

Cardiorespiratory Fitness Attenuates the Effects of the Metabolic Syndrome on All-Cause and Cardiovascular Disease Mortality in Men

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Background: The metabolic syndrome is a prevalent condition that carries with it an increased risk of type 2 diabetes mellitus, cardiovascular disease (CVD), and mortality.

Objective: To determine the relationship between cardiorespiratory fitness (CRF) and mortality in healthy men and in those with the metabolic syndrome.

Methods: The sample included 19 223 men, aged 20 to 83 years, who received a clinical evaluation between 1979 and 1995 with mortality follow-up through December 31, 1996. There were 15 466 healthy men (80.5%) and 3757 men with the metabolic syndrome (19.5%).

Results: A total of 480 deaths (161 due to CVD) occurred during 196 298 man-years of follow-up. After adjustment for age, year of examination, smoking status, alcohol consumption, and parental CVD, the relative risks

(RRs) (95% confidence interval) of all-cause and CVD mortality were 1.29 (1.05-1.57) and 1.89 (1.36-2.60), respectively, for men with the metabolic syndrome compared with healthy men. After the inclusion of CRF, the associations were not significant. The RRs comparing unfit with fit men for all-cause mortality were 2.18 (1.66-2.87) in healthy men and 2.01 (1.38-2.93) in men with the metabolic syndrome, whereas the RRs for CVD mortality for unfit vs fit men were 3.21 (2.03-5.07) in healthy men and 2.25 (1.27-3.97) in men with the metabolic syndrome. A significant dose-response relationship between CRF and mortality was also observed in men with the metabolic syndrome.

Conclusion: In this sample, CRF provided a strong protective effect against all-cause and CVD mortality in healthy men and men with the metabolic syndrome.

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RISK FACTORS FOR CHRONIC diseases tend to cluster within individuals,^{1,2} and the metabolic syndrome is such a constellation of risk factors that predispose toward the development of type 2 diabetes mellitus and cardiovascular disease (CVD). Ford et al³ estimate that the prevalence of the metabolic syndrome is approximately 22% among adults in the United States, which translates into 47 million people having the condition in 2000. The metabolic syndrome is hypothesized to result from insulin resistance in several organ systems and pathways, and abdominal obesity is a central feature.⁴ Given that the prevalence of obesity among adults in the United States has increased from 15% in the 1976-1980 period to 30.5% in 1999-2000,⁵ studies of the medical sequelae of obesity such as the metabolic syndrome are important and timely.

An operational definition of the metabolic syndrome was proposed by the National Cholesterol Education Program Adult Treatment Panel III (ATP III)⁶ and recently validated.⁷ A 2002 study⁸ has reported that middle-aged Finnish men diagnosed with the metabolic syndrome under the ATP III criteria have a significantly elevated risk of all-cause and CVD mortality. There is a need to replicate these results in other populations. A major new feature in the updated ATP III guidelines is the focus on the primary prevention of coronary heart disease in people with multiple risk factors. The guidelines highlight the importance of therapeutic lifestyle changes, including increased physical activity and reduction of body weight, in the treatment and prevention of metabolic disorders and coronary heart disease. However, little is known about the effects of cardiorespiratory fitness (CRF) on attenuating the mortality risk associated with the metabolic syndrome.

PARTICIPANTS

The sample included 19 223 men, aged 20 to 83 years (mean [SD] age, 43.1 [9.7] years), from the Aerobics Center Longitudinal Study (ACLS)⁹ who had complete data for CRF and the metabolic syndrome. The sample was restricted to men with no personal history of coronary heart disease, stroke, or cancer at the time of the baseline examination. The participants were well educated (approximately 75% were college graduates) and were predominantly non-Hispanic whites. All participants attended the Cooper Clinic in Dallas, Tex, for clinical evaluations between 1979 and 1995. Although baseline data collection for the ACLS began in 1970, the required clinical measurements for diagnosing the metabolic syndrome were only available for participants beginning in 1979. All men gave their informed consent to participate in the clinical examination and subsequent follow-up study. All study protocols were approved annually by The Cooper Institute institutional review board.

