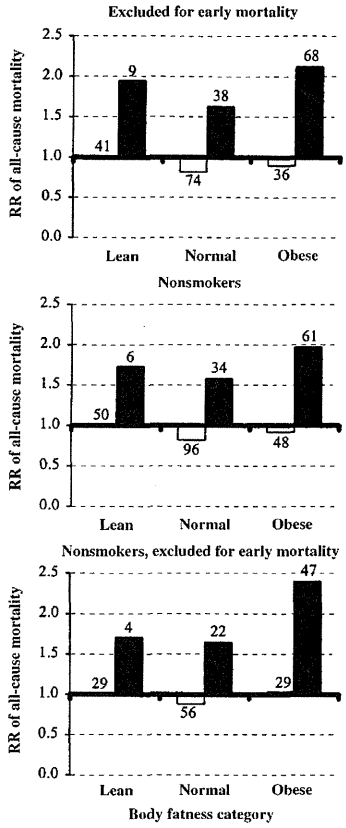

FIGURE 2. Body fatness and relative risks (RRs) of all-cause mortality by cardiorespiratory fitness categories in men: □, fit; ■, unfit. Fit, lean men comprised the reference category, represented by the heavy line at 1.0. Unfit men were the least-fit 20% of each age group, and fit refers to all other men (18). RRs were adjusted for age (single year), examination year, smoking habit, alcohol intake, and parental history of ischemic heart disease. Early mortality indicates the first 5 y of follow-up. Body fatness categories were, in percentage body fat, lean (<16.7%), normal (16.7% to <25.0%), and obese (≥25.0%). Numbers above or below the bars represent the number of deaths.

fatness interactions, and all were significant ($P \leq 0.001$) except height, diastolic blood pressure, and serum glucose.

All-cause and CVD death rates per 10000 man-years of follow-up, adjusted for age and examination year across body fatness categories, are shown in **Figure 1**. There was a direct relation between body fatness and all-cause ($P = 0.01$ for linear trend) and CVD ($P = 0.004$ for linear trend) death rates.

The associations among cardiorespiratory fitness, body fatness, and all-cause and CVD mortality are shown in **Table 2**. Cox proportional hazards regression analyses, adjusted for age and examination year, showed that fit men had lower death rates than did their unfit counterparts within lean, normal, and obese categories. Unfit, lean men had twice the risk of all-cause mortality as did fit, lean men ($P = 0.02$) and also had higher risk (2.2 times) of all-cause mortality when compared with fit, obese men ($P = 0.008$). The all-cause mortality rate of fit, obese men was not significantly different from that of fit, lean men. These results were similar after additional adjustment for cigarette smoking, alcohol intake, and parental history of IHD. To evaluate further the possible bias of subclinical disease at baseline, we constructed another multivariate model by adding baseline electrocardiographic status (normal or abnormal). This analysis led to adjusted RRs that were nearly identical to those reported in Table 2. Exclusion for early mortality also made little difference in these results (**Figure 2**).

We observed similar associations among cardiorespiratory fitness, body fatness, and all-cause mortality in nonsmokers and in nonsmokers with exclusion for early mortality and adjustment for age, examination year, alcohol intake, and parental history of IHD (Figure 2). Of nonsmokers, unfit, lean men had 1.7 times the risk of all-cause mortality of fit, lean men, with the highest all-cause mortality in unfit, obese men (RR: 1.97; 95% CI: 1.35, 2.88). Unfit nonsmokers in all body-composition groups had higher mortality risks than did fit nonsmokers after further exclusion for early mortality.

Unfit, lean men also had a high risk of CVD mortality when compared with their fit counterparts in all body fatness categories (Table 2). After multivariate adjustment for age, examination year, cigarette smoking, alcohol intake, and parental history of IHD, we observed that fit, lean men had the lowest CVD mortality, and that unfit, obese men had the highest. Unfit, lean men had 3.2 times the risk of CVD mortality of fit, lean men (95% CI: 1.12, 8.92; $P = 0.03$). However, fit, obese men had a lower risk of CVD mortality than did unfit, lean men.

When we further examined the relation of estimated $\dot{V}O_2$max (in mL·kg FFM^{-1}·min^{-1}) and body fatness with all-cause and

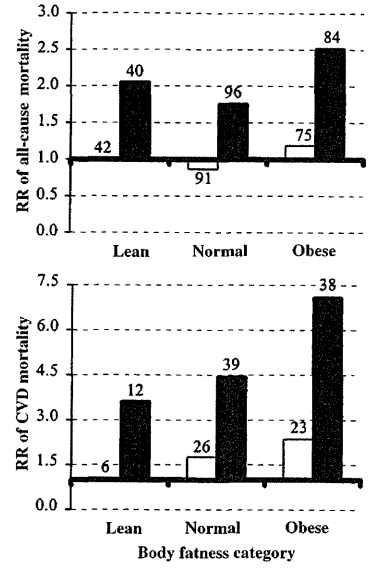

FIGURE 3. Body fatness and relative risks (RRs) of all-cause and cardiovascular disease (CVD) mortality by cardiorespiratory fitness categories in men: □, fit; ■, unfit. Fit, lean men comprised the reference category, represented by the heavy line at 1.0. Unfit men were the lowest quartile of oxygen uptake (mL•kg FFM^{-1}•min^{-1}) in each age group, and fit refers to all other men. RRs were adjusted for age (single year), examination year, smoking habit, alcohol intake, and parental history of ischemic heart disease. Body fatness categories were, in percentage body fat, lean (<16.7%), normal (16.7% to <25.0%), and obese (≥25.0%). Numbers above or below the bars represent the number of deaths.

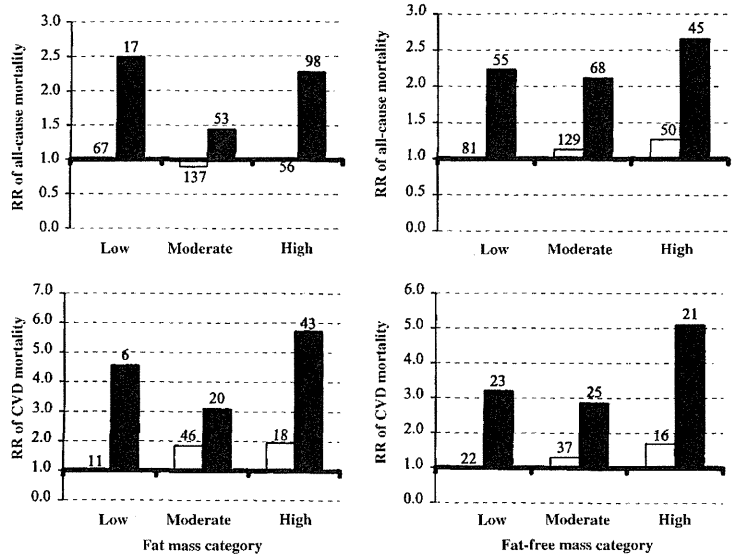

FIGURE 4. Fat mass, fat-free mass, and relative risks (RR) of all-cause and cardiovascular disease (CVD) mortality by cardiorespiratory fitness categories in men; □, fit; ■, unfit. Fit, lean men comprised the reference category, represented by the heavy line at 1.0. Unfit men were the least-fit 20% of each age group, and fit refers to all other men (18). RRs were adjusted for age (single year), examination year, smoking habit, alcohol intake, and parental history of ischemic heart disease. Fat mass measurements across low, moderate, and high categories were <12.8, 12.8 to <21.7, and ≥21.7 kg; fat-free mass measurements across these categories were <60, 60 to <70, and ≥70 kg. Numbers above or below the bars represent the number of deaths.

CVD mortality (**Figure 3**), similar results were obtained as for analyses in which fitness was expressed in $mL \cdot kg^{-1} \cdot min^{-1}$. Mortality risk was elevated in unfit, lean men, with the highest all-cause and CVD mortality in unfit, obese men. Unfit men had substantially higher risk of CVD in all fatness categories, but there also was a direct association between body fatness and CVD mortality in fit men ($P = 0.05$ for linear trend).

We also examined the relations of cardiorespiratory fitness, fat mass, and FFM to all-cause and CVD mortality (**Figure 4**). Unfit men had a higher risk of all-cause and CVD mortality than did fit men in all fat mass and FFM categories. Unfit men in the lowest quartile of fat mass and FFM had a greater risk of all-cause and CVD mortality than did fit men in the highest quartile of fat mass and FFM.

We also observed results similar to the analyses presented above when the men were stratified by waist circumference. There were 162 deaths (40 from CVD, 54 from cancer, and 68 from other causes) during an average of 5.6 y of follow-up (78 008 man-years of observation) in the subgroup of 14 043 men who had waist girth assessed at baseline. We calculated all-cause and CVD death rates per 10 000 man-years of follow-up and adjusted for age and examination year across waist circumference categories. All-cause and CVD death rates directly increased with larger sizes of waist girth, although the trends were not significant (**Figure 5**).

The associations among cardiorespiratory fitness, waist circumference, and all-cause mortality are shown in **Table 3**. After multivariate adjustment for age, examination year, cigarette smoking, alcohol intake, and parental history of IHD, we observed that fit men had lower risk of all-cause mortality in all waist circumference categories than unfit men. Unfit men in the lowest quartile of waist girth had 4.9 times ($P < 0.001$) the risk of all-cause mortality of their peers who were fit. In contrast, fit men in the highest quartile of waist girth had no elevated risk of all-cause mortality and had much lower mortality risk than unfit men in the lowest quartile of waist girth.

