Metabolic Syndrome, Obesity, and Mortality

Impact of cardiorespiratory fitness

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OBJECTIVE — To determine in normal weight, overweight, and obese men the risk of all-cause and cardiovascular disease (CVD) mortality associated with the metabolic syndrome (MetS) and the influence of cardiorespiratory fitness (CRF).

RESEARCH DESIGN AND METHODS — This observational cohort study included 19,173 men who underwent a clinical examination, including a maximal exercise test. MetS was defined according to National Cholesterol Education Program guidelines.

RESULTS — At baseline 19.5% of the men had MetS. The ORs of the metabolic syndrome at baseline were 4.7 (95% CI 4.2–5.3) in overweight and 30.6 (26.7–35.0) in obese men compared with normal weight men. A total of 477 deaths (160 CVD) occurred in 10.2 years of follow-up. The risks of all-cause mortality were 1.11 (0.75–1.17) in normal weight, 1.09 (0.82–1.47) in overweight, and 1.55 (1.14–2.11) in obese men with MetS compared with normal weight healthy men. The corresponding risks for CVD mortality were 2.06 (0.92–4.63) in normal weight, 1.80 (1.10–2.97) in overweight, and 2.83 (1.70–4.72) in obese men with the MetS compared with normal weight healthy men. After the inclusion of CRF in the model, the risks associated with obesity and MetS were no longer significant.

CONCLUSIONS — Obesity and MetS are associated with an increased risk of all-cause and CVD mortality; however; these risks were largely explained by CRF.

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The metabolic syndrome (MetS) is a constellation of hypertension, dyslipidemia, and diabetes risk factors that cluster within individuals. It is currently recommended that individuals with MetS be targeted for therapeutic lifestyle changes, which consist mainly of increases in physical activity and improvements in diet (1,2). The aggressive treatment of MetS is important because it is associated with an increased risk of type 2 diabetes (3,4), cardiovascular disease (CVD) (3,5), and premature mortality (5–7).

It is commonly observed that the probability of having metabolic abnormalities, including MetS, increases with the level of obesity. For example, by comparison with normal weight men, the odds of having MetS ranged from 5.2 to 25.2 to 67.7 times across overweight, moderately obese, and severely obese men in the National Health and Nutrition Examination Survey III (NHANES III) (8). It is also known that the risk of having MetS is higher in those with lower levels of cardiorespiratory fitness (CRF) (9,10) and that overweight and obese individuals have lower levels of CRF than normal weight individuals (11,12). Further, recent studies have demonstrated that physically fit men and women, as compared with physically unfit men and women, have a lower amount of total and abdominal fat for a given BMI (13–15). Thus, CRF may play an important role in explaining the increased risk of morbidity and mortality associated with MetS across levels of body weight.

To our knowledge no studies have examined differences in the risk of mortality due to MetS across normal weight, overweight, and obese categories. We have previously reported on the usefulness of CRF as a predictor of mortality in men with and without MetS (16). Here we examine differences in the risk of all-cause and CVD mortality among normal weight, overweight, and obese men with and without MetS, as well as the effect of CRF on the observed relationships. For the purpose of this study, we used the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (1) criteria for MetS.

RESEARCH DESIGN AND METHODS

— The sample included 19,173 men 20–83 years of age (average 43.1 ± 9.7 years) from the Aerobics Center Longitudinal Study (ACLS) who had complete data for CRF, body weight status, and the components of MetS. All participants attended the Cooper Clinic in Dallas, Texas, for clinical evaluations between 1979 and 1995. Baseline data collection for the ACLS began in 1970; however, all required measurements for diagnosing MetS were obtained begin-

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Abbreviations: ACLS, Aerobics Center Longitudinal Study; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; ECG, electrocardiogram; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; NIH, National Institutes of Health.

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

ning in 1979. The sample was restricted to men with a BMI of ≥18.5 kg/m^2 and no history of coronary heart disease, stroke, or cancer at the time of the baseline clinical examination. The sample as a whole was well educated (~75% were college graduates) and consisted of predominantly non-Hispanic whites. All participants provided their informed consent to participate in the clinical examination and follow-up study. All study protocols were approved annually by The Cooper Institute Institutional Review Board.

Clinical examination

The clinical evaluation included a medical history questionnaire, physical examination, electrocardiogram (ECG), phlebotomy, anthropometric and blood pressure measurements, and a maximal exercise test. All clinical measurements were made in the morning following at least a 12-h fast.

