Table 3. Multivariate analysis using CRF, BMI, age, baseline health status, and smoking status of 9925 women (Aerobics Center Longitudinal Study, 1970 to 1996)

Variable	RR (95% CI)	*p* value
CRF (Maximal METs)		
Low	1.0 (Referent)	
Moderate	0.49 (0.35, 0.69)	0.0001
High	0.57 (0.40, 0.83)	0.003
BMI (kg/m^2)		
Normal	1.0 (Referent)	
Overweight	0.84 (0.56, 1.26)	0.39
Obese	1.21 (0.71, 2.05)	0.48
Age (years)	1.08 (1.07, 1.09)	0.0001
Baseline health status		
Healthy	1.0 (Referent)	
Unhealthy	0.76 (0.55, 1.05)	0.10
Smoking status		
Never	1.0 (Referent)	
Quitter	1.12 (0.81, 1.56)	0.49
Current	1.83 (1.26, 2.67)	0.002

Each variable has been adjusted for all other variables in the model.

CRF, cardiorespiratory fitness; BMI, body mass index; RR, relative risk; CI, confidence interval; MET, metabolic equivalent.

25% increase in maximal oxygen uptake was seen in sedentary women (19). It should also be noted that moderate CRF is attainable even for obese women, as evidenced by the fact that 50.5% of women with BMIs between 31.1 and 33 kg/m^2 were classified as having at least a moderate level of CRF (Figure 3).

The current study has certain limitations. Women in the ACLS do not represent a random sample of the population; rather they are primarily white and college educated. We cannot say for certain that our observations extend to nonwhite women and/or women with lower levels of education. At the present time, there are no national norms in the United States for CRF that are based on a random sample of the population. However, median estimated maximal oxygen consumption for women in the ACLS is remarkably similar to a random sample of women in the Canada Fitness Survey (20). Thus, it would seem that women in the ACLS are not a select group of fitness enthusiasts and are similar to other groups of North American women.

In this study, we used treadmill time to estimate maximum $V\text{O}_2$ (and METs) rather than a direct measurement of oxygen uptake. Whereas our group has previously shown that the correlation between treadmill time and directly measured maximum $V\text{O}_2$ in women is 0.94 (12), most of the women in that particular study were in the normal BMI category. Although currently we have no evidence to the contrary, we cannot say for certain that the correlation between treadmill time and maximum $V\text{O}_2$ is as high in overweight and obese women. Therefore, it is possible that some overweight and obese women might have been misclassified with regard to CRF category.

We used baseline measurements to determine CRF and BMI categories. It is possible that some women may have changed their CRF or BMI category during the study, and we did not measure changes in these variables in the present study.

It is also important to note that there are various classes of obesity. Our observations extend primarily to women who are normal weight, overweight, Class 1 obese (BMI, 30 to 34.9 kg/m^2), and Class 2 obese (BMI, 35.0 to 39.9 kg/m^2). We do not have sufficient data to make any observations on women who are Class 3 obese (BMI, $\geq$40 kg/m^2). It is likely from the trend observed in Figure 3 that the vast majority of women who are Class 3 obese are sedentary and unfit, and thus are at significantly increased risk for all-cause mortality.

Because of the limited number of deaths in this cohort, we were not able to examine the effects of CRF and BMI on specific causes of mortality. We await additional mortality data for this purpose.

In summary, a low level of CRF as measured by a maximal treadmill exercise test was a more important predictor of all-cause mortality in ACLS women than was baseline BMI. Because previous work by our group has shown that unfit men who become fit enjoy a substantial reduction in mortality (21), it seems reasonable to suggest that a much stronger emphasis should be placed on increasing the CRF level of all unfit women as well. From an all-cause mortality perspective, we strongly suggest that clinicians and other health professionals spend at least as much time encouraging sedentary women to become more physically active as encouraging overweight and obese women to lose weight.

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論文名	The relation of body mass index, cardiorespiratory fitness, and all-cause mortality in women						
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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	女性	( )		( )		( )
	年齢	平均42.9歳			( )		前向き研究
	対象数	5000～10000	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)	目的：女性におけるBMI、全身持久性体力（CRF）、および全死亡原因の関係を調査すること。研究方法と手順：同じコホートの女性（42.9±10.4歳）において、CRF、身長、および体重が評価された。参加者は3つのBMIカテゴリ（標準体重、過体重、肥満）および3つのCRFカテゴリ（低い、普通、高い）に分類された。年齢、喫煙、およびベースライン時の健康状態補正後、全死亡原因の相対リスク（RR）をグループごとに決定した。多変量解析は、他のすべての予測因子を制御し、全死亡原因に対するそれぞれの予測因子（例えば、年齢、BMI、CRF、喫煙状態、およびベースライン時の健康状態）の貢献度をみる目的で施行された。結果：追跡調査（113145女性年）の間、全死亡原因で195の死亡が発現した。標準体重（RR=1.0）と比べて、過体重（RR=0.92）および肥満（RR=1.58）は全死亡リスクを有意に増加することはなかった。低いCRF（RR=1.0）と比べて、普通（RR=0.48）および高い（RR=0.57）CRFは下位の死亡リスクで有意（p=0.002）な相関関係を示した。多変量解析では、低いCRFと比べて、普通（RR=0.49）および高い（RR=0.57）CRFは強く死亡率の減少に関連づけられた（p=0.003）。標準体重（RR=1.0）と比べて、過体重（RR=0.84）および肥満（RR=1.21）は全死亡原因との間に有意な関係はみられなかった。議論：女性における低いCRFは全死亡原因の重要な予測因子となった。						
結 論 (200字まで)	女性においても男性と同様に、最大負荷運動試験で評価した心肺体力は、肥満の程度と比較して、総死亡のより強力な予測因子であった。						
エキスパートによるコメント (200字まで)	女性を対象として心肺体力と死亡リスクの関連について調べた貴重な研究。肥満との関連については今後の検討が必要。						

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Cardiorespiratory Fitness, Different Measures of Adiposity, and Cancer Mortality in Men

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Abstract

FARRELL, STEPHEN W., GINA M. CORTESE, MICHAEL J. LAMONTE, AND STEVEN N. BLAIR. Cardiorespiratory fitness, different measures of adiposity, and cancer mortality in men. *Obesity.* 2007;15:3140–3149.

Objective: The purpose was to examine the prospective relationship among cardiorespiratory fitness level (CRF), different measures of adiposity, and cancer mortality in men.

Research Methods and Procedures: Participants were 38,410 apparently healthy men who completed a comprehensive baseline health examination between 1970 and 2001. Clinical measures included BMI, waist circumference (WC), percent body fat, and CRF quantified as duration of a maximal treadmill exercise test. Participants were divided into fifths of CRF, BMI, WC, and percent body fat. Hazard ratios were computed with Cox regression analysis.

Results: During a mean follow-up period of 17.2 ± 7.9 years, 1037 cancer deaths occurred. Adjusted hazard ratios across incremental BMI quintiles were 1.0, 1.23, 1.15, 1.39, and 1.72; those of WC were 1.0, 1.05, 1.03, 1.31, and 1.64; those of percent body fat were 1.0, 1.24, 1.17, 1.23, and 1.50; and those of CRF were 1.0, 0.70, 0.67, 0.70, and 0.49 (trend $p < 0.01$ for each). Further adjustment for CRF eliminated the significant trend in mortality risk across percent body fat groups and attenuated the trend in risk across BMI and WC groups. Adjustment of CRF for adiposity measures had little effect on mortality risk. When grouped into categories of fit and unfit (upper 80% and lower 20% of CRF distribution, respectively), mortality rates (per 10,000 man-years) were significantly lower in fit compared with unfit men within each stratum of BMI, WC, and percent body fat.

Discussion: Higher levels of CRF are associated with lower cancer mortality risk in men, independently of several adiposity measures.

Key words: body composition, exercise, waist circumference, skinfold thickness, BMI

Introduction

Cancer is the second leading cause of death for U.S. men, accounting for ~285,000 deaths annually (1). In addition to its physical and emotional toll, cancer also is associated with a significant economic burden to society. The NIH has estimated total U.S. healthcare expenditures of $210 billion for cancer in 2004; approximately $74 billion in direct costs such as medication, hospital, physician, and nursing services; and approximately $136 billion in indirect costs related to lost productivity and the like (1).

Traditionally known modifiable risk factors for cancer include tobacco use (2) and poor diet (3), as well as environmental and occupational exposures (4,5). More recently, adiposity (6–9) and low levels of physical activity or cardiorespiratory fitness (CRF)[1] also have been shown to be associated with cancer mortality in men (10–14). Overweight and obesity (15), as well as physical inactivity (16), are highly prevalent in the U.S. population. Most studies on adiposity and cancer mortality have used self-reported or measured BMI as the measure of adiposity (6,7,9,14,17,18). Few studies have reported on associations between cancer mortality and clinical adiposity measures, such as waist circumference (WC) (8) or percent body fat. Studies on physical activity and cancer mortality have relied almost exclusively on self-reported assessment of physical activity habits (7,12,19). There is a paucity of reported data relating an objective measure of CRF with cancer mortality (11,14).

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[1] Nonstandard abbreviations: CRF, cardiorespiratory fitness; WC, waist circumference; ACLS, Aerobics Center Longitudinal Study; HR, hazard ratio; CI, confidence interval.