DISCUSSION

Although there is a strong direct relation between BMI and mortality (27), there has been little research on the relation between measured body fatness and mortality (16). We examined

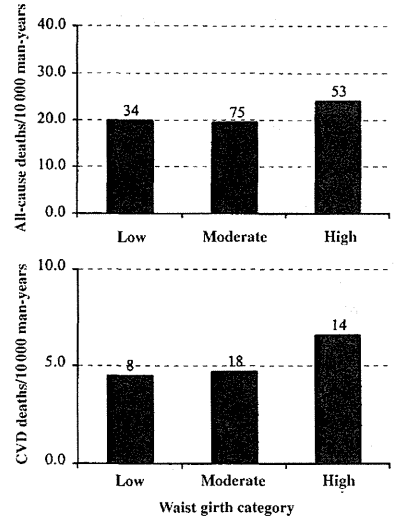

FIGURE 5. All-cause and cardiovascular disease (CVD) death rates per 10 000 man-years of follow-up, adjusted for age (single year) and examination year, across waist girth categories. Waist girth categories were low (<87 cm), moderate (87 to <99 cm), and high (≥99 cm). Numbers atop the bars represent the number of deaths.

TABLE 3
Waist circumference and relative risks (RRs) of all-cause mortality by cardiorespiratory fitness level in 14043 men[1]

Waist circumference category and cardiorespiratory fitness level	Deaths	Man years of follow-up	RR of death (95% CI)[2]	Multivariate RR of death (95% CI)[3]
	n	*man-y (%)*		
Low waist circumference (<87 cm)				
Fit (*n* = 3247)	26	18579 (23.8)	1.00	1.00
Unfit (*n* = 136)	8	1022 (1.3)	4.71 (2.13, 10.43)	4.88 (2.20, 10.83)
Moderate waist circumference (87 to <99 cm)				
Fit (*n* = 6237)	60	34189 (43.8)	1.08 (0.68, 1.71)	1.05 (0.66, 1.67)
Unfit (*n* = 616)	15	4211 (5.4)	2.08 (1.10, 3.93)	2.05 (1.08, 3.87)
High waist circumference (≥99 cm)				
Fit (*n* = 2645)	24	12994 (16.7)	0.98 (0.56, 1.72)	0.95 (0.54, 1.66)
Unfit (*n* = 1162)	29	7013 (9.0)	2.47 (1.45, 4.19)	2.40 (1.41, 4.07)

[1]Cardiorespiratory fitness level (fit or unfit) from reference 18.
[2]Adjusted for age (single year) and examination year.
[3]Adjusted for age (single year), examination year, smoking, alcohol intake, and parental history of ischemic heart disease.

the health effects of body composition among 21925 men after taking cardiorespiratory fitness into account. Our database is unique, with measures of body composition and maximal exercise test data on a large sample of men. We observed a direct relation between body fatness and all-cause and CVD mortality. However, being fit apparently decreased high mortality risk in obese men. This association was similar in nonsmokers and after exclusion for early mortality in both the entire population and in nonsmokers.

We observed similar results across strata of fat mass and FFM. Unfit men in the lowest quartile of fat mass and FFM had a greater risk of all-cause and CVD mortality than their fit counterparts. Fit men in the highest quartile of fat mass and FFM had a lower risk of all-cause and CVD mortality than did unfit, lean men. Our data indicate that cardiorespiratory fitness levels in men influence the health effects of obesity. We did not observe elevated mortality risk in men with high amounts of fat mass and FFM if they also were fit.

Several studies report that abdominal obesity is associated with elevated death rates (11–13). Although WHR has been commonly used to examine abdominal obesity, some studies suggest that waist girth rather than WHR is a better predictor of abdominal obesity (28–30). Measurement of waist girth instead of WHR for risk stratification is recommended in recent guidelines from the US National Institutes of Health and the World Health Organization (31, 32). Björntorp (33) reports that abdominal obesity, rather than peripheral obesity, also is associated with increased risk. Some studies show higher death rates in those with abdominal obesity who were underweight (a low BMI and high WHR) than in those without abdominal obesity who were overweight (a high BMI and low WHR) (11–13). No prior studies have reported the health effects of waist girth while also considering cardiorespiratory fitness. Our data show that fit men with low waist girth had lower risk of all-cause mortality than did unfit men in the same waist girth category. Unfit men with a high waist girth had a death rate 2.4 times greater than did the fit men with low waist girth, and fit men in the high waist girth category had a rate of all-cause mortality similar to fit men with low waist girth.

Our results support the hypothesis that moderate-to-high cardiorespiratory fitness reduces mortality risk across categories of body composition. Although most researchers agree that obesity is associated with health hazards and leanness is associated with health benefits, lean men in our study had increased longevity only if they were physically fit; furthermore, obese men who were fit did not have elevated mortality. In general, unfit, lean men were inactive and had low aerobic power despite their favorable IHD risk factor profiles at baseline, whereas fit, obese men were highly active and had high aerobic power at baseline.

A limitation of our study was that our subjects were white men in the middle and upper socioeconomic levels, although this homogeneity reduces the likelihood of confounding by socioeconomic characteristics. We hope that other investigators will examine these issues in other populations. The possibility of bias due to baseline health status is a consideration in all observational studies, including this one, but we think that serious bias is unlikely in this case because all study participants were given extensive medical examinations at baseline, which enabled us to exclude those with a history of myocardial infarction, stroke, or cancer. In addition, men who failed to achieve ≥85% of their age-predicted maximal heart rate on the maximal exercise test were excluded; this should have eliminated men who did not have a history of disease but were not feeling well as a result of an undiagnosed condition. We also adjusted the analyses for presence or absence of an abnormal electrocardiogram result. This exclusion eliminated men with angina, arrhythmia, or electrocardiographic abnormalities on the treadmill test, as well as resting electrocardiographic abnormalities. The effect of all these exclusion criteria was to minimize the possible bias of baseline subclinical disease. Another limitation of our study was that we estimated, rather than directly measured, residual lung volume during underwater weighing. Morrow et al (34) reported that the prediction accuracy of body fatness measured by densitometry when residual lung volume was estimated was only slightly better than anthropometric assessments. Nonetheless, the densitometry and skinfold-thickness estimates of body composition were likely to be more accurate measures of body fatness than BMI or height-weight indexes. Finally, we had only a one-time assessment of the exposure variables of cardiorespiratory fitness and body composition, and we do not know the extent to which these characteristics might have changed during follow-up. However, changes in the exposure variables during follow-up would cause misclassification and would be likely to lead to underestimates of RRs. Therefore, the true associations between fitness or body fatness and mortality may have actually been stronger than indicated by our results.

In summary, we found that obesity did not appear to increase mortality risk in fit men. For long-term health benefits we should focus on improving fitness by increasing physical activity rather than relying only on diet for weight control. Aerobic exercise improves IHD risk factors (35), and increases in physical activity or fitness extend longevity (18, 36). Although some studies show that there is no difference between diet and aerobic exercise in reducing IHD risk factors (37–39), or even report that diet is better than aerobic exercise for improving IHD risk factors in overweight men (40), our data show that fit men had greater longevity than unfit men regardless of their body composition or risk factor status. Obese men should be encouraged to increase their cardiorespiratory fitness by engaging in regular, moderate-intensity physical activity; this should benefit them even if they remain overweight.

We thank the physicians and technicians of the Cooper Clinic for collecting the data for this study; Kenneth H Cooper, for initiating the Aerobics Center Longitudinal Study; Carolyn E Barlow, for data management support; and Melba S Morrow, for editorial assistance. We are grateful for the guidance of the Scientific Advisory Board of the Cooper Institute for Aerobics Research.

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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男性	( )		( )		( )
	年齢	30-83の43.8歳			( )		前向き研究
	対象数	10000以上	空白		( )		( )
調査の方法	実測	( )					
アウトカム	予 防	な し	な し	な し	な し	(死亡)	( )
	維持・改善	な し	な し	な し	な し	( )	( )
図 表							
図表掲載箇所							
概 要 (800字まで)	背景:全身持久性体力と肥満はいずれも健康に関連するが、全死亡原因や心血管疾患(CVD)に対する相互関係は知られていない。目的:我々は、全身持久性体力を考慮すると同時に、痩せの健康利益と肥満の危険性をについて調査した。デザイン:これは、観察型コホートスタディであった。我々は、トレッドミルによる最大運動負荷テストおよび身体組成の評価を受けた30-83歳の21925名の男性を追跡調査した。平均8年間の追跡調査(176742人/年)で、428の死亡(CVDで144名、ガンで143名、他の原因で141名)が確認された。結果:年齢、調査年数、喫煙、アルコール摂取、虚血性心疾患の家族歴、低体力者(最大運動負荷テストにより低い全身持久性体力とされた者)等による補正後、痩せの者は、高体力者の全死亡率の2倍のリスクを持っていた(相対リスク2.07[1.16-3.69]95%信頼区間、P=0.01)。低体力者においても、痩せの者は、高体力で肥満である者より全死亡原因とCVDによる死亡で高いリスクがあった。我々は、死亡率に関して、脂肪と除脂肪において同様の結果を観察した。低体力の者は、すべての脂肪と除脂肪の範囲で高体力者に比べて、全死亡原因とCVDによる死亡に高いリスクがあった。同様に、低いウエスト(87cm以下)で低体力の者は、高いウエスト(99cm以上)で高体力者より全死亡率で高いリスクを持っていた。結論: 痩せの健康利益は体力が低いと少なくなり、、体力が高ければ肥満の危険を減少させる可能性がある。						
結 論 (200字まで)	普通以上の心肺体力を有する人では肥満は死亡を増加させる要因ではない。食事による肥満予防以上に、身体活動増加による体力改善が、健康増進に有用である。肥満の人は、習慣的運動により体力を増進させることが肝要である。						
エキスパートによるコメント (200字まで)	体力を高く保つことは有用であるが、肥満者の場合は体力を高めるための運動に加えて体重を落とすための食事介入をあわせて行わなければ、やせることは難しい。食事と運動の介入の両方が肥満者には必要。						

担当者　宮地 劉

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US weight guidelines: Is it also important to consider cardiorespiratory fitness?