Definition of exposure variables

The three main exposure variables considered in this study were the presence or absence of MetS, BMI status (normal weight, overweight, or obese), and CRF level. All exposures were evaluated at the baseline clinic visit.

MetS

MetS was diagnosed using the criteria recommended by the NCEP Adult Treatment Panel III (1), which include the presence of at least three of the following risk factors: high blood pressure (≥130/80 mmHg), central obesity (waist circumference >102 cm), high triglycerides (≥1.69 mmol/l), low HDL cholesterol (<1.04 mmol/l), and high fasting plasma glucose level (≥6.1 mmol/l) (1). Waist circumference was obtained at the level of the umbilicus with a plastic anthropometric tape. Systolic and diastolic blood pressures were obtained with a mercury sphygmomanometer and auscultory methods following the American Heart Association protocol (17). A fasting blood sample was obtained by venipuncture, and serum triglycerides, HDL cholesterol, and plasma glucose were assayed with automated techniques at the Cooper Clinic Laboratory, which participates in and meets the quality control standards of the U.S. Centers for Disease Control and Prevention Lipid Standardization Program.

Men with normal blood pressure or fasting plasma glucose at the clinical evaluation who indicated a history of physician-diagnosed hypertension (n = 859) or type 2 diabetes (n = 32) were also coded as positive for these risk factors, which increased the number of men with MetS by 208 (from 3,537 with MetS but without hypertension or diabetes). The results obtained when these men were excluded from all analyses were virtually identical to those reported here.

BMI status

Body mass and stature were measured using a standard physician's scale and stadiometer, and the BMI (kg/m^2) was calculated. Participants were classified as normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), or obese (≥30 kg/m^2) following the recommendations of the U.S. National Institutes of Health (18).

CRF

CRF was assessed by a maximal exercise test on a treadmill using a modified Balke protocol (19). Participants began walking at 88 m/min (3.3 miles/h) with no elevation. After the 1st minute, the incline was increased to 2% then by 1% each minute thereafter until the 25th minute. For men still able to continue the test beyond the 25th minute, the speed was increased by 5.4 m/min (0.2 miles/h) each minute until exhaustion or the test was terminated by the supervising physician for medical reasons. Time to completion of the treadmill test using this protocol is highly correlated (r = 0.92) with measured maximal oxygen uptake ($V\mathrm{O}_{2\mathrm{max}}$) (20). Time to completion on the treadmill was used to estimate $V\mathrm{O}_{2\mathrm{max}}$ in metabolic equivalents (METs) (one MET = 3.5 ml $\mathrm{O}_2 \cdot \mathrm{kg}^{-1} \cdot \mathrm{min}^{-1}$) from the Balke protocol using the following formula: $V\mathrm{O}_{2\mathrm{max}}$ = [1.44 × (minutes on treadmill) + 14.99]/3.5 (20).

Covariates

Individuals who indicated a personal history of coronary heart disease, stroke, or cancer at the baseline examination were excluded from the analyses. However, those with an indication of possible CVD were retained in the analyses, and a variable that was coded as either 0 (no indication of possible CVD) or 1 (possible CVD) was created. Indications of possible CVD at baseline included an abnormal ECG at rest or during exercise (6.2% of sample) or failure to achieve at least 85% of age-predicted maximal heart rate (220 − age) during the exercise test (2.7% of sample). Information on cigarette smoking, alcohol consumption, and parental history of CVD were collected from a medical history questionnaire. Cigarette smoking was coded as never, former, or current smoker. 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 (355 ml [12 oz]), a glass of wine (148 ml [5 oz]), or one shot of hard liquor (44 ml [1.5 oz]). Parental history of premature 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).

Mortality surveillance

Participants were followed until 31 December 1996 or until they died in the case of decedents. Deaths were identified from the National Center for Health Statistics National Death Index (NDI), and the cause of death was determined from official death certificates obtained from departments of vital records in the states of deceased participants. The NDI has established validity for use in cohort studies, with a sensitivity of 96% and specificity of 100% (21). 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.