Even fewer studies have reported on the joint exposures of adiposity and physical activity or fitness with subsequent cancer mortality (14,20). Thus, the primary purpose of this investigation is to examine the relationship among CRF, several measures of adiposity, and cancer mortality in a large cohort of initially cancer-free men who are enrolled in the Aerobics Center Longitudinal Study (ACLS).

Research Methods and Procedures

Study Participants and Measurements

The ACLS is a prospective epidemiological follow-up of patients who have completed a comprehensive health examination at the Cooper Clinic in Dallas, TX (21). Participants in the present study were 38,410 men who completed baseline examinations during the interval between 1970 and 2001. All participants were U.S. residents, and the majority of men were white and from middle to upper socioeconomic strata. After receiving written informed consent from each participant, a clinical evaluation was performed and included an examination by a physician, fasting blood chemistry assessment, personal and family health history, anthropometry, resting blood pressure and electrocardiogram, and a maximal graded treadmill exercise test. Height and weight were measured using a stadiometer and standard physician's scale. BMI was calculated as weight in kilograms divided by height in meters squared. Participants were grouped into fifths of the BMI distribution as follows: BMI <23.50, 23.50 to 25.10, 25.11 to 27.00, 27.01 to 29.80, and >29.80 kg/m^2. Percent body fat was assessed with hydrostatic weighing, with skinfold measures, or with both following standardized procedures (22). Body fat was estimated from hydrodensitometry using the Siri Equation (23) or from the sum of seven skinfolds using a generalized equation (22). In accord with our previously published study methods (24) and to standardize the body fat estimates, we developed a prediction model for hydrostatically determined percent of body fat from percent of fat determined from the skinfold measures in men who had both assessments (n = 13,234). Regression analysis resulted in the following equation: Percent body fat = 1.448 + 0.945 × skinfold percent fat (r = 0.83, standard error of the estimate = 3.77). Men were grouped into fifths of percent body fat distribution as follows: percent body fat <17.50%, 17.50% to 21.50%, 21.51% to 24.60%, 24.61% to 28.00%, and >28.0%. Waist circumference was measured at the level of the umbilicus using a cloth tape measure. The measurement of WC was not included in the clinical examination until the 1980s and, thus, is only available in a subset of study participants (n = 27,881). Men were assigned to fifths of the WC distribution as follows: WC <85.00 cm, 85.00 to 90.80 cm, 90.81 to 95.90 cm, 95.91 to 102.00 cm, and >102.00 cm. All procedures were administered by trained technicians who followed standardized measurement protocols.

CRF was quantified as the duration of a maximal treadmill exercise test using a modified Balke protocol (25). The treadmill test began at a speed of 88 m/min and 0% elevation. At the end of the first minute, elevation was increased to 2%, then by 1% each minute thereafter. After 25 minutes, elevation remained at 25% while speed was increased 5.4 m/min each minute until volitional fatigue. Exercise duration from this protocol has been shown to correlate highly (r = 0.92) with directly measured maximal oxygen uptake in men (26). Patients were given verbal encouragement to achieve a maximal effort during the test, and those that did not achieve at least 85% of age-predicted maximal heart rate were excluded from the analyses. To standardize exercise test performance, we computed maximal metabolic equivalent (1 metabolic equivalent = 3.5 mL O_2 uptake/kg/min) levels of CRF based on the final treadmill speed and grade (27).

Smoking history was obtained from a standardized questionnaire and grouped categorically for analysis (never, past, or current smoker). Chronic illness at baseline was defined as the presence of 1) dyslipidemia based on a history of physician-diagnosed high cholesterol or triglyceride, or measured fasting total cholesterol ≥240 mg/dL, or triglyceride ≥200 mg/dL, or high density lipoprotein <50 mg/dL; 2) diabetes based on a history of physician diagnosis or insulin use, or measured fasting glucose ≥126 mg/dL; 3) hypertension based on a history of physician diagnosis, resting systolic blood pressure ≥140 or resting diastolic blood pressure ≥90 mm Hg; 4) a history of physician diagnosed myocardial infarction or stroke; or 5) an abnormal resting electrocardiogram. Men with previously diagnosed cancer at baseline were excluded from the analyses.

Mortality Surveillance

Vital status was ascertained primarily using the National Death Index. Cancer deaths were identified using the International Classification of Diseases, ninth revision (codes 140–208) for deaths occurring before 1999 and 10th revision (codes C00-C97 for deaths during 1999 to 2003).

Statistical Analyses

We followed study participants for mortality from the date of their examination to the date of death for decedents or to December 31, 2003 for survivors. We computed man-years of exposure as the sum of follow-up time among decedents and survivors. There were 1037 cancer deaths identified during an average of 17.2 ± 7.9 years of follow-up and 660,652 man-years of exposure. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer mortality according to exposure categories. In our primary analysis, each adiposity exposure was grouped according to fifths of the sample-specific distribution as described above. CRF was grouped according to age-standard-

Table 1. Baseline characteristics for all men and by vital status in 38,410 men who were followed an average of 17.2 years: Aerobics Center Longitudinal Study, 1970 to 2003

Characteristic	All	Decedents	Survivors
N	38,410	1037	37,373
Man-years exposure	660,652	16,592	644,060
Age (yrs)	43.8 ± 9.9	50.7 ± 9.2	43.6 ± 9.8*
BMI (kg/m^2)	26.5 ± 3.8	26.5 ± 3.5	26.5 ± 3.8
Waist circumference† (cm)	94.2 ± 10.8	96.6 ± 10.8	94.1 ± 10.8*
Percent body fat‡	22.8 ± 6.4	24.1 ± 6.5	22.8 ± 6.4*
Treadmill time (min)	17.6 ± 5.2	14.6 ± 4.9	17.7 ± 5.2*
Maximal METs	12.2 ± 2.5	10.1 ± 2.3	12.5 ± 2.5*
BMI-defined weight groups (%)			
Normal-weight (18.5 to 24.99 kg/m^2)	38.5	36.5	38.6
Overweight (25 to 29.99 kg/m^2)	46.8	48.8	46.7
Obese (≥30 kg/m^2)	14.5	14.7	14.5
Waist circumference ≥102 cm (%)	21.0	28.0	20.9*
Smoking status (%)			
Never	47.8	31.4	48.3*
Past	33.7	39.3	33.6*
Current	18.5	29.3	18.1*
Chronic illness (%)§	75.1	87.9	74.7*

MET, metabolic equivalent. Data are mean ± standard deviation.
* $p < 0.05$ with decedents.
† Waist circumference: n = 27,881 (489 deaths).
‡ Percent body fat: n = 36,885 (960 deaths).
§ Chronic illness was defined as the presence of 1) dyslipidemia (history of physician-diagnosed high cholesterol or triglyceride or measured fasting total cholesterol >240 mg/dL, or triglyceride >200 mg/dL or high-density lipoprotein <50 mg/dL); 2) diabetes (history of physician diagnosis or use of insulin or measured fasting glucose >126 mg/dL); 3) hypertension (history of physician diagnosis or resting systolic blood pressure ≥140 or diastolic blood pressure ≥90); 4) prevalent cardiovascular disease (history of physician-diagnosed myocardial infarction or stroke); or 5) an abnormal resting echocardiogram.

ized quintiles of maximal exercise duration as described elsewhere (21). Multivariable analyses included age (years), examination year, smoking status (never, past, current smoker), and chronic illness at baseline (present or not). These four factors will henceforth be referred to as covariables. Tests of linear trends in mortality rates and risk estimates across exposure categories were computed using ordinal scoring. We also examined the joint associations of adiposity and CRF exposures with cancer mortality. In these analyses, adiposity exposure groups were based on standardized definitions for BMI (normal-weight 18.50 to 24.99, overweight 25.0 to 29.99, and obese ≥30 kg/m^2), WC (normal <102 and abdominal obesity ≥102 cm), and percent body fat (normal <25% and obese ≥25%) (28). CRF was grouped as fit and unfit based on the upper 80% and lower 20% of the age-standardized CRF distribution, as previously reported in the ACLS (24). We assessed interaction among exposure groups using likelihood ratio tests of nested models. All p values are 2-sided, and $p < 0.05$ was regarded as statistically significant.