CLINICAL EXAMINATION

Metabolic Syndrome

All clinical measurements were made in the morning following at least a 12-hour fast. Waist circumference (WC) was measured at the level of the umbilicus with a plastic anthropometric tape, and blood pressure measurements were obtained with a mercury sphygmomanometer using auscultatory methods. A fasting blood sample was obtained by venipuncture, and serum triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and plasma glucose levels were assayed with automated techniques at the Cooper Clinic Laboratory, which participates in and meets the quality control standards of the US Centers for Disease Control and Prevention Lipid Standardization Program. Metabolic syndrome was defined according to the criteria established by ATP III.⁶

Participants were diagnosed as having the metabolic syndrome if they had 3 or more of the following 5 risk factors: (1) high blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic); (2) central obesity (WC > 102 cm [> 40 in]); high TG level (≥ 1.69 mmol/L [≥ 150 mg/dL]); low HDL-C level (< 1.04 mmol/L [< 40 mg/dL]); and high fasting plasma glucose level (≥ 6.1 mmol/L [≥ 110 mg/dL]). Men with normal blood pressure or fasting plasma glucose who indicated a history of physician-diagnosed hypertension ($n = 861$) or type 2 diabetes mellitus ($n = 32$), respectively, were also coded as positive for high blood pressure or high fasting plasma glucose, which added an additional 208 men to the metabolic syndrome category. It should be noted that the results obtained were virtually identical to those reported in this study when these men were excluded.

Cardiorespiratory Fitness

Cardiorespiratory fitness was assessed by a maximal treadmill exercise test using a modified Balke protocol.¹⁰ Time until exhaustion on the treadmill was used to estimate the maximum oxygen uptake ($\dot{V}O_{2max}$) in metabolic equivalents (MET = 3.5 mL of oxygen/kg per minute) from the Balke protocol using the following formula: $\dot{V}O_{2max} = (1.44 \times [\text{No. of minutes on treadmill}] + 14.99) / 3.5$.¹¹ Participants were assigned to either unfit or fit categories using age-adjusted maximum METs. Men in the lower quintile (20%) were classified as unfit, whereas men in the upper 4 quintiles (80%)

were classified as fit. These fitness criteria are from previous reports on the cohort.¹²

Covariates

Information on cigarette smoking, alcohol consumption, and parental history of CVD were 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 age 50 years). Cigarette smoking status was coded as never smoked, former smoker, or current smoker. Alcohol consumption was coded as none, light (< 15 units/wk), moderate (15-30 units/wk), and heavy (> 30 units/wk). 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]).

MORTALITY SURVEILLANCE

Follow-up continued until participants died or until December 31, 1996, for survivors. Deaths were identified from the National Center for Health Statistics National Death Index, and the cause of death was determined from official death certificates obtained from departments of vital records in the states of deceased participants. The National Death Index has established validity for use in cohort studies, with a sensitivity of 96% and specificity of 100%.¹³ A nosologist coded the death certificates for the underlying and up to 4 contributing causes of death, and CVD mortality was defined as codes 390 to 449.9 of the *International Classification of Diseases, Ninth Revision*.

STATISTICAL ANALYSES

Cox proportional hazards regression was used to estimate the adjusted relative risk (RR) of mortality associated with the metabolic syndrome, including age, year of examination, smoking status, alcohol consumption, and parental history of CVD as covariates. Cardiorespiratory fitness (in METs) was then added to the model as a continuous variable to examine its effect on the relation between the metabolic syndrome and mortality. Given that abdominal obesity is a key component of the metabolic syndrome, the body mass index (BMI) was not included as a covariate in these models owing to the high degree of covariation between BMI and WC.

Mortality rates (per 10 000 man-years of follow-up), adjusted for age and year of examination, were calculated for unfit and fit healthy men and men with the metabolic syndrome. Cox proportional hazards regression was also used to evaluate the relationship between fitness category (unfit vs fit) and mortality after stratifying the sample into healthy men and men with the metabolic syndrome. The BMI was included as a covariate in these models to examine the influence of body weight status on the observed relationships. The dose-response relationship between CRF and mortality was examined in men with the metabolic syndrome by dividing this group into lower, middle, and upper tertiles of age-adjusted CRF (METs). For this analysis, the residuals from a regression of CRF on age were used as age-adjusted values. All analyses were conducted using SAS statistical software and procedures (SAS Institute, Cary, NC), and mortality data were restricted to those dying at least 1 year after their clinical evaluation.