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BACKGROUND: The health consequences of weight ranges across low to moderate and high levels of cardiorespiratory fitness are unknown.
OBJECTIVE: To evaluate the validity of the 1995 US weight guidelines, while considering cardiorespiratory fitness.
METHODS: We followed 21 856 men, aged 30–83 y, who had a complete preventive medical examination, including a maximal treadmill exercise test and body composition assessment. There were 427 deaths (144 cardiovascular disease (CVD); 143 cancer; 140 others) during an average of 8.1 y of follow-up. We used Cox proportional hazards regression to examine the relations among cardiorespiratory fitness, body mass index (BMI, kg/m^2), and all-cause and CVD mortality.
RESULTS: After adjustment for age, examination year, cigarette smoking and alcohol intake, we observed that men with a BMI of 19.0 to <25.0 and who were unfit had 2.3 times the risk of all-cause mortality (95% confidence interval (95% CI), 1.59–3.17, $P<0.001$) compared with fit men in this BMI group (reference category). Unfit men with a BMI of 25.0 to <27.8 also had a greater risk of all-cause mortality than fit men in the same BMI category. Fit but overweight men (BMI ≥ 27.8) had a similar rate of all-cause mortality as physically fit men of normal weight (BMI 19.0 to <25.0) and had a lower risk of all-cause mortality than unfit and normal weight men. Fit men of normal weight had the lowest CVD mortality, while unfit and overweight men experienced the highest CVD mortality. Unfit men had substantially higher CVD mortality than fit men in each BMI group.
CONCLUSIONS: Unfit men had higher all-cause and CVD mortality than fit men. The health benefits of normal weights appear to be limited to men who have moderate or high levels of cardiorespiratory fitness. These data suggest that the 1995 US weight guidelines may be misleading unless cardiorespiratory fitness is taken into account.

Keywords: cardiorespiratory fitness; BMI; mortality; weight standards; obesity

Introduction

According to the 1995 weight guidelines,[1] healthy weights for men and women are defined as body mass index (BMI, kg/m^2) from 19–25 kg/m^2, but the validity of these guidelines in relation to longevity remains less clear. Some studies show that the lowest all-cause mortality is associated with below-average weight[2,3] and another study shows an increased coronary heart disease (CHD) morbidity within the normal weight range.[4] We believe that cardiorespiratory fitness should also be considered when defining body weight standards. Cardiorespiratory fitness is an important mortality predictor,[5,6] is associated with weight control,[7] and may confound the relationship between BMI and mortality. Recent preliminary data from the Aerobics Center Longitudinal Study show a high BMI that is not associated with increased mortality in men who have moderate to high levels of cardiorespiratory fitness.[8] Extension of this earlier work with more detailed analyses confirms a protective association of fitness in those with a high BMI.[9] It appears, therefore, that being fit provides protection against all-cause mortality even in overweight or obese individuals.

The health consequences of weight guidelines need further investigation considering cardiorespiratory fitness. The purpose of this study is to extend our earlier analyses on the associations among cardiorespiratory fitness, BMI and mortality in men. We specifically assess the validity of the 1995 US weight guidelines, after taking cardiorespiratory fitness into account.

Methods

Study participants and measurements

Study participants included 21 856 men, aged 30–83 y, who had a preventive medical evaluation and body composition assessment between 1971 and 1989 at the Cooper Clinic in Dallas, Texas. All participants were residents of the US and had no personal history of myocardial infarction, stroke or cancer, at baseline. Participants gave their informed written consent for the medical evaluation and subsequent registration in the follow-up study, and the protocol was reviewed

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and approved annually by the Institutional Review Board.

The medical evaluation, performed after an overnight fast of at least 12 h, included a physical examination, anthropometry, electrocardiography, blood chemistry analysis, blood pressure assessment, a maximal exercise treadmill test, self-report of health habits, and demographic characteristics. Additional details of examination procedures are published elsewhere.[5,10]

Body weight and stature were measured with a standard physician's scale and stadiometer (Heathometer). BMI (kg/m^2) was used as an index of overweight and was classified as normal-weight (19.0–<25.0), mild-overweight (25.0–<27.8) and overweight (≥ 27.8), as specified in the US guidelines.[1] Body composition was assessed further by either hydrostatic weighing or measurement of skinfold fat, or both. We determined percent body fat by hydrodensitometry using Siri's two-component model.[11] Underwater weight was measured with a Chatillon 15 kg-scale following standard procedures.[12] The highest underwater weight of three trials was used to determine body volume. Residual lung volume was estimated from Goldman and Becklake.[13] The sum of seven skinfolds ($\Sigma 7$) was used to estimate percent body fat (%fat) from a generalized body density equation.[14] Skinfold fat was measured at chest, abdomen, thigh, axilla, triceps, subscapular and suprailium, with a Lange caliper (Cambridge Scientific Industries, Cambridge, MD) to the nearest 1 mm. We used either skinfold fat in men who had only the $\Sigma 7$ skinfold measurements, or hydrostatistically determined %fat in men who underwent hydrostatic weighing or who provided both hydrostatic weighing and $\Sigma 7$ skinfold measurements. The mean and standard deviation (s.d.) for %fat were nearly identical for the two methods in the men who had both measurements. We also did not find any differences of mortality rates in these two methods when we included a dummy variable ($\Sigma 7$ skinfolds or densitometry) in the multivariate analysis.

Alcohol intake and cigarette smoking habit were assessed with a self-reported questionnaire. Alcohol consumption was classified according to weekly alcohol intake: none, light (<15 units), moderate (15–≤ 30 units), and heavy (≥ 31 units). One unit of alcohol intake was defined as a bottle/can of beer (12 oz), a glass of wine (5 oz), or 1.5 oz of hard liquor. Smoking status was classified as never smokers, former smokers or current smokers, at three levels (<20, 20–<40 and ≥ 40 cigarettes/d).

Cardiorespiratory fitness was measured by a maximal treadmill exercise test as described previously.[5] All participants achieved at least 85% of their age-predicted maximal heart rate (220 – age in years) during the treadmill test. Total treadmill endurance time was used as an index of aerobic power, with time on treadmill with this protocol correlated highly with maximal oxygen uptake ($r = 0.92$).[15] Men in the least-fit 20% of each age group were classified as physically unfit, and all others as physically fit.[6] All participants were cross-tabulated by BMI categories and cardiorespiratory fitness levels as follows: (1) normal-weight and physically fit, (2) normal-weight and unfit, (3) mild-overweight and fit, (4) mild-overweight and unfit, (5) overweight and fit, and (6) overweight and unfit.

Mortality surveillance

All participants were followed for mortality from the baseline examination to the date of death or to 31 December 1989. Deaths among study participants were identified from the National Death Index, and official death certificates of decedents were obtained from the department of vital records in the respective state. The underlying cause of death was coded by a nosologist according to the *International Classification of Diseases* (*Revised 9th edn*, US Govt Printing Office, Washington, 1979), with cardiovascular disease (CVD) defined as codes 390–449.9.

Statistical analysis

All-cause and CVD death rates per 10 000 man-years of follow-up, adjusted for age and examination year, were calculated across BMI categories. Proportional hazards regression was used to examine the relations among cardiorespiratory fitness, BMI, and all-cause and CVD mortality.[16] The empirical cumulative hazard plots documented that the proportional hazards assumption was met. Separate models were also computed to examine this relation in nonsmokers and in nonsmokers with an additional exclusion for early mortality (the first five years of follow-up). Men who were normal weight and fit were selected as the reference category. The relative risks (RRs) of all-cause and CVD mortality were estimated after adjustment for age and examination year, and further adjustment for cigarette smoking and alcohol use. We did not control for the obesity-related biological factors such as hypertension, diabetes and hypercholesterolemia at baseline, as recommended by Manson *et al*,[2] although the RR showed little change when these factors were included in the multivariate model. The 95% confidence interval (95% CI) for each RR were calculated. All statistical procedures were performed by Statistical Analysis Systems software.[17]

Results

We followed 21 856 men, aged 30–83 y at baseline. There were 427 deaths (144 CVD; 143 cancer; 140 others) during 176 189 man years of observation. General descriptive and physiological characteristics of the baseline participants by BMI categories (19–<25, 25–<27.8 and ≥ 27.8) across cardiorespiratory fitness levels (fit and unfit) are presented in Table 1. Treadmill time was progressively lower with higher

Table 1 Baseline characteristics (mean ± s.d.) of participants by body mass index (BMI) and cardiorespiratory fitness levels in men, Aerobics Center Longitudinal Study, 1971–1989