Results

Baseline characteristics of the overall cohort and according to vital status are presented in Table 1. On average, decedents were older and had greater levels of adiposity, lower CRF, and a higher prevalence of smoking and chronic illness than survivors. With the exception of age, each of the other baseline characteristics was significantly ($p < 0.001$ each) associated with categories of CRF (Table 2). Rates of cancer mortality according to exposure groups are presented in Table 3. Significant positive associations with cancer mortality were seen across incremental categories of adiposity measures and of age (p for trend = 0.001 each). Mortality rates also were significantly higher in current and past smokers compared with non-smokers (p for trend <0.001) and in men who had chronic illness at baseline

Table 2. Baseline characteristics by cardiorespiratory fitness quintiles for 38,410 men who were followed an average of 17.2 years: Aerobics Center Longitudinal Study, 1970 to 2003

Characteristic	Cardiorespiratory fitness quintiles					
	1 (low)	2	3	4	5 (high)	*p* trend
N	7220	7820	7536	8009	7825	
Man-years	138,624	139,857	130,373	128,945	122,853	
Age (yrs)	43.6 ± 9.5	43.5 ± 9.7	44.6 ± 9.7	43.8 ± 10.0	43.5 ± 10.3	0.87
BMI (kg/m^2)	29.3 ± 5.1	27.1 ± 3.5	26.3 ± 3.0	25.5 ± 2.7	24.3 ± 2.3	<0.0001
Waist circumference (cm)	104.3 ± 13.1	97.8 ± 9.8	94.9 ± 8.7	91.7 ± 8.0	86.9 ± 7.1	<0.0001
Percent body fat	27.2 ± 6.3	24.7 ± 5.6	23.3 ± 5.5	21.3 ± 5.4	18.2 ± 5.3	<0.0001
Treadmill time (min)	11.0 ± 2.7	14.8 ± 2.2	17.1 ± 2.2	19.9 ± 2.3	24.4 ± 3.0	<0.0001
Maximal METs	8.4 ± 1.3	10.2 ± 1.0	11.2 ± 1.0	12.5 ± 1.1	14.9 ± 1.9	<0.0001
BMI-defined weight groups (%)						<0.0001
Normal-weight (18.5 to 24.99 kg/m^2)	18.6	27.9	34.4	45.4	65.1	
Overweight (25 to 29.99 kg/m^2)	44.3	53.5	53.9	48.9	33.6	
Obese (≥30 kg/m^2)	36.9	18.7	11.7	5.7	1.3	
Waist circumference ≥102 cm (%)	54.6	32.2	20.6	10.4	2.5	<0.0001
Smoking status (%)						<0.0001
Never	36.7	43.6	47.8	53.2	56.8	
Past	31.7	32.8	34.5	34.3	35.3	
Current	31.6	23.7	17.7	12.6	7.9	
Chronic illness (%)*	91.8	83.6	77.9	68.6	55.1	<0.0001
Deaths (%)	4.4	2.8	2.4	1.9	1.5	<0.0001

MET, metabolic equivalent. Data are mean ± standard deviation.

* Chronic illness was defined as the presence of 1) dyslipidemia (history of physician-diagnosed high cholesterol or triglyceride or measured fasting total cholesterol >240 mg/dL, or triglyceride >200 mg/dL or high-density lipoprotein <50 mg/dL); 2) diabetes (history of physician diagnosis or use of insulin or measured fasting glucose >126 mg/dL); 3) hypertension (history of physician diagnosis or resting systolic blood pressure ≥140 or diastolic blood pressure ≥90); 4) prevalent cardiovascular disease (history of physician-diagnosed myocardial infarction or stroke); or 5) an abnormal resting echocardiogram.

($p = 0.048$). A significant inverse gradient of cancer mortality rates was seen across incremental CRF categories ($p < 0.0001$).

We next computed HRs and 95% CIs as measures of the strength of association for adiposity and CRF exposure categories with cancer mortality (Table 4). After adjusting for covariables, HRs of cancer mortality across incremental quintiles of CRF were 1.0, 0.71, 0.69, 0.73, and 0.53; *p* for trend <0.0001. Further adjustment for BMI, WC, or percent body fat had little effect on the pattern or strength of association. Table 4 also shows the risk of cancer mortality across quintiles of BMI, WC, and percent body fat. When adjusted for covariables, a significant trend for higher mortality risk was seen across incremental levels of BMI (HRs = 1.0, 1.23, 1.09, 1.31, and 1.60; *p* for trend <0.0001), WC (HRs = 1.0, 1.02, 0.95, 1.19, and 1.51; *p* for trend = 0.001), and percent body fat (HRs = 1.0, 1.23, 1.13, 1.16, and 1.41; *p* for trend <0.01). After further adjustment for CRF, mortality risk was attenuated across BMI and WC levels and was no longer significant across levels of percent body fat ($p = 0.81$). Restricting the analyses to men who had at least 3 years of follow-up did not materially change the strength or patterns of the above associations (data not shown). Furthermore, restricting analyses on BMI and cancer mortality to only non-smokers and only apparently healthy men did not strengthen the CRF-adjusted association between BMI and mortality (data not shown).

To place our findings into a more clinically relevant perspective, we jointly regressed mortality rates on adiposity and CRF exposures grouped according to standardized definitions (Figures 1 to 3). Cancer mortality rates were significantly lower in fit compared with unfit men within each stratum of adiposity exposure, including men with BMI-defined obesity and with abdominal obesity. As shown in Figure 1, cancer mortality rates (per 10,000 man-years)

Table 3. Rates of cancer mortality according to exposure groups in 38,410 men followed an average of 17.2 years: Aerobics Center Longitudinal Study, 1970 to 2003

	Man-years	Deaths	Rate* (per 10,000 man-years)
BMI (kg/m^2) quintiles			
<23.5	145,625	176	12.3
23.50 to 25.10	139,467	223	15.2
25.11 to 27.00	153,020	230	14.1
27.01 to 29.80	109,263	185	17.1
>29.80	115,140	223	21.1
p linear trend			<0.0001
Waist circumference† (cm) quintiles			
<85.00	74,280	59	10.2
85.00 to 90.80	91,873	94	10.7
90.81 to 95.90	81,703	88	10.3
95.91 to 102.00	75,885	111	13.4
>102.00	77,365	137	16.7
p linear trend			<0.0001
Percent body fat‡ quintiles			
<17.50	136,375	142	12.6
17.50 to 21.50	131,718	189	15.6
21.51 to 24.60	122,186	182	14.8
24.61 to 28.00	117,426	194	15.5
>28.00	116,095	253	18.9
p linear trend			<0.001
Treadmill time§ (min) quintiles			
<13.50	138,624	314	21.9
13.50 to 16.10	139,978	216	15.3
16.11 to 19.00	130,373	203	14.6
19.01 to 22.30	128,945	185	15.3
>22.30	122,853	119	10.7
p linear trend			<0.0001
Age (yrs)			
18 to 30	44,324	6	1.2
30 to 40	211,895	106	4.5
40 to 50	241,197	369	14.6
50 to 60	128,917	382	29.6
60+	35,301	174	56.9
p linear trend			<0.001
Smoking status			
Never	301,169	326	11.6
Past	233,064	407	15.3
Current	128,474	304	25.8
p linear trend			<0.001
Chronic illness			
No	146,359	126	13.4
Yes	516,308	911	16.3
p difference			0.048

* Adjusted for age and examination year.

† Waist circumference: n = 27,881 (489 deaths).

‡ Percent body fat: n = 36,885 (960 deaths).

§ Quintiles of fitness were based on the distribution of treadmill exercise duration standardized to the following age groups: 18 to 39 years, 40 to 49 years, 50 to 59 years, and 60+ years in the overall Aerobics Center Longitudinal Study population of men. The tabulated values reflect the average value for the men included in this analysis. The associated metabolic equivalent (MET) ranges for each fitness quintile were <9.9, 9.9 to 10.8, 10.9 to 12.6, 12.7 to 14.0, and >14.0.

Table 4. Risk of cancer mortality by quintiles of cardiorespiratory fitness, BMI, waist circumference, and percent body fat: Aerobics Center Longitudinal Study, 1970 to 2003

	Exposure quintiles					
	1 (low)	**2**	**3**	**4**	**5 (high)**	***p* trend**
Cardiorespiratory fitness						
Adjusted for covariables*	1.00 (referent)	0.71 (0.60 to 0.85)	0.69 (0.58 to 0.83)	0.73 (0.61 to 0.89)	0.53 (0.43 to 0.67)	<0.0001
+ BMI†	1.00 (referent)	0.73 (0.62 to 0.88)	0.72 (0.60 to 0.87)	0.79 (0.65 to 0.97)	0.59 (0.47 to 0.76)	<0.001
+ waist circumference†	1.00 (referent)	0.68 (0.52 to 0.90)	0.63 (0.48 to 0.85)	0.74 (0.56 to 0.99)	0.53 (0.38 to 0.75)	0.004
+ percent body fat†	1.00 (referent)	0.68 (0.57 to 0.83)	0.65 (0.54 to 0.79)	0.70 (0.58 to 0.87)	0.50 (0.39 to 0.65)	<0.0001
BMI						
Adjusted for covariables	1.00 (referent)	1.23 (1.01 to 1.49)	1.09 (0.89 to 1.32)	1.31 (1.10 to 1.60)	1.60 (1.30 to 1.91)	<0.0001
+ cardiorespiratory fitness	1.00 (referent)	1.19 (0.98 to 1.46)	1.03 (0.84 to 1.26)	1.20 (0.97 to 1.49)	1.40 (1.13 to 1.50)	<0.01
Waist circumference						
Adjusted for covariables	1.00 (referent)	1.02 (0.74 to 1.42)	0.95 (0.68 to 1.32)	1.19 (0.87 to 1.60)	1.51 (1.10 to 2.18)	0.001
+ cardiorespiratory fitness	1.00 (referent)	0.98 (0.71 to 1.37)	0.88 (0.63 to 1.23)	1.07 (0.77 to 1.50)	1.25 (0.89 to 1.80)	0.09
Percent body fat						
Adjusted for covariables	1.00 (referent)	1.23 (0.98 to 1.52)	1.13 (0.90 to 1.41)	1.16 (0.93 to 1.53)	1.41 (1.12 to 1.80)	<0.01
+ cardiorespiratory fitness	1.00 (referent)	1.15 (0.92 to 1.43)	1.00 (0.80 to 1.26)	0.98 (0.78 to 1.24)	1.11 (0.88 to 1.40)	0.81

Data are hazard ratio (95% confidence interval).

