards Models: Cardiovascular Mortality

Predictor	Men			Women		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age	1.10	1.09–1.11	<0.001	1.10	1.09–1.12	<0.001
Smoking history*	1.46	1.22–1.76	0.001	1.28	1.10–1.49	<0.002
White race†	1.71	0.59–4.98	0.32	2.75	0.70–10.90	0.15
African American race†	2.24	0.71–7.07	0.17	3.00	0.71–12.60	0.13
<12 y of school completed‡	1.37	1.01–1.87	0.05	1.49	1.13–1.96	0.005
12 y of school completed‡	1.30	0.99–1.71	0.06	1.14	0.86–1.51	0.35
BMI§	1.02	0.99–1.05	0.29	1.00	0.98–1.02	0.92
WHR (0.1 change)‖	1.63	1.19–2.22	0.003	1.79	0.99–1.00	<0.001
WHR^2 (0.01 change)‖	0.89	0.81–0.98	0.02	0.79	0.70–0.91	0.002

BMI = body mass index; HR = hazard ratio; WHR = waist-to-hip ratio.
* Smoking variable was treated in the model as continuous, using 0 as never smoked, 1 as former smoker, and 2 as current smoker.
† Other race was used as the reference value.
‡ Education reference value was >12 y of school completed.
§ Centered at 27 kg/m^2.
‖ Centered at 0.92.