	Cardiorespiratory fitness and BMI (kg/m²)						
	Normal-weight (19.0– < 25.0)		*Mild-overweight (25.0– < 27.8)*		*Overweight (BMI ≥ 27.8)*		
Variable	*Fit*	*Unfit*	*Fit*	*Unfit*	*Fit*	*Unfit*	*All men (n = 21856)*
Age (y)	43.2 ± 9.0	43.2 ± 9.1	44.4 ± 8.9	43.5 ± 8.5	45.3 ± 8.9	43.3 ± 8.2	43.9 ± 8.9
Height (cm)	178.9 ± 6.3	177.6 ± 6.6	178.9 ± 6.3	178.0 ± 6.5	178.9 ± 6.5	178.3 ± 6.5	178.7 ± 6.4
Weight (kg)	74.4 ± 6.6	73.9 ± 6.9	84.1 ± 6.5	83.7 ± 6.6	95.8 ± 9.3	100.8 ± 13.9	83.4 ± 12.3
Treadmill time (min)	20.5 ± 4.5	11.7 ± 2.7	18.4 ± 3.9	11.6 ± 2.5	16.6 ± 3.4	11.0 ± 2.5	17.5 ± 5.1
Systolic BP (mmHg)	118.9 ± 13.4	120.1 ± 14.2	120.9 ± 13.2	123.2 ± 13.9	123.8 ± 13.3	126.2 ± 13.8	121.2 ± 13.6
Diastolic BP (mmHg)	78.6 ± 9.1	79.9 ± 9.4	80.8 ± 9.2	82.5 ± 9.4	83.4 ± 9.3	85.5 ± 9.9	81.0 ± 9.5
Triglycerides (mmol/L)	1.2 ± 0.9	1.7 ± 1.9	1.5 ± 1.1	2.0 ± 1.7	1.8 ± 1.3	2.4 ± 1.9	1.6 ± 1.3
Serum glucose (mmol/L)	5.4 ± 0.7	5.6 ± 1.3	5.6 ± 0.7	5.7 ± 1.0	5.7 ± 0.9	5.9 ± 1.5	5.6 ± 0.9
Total cholesterol (mmol/L)	5.3 ± 1.2	5.6 ± 1.0	5.6 ± 1.1	5.8 ± 1.1	5.7 ± 1.1	5.8 ± 1.1	5.5 ± 1.2
BMI (kg/m²)	23.2 ± 1.3	23.4 ± 1.3	26.3 ± 0.8	26.4 ± 0.8	29.9 ± 1.9	31.7 ± 3.6	26.1 ± 3.4
Percent body fat	16.9 ± 5.4	21.1 ± 6.6	21.1 ± 4.9	23.7 ± 5.4	25.7 ± 4.9	28.6 ± 5.7	21.1 ± 6.6
Inactive (%)	24.4	73.1	30.2	73.5	34.8	68.0	36.8
Systolic BP ≥ 140 mmHg (%)	7.8	11.4	9.8	13.7	13.0	18.7	10.7
Fasting glucose ≥ 6.7 mmol/L (%)	2.1	4.4	3.7	6.6	6.7	11.9	4.5
Abnormal electrocardiogram (%)	5.5	11.3	6.2	11.2	7.1	7.9	6.7
Family history of CHD (%)	26.8	28.3	29.4	29.5	30.2	29.8	28.6
History of hypertension (%)	10.2	16.3	16.0	22.2	21.8	29.7	16.4
History of diabetes (%)	1.9	5.5	2.1	5.4	1.8	5.0	2.6
Current smoker (%)	15.6	41.2	18.7	40.1	17.1	31.3	20.8
Past smoker (%)	29.2	19.4	29.9	19.8	29.7	23.1	27.9

BP = blood pressure; CHD = coronary heart disease.

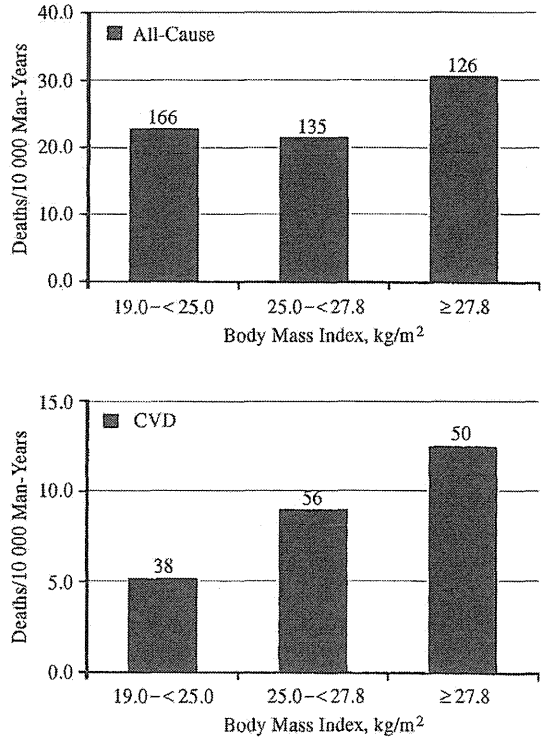

Figure 1 All-cause and cardiovascular disease (CVD) death rates per 10 000 man-years of follow-up, adjusted for age (single year) and examination year, across body mass index (BMI, kg/m²) categories. Numbers above the bars represent number of deaths.

BMIs in fit men, but maintained a constant trend across BMI categories in unfit men. Men who were normal weight and physically fit had the longest average treadmill time. Body fatness was greater in higher BMI groups in both fit and unfit men, but fit men had a lower degree of body fatness compared with their unfit counterparts in each BMI group. In general, unfit men had less favorable CVD risk factor profiles than their fit counterparts in the same BMI category, with a higher prevalence of physical inactivity, elevated systolic blood pressure, fasting glucose, abnormal electrocardiogram and history of hypertension and diabetes.

Figure 1 presents all-cause and CVD death rates per 10 000 man-years of follow-up, adjusted for age and examination year, across BMI categories. All-cause and CVD death rates were higher in men with a BMI of $\geq 27.8\,kg/km^2$. Men in the normal weight group had a low death rate for all-cause and CVD, while overweight men had a high death rate for all-cause and CVD.

Table 2 presents the relations among cardiorespiratory fitness, BMI, and all-cause mortality. The RRs of all-cause mortality for BMI categories across cardiorespiratory fitness levels are provided for all men. After adjustment for age and examination year, unfit men were at higher risk of all-cause mortality than their fit counterparts in all BMI categories, with RRs being from 1.7–2.2 higher in the unfit. Fit and overweight men had a similar rate of all-cause mortality as fit, normal weight men, but had a lower rate of all-cause mortality when compared with unfit and normal weight men. These results were similar after additional adjustment for cigarette smoking and alcohol intake.

The associations also remained in nonsmokers and in nonsmokers with exclusion for early mortality, with adjustment for age, examination year and alcohol intake (Figure 2). For nonsmokers, fit and normal weight men experienced the lowest all-cause mortality,

Table 2 Body mass index (BMI, kg/m^2) and relative risks of all-cause mortality by cardiorespiratory fitness levels in men, Aerobics Center Longitudinal Study

Fitness[a]	*BMI*	*Deaths (n)*	*Subjects (n)*	*Man years of follow-up (%)*	*RR of death (95% CI)*[b]	*Multivariate RR of death (95% CI)*[c]
Fit	19.0– < 25.0[d]	121	8123	64 233 (37)	1.00	1.00
Unfit	19.0– < 25.0[d]	45	939	10 412 (6)	2.24 (1.59–3.16)	2.25 (1.59–3.17)
Fit	25.0– < 27.8	89	6073	45 877 (26)	0.96 (0.73–1.26)	0.96 (0.73–1.26)
Unfit	25.0– < 27.8	46	1296	14 358 (8)	1.68 (1.19–2.36)	1.68 (1.19–2.37)
Fit	≥ 27.8	49	3307	21 683 (12)	1.08 (0.77–1.50)	1.08 (0.77–1.50)
Unfit	≥ 27.8	77	2118	19 626 (11)	2.24 (1.68–2.98)	2.24 (1.68–2.98)

[a] Cardiorespiratory fitness (fit *vs* unfit[6]).
[b] Adjusted for age (single year) and examination year.
[c] Adjusted for age (single year), examination year, smoking habit (never, former, or current (< 20, 20– < 40 or ≥ 40 cigarettes/d)) and alcohol intake (none, light, moderate or heavy).
[d] US weight guidelines: US Department of Agriculture.[3]
RR = relative risk; 95% CI = 95% confidence interval.

while unfit and overweight men experienced the highest all-cause mortality. However, unfit, normal weight men had 2.1 times the risk of all-cause mortality of fit and normal weight men (95% CI, 1.35–3.41, $P = 0.001$). When we excluded the first five years of follow-up among nonsmokers, unfit, normal weight men still had a greater risk of all-cause mortality, with a RR of 2.2 compared with their fit counterparts (95% CI = 1.24–3.83, $P = 0.007$). Men who were unfit and overweight had the highest all-cause mortality (RR = 2.88, 95% CI, 1.89–4.40, $P = 0.001$). However, fit and overweight men were at lower risk of all-cause mortality than unfit and normal weight men.

Figure 2 also presents the associations among BMI, cardiorespiratory fitness, and CVD mortality, with adjustment for age, examination year, smoking status and alcohol intake. Men who were fit and normal weight experienced the lowest CVD mortality, while men who were unfit and overweight experienced the highest CVD mortality. Unfit, normal weight men also had a greater risk of CVD mortality, with RR of 2.8 (95% CI, 1.43–5.49, $P = 0.003$) compared with the reference group. The RRs of CVD mortality increased with increasing BMIs in both fit and unfit men, respectively. Men who were unfit and overweight had 4.8 (95% CI, 2.85–8.05, $P < 0.001$) times the risk of CVD mortality of fit, normal weight men. In contrast, fit and overweight men had less risk of CVD mortality than unfit men of normal weight. In the mild-overweight range, unfit men had 3.7 times (95% CI, 2.05–6.50, $P < 0.001$) and fit men had 1.8 times (95% CI, 1.07–3.01, $P = 0.03$) the risk of CVD mortality of fit and normal weight men.