* Age, examination year, smoking status, and chronic illness at baseline.

† BMI, waist circumference, and percent body fat were separately entered into a model with cardiorespiratory fitness and the covariables.

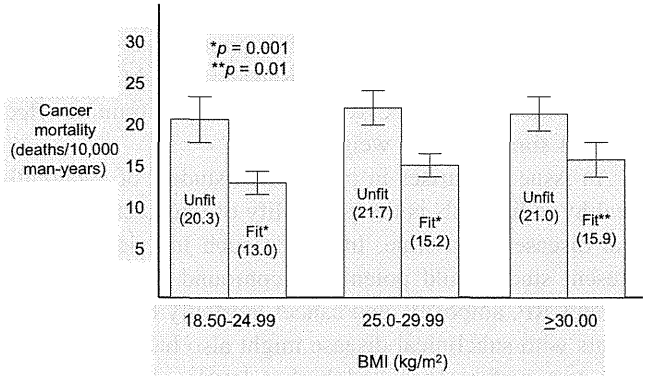

Figure 1: Joint association of CRF and BMI with the age- and examination year-adjusted rates of cancer mortality: ACLS, 1970 to 2003. Error bars represent standard error. Likelihood ratio test for interaction, χ^2, $df_1 = 0.43$, $p = 0.51$. Numbers shown in bars represent cancer mortality rates.

were significantly higher in unfit (20.3, 21.7, and 21.0, respectively) than fit men (13.0, 15.2, and 15.9, respectively) across incremental BMI categories ($p = 0.01$). As shown in Figure 2, mortality rates were also significantly higher in unfit (15.6 and 20.9, respectively) than fit men (10.4 and 13.8, respectively) across incremental categories of WC ($p = 0.02$). Finally, as shown in Figure 3, mortality rates were significantly higher in unfit (19.6 and 25.0, respectively) than fit men (12.2 and 16.3, respectively) across incremental categories of percent body fat ($p = 0.001$). There was no statistical evidence of interaction between CRF and the adiposity measures (BMI, χ^2 $df_1 =$ 0.43, $p = 0.51$; WC χ^2 $df_1 = 0.07$, $p = 0.78$; and, percent body fat, χ^2 $df_1 = 0.09$, $p = 0.77$).

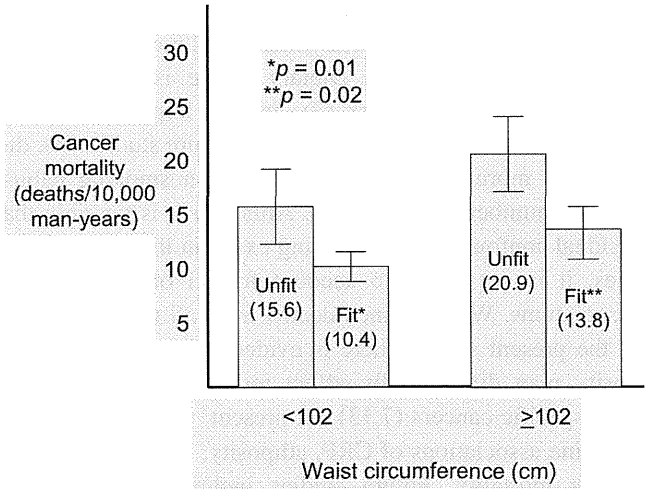

Figure 2: Joint association of CRF and waist circumference with the age- and examination year-adjusted rates of cancer mortality: ACLS, 1970 to 2003. Error bars represent standard error. Likelihood ratio test for interaction, χ^2, $df_1 = 0.07$, $p = 0.78$. Numbers shown in bars represent cancer mortality rates.

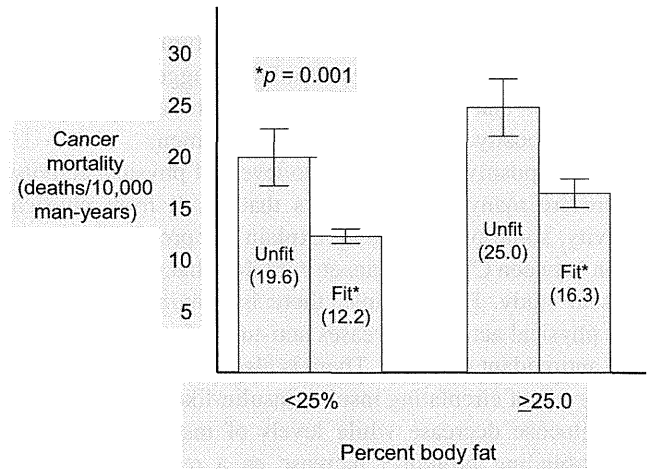

Figure 3: Joint association of CRF and percent body fat with the age- and examination year-adjusted rates of cancer mortality: ACLS, 1970 to 2003. Error bars represent standard error. Likelihood ratio test for interaction, χ^2, $df_1 = 0.09$, $p = 0.77$. Numbers shown in bars represent cancer mortality rates.

Discussion

In the present study, rates of cancer mortality were positively associated with BMI, WC, and percent body fat. The association persisted after adjusting for baseline differences in age, smoking, and health status. However, further adjustment for CRF attenuated the significant mortality risk associated with BMI to only men in the highest BMI quintile, attenuated the association between cancer mortality and WC, and eliminated the associations between cancer mortality and percent body fat. CRF was inversely associated with cancer mortality independently of several confounding factors, including each of the adiposity measures. Based on joint regression analysis, men with low CRF and high adiposity experienced the highest rates of cancer mortality, whereas men who were fit had lower rates of mortality than their unfit peers, irrespective of adiposity levels. Our findings are consistent with and expand on an earlier report from the ACLS (11) and a more recent report on CRF, BMI, and cancer mortality in the Lipid Research Clinics Mortality Follow-up Study (14). In the Lipid Research Clinics Mortality Follow-up Study, a significantly lower risk of cancer mortality was seen only in men in the highest CRF quintile. The somewhat different findings seen in the Lipid Research Clinics Mortality Follow-up Study and the present study may be explained, in part, by differences in the distribution of CRF, BMI, and baseline health status among men in the 2 studies. In the present study, the reduction in cancer mortality risk across quintiles of CRF was materially unchanged after adjustment for BMI, WC, and percent body

fat. Furthermore, cancer mortality rates were much lower among fit vs. unfit men within each stratum of BMI, WC, and percent body fat. These findings suggest that higher CRF levels can significantly attenuate the association between adiposity and cancer mortality in men.

CRF is positively correlated to levels of physical activity. There are many health benefits that result from physical activity, some of which may explain the protective association between CRF and cancer mortality that was seen in the present study. For example, there is convincing evidence that physical activity increases anti-tumor immune defenses and antioxidant defenses. There is also convincing evidence that levels of circulating insulin, insulin-like growth factors, and glucose decrease while levels of insulin-like growth factor-binding protein-3 increase as a result of physical activity (29).

The mechanisms by which adiposity contributes to cancer development may be similar to some of those that are potentially associated with low levels of physical activity. For instance, excess body fat has been shown to increase circulating levels of insulin-like growth factors, insulin, glucose, and sex hormones. Additionally, adipocytes produce estrogen and can store carcinogens (30,31).

An important point to consider when interpreting the joint associations of CRF and measures of adiposity with cancer mortality is the method in which CRF was grouped for this analysis. Currently, there is not a widely accepted method of defining CRF levels for use in clinical or public health research. In the ACLS, we have standardized the definition of low fitness (unfit) according to the bottom 20% of the age-standardized distribution of maximal exercise duration within the overall ACLS population; individuals in the remaining 80% of the distribution are considered to be fit (10,21). By our definition, it would thus seem that even modest levels of CRF are associated with lower risk of cancer mortality. For example, a 50- to 59-year-old man would need to achieve a maximal metabolic equivalent (MET) level of 8.9 or higher to qualify for the fit category. This is equivalent to covering ~1.2 miles in the Cooper 12 Minute Run-Walk Test (32) or achieving a treadmill time of ~8.5 minutes on a standard Bruce Treadmill Test (27). This level of CRF can be achieved by many, perhaps even most, apparently healthy adults through moderate amounts and intensities of regular physical activity such as brisk walking (33). In a study comparing the effects of weight loss and aerobic exercise training on coronary artery disease risk factors in sedentary, obese middle-aged and older men, Katzel et al. (34) showed a 17% mean increase ($p < 0.001$) in maximal oxygen consumption in 49 subjects who completed 9 months of moderate aerobic training. In a supervised setting, subjects used treadmills and stationary bicycles with an initial training load of 30 minutes, 3 days per week at 50% to 60% of heart rate reserve. The group progressed to performing 45 minutes of cycling, 3 days per week at 70% to 80% of heart rate reserve. The significant increase in maximal oxygen consumption in the aerobic training group occurred in the absence of weight loss, showing that the increase in CRF was due to a true training effect and not simply due to weight loss.

