

The Importance of Waist Circumference in the Definition of Metabolic Syndrome

Prospective analyses of mortality in men

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OBJECTIVE — The purpose of this study was to compare the predictive ability of the National Cholesterol Education Panel (NCEP), revised NCEP (NCEP-R), and International Diabetes Federation (IDF) metabolic syndrome criteria for mortality risk, and to examine the effects of waist circumference on mortality within the context of these criteria.

RESEARCH DESIGN AND METHODS — The sample included 20,789 white, non-Hispanic men 20–83 years of age from the Aerobics Center Longitudinal Study. The main outcome measures were all-cause and cardiovascular disease (CVD) mortality over 11.4 years of follow-up.

RESULTS — The proportions of men with the metabolic syndrome were 19.7, 27, and 30% at baseline, according to NCEP, NCEP-R, and IDF criteria. A total of 632 deaths (213 CVD) occurred. The relative risks (RRs) and 95% CIs of all-cause mortality were 1.36 (1.14–1.62), 1.31 (1.11–1.54), and 1.26 (1.07–1.49) for the NCEP, NCEP-R, and IDF definitions, respectively. The corresponding RRs for CVD mortality were 1.79 (1.35–2.37), 1.67 (1.27–2.19), and 1.67 (1.27–2.20). Additionally, there was a significant trend for a higher risk of CVD mortality across waist circumference categories (<94, 94–102, and >102 cm) among men with at least two additional metabolic syndrome risk factors ($P = 0.01$).

CONCLUSIONS — The prediction of mortality with IDF and NCEP metabolic syndrome criteria was comparable in men. Waist circumference is a valuable component of metabolic syndrome; however, the IDF requirement of an elevated waist circumference warrants caution given that a large proportion of men with normal waist circumference have multiple risk factors and an increased risk of mortality.

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Individuals with metabolic syndrome are at increased risk of all-cause and cardiovascular disease (CVD) mortality (1–3). Over the last decade several clinical criteria for metabolic syndrome have been developed (4–6). Clinically defined metabolic syndrome criteria were proposed by the National Cholesterol Education Program (NCEP) (5) and were subsequently revised (NCEP-R) (7) by lowering

the threshold for blood glucose to correspond to the impaired fasting glucose cut-off of the American Diabetes Association (8). Most recently, the International Diabetes Federation (IDF) proposed consensus criteria for identification of metabolic syndrome (9). The IDF definition builds upon the NCEP-R criteria, but differs in two key aspects. First, the IDF has lowered the threshold for waist circumfer-

ence from 102 to 94 cm. Second, waist circumference is a required component of metabolic syndrome under the IDF criteria, rather than an optional component as used by the NCEP. Previous studies have shown that using a lower waist circumference threshold within the context of metabolic syndrome increases the prevalence, but decreases the risk of mortality (1) and type 2 diabetes (10). However, the effects of establishing waist circumference as a required versus an optional component of metabolic syndrome are unknown.

Given the high and increasing prevalence of metabolic syndrome in North America (11,12), the effects of including waist circumference as a mandatory component of metabolic syndrome has important implications that require further evaluation. Thus, the purpose of this study was twofold. First, the impact of the NCEP, NCEP-R, and IDF definitions of metabolic syndrome on all-cause and CVD mortality in men was examined. Second, the effects of waist circumference within the context of metabolic syndrome on the risk of all-cause and CVD mortality were determined.

RESEARCH DESIGN AND METHODS

Two samples were used to accomplish the aims. First, the relative risks (RRs) of mortality associated with metabolic syndrome were estimated in the Aerobics Center Longitudinal Study (ACLS). Second, population prevalences of metabolic syndrome were obtained from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) to estimate the impact of metabolic syndrome on the population.

ACLS

The sample included 20,789 men 20–83 years of age. All participants attended the Cooper Clinic in Dallas, Texas, for clinical evaluations between 1979 and 1997. The sample was well educated (~75% college graduates) and consisted of non-Hispanic whites. All participants provided their informed consent to participate in the clinical examination and subsequent

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Abbreviations: ACLS, Aerobics Center Longitudinal Study; CVD, cardiovascular disease; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Panel; NCEP-R, revised NCEP; NHANES, National Health and Nutrition Examination Survey; PAF, population-attributable fraction.