Discussion

The purpose of this study was to examine the relation of the 1995 US weight guidelines to mortality, after taking cardiorespiratory fitness into account. The major finding is that men, within the recommended US weight guidelines but who were unfit, had a high risk of all-cause and CVD mortality when compared with overweight men who were fit. Unfit and mildly overweight men also had a greater risk of all-cause and CVD mortality than their fit peers.

We observed similar results in nonsmokers and in nonsmokers with exclusion for early mortality. For nonsmokers, fit and normal weight men had the lowest all-cause mortality, but normal weight men who were unfit had a high risk of all-cause mortality. When we additionally excluded the first five years of follow-up, similar results were obtained.

Although the current US weight guidelines recommend healthy weights as BMIs from 19–25 kg/m^2, the optimal level of body weight in relation to longevity still remains controversial. Some studies show that the lowest all-cause mortality is associated with the normal weight range,[18,19] while others show that the lowest all-cause mortality is associated with leanness.[2,4] According to the American Cancer Study,[18] the lowest all-cause mortality occurs in those with a BMI from 20–25 kg/m^2, which is similar to the Norwegian experience[19] of BMI from 21–25 kg/m^2. However, these findings are limited, due to the lack of controlling for either smoking effect or illness-related early mortality.[20] Conversely, recent data from the Nurses' Health Study[4] showed elevated CHD morbidity across the normal weight range. Our data show that the health benefits of weight in this range are limited to the men who have moderate or high levels of cardiorespiratory fitness. We observed a low risk of all-cause and CVD mortality in fit men with a BMI of 19–25 kg/m^2, but this was not the case with the unfit in this BMI group. Thus, the current US weight guidelines may be misleading, unless cardiorespiratory fitness is also considered. These data suggest that it may be desirable to obtain healthy weights with aerobic exercise rather than to diet for weight loss. In fact, it is clear that aerobic exercise increases aerobic power and preserves fat-free mass, while diet does not.[21–24]

An interesting finding of this study is that overweight but fit men were at low risk of all-cause mortality. These fit but overweight men had lower

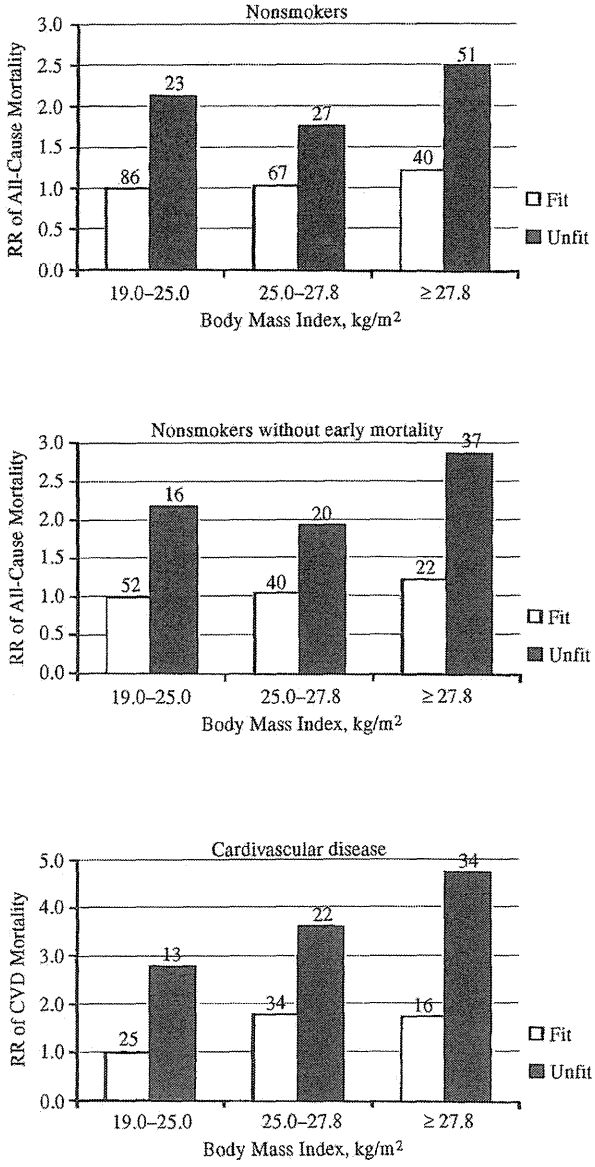

Figure 2 Body mass index (BMI, kg/m^2) and relative risks (RR) of all-cause and cardiovascular disease (CVD) mortality by cardiorespiratory fitness levels in men. For nonsmokers, the RR has been adjusted for age (single year), examination year, and alcohol intake (none, light, moderate or heavy). For CVD mortality, the RR has been adjusted for age (single year), examination year, smoking habit (never, former or current (<20, 20 to <40 or ≥ 40 cigarettes/d)), and alcohol intake (none, light, moderate or heavy). Early mortality indicates the first five years of follow-up. Numbers above the bars represent number of deaths. Unfit men are the least-fit 20% of each age group, and fit refers to all other men.[6]

%fat and higher aerobic power than unfit, overweight men (Table 1). When we further analyzed the mortality rates of these fit and unfit overweight men including either BMI or %fat as continuous variables with other risk factors in the multivariate analysis, the mortality differences between fit and unfit men in the overweight category was unchanged. Thus, it seems that the increased longevity we observed in overweight but fit men may be due to high fitness rather than differences in body fatness in the two fitness groups.

In this study, we do not intend to minimize the risk of overweight, but we do emphasize that increasing fitness may be more important than maintaining healthy weights. It is well documented that higher levels of physical fitness are associated with lower incidence of all-cause and CVD mortality.[5,25] It is also established that an increase in fitness improves CVD risk factors[26] and extends longevity.[6] Thus, we strongly recommend to public health policy makers the importance of maintaining acceptable levels of cardiorespiratory fitness.

Although our findings are limited to Caucasian men in middle and upper socioeconomic levels, this is the first study that presents data on longevity for the US weight guidelines categories, combined with cardiorespiratory fitness levels. Our data clearly show that greater longevity in men meeting the normal weight criterion of the 1995 US weight guidelines is limited to men who have moderate or high levels of cardiorespiratory fitness. These data suggest that cardiorespiratory fitness should be considered when defining body weight standards.

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対象の内訳		ヒト	動物	地　域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男性	( )		( )		( )
	年齢	30-83歳			( )		前向き研究
	対象数	10000以上	空白		( )		( )
調査の方法	実測	( )					
アウトカム	予　防	心疾患予防	なし	なし	なし	( )	( )
	維持・改善	なし	なし	なし	なし	( )	( )
図　表							
図表掲載箇所							
概　要 (800字まで)	背景：低～中水準および高水準の体力における体重範囲からみた健康の意義については知られていない。目的：1995年の米国における体力を考慮した標準体重のガイドラインの妥当性を検討すること。方法：最大トレッドミル負荷テストや身体組成評価を含む予防診察を終えた30-83歳の21856人の男性を追跡調査した。427名の死亡（心血管疾患（CVD）で144名；ガンで143名；その他で140名）が、平均8.1年の期間で確認された。我々は、体力、BMI、全死亡率およびCVDによる死亡率でそれぞれの関係を検討するため、Coxの比例ハザード回帰モデルを使用した。結果：年齢、調査年、喫煙、およびアルコール摂取量による補正後、BMI が19.0 < 25.0の中で、体力のある人とない人を比較したところ、全死亡率が2.3倍（95%信頼区間 1.59-3.17, P< 0.001）であることを観測した。また、BMIが25.0 < 27.8で体力の低い者は、同じカテゴリーで体力の高い者に比べ全死亡においてより高いリスクであった。体力は高いが過体重の人（BMI ≧ 27.8）は、体力が高く標準体重の人（BMI：19.0 < 25.0）と全死亡原因で同率であり、体力の低い標準体重の人に比べて低率であった。標準体重で体力の高い人は、低いCVDによる死亡率であったが、過体重で体力の低い人は高いCVDによる死亡率であった。体力の低い人は、おのおののBMI群において、体力の高い人よりも大体は高いCVDによる死亡率であった。結論：体力の低い人は、体力の高い人より全死亡原因とCVDによる死亡率は高かった。標準体重による健康利益は、中程度または高水準の体力を持っている人（男性）ではあまり顕著ではないように思われる。これらのデータより、1995年の米国における標準体重のガイドラインは、体力が考慮に入れられない限り誤解を招くかもしれない。						
結　論 (200字まで)	全体として、低体力者は、標準体力者に比べて高い総死亡および循環器病死亡率であった。従って、標準体重である利益は、標準以上の心肺体力を有している者に限って認められる(やせていればすべてよし、という訳ではない)。健康のための体重のガイドラインを作成するに当たって、体重のみでなく、心肺機能も考慮に入れるべきである。						
エキスパートによるコメント (200字まで)	フィットネスかファットネスか？どちらも独立して生活習慣病予防に寄与することを示した価値のある研究。						

担当者　宮地 劉

ORIGINAL ARTICLE

The Association Between Cardiorespiratory Fitness and Risk of All-Cause Mortality Among Women With Impaired Fasting Glucose or Undiagnosed Diabetes Mellitus

G. William Lyerly, PhD; Xuemei Sui, MD; Carl J. Lavie, MD; Timothy S. Church, MD, PhD; Gregory A. Hand, PhD; and Steven N. Blair, PED