An issue that arises in prospective studies of apparently healthy individuals is the possibility of undetected subclinical disease at baseline. Including such individuals in the present study could potentially confound the relation between CRF, adiposity, and cancer mortality because participants with subclinical disease might also have lower exercise test performance and higher levels of adiposity. In contrast to most other epidemiological cohort studies on this topic is the extensive baseline clinical examination including a physician-given examination, detailed health history interview, and other tests that make it less likely that undetected subclinical disease was present in our study participants. When we performed additional analyses restricted only to those men with three or more years of follow-up, the primary findings were materially unchanged. This enhances our confidence that our primary observations were not explained entirely by undetected disease at baseline.

Among the strengths of the current study is a large and well-characterized cohort of men, an extensive follow-up with a relatively large number of cancer deaths for analysis, and the use of objective measures for CRF and adiposity exposures. This study also has limitations. The cohort is primarily white and from middle to upper socioeconomic strata; therefore, our findings must be cautiously interpreted when generalized to other populations. However, the homogeneity of socio-demographic factors in our population sample strengthens the internal validity of our findings by reducing potential confounding by these issues. We did not have sufficient data for dietary intake and medication use to include in this analysis. Dietary intake is an important determinant of cancer risk (3), and we hope to include a measure of this important exposure in future studies. We did not have more extensive information on smoking habits, such as number of pack-years. Although it is possible that residual confounding by smoking exists in the present analyses, it is not likely to account for all of the observed associations. We examined deaths from all types of cancer in the present study. There is evidence that CRF and adiposity may differentially affect mortality risk associated with specific cancers (7,13). At present, we were unable to examine associations of CRF, adiposity, and cause-specific cancer mortality. Future studies including work in the ACLS cohort should attempt to address issues pertaining to site-specific cancer mortality.

Our group has previously shown that CRF is a stronger predictor than adiposity for all-cause (35) and cardiovascular disease mortality (24) in non-diabetic men as well as for

all-cause mortality in men with type 2 diabetes (36). The results of the current study underscore the need for health professionals to place at least as much emphasis on enhancing physical activity as on weight management when counseling individuals on healthy lifestyle habits that may lower cancer mortality risk.

In summary, CRF is significantly and inversely associated with cancer mortality in men. This association is steep, graded, and relatively unchanged after adjustment for adiposity. While each adiposity measure was significantly and directly associated with cancer mortality, this association was attenuated or eliminated after adjustment for CRF. When regressed jointly, mortality rates were significantly lower in fit compared with unfit men within stratum of standard clinical groupings for BMI, WC, and percent body fat. These data suggest that attaining a moderate to high level of CRF may attenuate some of the cancer mortality risks associated with increased adiposity. A strong emphasis should be placed on encouraging sedentary individuals of all adiposity levels to become at least moderately active, presumably thereby increasing their CRF level to decrease the risk of cancer mortality.

Acknowledgments

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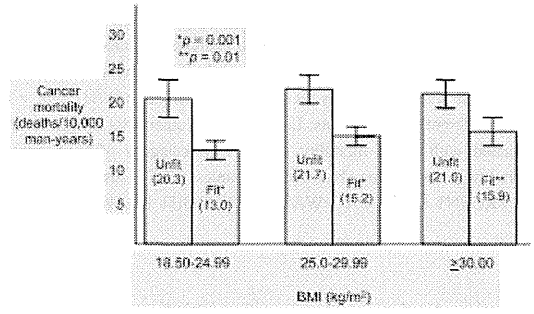
論文名	Cardiorespiratory fitness, different measures of adiposity, and cancer mortality in men						
著 者	Farrell SW, Cortese GM, LaMonte MJ, Blair SN.						
雑誌名	Obesity (Silver Spring, Md)						
巻・号・頁	15(12)　3140-3149						
発行年	2007						
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/18198325						
対象の内訳		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	43.8歳			( )		前向きコホート
	対象数	10000以上			( )		( )
調査の方法	実測	( )					
アウトカム	予 防	なし	なし	ガン予防	なし	(死亡)	( )
	維持・改善	な し	な し	な し	なし	(	( )
図 表	 *Figure 1:* Joint association of CRF and BMI with the age- and examination year-adjusted rates of cancer mortality: ACLS, 1970 to 2003. Error bars represent standard error. Likelihood ratio test for interaction, χ^2, $df_1 = 0.43$, $p = 0.51$. Numbers shown in bars represent cancer mortality rates.						
図表掲載箇所	P3146, Figure 1						
概 要 (800字まで)	本研究は、Aerobics Center Longitudinal Studyの健康な男性38,410名を対象に、17.2年間の追跡を行い、ガン死亡に対する肥満と体力との関連を検討した。体力は、トレッドミル運動負荷試験(modified Balke protocol)により心肺体力として評価され、年齢標準化された分位によりカテゴリー化された。心肺体力が、8.4メッツ、10.2メッツ、11.2メッツ、12.5メッツ、14.9メッツのグループでは、ガン死亡に対するリスクがそれぞれ、1.0、0.71(0.6-0.85)、0.69(0.58-0.83)、0.73(0.61-0.89)、0.53(0.43-0.67)であり、最も心肺体力が低いグループ(8.4メッツ)と比較して、10.2メッツを有するグループにおいてガン死亡のリスクの有意な低下が認められた。また、BMIや腹囲、体脂肪率により調整された後においても、心肺体力はガン死亡のリスク低下と関連していた。						
結 論 (200字まで)	高い心肺体力は、男性におけるガンの死亡のリスク低下と関連しており、これらはいくつかの肥満の指標と独立していた。高い心肺体力を有することはガンによる死亡のリスクを低下させる。						
エキスパートによるコメント (200字まで)	ガンによる死亡は、現在の我が国における最も多い死亡原因であり、これらを高い心肺体力を有することで予防可能であることが示されたことは非常に重要な知見である。						

担当者　村上晴香

Cardiorespiratory Fitness, Adiposity, and All-Cause Mortality in Women

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ABSTRACT

FARRELL, S. W., S. J. FITZGERALD, P. A. McAULEY, and C. E. BARLOW. Cardiorespiratory Fitness, Adiposity, and All-Cause Mortality in Women. *Med. Sci. Sports Exerc.*, Vol. 42, No. 11, pp. 2006–2012, 2010. **Purpose**: To determine the prospective associations among cardiorespiratory fitness (CRF), different measures of adiposity, and all-cause mortality in women. **Methods**: A total of 11,335 women completed a comprehensive baseline examination between 1970 and 2005. Clinical measures included body mass index (BMI), waist circumference (WC), waist-to-height ratio (W/HT), waist-to-hip ratio (W/Hip), percent body fat (%BF), and CRF quantified as duration of a maximal exercise test. Participants were classified by CRF as low (lowest 20%), moderate (middle 40%), and high (highest 40%) as well as by standard clinical cut points for adiposity measures. Hazard ratios (HR) were computed using Cox regression analysis. **Results**: During a mean follow-up of 12.3 ± 8.2 yr, 292 deaths occurred. HR for all-cause mortality were 1.0, 0.60, and 0.54 for low, moderate, and high fit groups, respectively (P for trend <0.01). Adjusted death rates of overweight/obese women within each adiposity exposure were somewhat higher compared with normal-weight women and approached statistical significance for BMI, %BF, and W/HT ($P = 0.08$, $P = 0.08$, and $P = 0.07$, respectively). When grouped for joint analyses into categories of fit and unfit (upper 80% and lower 20% of CRF distribution, respectively), HR were significantly higher in unfit women within each stratum of BMI compared with fit–normal BMI women. Fit women with high %BF (HR = 1.0), high WC (HR = 0.9), and high W/HT (HR = 1.2) had no greater risk of death compared with fit–normal-weight women (referent). **Conclusions**: Low CRF in women was a significant independent predictor of all-cause mortality. Higher CRF was associated with lower mortality within each category of each adiposity exposure. Using adiposity measures as predictors of all-cause mortality in women may be misleading unless CRF is also considered. **Key Words:** BODY MASS INDEX, WAIST CIRCUMFERENCE, PERCENT BODY FAT, WAIST-TO-HEIGHT RATIO, WAIST-TO-HIP RATIO

BASIC SCIENCES

Overweight is an increasingly prevalent disorder in the United States and elsewhere. According to recent body mass index (BMI) data from the National Health and Nutrition Examination Survey, the prevalence of overweight (BMI $\geq$ 25 kg·m^{-2}) for US female adults is estimated to be 62% (23). Recent data from the Behavioral Risk Factor Surveillance System show the prevalence of obesity (BMI $\geq$ 30 kg·m^{-2}) among US adults to be ≥30% in several states.