RESULTS

The characteristics of the participants at baseline are summarized in **Table 1**. The prevalence of the metabolic syndrome in the sample was 19.5%. Fit men within each

Table 1. Baseline Characteristics in 19223 Men Across Cardiorespiratory Fitness Categories in Healthy Men and Men With the Metabolic Syndrome*

Characteristic	Healthy Men		Men With Metabolic Syndrome	
	Fit (n = 14 028)	Unfit (n = 1438)	Fit (n = 2494)	Unfit (n = 1263)
Age, y	42.4 ± 9.7	42.3 ± 9.5	46.8 ± 9.5	44.4 ± 9.1†
Height, cm	178.8 ± 6.5	177.1 ± 6.6†	179.6 ± 6.7	179.0 ± 6.8†
Weight, kg	81.0 ± 10.3	86.9 ± 14.4†	92.7 ± 12.6	102.2 ± 16.3
Body mass index‡	25.3 ± 2.7	27.6 ± 4.1†	28.7 ± 3.2	31.8 ± 4.5†
Waist circumference, cm	90.5 ± 8.2	97.5 ± 10.9†	101.3 ± 9.2	109.5 ± 11.8†
Triglycerides, mmol/L	1.2 ± 0.7	1.6 ± 0.8†	2.5 ± 1.1	2.6 ± 1.1†
HDL cholesterol, mmol/L	1.2 ± 0.3	1.1 ± 0.3†	0.9 ± 0.2	0.9 ± 0.2†
Fasting glucose, mmol/L	5.4 ± 0.6	5.5 ± 0.9†	6.0 ± 1.3	6.2 ± 1.7†
Diastolic blood pressure, mm Hg	78.9 ± 8.8	80.2 ± 8.7†	86.5 ± 8.8	86.7 ± 9.2
Systolic blood pressure, mm Hg	118.4 ± 12.1	118.4 ± 11.9	127.7 ± 12.9	126.9 ± 12.7
Maximal METs	12.6 ± 1.8	9.1 ± 1.1†	11.1 ± 1.4	8.7 ± 1.1†
Alcohol consumption, %§				
None	24.3	29.8	27.9	34.2
Light	31.3	26.3	27.2	26.4
Moderate	22.1	18.2	19.5	15.1
Heavy	22.3	25.8	25.3	24.2
Smoking, %§				
Never	48.6	34.8	42.9	33.5
Former	36.5	30.4	40.7	36.7
Current	14.9	34.8	16.4	29.8

Abbreviations: HDL, high-density lipoprotein; MET, metabolic equivalent (3.5 mL of oxygen/kg per minute).

SI conversion factors: To convert reported triglyceride levels to conventional units (mg/dL), divide by 0.0113; HDL cholesterol (mg/dL), divide by 0.0259; and fasting glucose (mg/dL), divide by 0.0555.

*Unless otherwise indicated, data are mean ± SD.

† $P < .05$, t test between fit and unfit men, within metabolic syndrome categories.

‡Calculated as the weight in kilograms divided by the square of height in meters.

§ $P < .05$, χ^2 test between fit and unfit men, within metabolic syndrome categories.

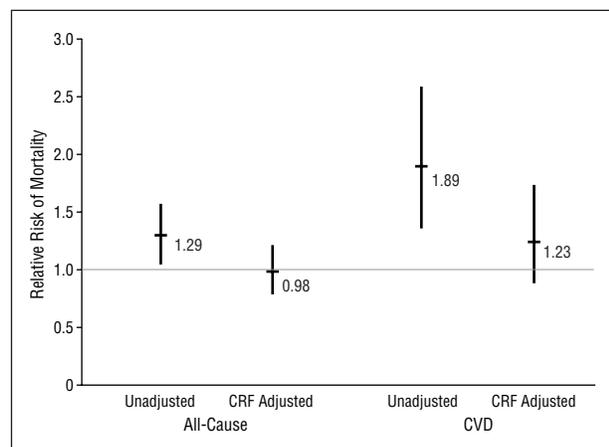


Figure 1. Relative risks of all-cause and cardiovascular disease (CVD) mortality associated with the metabolic syndrome before and after the inclusion of cardiorespiratory fitness (CRF) as a covariate in 19223 men aged 20 to 83 years from the Aerobics Center Longitudinal Study. All models include age, year of examination, smoking status, alcohol consumption, and family history of CVD as covariates. Error bars represent 95% confidence intervals.

metabolic syndrome category had a better metabolic fitness profile than unfit men (ie, significantly smaller WCs, lower TG and plasma glucose levels, and higher HDL-C levels). During 196 298 person-years of follow-up, there were 480 deaths (161 due to CVD). After adjustment for age, smoking status, alcohol consumption, and parental history of CVD, the RRs (95% confidence interval [CI])

of all-cause and CVD mortality were 1.29 (1.05-1.57) and 1.89 (1.36-2.60), respectively, in men with the metabolic syndrome compared with healthy men. After the further inclusion of CRF (METs) as a covariate, the RRs (95% CI) of all-cause and CVD mortality were reduced to 0.98 (0.79-1.21) and 1.23 (0.88-1.73), respectively, and were no longer statistically significant (**Figure 1**).