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

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Table 1—Descriptive baseline characteristics of 20,879 men 20–83 years of age from the ACLS across categories of NCEP, NCEP-R, and IDF definitions of the metabolic syndrome

| | Entire cohort | NCEP | | NCEP-R | | IDF | |
|---------------------------------|---------------|---------------|--------------|--------------|--------------|--------------|--------------|
| | | No | Yes | No | Yes | No | Yes |
| n (%) | 20,789 (100) | 16,692 (80.3) | 4,097 (19.7) | 15,194 (73) | 5,595 (27) | 14,546 (70) | 6,243 (30) |
| Age (years) | 43.3 ± 9.7 | 42.6 ± 9.7 | 46.2 ± 9.4 | 42.4 ± 9.6 | 45.8 ± 9.5 | 42.2 ± 9.7 | 45.9 ± 9.3 |
| BMI (kg/m ²) | 26.4 ± 3.6 | 25.6 ± 2.9 | 29.8 ± 4.1 | 25.4 ± 2.8 | 29.2 ± 4.1 | 25.1 ± 2.8 | 29.5 ± 3.5 |
| Waist circumference (cm) | 93.9 ± 10.6 | 91.4 ± 8.8 | 104.3 ± 11.0 | 90.7 ± 8.4 | 102.5 ± 11.1 | 89.7 ± 8.3 | 103.8 ± 8.6 |
| Systolic blood pressure (mmHg) | 120.3 ± 12.8 | 118.5 ± 12.1 | 127.9 ± 12.9 | 118.0 ± 11.9 | 126.6 ± 13.0 | 118.0 ± 11.9 | 125.7 ± 13.1 |
| Diastolic blood pressure (mmHg) | 80.6 ± 9.3 | 79.1 ± 8.8 | 86.8 ± 8.9 | 78.7 ± 8.7 | 85.7 ± 9.2 | 78.7 ± 8.7 | 85.1 ± 9.3 |
| HDL cholesterol (mmol/l) | 1.17 ± 0.30 | 1.22 ± 0.29 | 0.93 ± 0.21 | 1.24 ± 0.29 | 0.96 ± 0.22 | 1.24 ± 0.30 | 1.01 ± 0.25 |
| Triglycerides (mmol/l) | 1.51 ± 0.94 | 1.27 ± 0.70 | 2.52 ± 1.09 | 1.20 ± 0.64 | 2.36 ± 1.08 | 1.22 ± 0.68 | 2.19 ± 1.09 |
| Glucose (mmol/l) | 5.63 ± 0.90 | 5.49 ± 0.63 | 6.17 ± 1.45 | 5.46 ± 0.64 | 6.08 ± 1.25 | 5.47 ± 0.70 | 6.00 ± 1.16 |

Data are means ± SD unless otherwise indicated.

mortality follow-up, and all study protocols were reviewed annually by the Cooper Institute Institutional Review Board.

Clinical examination

All participants underwent a clinical examination after fasting for at least 12 h. Waist circumference was measured at the level of the umbilicus, and systolic and diastolic blood pressures were obtained with a mercury sphygmomanometer using auscultatory methods. A fasting blood sample was obtained, and concentrations of triglycerides, HDL cholesterol, and glucose were assayed using automated techniques at the Cooper Clinic Laboratory, which participates in and meets the standards of the Centers for Disease Control and Prevention Lipid Standardization Program.

Definitions of metabolic syndrome

According to the NCEP definition, metabolic syndrome is present if a man has three or more of the following: high waist circumference values (>102 cm), high triglyceride levels (≥ 1.69 mmol/l), low HDL cholesterol levels (<1.04 mmol/l), elevated blood pressure ($\geq 130/85$ mmHg), and elevated glucose values (≥ 6.1 mmol/l) (5). Men were also classified with a revised definition (NCEP-R) which uses a glucose threshold of 5.6 mmol/l (12) to correspond to the American Diabetes Association definition of impaired fasting glucose (7). According to the IDF definition, metabolic syndrome is present if a man has a waist circumference ≥ 94 cm in addition to two or more of the following: high triglyceride level, low HDL cholesterol level, elevated blood pressure, and elevated glucose value (8). In addition to the clinical criteria, men who indicated a history of hypertension

or diabetes were classified as having elevated blood pressure and glucose, respectively, for all three metabolic syndrome definitions.

Covariates

Information about cigarette smoking, alcohol consumption, and parental history of CVD was collected using a medical history questionnaire. Parental history of CVD was coded as a dichotomous variable (0 = no history, 1 = either parent had a stroke or coronary event before the age of 50 years). Smoking status was categorized as never, former, or current. Alcohol consumption was coded as none, light (<15 units/week), moderate (15–30 units/week), or heavy (>30 units/week). One unit of alcohol was defined as one bottle or can of beer, a glass of wine, or one shot of hard liquor.