Various measures of adiposity such as BMI, waist-to-hip ratio (W/Hip), waist circumference (WC), and waist-to-height ratio (W/HT) have shown overweight to be associated with increased cardiovascular morbidity (25,30,32) and mortality (9,17,18,21,26,28,30,32), as well as increased all-cause mortality (9,14,16,21,26) for women in several prospective studies. Although some studies have investigated associations of multiple measures of adiposity with all-cause mortality (9,14,16), none of these measured cardiorespiratory fitness (CRF) level. Because low CRF is an important independent predictor of all-cause mortality in women (3,4,8,12,22), failure to adjust for CRF potentially confounds the relationship between levels of adiposity and mortality. Failure to measure CRF may be due in part to an underlying assumption that all overweight individuals are unfit, an assumption that is not always valid. Earlier, our group (8) examined the relation of CRF and BMI to all-cause mortality in women who were enrolled in the Cooper Center Longitudinal Study (CCLS). We found that approximately 25% of women with class II obesity (BMI = 35–39.9 kg·m^{-2}) had a moderate to high level of CRF. In these same analyses, CRF was strongly and inversely associated with all-cause mortality; however, BMI was not significantly associated with mortality after adjustment for CRF. Using a subset of CCLS women who had either impaired fasting glucose or undiagnosed diabetes mellitus at baseline, Lyerly et al. (20) recently reported on the independent and joint associations among CRF, BMI, and all-cause mortality. Moderate and high levels of CRF were associated with a significant reduction in risk of all-cause mortality, relative to low levels of CRF. Before and after adjustment for CRF, BMI was not a significant predictor of all-cause mortality in women with impaired fasting glucose or undiagnosed diabetes mellitus. The present study

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expands on these findings by using a much larger sample of women who were apparently healthy at baseline and by using multiple measures of adiposity. Thus, the purpose of the present study was to extend previous observations by simultaneously quantifying the associations of CRF and different clinical measures of adiposity with all-cause mortality in a large cohort of adult women.

METHODS

Study participants and measurements. The CCLS is an updated continuation of the previously described Aerobics Center Longitudinal Study (3). The CCLS includes mortality data collected through 2006, as well as additional clinical variables. Briefly, the aim of the CCLS was to examine prospectively the relation of physical activity and physical fitness to health in men and women. Participants in the present study included 11,335 women who completed a baseline comprehensive medical examination at the Cooper Clinic in Dallas, TX, during the interval between 1970 and 2005. All participants were US residents, and the majority of women were white and from the middle to upper socioeconomic strata. After receiving written informed consent from each participant, a clinical evaluation was performed and included an examination by a physician, fasting blood chemistry assessment, personal and family health history, anthropometry, resting blood pressure and ECG, and a maximal graded treadmill exercise test. A standard physician's scale and stadiometer were used to measure weight and height. BMI was calculated as weight in kilograms divided by height in meters squared. We categorized women as normal weight (BMI = 18.5–24.9 $kg \cdot m^{-2}$) or overweight/obese (BMI $\geq$ 25 $kg \cdot m^{-2}$). WC was measured at the umbilicus using a cloth tape measure. A WC of <88 cm was categorized as normal, whereas a WC of $\geq$88 cm was categorized as high. The W/HT was calculated by dividing the WC by height. A W/HT of <0.5 was categorized as normal, whereas a W/HT of $\geq$0.5 was categorized as high. We estimated %BF using a generalized equation for the sum of seven skinfolds (13). A %BF of <30% was categorized as normal, whereas a %BF $\geq$30% was categorized as high (5). Because hip circumference measurement was not included as part of the physical examination until the mid 1980s, only a subset of women (n = 7653) in the cohort underwent measurement of both waist and hip circumferences. The W/Hip ratio was calculated by dividing the WC by the hip circumference. A W/Hip ratio of $\leq$0.75 was categorized as normal, whereas a W/Hip ratio of >0.75 was categorized as high.

CRF was quantified as the duration of a maximal treadmill exercise test using the modified protocol of Balke and Ware (2) as previously described (3). Exercise duration from this protocol has been shown to correlate highly with directly measured maximal oxygen update in women (24). All participants were encouraged to provide a maximal effort performance, and those who did not achieve at least 85% of age-predicted maximal heart rate were excluded from the analyses. To standardize exercise test performance, we used standard equations to compute maximal metabolic equivalent (1 MET = 3.5 mL O_2 uptake$\cdot kg^{-1}$ body weight$\cdot min^{-1}$) levels of CRF on the basis of the final treadmill speed and grade (1).

Cooper Clinic laboratory technicians analyzed blood chemistry using automated techniques. This laboratory participates in and meets quality control standards of the Centers for Disease Control and Prevention Lipid Standardization Program. All procedures were administered by trained technicians who followed standardized procedures. The CCLS undergoes annual review and approval by the institutional review board of The Cooper Institute.

All women completed a thorough medical history questionnaire that consisted of a comprehensive review of systems. From this questionnaire, an absence of a history of physician-diagnosed myocardial infarction, high blood pressure, stroke, diabetes, or cancer, along with normal resting and exercise treadmill ECG responses, was used to define "apparently healthy" status.

Mortality surveillance. We observed study participants for mortality from the date of their baseline examination to the date of either death or survival up to December 31, 2006. The National Death Index was used to ascertain vital status. The National Death Index has a sensitivity of 96% and a specificity of 100% for determining deaths in the general population (27). Once we identified possible decedents, Departments of Vital Statistics in the appropriate states were contacted, and official copies of death certificates were requested. We compared information on the death certificates with clinical records to confirm that the death certificate matched the individual. A nosologist coded the underlying and potentially four other contributing causes of death according to the *International Classification of Diseases, Ninth and Tenth Editions, Revised.*

Statistical analyses. We computed woman-years of exposure as the sum of follow-up time among decedents and survivors. There were 292 deaths identified during an average of 12.3 ± 8.2 yr of follow-up and 138,537 total woman-years of exposure. We first compared descriptive characteristics of women according to vital status and CRF level. Next, we calculated adjusted all-cause mortality rates per 10,000 woman-years of observation across low, moderate, and high CRF categories, categories of different adiposity measures, and smoking and health status.

We used Cox proportional hazards regression to calculate multivariable adjusted hazard ratios (HR) for all-cause mortality. These models included age (yr), examination year, smoking status (current, former, or never), and health status (apparently healthy or not). These four factors will subsequently be called covariables. Separate models were then calculated for CRF as well as each adiposity parameter (BMI, W/HT, WC, and %BF). Because of the limited amount of follow-up and the relatively small number of deaths (n = 70) in the subset of women who had values for

W/Hip, this adiposity exposure was not included in the multivariate mortality analyses.

We also examined the joint association of the various adiposity exposures and CRF exposure with all-cause mortality. In these analyses, adiposity exposure groups were based on standardized definitions mentioned previously. CRF was grouped as fit and unfit on the basis of the upper 80% and lower 20% of the age-standardized CRF distribution, as previously reported in the CCLS (19).

The 95% confidence intervals (CI) around all risk estimates were also calculated. To avoid bias from undetected illness at baseline, all analyses were performed after excluding those who had <1 yr of follow-up. All P values are two-sided, and $P < 0.05$ was regarded as statistically significant. We conducted all data analyses using SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline characteristics of the cohort according to vital status are presented in Table 1. On average, decedents were older, had a higher %BF, had lower CRF levels, had a higher prevalence of smoking, and had a higher alcohol intake than survivors ($P < 0.05$). Higher values for decedents than survivors were also seen for W/HT and W/Hip; these differences approached statistical significance ($P = 0.07$ and $P = 0.05$, respectively). Baseline characteristics of the cohort across CRF categories are presented in Table 2. Each of the baseline characteristics was significantly associated with categories of CRF. Higher levels of CRF were strongly associated with more favorable risk status (P for trend <0.001).

Adjusted rates of all-cause mortality according to exposure groups are presented in Table 3. There were no significant differences in mortality rates seen between categories of WC. Differences in mortality rates between women with a high BMI, %BF, or W/HT compared with those with a normal BMI, %BF, or W/HT approached statistical significance ($P = 0.08$, $P = 0.08$, and $P = 0.07$, respectively). Mortality rates were significantly higher in current smokers compared with nonsmokers (45.5 and 18.4 deaths per 10,000 woman-years, respectively, $P < 0.001$). A significant inverse trend of all-cause mortality rates was seen across incremental CRF categories (34.7, 20.2, and 18.8 deaths per 10,000 woman-years for low, moderate, and high fit women, respectively, $P < 0.001$).

Results of multivariate analyses are presented in Tables 4a and 4b. In Table 4a, after adjusting for covariables and using the low CRF group as the referent, HR for moderate and high CRF groups were 0.60 and 0.54, respectively ($P < 0.001$). Further adjustment for BMI, W/HT, WC, and %BF in separate models had little effect on the pattern or strength of association. In Table 4b, before and after adjustment for CRF, none of the adiposity exposures had a significant association with all-cause mortality. In Table 5, we present the MET levels for low, moderate, and high CRF categories by age group.

To place our findings into a more clinically relevant perspective, we jointly regressed mortality rates on adiposity and CRF exposures grouped according to standardized definitions (Figs. 1–4). As shown in Figure 1, HR across incremental BMI categories of normal, overweight, and obese were significantly higher in unfit (1.5, 1.9, and 2.5, respectively) than fit women (1.0, 1.1, and 0.5, respectively;

TABLE 1. Baseline characteristics[a] on the basis of vital status in 11,335 women (CCLS, 1979–2006).

	Survivors	Decedents	P
n	11,043	292	
Follow-up (yr)	12.2 ± 8.4	14.8 ± 7.0	<0.001
Age (yr)	44.8 ± 10.2	53.4 ± 10.9	<0.001
BMI (kg·m^{-2})	23.7 ± 4.2	23.5 ± 3.6	0.92
WC (cm)	74.4 ± 10.7	74.8 ± 10.1	0.16
W/HT	0.45 ± 0.06	0.46 ± 0.06	0.07
%BF	26.2 ± 6.3	29.1 ± 6.0	<0.001
W/Hip	0.77 ± 0.10	0.78 ± 0.06	0.05
CRF (METs)	9.7 ± 2.1	8.2 ± 2.0	<0.001
Healthy (%)	77.6	76.4	0.61
Current smoker (%)	8.1	18.2	<0.001
Alcohol (drinks per week)[b]	0 (0–1)	2 (0–7)	<0.001

[a] Mean ± SD, unless indicated.
[b] Median (25th–75th percentile).