Statistical analysis

Logistic regression was used to examine the association between BMI category and MetS at baseline. Mortality rates per 10,000 person-years are reported as adjusted by Cox proportional hazards regression for age and year of examination. Cox regression was used to estimate the adjusted relative risks (RRs) of all-cause and CVD mortality associated with having MetS in obese, overweight, and normal weight men. Age, year of examination, smoking status, alcohol consumption, possible CVD, and parental history of CVD were included as covariates, and maximal METs was added as a covariate in specified models to examine the influence of CRF on the relationships. All analyses were conducted using SAS software and procedures (SAS Institute, Cary, NC), and mortality data were re-

Table 1—*Baseline characteristics of 19,173 normal weight, overweight, and obese men from the ACLS

	Normal weight		Overweight		Obese	
	Healthy	MetS	Healthy	MetS	Healthy	MetS
n	7,153	352	7,256	1,792	1,019	1,601
Age (years)	41.4 ± 10.0	47.0 ± 10.1	43.4 ± 9.3	46.8 ± 9.4	43.2 ± 9.3	44.9 ± 9.1
BMI (kg/m^2)	23.2 ± 1.3	23.7 ± 1.1	26.9 ± 1.3	27.7 ± 1.4	32.2 ± 2.4	33.2 ± 2.9
Waist circumference (cm)	85.4 ± 5.9	88.6 ± 5.5	94.7 ± 5.6	99.8 ± 6.1	107.1 ± 9.2	111.9 ± 9.2
Triglycerides (mmol/l)	1.11 ± 0.61	2.41 ± 0.92	1.39 ± 0.76	2.58 ± 1.11	1.37 ± 0.63	2.49 ± 1.11
HDL cholesterol (mmol/l)	1.27 ± 0.31	0.92 ± 0.17	1.19 ± 0.28	0.92 ± 0.21	1.19 ± 0.25	0.95 ± 0.22
Glucose (mmol/l)	5.38 ± 0.64	6.00 ± 1.14	5.47 ± 0.60	6.06 ± 1.38	5.50 ± 0.54	6.13 ± 1.52
Systolic blood pressure (mmHg)	117.2 ± 12.0	127.2 ± 12.9	119.1 ± 12.1	127.3 ± 13.0	121.1 ± 11.1	127.5 ± 12.7
Diastolic blood pressure (mmHg)	77.7 ± 8.7	85.5 ± 8.1	79.9 ± 8.7	86.3 ± 8.8	82.0 ± 8.8	87.1 ± 9.2
Maximal METs	13.0 ± 2.0	11.4 ± 2.0	11.8 ± 1.8	10.6 ± 1.6	10.6 ± 1.6	9.7 ± 1.5
Cigarette smoking (%)						
Never	50.9	40.1	44.2	39.7	43.9	39.6
Former	34.2	38.1	37.2	39.1	38.6	40.1
Current	14.8	21.9	18.6	21.3	17.6	20.3
Alcohol Use (%)						
None	25.3	29.3	23.6	28.1	29.6	32.2
Light	32.7	27.8	29.3	26.4	28.2	27.4
Moderate	22.4	17.6	21.6	19.2	18.8	17.0
Heavy	19.7	25.3	25.5	26.3	23.4	23.4
Possible CVD (%)†	5.8	15.9	7.5	13.7	8.4	14.7

Data are means ± SD. *With the exception of smoking (%) and alcohol use (%) in obese men, all comparisons between healthy men and men with the MetS within body weight categories were significant ($P < 0.05$.). †Failure to achieve 85% predicted maximal heart rate on fitness text or abnormal ECG at rest or exercise.

stricted to those with at least 1 year of follow-up.

RESULTS — The present sample of 19,173 men included 3,745 men (19.5%) at baseline who were classified as having MetS according to NCEP criteria. The descriptive characteristics of the sample are presented in Table 1. The prevalence of MetS was progressively higher across normal weight (4.7%), overweight (19.8%), and obese (61.1%) categories. As expected, men who had MetS were significantly older and had higher values (lower for HDL cholesterol) for all metabolic variables than healthy men in all BMI categories ($P < 0.05$). There was also a greater proportion of smokers and heavy alcohol users in the MetS group among normal weight and overweight ($P < 0.05$) men, but not among obese men. Cross-sectional logistic regression analysis of BMI category and MetS at baseline, adjusted for age, year of examination, smoking, and alcohol consumption, indicated that the odds ratios (ORs) for the presence of MetS were 4.7 (95% CI 4.2–5.3) in overweight and 30.6 (26.7–35.0) in obese men.

The average mortality follow-up interval was 10.2 years (range 1.0–19.3 years). A total of 477 deaths occurred during 195,783 person-years of follow-up, of which 160 deaths were from CVD. Figure 1 presents all-cause and CVD death rates per 10,000 person-years of follow-up, adjusted for age and year of clinical examination. Within each BMI category, men with MetS had a higher mortality rate than healthy men. Independent of MetS status, obese men had higher mortality rates than overweight and normal weight men.