Individuals who indicated a history of CHD, stroke, or cancer on the medical history questionnaire were excluded from the analyses. However, men with an indication of CVD at the baseline examination were retained and coded as 0 (no indication of CVD) and 1 (possible indication of CVD). Indications of possible CVD were an abnormal electrocardiogram at rest or during exercise (6.2% of sample) or failure to achieve at least 85% of age-predicted maximal heart rate ($220 - \text{age}$) during an exercise treadmill test (2.7% of sample).

Mortality surveillance

Participants were followed until death or until 31 December 1998 in the case of survivors. Deaths were identified using the National Death Index and causes of death were determined from death certificates obtained from the departments of vital statistics in the states of decedents. A

nosologist coded the death certificates for the underlying and up to four contributing causes of death, and CVD mortality was defined as codes 390–449.9 of the ICD-9. All analyses were limited to participants with at least 1 year of follow-up.

Statistical analysis

Cox regression was used to estimate the RR of mortality associated with the NCEP, NCEP-R, and IDF definitions of metabolic syndrome. Age, year of examination, smoking status, alcohol consumption, parental history of CVD, and possible CVD at baseline were included as covariates in multivariable models. To examine the effects of waist circumference on mortality within the context of metabolic syndrome, the sample was divided into groups by waist circumference (<94, 94–102, and >102 cm) and by the presence or absence of two or more additional metabolic syndrome risk factors. Mortality rates per 10,000 man-years of follow-up are reported as adjusted by Cox regression for age and year of examination. The ability of metabolic syndrome criteria to predict 10-year all-cause and CVD mortality was compared using C statistics derived from logistic regression, including age and year and examination as covariates and then adding smoking status, alcohol consumption, parental history of CVD, and possible CVD at baseline as covariates in multivariable models. The C statistic is equivalent to the Wilcoxon two-sample statistic for comparing the locations of event and nonevent distributions. All analyses were conducted using SAS software (SAS Institute, Cary, NC).

NHANES

NHANES is the most recent population health survey that measures metabolic

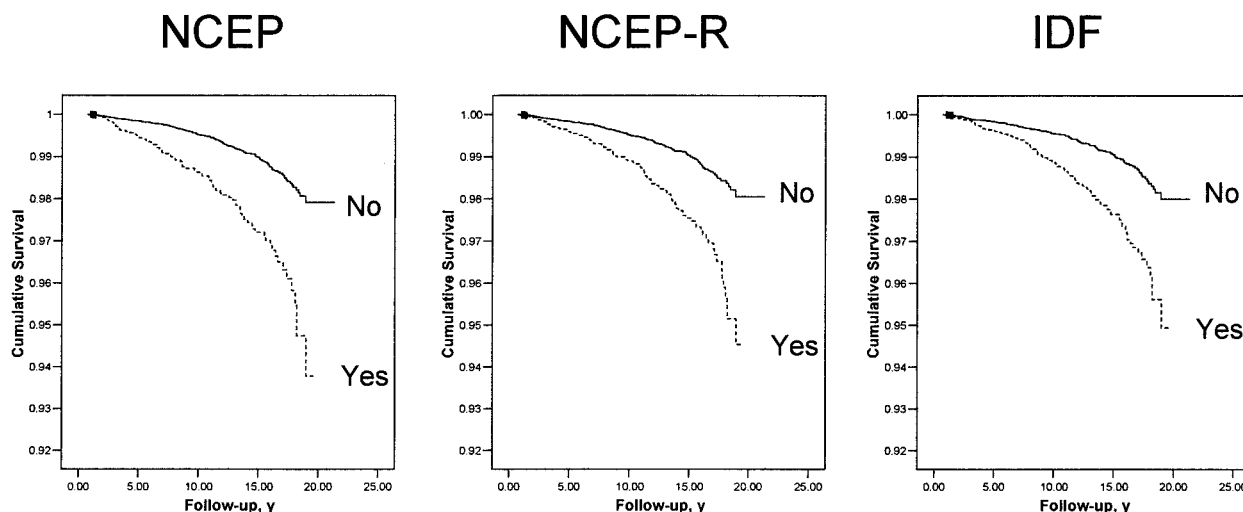


Figure 1—Unadjusted Kaplan-Meier hazard curves for CVD mortality among 20,789 men 20–83 years of age from the ACLS.

syndrome risk factors. NHANES uses a multistage, stratified, and weighted sampling design to select participants who are representative of the civilian noninstitutionalized U.S. population. Complete details of the survey design and strategy are available elsewhere (13). To estimate the impact of metabolic syndrome on the population, data from NHANES (1999–2002) were used to calculate prevalences of metabolic syndrome.