OBJECTIVE: **To evaluate the independent and joint associations among cardiorespiratory fitness (CRF), body mass index, and risk of mortality from any cause among women with impaired fasting glucose (IFG) or undiagnosed diabetes mellitus (DM).**

PATIENTS AND METHODS: **Female patients (N=3044; mean age, 47.4 years) with IFG or undiagnosed DM completed a maximal exercise treadmill test (between January 26, 1971, and March 21, 2001). The women had no history of a cardiovascular disease event or diagnosed DM at baseline. Cardiorespiratory fitness was defined categorically as low (bottom 20%), moderate (middle 40%), or high (upper 40%) according to previously published Aerobics Center Longitudinal Study guidelines. Body mass index was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2).**

RESULTS: **During a 16-year follow-up period, 171 deaths occurred. There was an inverse association between CRF and all-cause mortality risk. Women with moderate or high CRF were at lower risk of mortality (moderate CRF, 35% lower; high CRF, 36% lower; P_{trend}=.03) than those with low CRF. An exercise capacity lower than 7 metabolic equivalents was associated with a 1.5-fold higher risk of death than an exercise capacity of 9 metabolic equivalents or higher (P_{trend}=.05). The multivariate adjusted hazard ratios (HRs), including adjustments for CRF, were higher for heavier patients than for patients of normal weight (overweight patients: HR, 0.86; 95% confidence interval, 0.57-1.30; obese patients: HR, 1.19; 95% confidence interval, 0.70-2.03; P_{trend}=.84). Combined analyses showed that women who were overweight or obese and unfit (low CRF) were at more than twice the risk of death than women who were of normal weight and fit (moderate or high CRF).**

CONCLUSION: **Cardiorespiratory fitness, not body mass index, is a significant predictor of all-cause mortality among women with IFG or undiagnosed DM. Assessing CRF levels provides important prognostic information independent of traditional risk factors.**

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ACLS = Aerobics Center Longitudinal Study; BMI = body mass index; CI = confidence interval; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; DM = diabetes mellitus; HR = hazard ratio; IFG = impaired fasting glucose; MET = metabolic equivalent

Impaired fasting glucose (IFG) has been associated with an elevated risk of premature mortality.[1,2] Recently, greater attention has been directed toward IFG in efforts to reduce the development of diabetes mellitus (DM) and cardiovascular disease (CVD). In 2003, the American Diabetes Association recommended that the definition of IFG be expanded to include fasting glucose concentrations between 100 mg/dL and 125 mg/dL (to convert to mmol/L, multiply by 0.0555), as opposed to the previous concentrations of 110 mg/dL to 125 mg/dL.[3] In 2002, 54 million people in the United States aged 20 years or older had IFG, representing 26% of the total US population; this number would be higher if the more stringent definition were used.[4] In 2005, 20.8 million people (7% of the total US population) in the same age group had DM.[4] Half of these cases of DM were expected to be undiagnosed and asymptomatic.[5] The risk of premature CVD and death is 2 to 4 times higher for persons with DM than for those of equivalent age without DM.[6,7] Therefore, the detection and treatment of CVD risk factors may be particularly important for preventing CVD among persons with asymptomatic IFG and DM.

A low cardiorespiratory fitness (CRF) level is a predictor of all-cause mortality among men with type 2 DM.[8] Recent studies[9,10] have also reported a strong and independent association between CRF and mortality among men with DM in all body mass index (BMI) and body fatness groups.[11] However, most previous studies have focused on the association between CRF and mortality among either men only or men and women who are sedentary but apparently healthy.[8,9,12]

For editorial comment, see page 776

There is a strong independent association between obesity and all-cause mortality among both men and women.[13-17] Most studies have found that this association is J-shaped or U-shaped. Like CRF studies, most obesity studies have focused on the association between obesity and mortality in women, men, or both men and women in the general population, regardless of any disease state.[13-16]

Few studies have focused on persons with IFG and undiagnosed DM, especially women. To our knowledge, no

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TABLE 1. **Stratification of CRF by Age Groups as Determined by Duration of Treadmill Exercise Test and Oxygen Uptake in METs Among the Aerobics Center Longitudinal Study Population**

Age (y)	CRF category	Duration (min)	METs
20-39	Low	<10.3	<8.2
	Moderate	10.3-15.0	8.2-10.4
	High	>15.0	>10.4
40-49	Low	<8.9	<7.6
	Moderate	8.9-13.0	7.6-9.4
	High	>13.0	>9.4
50-59	Low	<7.0	<6.7
	Moderate	7.0-10.7	6.7-8.5
	High	>10.7	>8.5
≥60	Low	<5.5	<5.8
	Moderate	5.5-9.0	5.8-7.6
	High	>9.0	>7.6

CRF = cardiorespiratory fitness; MET = metabolic equivalent.
Adapted from *Am J Epidemiol*,[22] with permission.

previous study has concurrently evaluated the association between CRF, overweight or obesity status as reflected by BMI, and death among women with IFG. Therefore, the primary aim of this study was to evaluate the association between CRF and risk of all-cause mortality among women with IFG or undiagnosed DM.

PATIENTS AND METHODS

The Aerobics Center Longitudinal Study (ACLS) is a prospective epidemiological investigation of patients who underwent an extensive clinical examination. We reviewed the records of 3044 female patients aged 20 to 79 years (mean, 47.4 years) who had IFG or undiagnosed DM and had completed a preventive medical evaluation for determination of baseline values between January 26, 1971, and March 21, 2001. Impaired fasting glucose was defined as a fasting glucose concentration of 100 mg/dL to 125.9 mg/dL,[18] and undiagnosed DM was defined as a fasting glucose concentration of 126 mg/dL or higher among patients with no history of DM and no current therapy with hypoglycemic medication. At baseline, no patients had experienced CVD (myocardial infarction or stroke), and all were able to complete an exercise stress test to at least 85% of their age-predicted maximal heart rate. Details of the study design and the characteristics of the cohort have been reported previously.[6,9,19] Most patients were white, well-educated, and from the middle or upper socioeconomic strata. The Institutional Review Board of the Cooper Institute reviewed and approved the study protocol annually.

Clinical Examination

After giving written informed consent, patients underwent a baseline clinical examination that included analyses of fasting blood chemistry, elicitation of personal and family health history, anthropometry, determination of resting blood pressure, and a maximal graded exercise test. Technicians administered all procedures according to a standard manual of operations. Height was measured with a stadiometer, and weight was measured with a standard physician's scale. Body mass index was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Patients who were underweight (BMI <18.5 kg/m^2) were excluded from the study. Patients were placed into BMI groups according to standard clinical definitions: normal weight, less than 25.0 kg/m^2; overweight, 25.0 to 29.9 kg/m^2; and obese, 30.0 kg/m^2 or more. Resting blood pressure was determined by auscultation and was recorded as the first and fifth Korotkoff sounds.[20] Patients were considered to have hypertension if they had a history of this diagnosis by a physician or if they had a resting systolic pressure of 140 mm Hg or higher or a diastolic pressure of 90 mm Hg or higher. Standardized automated bioassays were used to determine serum concentrations of lipids and glucose. Hypercholesterolemia was defined as a total cholesterol concentration of 240 mg/dL (to convert to mmol/L, multiply by 0.0259) or higher. Information about smoking habits (current smoker or not), alcohol intake (number of drinks per week), and family history of DM was obtained with a standardized questionnaire.

Cardiorespiratory fitness was defined as low, moderate, or high according to previously published age-specific distributions of maximal exercise duration from the ACLS population[21,22] (Table 1). These categories are determined by the time (in minutes) on a treadmill exercise test and by oxygen uptake (in metabolic equivalents [METs]). The test of symptom-limited maximal treadmill exercise was performed according to a modified Balke protocol.[21,23] Patients began walking at a speed of 88 m/min without elevation. After the first minute, the elevation was increased to 2%; thereafter, the elevation was increased by 1% per minute until the 25th minute. After 25 minutes, the elevation did not change but the speed was increased by 5.4 m/min each minute until the test end point. Patients were encouraged to give maximal effort. The test end point was volitional exhaustion or termination by the physician for medical reasons. Exercise duration on this protocol is strongly positively correlated (r=0.94) with measured maximal oxygen uptake.[24] One MET is equal to an uptake of 3.5 mL of oxygen per kilogram of body weight per minute, as calculated from the final treadmill speed and grade.[25]

A Framingham risk score was computed for each patient by using the sex-specific algorithm for total cholesterol concentration.[26] Risk points were assigned to risk factor categories and were then summed. The point total was used to assign 10-year probabilities of primary CVD events; the probabilities were lower than 10% for the low-risk group, 10% to 19% for the intermediate-risk group, and 20% or higher for the high-risk group.[27]

Mortality Surveillance

Patients were followed up from the date of their baseline examination to the date of their death or, for survivors, until December 31, 2003. Vital status was ascertained primarily by using the National Death Index. When this method is used, more than 95% of mortality follow-up is complete. The underlying cause of death was coded according to the *International Classification of Diseases, Ninth Revision* (CVD, 390-449.9) before 1999 and according to the *Tenth Revision* (CVD, I00-I78) from 1999 to 2003. We restricted the analyses to women who had been followed up for least 1 year so that we could eliminate any possibility of increased risk due to undetected disease at baseline.