TABLE 2. Baseline characteristics on the basis of CRF level in 11,335 women (CCLS, 1979–2006).

	Low Fit	Moderate Fit	High Fit	P
n	1068	3679	6588	
Follow-up (yr)	14.4 ± 9.0	13.3 ± 8.8	11.3 ± 7.9	<0.001
Age (yr)	44.4 ± 10.2	45.0 ± 10.5	45.1 ± 10.2	0.05
BMI (kg·m^{-2})	28.2 ± 6.3	24.6 ± 4.4	22.5 ± 2.8	<0.001
WC (cm)	84.4 ± 14.1	76.6 ± 10.8	71.6 ± 8.4	<0.001
W/HT	0.52 ± 0.08	0.46 ± 0.07	0.43 ± 0.05	<0.001
%BF	32.6 ± 5.2	28.8 ± 5.4	23.7 ± 5.7	<0.001
W/Hip[a]	0.81 ± 0.07	0.78 ± 0.12	0.76 ± 0.09	<0.001
BMI ≥ 25 kg·m^{-2} (%)	61.8	36.9	15.7	<0.001
WC ≥ 88 cm (%)	38.2	14.7	4.8	<0.001
W/HT ≥ 0.5	53.8	26.2	9.6	<0.001
%BF ≥ 30 (%)	71.8	43.8	14.8	<0.001
CRF (METs)	6.6 ± 0.8	8.4 ± 1.0	10.9 ± 1.7	<0.001
Healthy (%)	69.8	75.6	80.0	<0.001
Current smoker (%)	14.4	11.0	6.1	<0.001
Alcohol (drinks per week)	0 (0–1)	0 (0–2)	0 (0–1)	0.02

[a] n = 7653. All other measures were performed on the entire cohort of 11,335 women.

TABLE 3. Adjusted[a] rates of all-cause mortality according to exposure groups in 11,335 women (CCLS, 1979–2006).

	Woman-Years	Deaths	Rate/10,000 Woman-Years[a]	P
BMI category				
Normal weight	107,614	214	19.9	0.08
Overweight/obese	30,923	78	25.1	
Normal WC	127,054	262	26.3	0.21
High WC	11,483	30	20.6	
Normal %BF	96,563	158	21.0	0.08
High %BF	41,974	134	21.3	
Normal W/HT	117,495	231	20.1	0.07
High W/HT	21,041	61	26.5	
CRF				
Low	15,365	64	34.7	<0.001
Moderate	48,935	110	20.2	
High	74,237	118	18.8	
Healthy	114,216	223	20.9	0.80
Unhealthy	24,321	69	21.7	
Nonsmoker	124,923	239	18.4[b]	$P < 0.001$
Current smoker	13,613	53	45.5[b]	

[a] Adjusted for age, examination year, smoking status, and baseline health status.
[b] Adjusted for age, examination year, and baseline health status.

TABLE 4a. Risk of mortality according to CRF and body composition groups in 11,335 women (CCLS, 1979–2006).

	HR[a] (95% CI)	HR[b] (95% CI)	HR[c] (95% CI)	HR[d] (95% CI)	HR[e] (95% CI)
CRF					
Low fit	1.0	1.0	1.0	1.0	1.0
Moderate fit	0.60 (0.44–0.82)	0.61 (0.44–0.84)	0.61 (0.45–0.84)	0.60 (0.44–0.83)	0.61 (0.44–0.83)
High fit	0.54 (0.40–0.75)	0.57 (0.41–0.79)	0.57 (0.41–0.80)	0.55 (0.40–0.77)	0.56 (0.40–0.79)

[a] Adjusted for age, examination year, current smoking status, and health status.
[b] Model 1 + BMI.
[c] Model 1 + W/HT.
[d] Model 1 + WC.
[e] Model 1 + %BF.

$P < 0.05$). In addition, fit–overweight (HR = 1.1) and fit–obese (HR = 0.5) women were no more likely to die than their fit–normal-weight BMI counterparts (referent). As shown in Figure 2, HR across incremental WC categories were significantly higher in unfit (HR = 1.7 and 2.0, respectively) than in fit–normal-WC women (referent), $P < 0.006$. In addition, fit–high-WC women were no more likely to die (HR = 0.9) than their fit–normal-WC counterparts. As shown in Figure 3, HR were not significantly different between fit (referent) and unfit (HR = 1.4) women within the normal %BF category; however, there was a significant difference between unfit–high %BF women (HR = 2.0) and fit–normal-%BF women ($P < 0.001$). In addition, fit–high-%BF women were no more likely to die (HR = 1.0) than their fit–normal-%BF (referent) counterparts. Finally, as shown in Figure 4, HR across incremental W/HT categories were significantly higher in unfit (HR = 1.8 and 1.9, respectively) than in fit–normal-W/HT women (referent), $P < 0.004$. In addition, fit–high-W/HT women were no more likely to die (HR = 1.2) than their fit–normal-W/HT counterparts.

DISCUSSION

To our knowledge, this is the first study that has examined an objective measure of CRF, multiple clinical measures of adiposity, and all-cause mortality in apparently healthy adult women of varying ages. CRF was strongly and inversely associated with all-cause mortality independently of several confounding factors, including the adiposity measures. Rates of all-cause mortality were significantly lower in fit–normal-BMI women than in unfit women within each stratum of BMI. In addition, fit women with high BMI, %BF, high WC, and high W/HT had no greater risk of death compared with their fit–normal counterparts.

TABLE 4b. Risk of mortality according to body composition groups in 11,335 women (CCLS, 1979–2006).

	Model 1[a]	Model 2[b]
	HR (95% CI)	HR (95% CI)
BMI		
Overweight	1.0	1.0
Normal weight	0.79 (0.61–1.03)	0.90 (0.68–1.19)
W/HT		
High	1.0	1.0
Normal	0.76 (0.57–1.02)	0.87 (0.64–1.19)
WC		
High	1.0	1.0
Normal	0.94 (0.63–1.40)	0.94 (0.63–1.41)
%BF		
High	1.0	1.0
Normal	0.91 (0.71–1.17)	0.92 (0.71–1.18)

[a] Model 1 adjusted for age, examination year, current smoking status, and health status.
[b] Model 2 adjusted for all variables in model 1 plus CRF.

Data on the joint effects of adiposity and CRF on mortality are sparse, as objective measures of CRF (i.e., maximal treadmill exercise testing) and data on %BF or W/HT are not widely available. Stratifying adiposity by CRF permits more rigorous analyses of combined subgroups than adjustment for either variable alone. The joint associations observed between various measures of adiposity, CRF, and all-cause mortality in women in the current study are somewhat difficult to compare with other studies. Using data from the National Institutes of Health-AARP Diet and Health Study, Koster et al. (17) found that high levels of physical activity (>7 $h \cdot wk^{-1}$) significantly attenuated, but did not eliminate, the increased mortality risk associated with obesity as measured by BMI and WC. In the Nurses' Health Study, Hu et al. (11) found that, although higher levels of physical activity (≥3.5 $h \cdot wk^{-1}$) did not eliminate excess mortality associated with obesity as measured by BMI, mortality rates were lower in highly active women than inactive women within each stratum of BMI. Similar results were seen by Weinstein et al. (30) during a prospective study of 38,987 participants in the Women's Health Study. A major difference between the CCLS and the aforementioned studies is the use of objectively measured CRF levels in the former and the use of self-reported physical activity in the latter. It has been reported in the literature that the correlation between self-reported physical activity and CRF is quite modest, ranging between 0.3 and 0.4 (31).

With regard to using an objective measure of baseline CRF and subsequent mortality, these results are in agreement with a recent meta-analysis performed by Kodama et al. (15). Using data from 33 eligible studies, 6910 cases of all-cause mortality were reported among 102,980 participants. A significant inverse trend in mortality was observed across low, intermediate, and high CRF

TABLE 5. MET levels by age group for low, moderate, and high CRF categories in 11,335 women (CCLS, 1979–2006).

Age Group (yr)	Low CRF (METs)	Moderate CRF (METs)	High CRF (METs)
20–39	<8.2	8.2–10.3	>10.3
40–49	<7.3	7.3–9.3	>9.3
50–59	<6.3	6.3–8.1	>8.1
60+	<5.9	5.9–7.2	>7.2

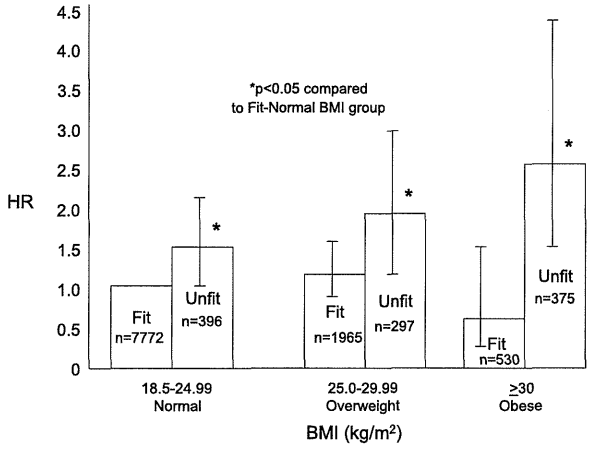

FIGURE 1—Joint association of CRF and BMI with the age and examination year adjusted HR for all-cause mortality: CCLS women, 1979–2006. *Error bars* represent 95% CI.