The current analysis was limited to 1,957 men aged 18+ years who had fasted for at least 8 h. A detailed explanation of the NHANES protocols is found elsewhere (13). The population-attributable fractions (PAFs) ($= [P(RR - 1)]/[1 + P(RR - 1)]$) associated with the three definitions of metabolic syndrome were calculated from the RRs obtained from the ACLS cohort and the population prevalences (P) from NHANES.

RESULTS— Table 1 presents the characteristics of the ACLS sample. The proportions of men with metabolic syndrome in the ACLS cohort were 19.7, 27, and 30%, according to NCEP, NCEP-R, and IDF criteria, respectively. Over an average of 11.4 years of follow-up there were 632 deaths (213 from CVD). The unadjusted Kaplan-Meier curves according to the three metabolic syndrome definitions are presented in Fig. 1 for CVD mortality, and Table 2 presents the RR of mortality associated with metabolic syndrome. In the multivariable models, the RRs (95% CIs) of all-cause mortality were 1.36 (1.14–1.62), 1.31 (1.11–1.54), and 1.26 (1.07–1.49) for the NCEP, NCEP-R, and IDF definitions, respectively. The corresponding values for CVD mortality were 1.79 (1.35–2.37), 1.67 (1.27–2.19), and 1.67 (1.27–2.20), respectively. The prevalences of NCEP, NCEP-R, and IDF

definitions of metabolic syndrome in NHANES were 24.3, 32.4, and 38.6%, respectively. The corresponding PAF using the RRs from the ACLS and the prevalences from NHANES for the NCEP, NCEP-R, and IDF definitions are 8, 9.1, and 9.1%, respectively, for all-cause and 16.1, 17.8, and 20.5%, respectively, for CVD mortality.

The C statistic for predicting 10-year all-cause mortality was 0.755 for all three of the NCEP, NCEP-R, and IDF criteria, from logistic regression models including age and year of examination. The C statistics were 0.769, 0.768, and 0.768 for the NCEP, NCEP-R, and IDF criteria, respectively, from the multivariable models. The corresponding values for CVD mortality were 0.802, 0.795, and 0.799, respectively, from models including age and year of examination and 0.821, 0.817, and 0.817 from the multivariable models.

Table 2—Relative risks of all-cause and CVD mortality associated with the NCEP, NCEP-R, and IDF definitions of the metabolic syndrome in 20,789 men 20–83 years of age from the ACLS

| | n | No. deaths (CVD) | Man-years of follow-up | All-cause mortality | | CVD mortality | |
|---------------|--------|------------------|------------------------|---------------------|------------------|------------------|------------------|
| | | | | RR (95% CI)* | RR (95% CI)† | RR (95% CI)* | RR (95% CI)† |
| NCEP | | | | | | | |
| No | 16,692 | 449 (134) | 193,748 | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) |
| Yes | 4,097 | 183 (79) | 43,063 | 1.46 (1.23–1.74) | 1.36 (1.14–1.62) | 2.03 (1.54–2.69) | 1.79 (1.35–2.37) |
| NCEP-R | | | | | | | |
| No | 15,194 | 399 (118) | 177,515 | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) |
| Yes | 5,595 | 233 (95) | 59,296 | 1.41 (1.21–1.67) | 1.31 (1.11–1.54) | 1.89 (1.44–2.47) | 1.67 (1.27–2.19) |
| IDF | | | | | | | |
| No | 14,546 | 385 (112) | 170,780 | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) |
| Yes | 6,243 | 247 (101) | 66,030 | 1.36 (1.16–1.60) | 1.26 (1.07–1.49) | 1.86 (1.42–2.44) | 1.67 (1.27–2.20) |

*Adjusted for age and year of examination. †Adjusted for age, year of examination, smoking, alcohol consumption, parental history of premature CVD, and possible CVD at baseline.