Statistical Analyses

Descriptive statistics were used to summarize baseline characteristics on the basis of vital status. Cox proportional hazards regression analysis was used to estimate rates (per 10,000 woman-years), hazard ratios (HRs), and 95% confidence intervals (CIs) for all-cause mortality according to exposure categories. Unless otherwise noted, all multivariable models included baseline age (years), examination year, current smoker (yes/no), alcohol intake (≥5 drinks per week or not), hypertension (yes/no), hypercholesterolemia (yes/no), and family history of DM (present or not). Tests of linear trends across exposure categories were computed by using ordinal scoring. To assess the shape of the CRF-mortality curve or the BMI-mortality curve, we examined the risk of overall death across increments of METs or BMI. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure; no appreciable violations were noted. All statistical analyses were performed with SAS software (version 9.1; SAS Institute, Cary, NC). *P* values are 2-sided; statistical significance was assigned at the level of $P<.05$.

RESULTS

During a mean follow-up period of 15.6 years, 171 deaths (48 due to CVD) occurred. On the basis of the Framingham risk scores, more than 90% of women in the study were members of the low-risk group. Of the entire group of women, 66.4% were of normal weight, 22.2% were overweight, and 11.4% were obese. Compared with survivors, decedents tended to be older, had a lower level of CRF, and were more likely to be current smokers or to have hypertension or hypercholesterolemia (Table 2). Univariate Cox regression analyses showed that both CRF and BMI were associated with a higher risk of mortality (Table 2). The risk of dying was more than 10 times higher for women aged 60 years or older than for women aged 20 to 39 years (Table 2).

Table 3 shows the independent association between CRF, BMI, and all-cause mortality. The all-cause death rate (adjusted for age and examination year) per 10,000 woman-years was 52.0% for women in the low CRF group, 33.3% for those in the moderate CRF group, and 31.0% for those in the high CRF group ($P_{trend}=.01$). After the analyses were adjusted for covariables (age, examination year, current smoking, alcohol intake, hypertension, hypercholesterolemia, and family history of DM), the risk of death was 35% lower for the moderate CRF group and 36% lower for the high CRF group than for the low CRF group ($P_{trend}=.03$). The inverse association was slightly attenuated but remained statistically significant after additional adjustments for BMI ($P_{trend}=.03$). The multivariable-adjusted HR (adjusted for age, examination year, current smoking, alcohol intake, hypertension, hypercholesterolemia, and family history of DM) for all-cause mortality was 1.00 for women with a BMI lower than 25.0 kg/m^2, 0.91 for women with a BMI of 25.0 to 29.9 kg/m^2, and 1.32 for women with a BMI of 30.0 kg/m^2 or higher ($P_{trend}=.51$), respectively. After an additional adjustment for baseline treadmill test duration, the association between BMI and mortality risk remained nonsignificant ($P_{trend}=.84$).

To further examine the dose-response characteristics of the association among CRF, BMI, and risk of all-cause mortality, we computed the age-adjusted death rates (per 10,000 woman-years) for CRF categories defined by 1-MET increments (Figure, left) and for BMI categories (2.5 units; Figure, right). An exercise capacity lower than 7 METs was associated with a 1.5-fold higher death risk than an exercise capacity of 9 METs or higher ($P_{trend}=.05$). The HR across the incremental METs group is 1.00; the HRs (95% CIs) for the categories of exercise capacities are as follows: 0.78 (95% CI, 0.51-1.20) for the group with an exercise capacity of 7.0 to 7.9 METs, 0.72 (95% CI, 0.49-1.08) for the group with an exercise capacity of 8.0 to 8.9 METs, and 0.67 (95% CI, 0.43-1.03) for the group with an exercise capacity of 9.0 METs or higher. No association trend was observed between BMI and death ($P_{trend}=.24$).

Finally, we examined the combined effect of CRF and BMI (Table 4) and found statistical evidence of an interaction between CRF and BMI in predicting all-cause mortality ($\chi^2=23.86$; $P<.001$). The death rates among unfit women with higher BMI (≥25 kg/m^2) were more than twice those among fit women with higher BMI. When fit women with normal BMI were used as the comparator group, the highest mortality risk was found for unfit women with higher BMI (HR, 2.26; 95% CI, 1.27-4.03).

DISCUSSION

We addressed the single and joint associations among CRF, BMI, and the risk of mortality among women with IFG

TABLE 2. **Characteristics of 3044 Study Patients at Baseline According to Their Survival Status: ACLS, 1971-2003**[a,b]

Characteristic	Study patients at baseline	Survivors (n=2873)	Decedents (n=171)	Crude hazard ratio (95% CI)[c]	*P* value[d]
Age (y)	47.4±10.1	47.0±10.0	53.7±9.7	1.09 (1.08-1.11)	<.001
20-39	693 (22.8)	678 (23.6)	15 (8.8)	1.00 (referent)	
40-49	1029 (33.8)	996 (34.7)	33 (19.3)	1.98 (1.08-3.65)	
50-59	971 (31.9)	896 (31.2)	75 (43.9)	5.45 (3.13-9.49)	
≥60	351 (11.5)	303 (10.5)	48 (28.1)	13.20 (7.36-23.68)	
Maximal METs	9.1±2.1	9.1±2.1	7.8±2.0	0.79 (0.72-0.86)	<.001
Body mass index (kg/m^2)	24.4±4.6	24.4±4.6	24.5±4.6	1.05 (1.02-1.08)	.002
Waist girth (cm)	71.6±21.8	71.6±21.8	70.7±21.2	1.01 (0.99-1.02)	.38
Lipid levels (mg/dL)					
Total cholesterol	210.3±40.5	209.4±40.1	224.7±44.2	1.01 (1.00-1.01)	<.001
HDL-C	61.5±15.8	61.6±15.8	60.7±17.1	1.00 (0.99-1.02)	.58
Triglycerides	107.8±78.1	106.9±77.5	122.8±86.3	1.001 (1.000-1.002)	.005
Fasting blood glucose (mg/dL)	106.6±11.0	106.3±9.9	110.6±22.8	1.01 (1.01-1.02)	<.001
Blood pressure (mm Hg)					
Systolic	117±16	117±15	125±19	1.03 (1.02-1.04)	<.001
Diastolic	78±10	78±10	79±11	1.02 (1.00-1.03)	.04
Current smoker	272 (8.9)	234 (8.1)	38 (22.2)	2.15 (1.50-3.09)	<.001
≥5 Alcohol drinks per week	530 (17.4)	521 (18.1)	9 (5.3)	0.84 (0.43-1.67)	.63
Hypertension	739 (24.3)	679 (23.6)	60 (35.1)	1.81 (1.32-2.48)	.0002
Hypercholesterolemia	646 (21.2)	588 (20.5)	58 (33.9)	1.86 (1.36-2.56)	.0001
Family history of diabetes	298 (9.8)	296 (10.3)	2 (1.2)	0.46 (0.11-1.88)	.28
Framingham risk score (10-y CVD risk) (%)[e]	3.8±3.9	3.5±3.6	8.1±6.7		
<10	2777 (91.2)	2667 (92.8)	110 (64.3)		
10-19	229 (7.5)	182 (6.3)	47 (27.5)		
≥20	38 (1.2)	24 (0.8)	14 (8.2)		

[a] Categorical data are presented as number (percentage) of patients and continuous data as mean ± SD. ACLS = Aerobics Center Longitudinal Study; CI = confidence interval; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; MET = metabolic equivalent.

[b] SI conversion factors: To convert total cholesterol and HDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113; to convert fasting blood glucose levels to mmol/L, multiply by 0.0555.

[c] Hazard ratios for continuous variables reflect an increase of 1 unit in magnitude.

[d] For univariate Cox regression analysis.

[e] Framingham risk was computed by using the sex-specific algorithm for total cholesterol.[26]

and undiagnosed DM. Low CRF was associated with a significantly higher risk of all-cause mortality, and this inverse association remained significant after the analyses were adjusted for age, year of examination, smoking status, alcohol intake, prevalence of hypertension, hypercholesterolemia, family history of DM, and BMI at baseline. No association was observed between being overweight or obese and overall deaths. The protective effect of CRF held true for overweight or obese women, whereas the death rate among unfit women with higher BMI (≥25 kg/m^2) was more than twice that among fit women with higher BMI.

We have found no previous reports of an association between CRF and risk of all-cause mortality among women with IFG or undiagnosed DM. Most of the few published studies focused on patients with abnormal glucose metabolism or on men only or a combination of women and men. Wei et al[8] examined this association among 1263 middle-aged men and found that the adjusted risk of all-cause mortality among men in the low CRF group was 2.1-fold higher (95% CI, 1.5- to 2.9-fold) than that of physically active men and that the adjusted risk of all-cause mortality among men classifying themselves as physically inactive was 1.7-fold higher (95% CI, 1.2-fold to 2.3-fold) than that among men who were physically active. They also found that both low CRF and physical inactivity were independent predictors of all-cause mortality among men with DM. A study by Church et al[9] involving 2196 middle-aged men with DM found that the mortality risk was 4.5 (95% CI, 2.6-7.6), 2.8 (95% CI, 1.6-4.7), and 1.6 (95% CI, 0.93-2.76) across the first 3 fitness quartiles; the fourth quartile served as the reference group (*P* for trend <.0001). This steep inverse association between CRF and all-cause mortality was found to be independent of BMI.[9] Kavanagh et al[28,29] also found an inverse association between CRF and risk of all-cause mortality among men who either had undergone a heart transplant or were candidates for cardiovascular rehabilitation. Most studies focusing on the association between CRF and mortality have focused on sedentary but apparently healthy persons.[12] Our results provide evidence that supports the formal assessment of CRF among women with IFG and the use of this

TABLE 3. **Rates and HRs (95% CIs) for All-Cause Mortality According to Baseline Cardiorespiratory Fitness and BMI[a]**