The all-cause and CVD death rates (per 10000 man-years of follow-up), adjusted for age and year of examination, for unfit and fit healthy men and men with the metabolic syndrome are presented in **Figure 2**. The overall death rates were higher in men with the metabolic syndrome, but they were greatly attenuated by CRF.

The adjusted RRs (95% CI) comparing unfit with fit men for all-cause mortality were 2.18 (1.66-2.87) in healthy men and 2.01 (1.38-2.93) in men with the metabolic syndrome, after including age, smoking status, alcohol consumption, parental history of CVD, and BMI as covariates. The corresponding RRs (95% CI) for CVD mortality were 3.21 (2.03-5.07) in healthy men and 2.25 (1.27-3.97) in men with the metabolic syndrome (**Table 2**). A dose-response relationship between CRF and mortality is clearly evident in men with the metabolic syndrome (**Figure 3**). Men in the middle and lower tertiles of CRF had 1.42 (95% CI, 0.84-2.39) and 2.70 (95% CI, 1.63-4.47) times the risk of all-cause mortality, respectively, of men in the upper tertile. Similarly, men in the middle and lower tertiles of CRF had 2.08 (95% CI, 0.90-4.80) and 3.48 (95% CI, 1.52-8.01) times the risk of CVD mortality of men in the upper tertile, re-

spectively. It should be noted that the analyses were re-run after taking BMI out of the adjusted models, and the results were unchanged.

COMMENT

As the prevalence of obesity increases in this and other countries, the ability to identify high-risk individuals for obesity-related disorders becomes increasingly important. The present study provides further evidence of the validity of the ATP III⁶ definition of the metabolic syndrome; men diagnosed with the metabolic syndrome were 1.29 times more likely to die of any cause and 1.89 times more likely to die of CVD than healthy men (Figure 1). These results support those of Lakka and colleagues,⁸ who recently reported that middle-aged Finnish men diagnosed as having the metabolic syndrome under the ATP III criteria were 4.26 (95% CI, 1.62-11.2) times more likely to die over 11 years of follow-up than healthy men. Our results also are consistent with those of 2 studies that examined the association between the metabolic syndrome (using different diagnostic criteria) and mortality rates.^{14,15} The metabolic syndrome, defined under the criteria of the World Health Organization,¹⁶ was associated with 2.96 times the risk of CVD mortality over 6.9 years of follow-up in a sample from Finland and Sweden.¹⁴ Additionally, a cluster of low HDL-C level and high blood pressure, blood glucose level, and TG level was associated with 2.49 times the risk of CVD death over an average of 7 years of follow-up in an Italian study.¹⁵ The somewhat lower relative risk of mortality observed in the present sample of well-educated, middle- to upper-class business executives and professionals might be owing to better medical care than that received by the participants in the 3 earlier studies. For example, the baseline data for the present study were collected during a preventive medicine examination. Nevertheless, our results show that even in this sample of men, most of whom had access to excellent medical care, the metabolic syndrome was still associated with mortality.

To our knowledge, the present study is the first to explicitly test the hypothesis that CRF attenuates the mortality risk associated with the metabolic syndrome. In healthy men and those with the metabolic syndrome, there was a substantially lower risk in fit men than in unfit men. The finding of a dose-response relationship between CRF and mortality in men with the metabolic syndrome, similar to what has been observed in the entire ACLS cohort,⁹ indicates that physical activity may be a valuable tool in the treatment of the metabolic syndrome and the prevention of further health problems.