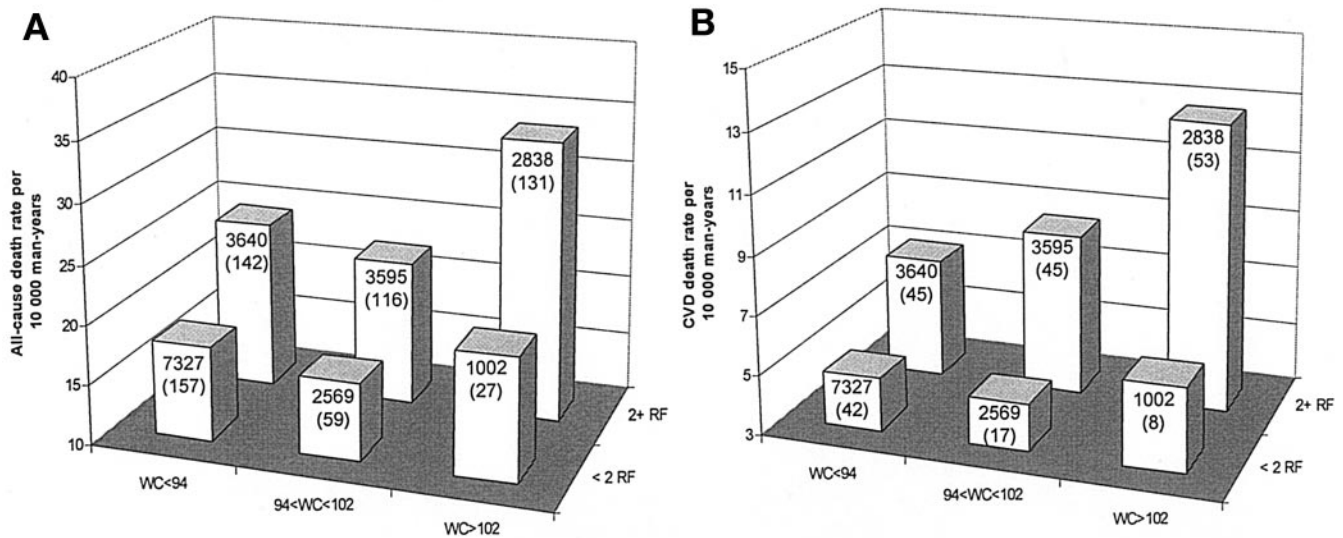


Figure 2—All-cause (A) and CVD (B) death rates according to categories of waist circumference (WC) and the presence or absence of two or more other metabolic syndrome risk factors. Death rates are adjusted for age and year of examination. Sample size number is shown in the bars, with number of deaths indicated in parentheses.

These results indicate that the predictive ability of the three metabolic syndrome criteria were quite similar.

All-cause and CVD death rates across waist circumference and risk factor categories are illustrated in Fig. 2, adjusted for age and year of examination. Approximately one-third of the men with a waist circumference <94 cm ($n = 10,967$) had two or more other metabolic syndrome risk factors ($n = 3,640$), whereas approximately one-fourth of the men with a waist circumference >102 cm ($n = 3,840$) had less than two metabolic syndrome risk factors ($n = 1,002$). All-cause and CVD death rates were higher in men with two or more additional risk factors, regardless of waist circumference level. There was a significant trend for higher all-cause ($P = 0.01$) and CVD ($P = 0.005$) mortality rates across waist circumference categories in men with two or more additional risk factors, but not for men with less than two risk factors. Men with a waist circumference <94 cm and two or more additional risk factors (RR = 1.29 [95% CI 1.03–1.63]) and men with a waist circumference >102 cm and two or more risk factors (1.68 [1.33–2.13]) had an elevated RR of all-cause mortality by comparison to men with a waist circumference <94 cm and less than two risk factors. For CVD mortality, the elevated RR of mortality was restricted to men with waist circumference between 94 and 102 cm (1.57 [1.03–2.39]) and >102 cm (2.31 [1.53–3.48]) with two or more additional risk factors. The trend

across waist circumference categories in the multivariable models was significant for CVD mortality ($P = 0.01$), but not for all-cause mortality ($P = 0.06$). The RR of CVD mortality in men with a waist circumference <94 cm and two or more risk factors was elevated but not statistically significant (1.38 [0.90–2.12]).