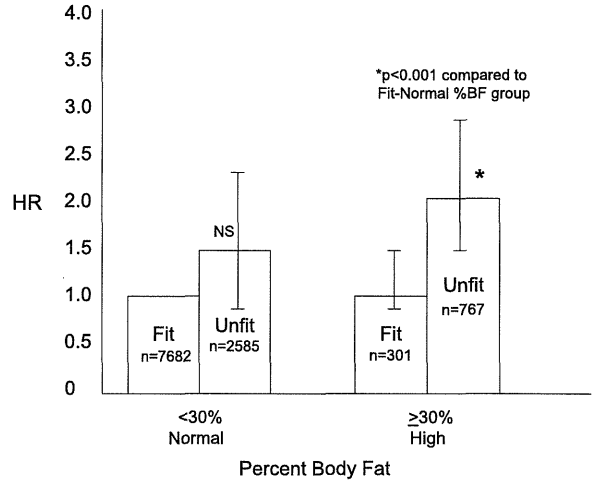

FIGURE 3—Joint association of CRF and %BF with the age and examination year adjusted HR for all-cause mortality: CCLS women, 1979–2006. *Error bars* represent 95% CI.

groups. Unlike our present study, however, this meta-analysis did not examine the effects of adiposity on mortality and the joint associations among adiposity, CRF, and mortality. Thus, we feel that our study adds significant value to the existing literature regarding CRF and mortality.

An important point to consider when interpreting these data is the method by which CRF was grouped for the analysis. In the CCLS, we have standardized the definition of low fit (unfit) as the bottom 20% of the age-standardized distribution of maximal exercise duration within the overall CCLS population; individuals in the remaining 80% of the distribution are defined as fit (19). Using this definition, it is apparent that even modest levels of CRF are associated with lower risk of all-cause mortality. For example, a 40- to 49-yr-old woman would need to achieve a maximal metabolic equivalent (MET) level ≥7.3 to qualify for the fit category. This is equivalent to covering 1.1 miles using the Cooper 12-min run–walk test (6) or achieving a treadmill time of 7.5 min on a standard Bruce treadmill test. This modest level of CRF can likely be achieved by most apparently healthy women by performing moderate amounts and intensities of regular aerobic activity such as brisk walking. For example, Duncan (7) randomized 102 sedentary women to one of four treatment groups: control, strollers, brisk walkers, and aerobic walkers. The three intervention groups progressively increased their distance and intensity until they could walk 3 miles five times per week at an assigned pace. Strollers, brisk walkers, and aerobic walkers trained at 3, 4, and 5 mph, respectively. Maximal oxygen

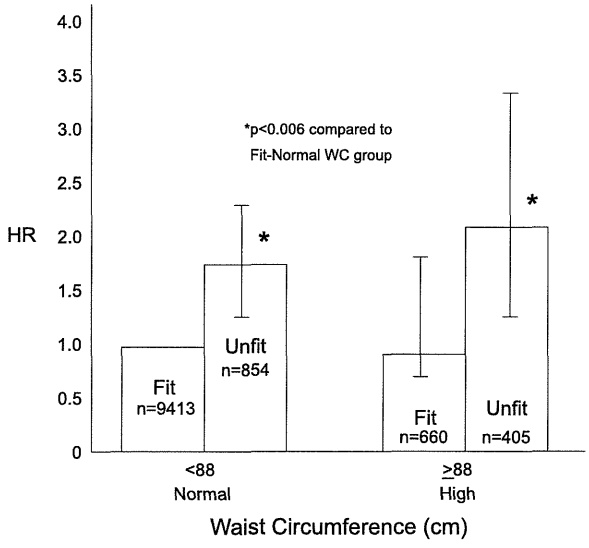

FIGURE 2—Joint association of CRF and WC with the age and examination year adjusted HR for all-cause mortality: CCLS women, 1979–2006. *Error bars* represent 95% CI.

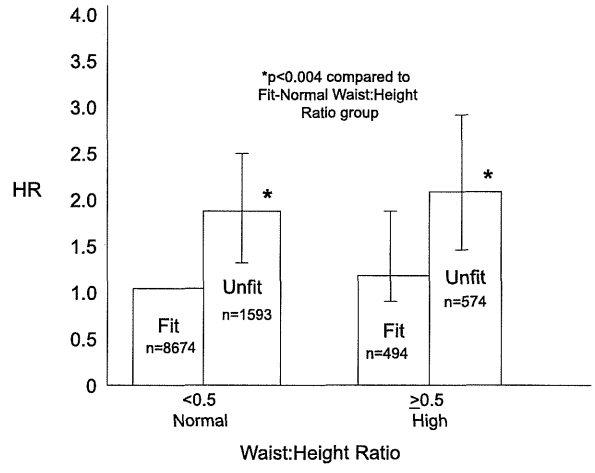

FIGURE 4—Joint association of CRF and W/HT with the age and examination year adjusted HR for all-cause mortality: CCLS women, 1979–2006. *Error bars* represent 95% CI.

consumption was increased in a dose–response manner by 4%, 9%, and 16%, respectively.

An issue that arises in prospective studies of apparently healthy individuals is the possibility of undetected subclinical disease at baseline. Including such individuals in the present study might confound the relationship among CRF, adiposity, and all-cause mortality because individuals with subclinical disease might have a lower treadmill test performance and higher levels of adiposity. Because of the extensive baseline health examination that was defined earlier in our article, it is not likely that undetected subclinical disease was present in a large number of our study participants. In addition, we excluded all women with <1 yr of follow-up, which enhances our confidence that our primary findings were not due solely to undetected disease at baseline.

Among the strengths of the current study is a large and well-characterized cohort of women, an extensive follow-up with a relatively large number of all-cause deaths for analysis, and the use of objective measures for CRF and several different adiposity exposures. Although BMI, WC, and W/HT are proxy measures of body fatness, all were significantly correlated with %BF (r = 0.73, r = 0.68, and r = 0.69, respectively; data not shown).

This study also has limitations. The cohort is primarily white and from the middle to upper socioeconomic strata; therefore, our findings must be cautiously interpreted when generalizing to other populations. This same limitation strengthens the internal validity of our findings by reducing potential confounding by these issues. Furthermore, median levels of CRF in CCLS women are very similar to median values recently reported using a representative sample of US women (29). Additional limitations include the absence of more extensive information on smoking habits, such as number of pack-years. Also, CCLS women are leaner than the general population. Using BMI as the criterion, the majority of our cohort (92%) was in the normal weight or overweight category. Although approximately 5.3% (n = 625) of the cohort were in the class I obese category, we have insufficient data to comment on the relation among CRF, adiposity, and mortality for class II (n = 204) or class III (n = 76) obese women. In addition, we are reporting only baseline data on adiposity exposures and CRF. It is possible that changes in these exposures will have occurred during the follow-up period, which, in turn, may have influenced our results. Because all Cooper Clinic patients received lifestyle counseling from their physician after the examination, this could be seen as a form of intervention. It is possible that fit individuals are more receptive to lifestyle counseling than unfit individuals. If this were true, then it is possible that it was not CRF *per se* but other interventions that were initiated at the time of baseline measurement that negated the impact of higher adiposity during follow-up. Because of the limited amount of follow-up and the relatively small number of deaths in women who underwent measurement of W/Hip, we have insufficient data to comment on the relation among CRF, W/Hip, and mortality in women. Using skinfold measurement to estimate %BF has an inherent level of error of ±3%. Because the study took place during a 35-yr period, many Cooper Clinic technicians were responsible for these measurements. Although all Clinic technicians undergo extensive training before having contact with patients, the fact that numerous personnel performed skinfold measurements may have introduced some additional degree of error as well. Finally, we were unable to evaluate medication use in this cohort. The current study examined all-cause mortality. Future analyses will focus on the relation between CRF, different measures of adiposity, and specific causes of mortality, i.e., cardiovascular disease and cancer.

In summary, these findings confirm a protective role of CRF on risk of all-cause mortality in women. Furthermore, only a relatively modest level of CRF is necessary to obtain significant protection. In the present study, a much greater incremental reduction in mortality risk was achieved comparing low to moderate CRF (~40% reduction) than from comparing moderate to high CRF (~10% reduction; Table 4a), supporting the premise that it may be possible to achieve a sizable reduction in all-cause mortality simply by encouraging women of low CRF levels, including those who are obese, to achieve moderate CRF levels. It is very likely that if women follow current public health guidelines for physical activity, i.e., 150 min·wk^{-1} of moderate-intensity aerobic exercise, then these modest moderate levels of CRF can be achieved by a substantial proportion of adult women (10).

Our findings also show that for various adiposity exposures, rates of all-cause mortality among fit–overweight/obese women are not significantly different from mortality rates of their fit–normal-weight counterparts. Physicians and other health care professionals should make a concerted effort to estimate or measure CRF levels before categorizing patients into risk strata on the basis of adiposity exposures only.

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