Although central obesity (large WC) is a component of the metabolic syndrome, the finding in the present study that CRF remained a significant predictor of mortality in men with the metabolic syndrome after the inclusion of BMI as a covariate suggests that CRF was associated with mortality risk independent of body weight status. The fact that the results were virtually identical when BMI was not included as a covariate indicates that body weight status was not an important modifier of mortality risk in this sample of men who were already diagnosed as having the metabolic syndrome once the ef-

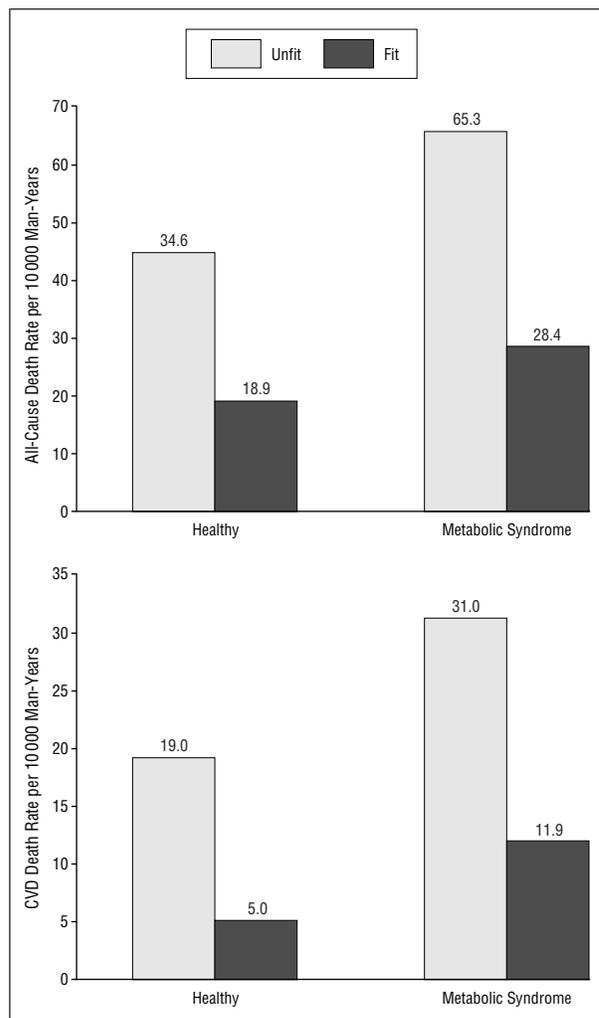


Figure 2. All-cause and cardiovascular disease (CVD) death rates per 10000 man-years of follow-up in fit and unfit healthy men and men diagnosed as having the metabolic syndrome, adjusted for age and year of examination. Results are from 19223 men aged 20 to 83 years from the Aerobics Center Longitudinal Study.

fects of CRF were accounted for. This finding further supports the notion that CRF is an independent determinant of health status, regardless of body weight. The mechanisms by which CRF provides a protective effect against the mortality risk associated with the metabolic syndrome still need to be determined.

The prevalence of the metabolic syndrome in this sample of predominantly well-educated professional men was 19.5%. This is slightly lower than the prevalence of the metabolic syndrome in the United States, which has been recently estimated at 24.0% in men, based on data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994).³ The lower prevalence of the metabolic syndrome in the present sample is mainly owing to a lower prevalence of abdominal obesity (large WC) (19.5% vs 30.5%) and high TG level (20.5% vs 35.1%) rather than differences in low HDL-C level (35.2% vs 36.8%), high blood pressure (41.7% vs 37.2%), or high blood glucose level (13.5% vs 15.6%). Given that the ACLS sample consists of men measured at baseline between 1979 and 1995 and the NHANES III

Table 2. Adjusted Relative Risks for All-Cause and Cardiovascular Disease Mortality by Fitness Group in Healthy Men and Men With the Metabolic Syndrome

Health and Fitness Group	Man-Years	No. of Deaths	All-Cause Mortality*		Cardiovascular Disease Mortality*	
			RR _{age}	RR _{all}	RR _{age}	RR _{all}
Healthy						
Fit	144 688	274	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Unfit	15 774	74	2.36 (1.82-3.05)	2.18 (1.66-2.87)	3.81 (2.48-5.86)	3.21 (2.03-5.07)
Metabolic syndrome						
Fit	23 556	67	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Unfit	12 280	65	2.30 (1.63-3.26)	2.01 (1.38-2.93)	2.61 (1.55-4.40)	2.25 (1.27-3.97)

Abbreviations: RR_{age}, relative risks adjusted for age and year of examination; RR_{all}, relative risks adjusted for age, year of examination, alcohol consumption, cigarette smoking, family history of cardiovascular disease, and body mass index.