Table 2 presents the results of the mortality follow-up proportional hazards regressions. In each analysis, the reference group was the normal weight men without MetS (RR = 1.00). After adjusting for age, year of examination, smoking, alcohol consumption, possible CVD at baseline, and parental history of premature CVD, the risk of all-cause mortality was higher in obese men with MetS (RR = 1.55, 95% CI 1.14–2.11) than in normal weight, healthy men. However, this difference disappeared after the inclusion of CRF as a covariate (0.93, 0.66–1.30). For CVD mortality, there was a higher risk among overweight men with MetS (1.80, 1.10–2.97) and among obese men both with MetS (2.83, 1.70–4.72) and without MetS (2.70, 1.40–5.19). After the inclusion of CRF as a covariate, all of the RR estimates for CVD mortality were attenuated and were no longer statistically significant. CRF was included in the models as a continuous variable (METS), and the RRs per each MET were 0.81 (95% CI: 0.77–0.86) for all-cause and 0.74 (0.67–0.82) for CVD mortality, indicating that higher CRF was associated with a significantly lower risk of mortality, after controlling for stratifications of BMI and MetS (Table 2).

CONCLUSIONS — Previous studies have documented an increased risk of mortality due to excess body weight (22,23) as well as MetS (5–7,16). This study extends these previous analyses by specifically comparing mortality rates among obese, overweight, and normal weight men with and without MetS. The results indicate that mortality rates are higher in those with MetS than in healthy participants within each BMI category. Furthermore, we observed higher mortality rates in obese men than in overweight or normal weight men. The results also demonstrate that there is a higher risk of CVD mortality attributable to obesity, even in men without MetS (RR = 2.70, 95% CI 1.40–5.19). However, CRF greatly attenuates the effect of MetS on