CONCLUSIONS— There is currently debate as to whether metabolic syndrome increases the risk of adverse health outcomes beyond the risk associated with the individual component risk factors (14–16). The existing diagnostic criteria for metabolic syndrome arose from deliberations of panels of experts rather than from the results of prospective epidemiological studies or an evidence-based process (16). Thus, studies are required to determine the effectiveness of metabolic syndrome at predicting health outcomes, albeit in a post hoc manner, to refine the clinical definitions and to either provide support for their use or discontinue their use. The results of this study demonstrate a higher risk of mortality associated with metabolic syndrome in white, non-Hispanic men and provide support for a role for waist circumference in the clinical criteria for metabolic syndrome. Although the prevalence of metabolic syndrome using the IDF criteria was about 50% higher than that with the original NCEP criteria, the predictive ability of the IDF and NCEP criteria were comparable. However, the requirement in the

IDF criteria that waist circumference be at least 94 cm warrants caution because approximately one-third of the men with a waist circumference <94 cm had multiple risk factors and a high risk of mortality.

A recent review and meta-analysis by Ford (17) indicated that the PAF associated with NCEP metabolic syndrome is about 6% for all-cause and 12% for CVD mortality. The PAF estimates from the present study range from 8 to 9.1% for all-cause and from 16.1 to 20.5% for CVD mortality for the three definitions of metabolic syndrome. A more recent analysis from the Hoorn Study compared several definitions of metabolic syndrome in the prediction of CVD and found that metabolic syndrome doubled the risk of incident CVD; however, there were minimal differences across metabolic syndrome definitions (18). These observations suggest that the public health burden associated with metabolic syndrome is substantial regardless of the metabolic syndrome criteria used.

It is not surprising that the prevalence of metabolic syndrome using the IDF criteria was ~50% higher than that using NCEP criteria, given the lower glucose and waist circumference thresholds. However, despite the higher prevalence, the predictive ability (C statistic) of IDF and NCEP definitions for mortality were similar. The IDF metabolic syndrome criteria identified a larger subset of the population that is at increased risk of mortality. On the other hand, because the IDF definition of metabolic syndrome re-

quires a waist circumference ≥ 94 cm, it failed to identify a substantial number of subjects at high mortality risk. Indeed, 8% of the population had multiple risk factors despite having a waist circumference < 94 cm. Together these observations suggest that lowering the glucose and waist circumference values within the metabolic syndrome context is beneficial for identifying men at risk; however, the optimal waist circumference threshold remains to be determined.

A novel aspect of this study was the analyses of waist circumference thresholds in the presence or absence of two or more other metabolic syndrome risk factors. The principal finding was twofold. First, the rate of CVD mortality increased across waist circumference categories in men with two or more other metabolic syndrome risk factors. Second, in the absence of multiple risk factors, risk did not increase across waist circumference categories. The results provide support for a valuable role for waist circumference in the clinical definition of metabolic syndrome; however, it is apparent that a high waist circumference value in the absence of additional risk factors may not indicate increased mortality risk. This is consistent with reports suggesting that the combination of high waist circumference value and high triglyceride level is a better predictor of CVD than either alone (19). These findings reinforce the recommendation that clinicians obtain all metabolic syndrome criteria to properly interpret the health risks associated with an elevated waist circumference.

The mechanisms whereby waist circumference is associated with risk in the presence of other risk factors are unclear. It is possible that waist circumference acts as a marker for risk factors not measured in this study (physical inactivity, insulin resistance, C-reactive protein, and others). Together these findings reinforce the notion that reductions in waist circumference should be a primary aim of strategies designed to reduce health risks associated with metabolic syndrome. Given that exercise is associated with substantial reductions in waist circumference (20–22), and that cardiorespiratory fitness significantly attenuates the mortality risk associated with metabolic syndrome (23), it is reasonable to suggest that physical activity be a cornerstone of strategies designed to treat metabolic syndrome.

There are several strengths and limitations of this study. A marked strength is the use of a large sample of men for whom

an extensive battery of measurements were obtained, which allowed the classification of metabolic syndrome under NCEP, NCEP-R, and IDF criteria. The predominantly white, middle-to-upper class sample of men limits the generalizability of the results; however, the homogenous nature of the sample ensures control over factors such as ethnicity and socioeconomic status. The use of NHANES to obtain national estimates of the prevalence of metabolic syndrome in men is also a strength of this study. However, further research is required to confirm these findings in women and in other ethnic and socioeconomic groups.

In summary, men with metabolic syndrome have a higher risk of all-cause and CVD mortality by comparison with men without metabolic syndrome. The results suggest that IDF metabolic syndrome criteria will identify a larger segment of the population at increased mortality risk than NCEP metabolic syndrome criteria. However, the IDF requirement that waist circumference be at least 94 cm warrants caution because a large segment of the population with multiple risk factors and at increased mortality risk have waist circumference values < 94 cm. The optimal waist circumference threshold value for predicting mortality within the context of the metabolic syndrome needs to be determined.

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