*Nonreferent values reported as relative risk (95% confidence interval).

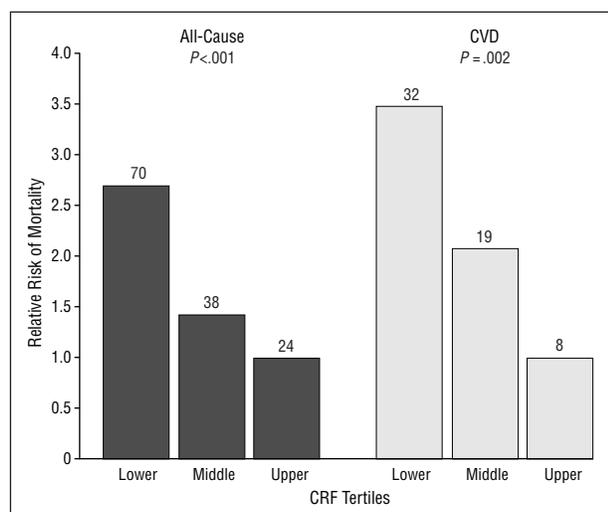


Figure 3. Relative risks of all-cause and cardiovascular disease (CVD) mortality in men diagnosed as having the metabolic syndrome across baseline tertiles (lower, middle, and upper) of cardiorespiratory fitness (CRF) in 3757 men aged 20 to 83 years from the Aerobics Center Longitudinal Study. Relative risks are adjusted for age, year of examination, smoking status, alcohol consumption, family history of CVD, and body mass index. Numbers atop bars indicate the number of deaths; *P* values are for tests of linear trend across the cardiorespiratory fitness categories.

occurred between 1988 and 1994, the recent increases in the prevalence of obesity in the United States are likely more represented in the NHANES III sample than in the ACLS cohort; 62% of the men in the present study (n=11846) were evaluated for baseline measures between 1979 and 1987. Nevertheless, men diagnosed as having the metabolic syndrome were 1.29 times more likely to die from any cause and 1.89 times more likely to die from CVD than healthy men.

Based on the results of this study, the estimated population attributable risk ($P[(RR-1)/RR]$, where *P* indicates population prevalence)¹⁷ of the metabolic syndrome in male residents of the United States is 5.4% for all-cause mortality and 11.3% for CVD mortality, assuming that 24% of men in the United States currently have the metabolic syndrome.³ This suggests that approximately 1 in 20 deaths and 1 in 10 CVD deaths in men are directly attributable to the metabolic syndrome. Thus, the results reinforce the stance of the ATP III guidelines⁶ that emphasize the treatment of patients

with multiple risk factors, including those with the metabolic syndrome. Furthermore, the public health burden associated with the metabolic syndrome is substantial, and the finding that physical fitness may greatly attenuate the relative risk of both all-cause and CVD mortality strengthens the argument for aggressive public health campaigns aimed at increasing physical activity levels in the population.

The present study has several strengths. First, the large sample size allowed for the examination of interactions between the metabolic syndrome and CRF through the cross-tabulation of these indices, which enhances the clinical utility of the findings. Second, the CRF data were obtained using a maximal treadmill test to exhaustion, and maximum treadmill time is highly correlated with directly measured maximum oxygen uptake ($r=0.92$).¹¹ This allowed for the objective quantification of mortality risk associated with CRF level while minimizing the introduction of technical errors and errors of measurement that can occur with fitness measurements obtained from submaximal exercise data or self-reported physical activity data from a questionnaire. Third, the use of measured clinical data on CVD risk factors allowed for the diagnosis of the metabolic syndrome using the recent ATP III guidelines, which also increases the clinical utility of the findings.

The main weakness of this study is that the sample was predominantly white, middle to upper class, and all male, which limits the generalizability of the results. Further, the lack of dietary information for the participants is a limitation in that dietary factors are known to influence the component risk factors in the metabolic syndrome.

In conclusion, the metabolic syndrome was significantly associated with mortality in this sample. Low CRF was an important risk factor for premature mortality in healthy men and men with the metabolic syndrome. In fact, CRF attenuated much of the risk associated with the metabolic syndrome, which indicates that the promotion of the measurement of CRF in clinical medicine may aid in risk stratification and that the promotion of physically active lifestyles should be a public health priority.

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