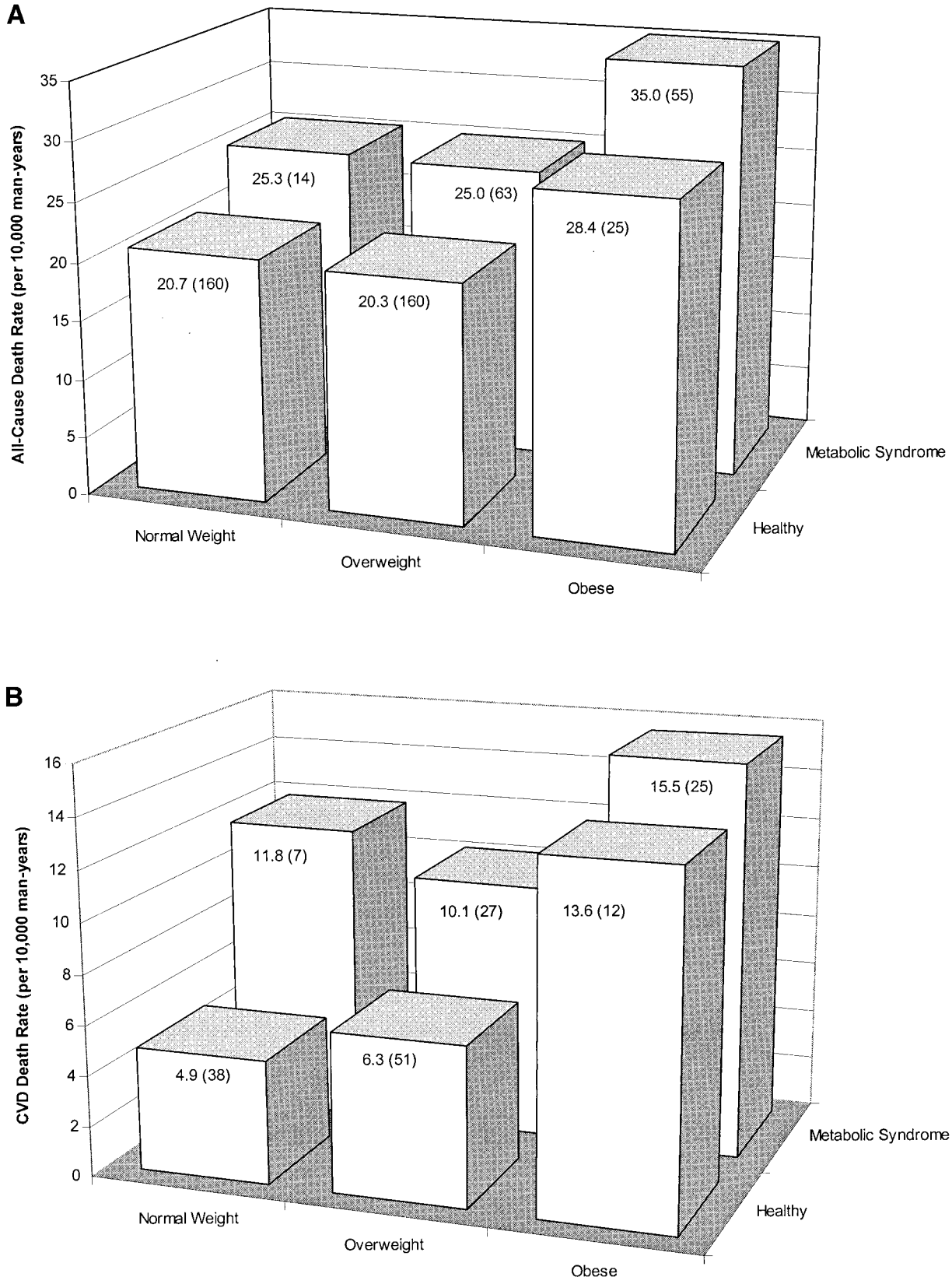

Figure 1—*BMI status and all-cause (A) and CVD (B) mortality in healthy men and men with MetS in the ACLS. The numbers in the bars are the death rates per 10,000 person-years of follow-up, adjusted for age and year of examination, and numbers in parentheses are the number of deaths. Normal weight is BMI 18.5–24.9 kg/m^2, overweight is BMI 25.0–29.9 kg/m^2, and obese is BMI ≥30.0 kg/m^2.*

Table 2—*RRs of all-cause and CVD mortality in 19,173 obese, overweight, and normal weight men with and without MetS from the ACLS*

	Man-years of follow-up [*n* (%)]	All-cause mortality			Cardiovascular disease mortality		
		Deaths (*n*)	RR of death (95% CI)*	CRF-adjusted RR of death (95% CI)†	Deaths (*n*)	RR of death (95% CI)*	CRF-adjusted RR of death (95% CI)†
Normal weight							
Healthy	77,225 (39.4)	160	1.00 (ref.)	1.00 (ref.)	38	1.00 (ref.)	1.00 (ref.)
MetS	3,708 (1.9)	14	1.11 (0.64–1.92)	0.92 (0.53–1.60)	7	2.06 (0.92–4.63)	1.60 (0.71–3.61)
Overweight							
Healthy	73,569 (37.6)	160	0.94 (0.75–1.17)	0.79 (0.63–0.99)	51	1.27 (0.83–1.94)	1.00 (0.65–1.54)
MetS	17,860 (9.1)	63	1.09 (0.82–1.47)	0.80 (0.59–1.08)	27	1.80 (1.10–2.97)	1.19 (0.72–1.99)
Obese							
Healthy	9,281 (4.7)	25	1.31 (0.86–2.01)	0.88 (0.57–1.36)	12	2.70 (1.40–5.19)	1.59 (0.81–3.12)
MetS	14,140 (7.2)	55	1.55 (1.14–2.11)	0.93 (0.66–1.30)	25	2.83 (1.70–4.72)	1.43 (0.82–2.49)
CRF							
MetS	—	—	—	0.81 (0.77–0.86)	—	—	0.74 (0.67–0.82)

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

all-cause and CVD mortality in all BMI categories.

Given that the prevalence of overweight and obesity exceeds 65% in the U.S. (24) and that overweight and obese individuals are at a substantially higher risk of having MetS, these results have important public health implications. Strategies to combat the increasing prevalence of overweight and obesity that also target those with elevated risk factor profiles, including sedentary habits and low CRF, are likely to be the most effective in improving the health of the population.

The finding in the present study that the odds of MetS increases across overweight (OR = 4.7) and obese categories (OR = 30.6) compared with normal weight categories supports results from NHANES III, in which the ORs for MetS were 5.2 (95% CI 3.9–6.9) in overweight, 25.2 (19.3–32.9) in obese class I, and 67.7 (40.5–113.3) in obese class II and III participants, as compared with normal weight men (8). However, in the present sample, it is also noteworthy that ~40% of obese men did not have MetS, whereas ~5% of normal weight men had MetS. Thus, although there is a robust relationship between level of obesity and the presence of multiple risk factors, there is considerable variability in the presence of MetS within BMI categories.