Variable	Cardiorespiratory fitness			*P* for trend[b]	BMI (kg/m²)			*P* for trend[b]
	Low	Moderate	High		<25.0	25.0-29.9	≥30.0	
No. of patients	517	1041	1486		2021	677	346	
Deaths	54	62	55		120	32	19	
Woman-years of observation	9668	17,687	19,987		33,872	8991	4484	
All-cause mortality rate[c]	52.0	33.3	31.0	.01	36.3	29.8	47.4	.51
HR (95% CI) for all-cause mortality								
Adjusted for age and examination year	1.0 (referent)	0.64 (0.44-0.92)	0.60 (0.40-0.88)	.01	1.0 (referent)	0.92 (0.62-1.37)	1.30 (0.80-2.12)	.51
Adjusted for multiple variables[d]	1.0 (referent)	0.65 (0.45-0.94)	0.64 (0.43-0.95)	.03	1.0 (referent)	0.91 (0.61-1.36)	1.32 (0.80-2.18)	.51
Adjusted for multiple variables, including BMI[e]	1.0 (referent)	0.63 (0.43-0.92)	0.61 (0.39-0.93)	.03				
Adjusted for multiple variables, including continuous treadmill test duration[f]					1.0 (referent)	0.86 (0.57-1.30)	1.19 (0.70-2.03)	.84

[a] BMI = body mass index; CI = confidence interval; HR = hazard ratio.
[b] This is the *P* value for overall comparison across 3 groups.
[c] Rate is expressed per 10,000 woman-years and adjusted for baseline age and examination year.
[d] Adjusted for age, examination year, current smoking, alcohol intake, hypertension, hypercholesterolemia, and family history of diabetes.
[e] Adjusted for age, examination year, current smoking, alcohol intake, hypertension, hypercholesterolemia, family history of diabetes, and BMI.
[f] Adjusted for age, examination year, current smoking, alcohol intake, hypertension, hypercholesterolemia, family history of diabetes, and treadmill test duration.

information in physical activity counseling aimed at reducing the risk of premature death.

Although it is well recognized that IFG is a risk factor for the development of DM, Barr et al[1] demonstrated that IFG is an independent risk factor for increased mortality, not simply an antecedent of DM. These findings suggest that strategies aimed at preventing premature mortality should focus on persons at earlier stages of metabolic dysfunction, such as IFG, and not only on those with frank DM. Thompson et al[30] found that young, urban Native American women with lower CRF levels were at a higher risk of IFG, but not of metabolic syndrome, when the statistical analyses were adjusted for BMI. This finding further supports the suggestion by Barr et al[1] that IFG is an important risk factor for premature mortality. The findings of these 2 studies also further support our recommendation that the CRF of women with IFG be assessed by formal treadmill testing for a determination of which groups are at higher risk of mortality. These women should be counseled to intensify their physical activity as a part of primary prevention efforts.

Obesity is an independent risk factor for mortality among women,[13-17] but little is known about the mortality risk of women with IFG and DM. The current study found

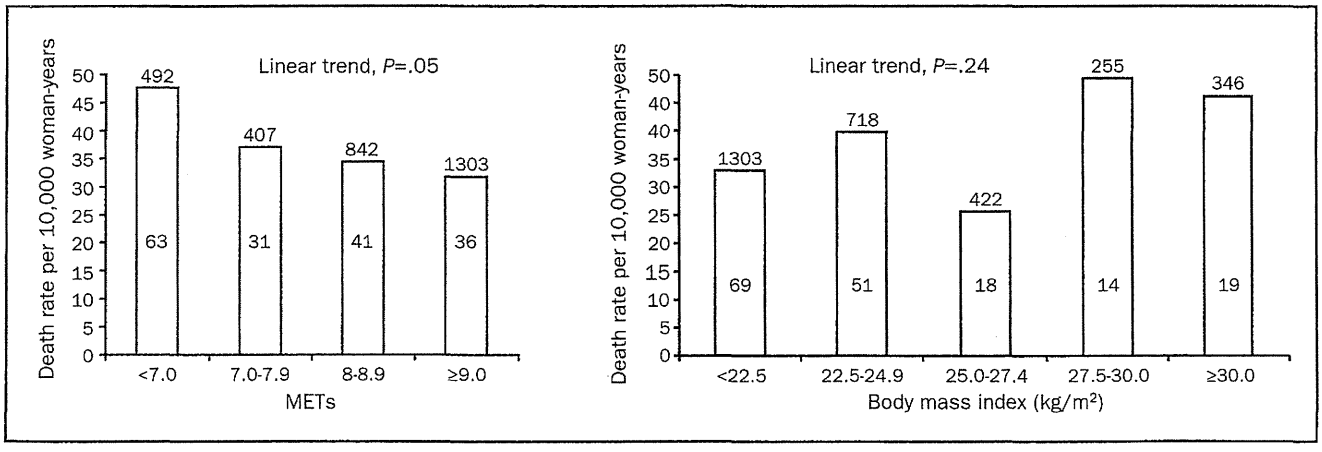

FIGURE. Age-adjusted all-cause mortality rates (per 10,000 woman-years) by cardiorespiratory fitness levels quantified in increments of 1 metabolic equivalent (MET) as determined by a maximal treadmill exercise test (left) and by body mass index levels in 2.5 kg/m² increments (right) in women. Number of patients at risk is located above each associated bar, and number of deaths is located within each associated bar.

TABLE 4. **All-Cause Mortality Rates and Hazard Ratios by BMI and Cardiorespiratory Fitness Categories**[a]

Variable	Normal weight (BMI <25.0 kg/m²)		Overweight (BMI ≥25.0 kg/m²)	
	Fit	Unfit	Fit	Unfit
No. of women, total	1817	204	710	313
Deaths	97	23	20	31
All-cause mortality rate (%)[b]	34.2	48.7	24.6	54.6
Hazard ratio (95% CI)				
Adjusted for age	1.00	1.43 (0.90-2.26)	0.72 (0.44-1.17)	1.60 (1.06-2.40)
Adjusted for multiple variables[c]	1.00	1.41 (0.87-2.31)	1.85 (0.99-3.45)	2.26 (1.27-4.03)

[a] BMI = body mass index; CI = confidence interval.
[b] Per 10,000 woman-years with adjustment for age.
[c] Adjusted for age, examination year, current smoking, alcohol intake, hypertension, hypercholesterolemia, and family history of diabetes.

no association between obesity and mortality, a finding that agrees with the observations of Johnson et al.[31] Some studies have also found an inverse association between BMI and mortality, a finding termed the *obesity paradox*.[32,33] The mechanism responsible for this paradox is currently unclear, but the finding is more common among patients with CVD.[32,33] This paradox may be explained by nonpurposeful weight loss before study participation or by dyspnea due to deconditioning (caused by factors other than CVD) among obese patients.[33]

Another explanation for the paradox may be the limitations associated with using BMI to define at-risk obesity. However, Lavie et al found that a higher percentage of body fat predicts a better prognosis for patients with heart failure[33] and coronary heart disease.[34] Further research is warranted in this area, but these findings are in direct contrast to those of most other studies, which have found either a J-shaped or a U-shaped association between BMI and mortality risk.[13-17] In the current study, low fitness was associated with a higher risk of mortality in 51% of obese patients, 20% of overweight patients, and 10% of patients of normal weight; these rates were higher than those of women with all other combinations of CRF and BMI (Table 4). This association between low fitness and higher risk of mortality was also found when the overweight and obese groups were combined. Higher fitness was associated with a lower risk of overall mortality for overweight or obese women but not for normal-weight women, although there was a nonsignificant trend in this direction.

Although CRF has a genetic component (25%-40% of cases),[12,35,36] the primary determinant of fitness is the physical activity routine. Recently, Church et al[37] reported that women with activity levels as low as 4 kcal/kg/wk (approximately 72 min/wk of moderate-intensity walking) experienced significant improvements in CRF when they were compared with women in a control group who did not exercise. Engaging in activities such as brisk walking, bicycling, or jogging for 30 minutes or more on most days of the week[30] would move most of these women out of the low fitness category.

This study has several strengths, including the extensive baseline examination aimed at detecting subclinical disease, the use of measured risk factors, the relatively long follow-up period (average, 15 years), and the broad age range of the study population (20-79 years).

One limitation of this study is homogeneity of the patient population: patients were predominantly white, well-educated, middle- to upper-class, and female. This homogeneity limits our ability to generalize our findings to a broader population but should not affect the internal validity of the study. There is no strong reason to assume that CRF assessment would have fewer benefits for men or other ethnic groups. Our previous studies, in which the number of deaths that occurred was sufficient to allow parallel analyses of women and men, showed that the inverse gradient of mortality across CRF groups is similar for men and women.[9,38-40] In terms of exposure assessment, we classified women according to CRF at the time of study enrollment, but in the current analysis we were unable to evaluate the effect on outcome of changes in fitness or BMI over time. During the follow-up interval, many women in the low fitness category may have increased their fitness levels, and many obese women may have decreased their BMI. Therefore, we cannot determine whether changes in fitness, obesity status, or both occurred during follow-up or if there were any other exposures. However, such misclassification of exposure would probably lead to an underestimation of the magnitude of the associations observed in the current study.

CONCLUSION

Cardiorespiratory fitness, but not BMI, is a significant predictor of all-cause mortality among women with IFG or undiagnosed DM, independently of traditional risk fac-

tors. Determining CRF levels with exercise stress testing, which has already been shown to be an effective tool for risk stratification of men with diabetes, may also be an effective tool for risk stratification of women with IFG. We encourage health care professionals to consider the potential preventive and diagnostic value of assessing CRF levels in this high-risk group of women.

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