The idea that some obese individuals appear healthy and display none of the traditional risk factors for chronic disease, including dyslipidemia and insulin resistance, has been reported previously (25–27). The results from our study indicate that the risk of CVD mortality was significantly higher in obese men, regardless of whether they had MetS, than in normal weight men without MetS (Table 2). However, the higher risk of all-cause mortality in obese men was limited to those with MetS (RR = 1.55, 95% CI 1.14–2.11). In addition, there was a higher risk of CVD mortality in overweight men with MetS (1.80, 1.10–2.97), but there was no higher risk of CVD mortality in healthy overweight men. It should also be noted that all of these differences disappeared after adjustment for CRF. Although indirect, these results support the existence of "metabolically normal" obese individuals, and they support the use of the NIH treatment algorithm for overweight and obesity, which suggests that weight loss is of particular importance for overweight individuals with two or more CVD risk factors (28). In sum, the results indicate that weight loss should be promoted in all obese individuals, but should be more aggressively pursued among overweight and obese individuals accompanied by other risk factors.

In the present study, the inclusion of CRF as a covariate in the regression models resulted in lower RR estimates for obesity and MetS to the point where they were no longer statistically significant. This suggests that CRF is an important effect modifier in the relationships among obesity, metabolic status, and mortality. These results extend earlier findings in this cohort (12,29) and others (30) that CRF is protective against premature mortality in those who are overweight and obese. Further, CRF provides a strong protective effect against both all-cause and CVD mortality in healthy men and men with MetS (16). Thus, the higher risk of mortality observed in normal weight, overweight, and obese men with MetS might in large part be explained by differences in CRF.

The mechanisms by which CRF influences the relationships among obesity, metabolic status, and mortality remain to be identified. It is clear that CRF has an effect on the risk of mortality that is independent of traditional risk factors for CVD, such as those that are included in the definition of MetS, including high blood pressure, high triglycerides, low HDL cholesterol, and high plasma glucose. There are several previously unknown, emerging risk factors for CVD, some of which may be positively affected by enhanced CRF. For example, C-reactive protein levels, which have been linked with an increase in CVD risk in apparently healthy individuals (31,32), have been shown to be inversely related to CRF (33,34). Recent studies have also demonstrated that C-reactive protein adds to MetS in the prospective prediction of CVD and diabetes (3,35). It is also possible that CRF has an effect on metabolic risk factors that would require more detailed procedures and measurements than were used in the present study. For example, oral glucose tolerance tests, hyperinsulinemic-euglycemic clamp proce-

dures, lipoprotein subfractions (HDL_2, HDL_3, etc.), and visceral and subcutaneous adipose tissue measurements may yield insights into the mechanisms whereby CRF influences health risk, independent of obesity. Further research is required to elucidate the mechanisms behind these observations.

The strengths and limitations of this study warrant discussion. The large sample size that allowed for stratification by BMI and MetS and the objective measurement of CRF are notable strengths, as is the large battery of clinical risk factor measurements used in the ACLS. The all-male, predominantly white, middle-to-upper class sample used in this study limits the generalizability of the results; however, this homogeneous sample also ensures a certain degree of control over factors such as ethnicity and socioeconomic status, which may impact the observed relationships. Although it is difficult to compare death rates across studies due to different baseline ages, follow-up periods, and cohort effects, the death rate in this study (24 per 10,000 person-years of follow-up) is lower than that reported in the Health Professionals Follow-up Study (53 per 10,000 person-years of follow-up, which is another study conducted using an all-male, predominantly well-educated cohort (22). The major difference between the two studies is that the average age at baseline was ~10 years older in the Health Professionals Follow-up Study compared with the ACLS (53 years vs. 43 years). Further research is needed to confirm these findings in women and in other socio-economic and ethnic groups.

In conclusion, we observed progressively higher odds of having MetS across the BMI categories of normal weight, overweight, and obesity in this sample. This observed positive trend translated into a higher risk of all-cause and CVD mortality than that of normal weight, metabolically normal men. However, the higher mortality risk was greatly attenuated after controlling for CRF. It appears that CRF provides a protective effect against premature mortality regardless of body weight status or the presence of MetS. The amount of physical activity required to achieve the levels of CRF that were protective in this study is ~30 min of moderate intensity activity on most days of the week (36), which are the currently recommended physical activity levels for health (37). Thus, these results highlight the importance of maintaining a physically active lifestyle, even in the face of obesity and metabolic disorders. Health promotion programs should specifically target those with low CRF levels for therapeutic lifestyle changes, given their high risk of death.

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