liter (250 mg per deciliter) for participants 30 to 39 years of age, and 3.38 mmol per liter (300 mg per deciliter) for those 40 or older; (4) those who reported at Visit 1 that they were currently taking lipid-lowering drugs; (5) participants with borderline elevations in cholesterol or triglyceride levels, or in both values (the definition of "borderline elevation" and the sampling frequency was age-, race-, and sex-specific for each clinic).[14] Altogether, 8200 men and women were screened at Visit 2, an average of 85 percent of those invited.

In 1977, the Lipid Research Clinics Mortality Follow-up Study of all participants who were examined at Visit 2 and who were 30 or older was begun in order to assess the relation of certain base-line characteristics to subsequent mortality, both overall and from a specific cause. This surveillance was carried out by mail and telephone. To date, 99 percent of the participants have been contacted successfully. No treatment of any kind has been provided, and no additional examinations have been performed. Because of the small number of nonwhites and very elderly subjects, and because of the low incidence of cardiovascular death among women, the present study was restricted to white men 30 to 69 years of age at base line.

Identification of Deaths

Beginning in 1977 and 1978, participants were contacted annually. When a participant was found to have died, a death certificate was obtained, and if cardiovascular disease was suspected, a witness (usually a physician) or the next of kin was interviewed. Two members of a panel of five cardiologists, who were unaware of the identity and base-line characteristics of the man, reviewed each case in which cardiovascular disease was suspected, and assigned a specific cause of death corresponding to codes 390 through 458 in the *International Classification of Diseases, Adapted* (ICDA), eighth edition, for death from cardiovascular disease and 410 through 414 for death from coronary heart disease. Disagreements between the two primary reviewers were adjudicated by the full panel. The present report is based on deaths identified during or before the 1983–1984 contact year, an average follow-up of 8.5 years.

Ascertainment of Risk Factors at Visit 2

Plasma lipid, lipoprotein, and glucose concentrations were measured after 12 or more hours of fasting. Information on smoking history, alcohol consumption, medications, regular physical activity (strenuous exercise or hard physical labor), and dietary intake with 24-hour recall was obtained by questionnaire.[14] The presence of angina was evaluated by the Rose questionnaire.[14] Height and weight were measured with the participants wearing light clothing but no shoes. Quetelet's index was calculated by dividing the weight in kilograms by the square of the height in meters. Resting blood pressures were measured after five minutes in a sitting position; the mean value of two random-zero measurements was recorded.[14]

The Exercise Test

A submaximal treadmill exercise test was administered at Visit 2 to all participants, according to a modified Bruce protocol[15,16] with seven three-minute stages in which the speed and inclination were increased in a stepwise fashion (stage 1: 2.7 km per hour [1.7 miles per hour] and 10 percent inclination; stage 2: 4 km per hour [2.5 miles per hour] and 12 percent inclination; stage 3: 5.5 km per hour [3.4 miles per hour] and 14 percent inclination). The electrocardiogram was monitored continuously, and blood pressure was measured at the end of each stage by the cuff technique. Heart rate was monitored continuously and was also recorded at the end of each stage, or earlier if a person stopped during a stage. The test was stopped when a precalculated target heart rate of 90 percent of the man's predicted maximal heart rate was attained.[15] The test was terminated before the attainment of the target heart rate if the participant was unable to continue because of chest pain, fatigue, dyspnea, or leg pain (a symptom-limited test) or because of abnormalities in the electrocardiogram (≥1 mm horizontal ST-segment change, major arrhythmias, or conduction defects), a decrease in systolic blood pressure, technical difficulties, or noncooperation by the participant.

The exercise electrocardiographic response was classified as negative, weakly positive, or strongly positive according to the degree of ST-segment displacement.[17]

Measurement of Fitness

The assessment of physical fitness, as measured on the treadmill, was restricted to men who were eligible for and performed at least one minute of the standard exercise-test protocol, were not using drugs that could interfere with the heart-rate response, and had their vital status ascertained at least once between 1977 and 1984. Men with signs or symptoms of cardiovascular disease (on the basis of history, physical examination, resting electrocardiography, or use of blood-pressure medication), referred to as the group with cardiovascular disease, and men without symptoms of cardiovascular disease, referred to as healthy, were analyzed separately. For healthy participants, the fitness variables used in our analysis were the heart rate measured at stage 2 of the exercise test, which was valid only if the participant exercised for at least one full minute at stage 2, and the amount of time on the treadmill. For healthy subjects, time on the treadmill was used as a relative measure of maximal oxygen uptake. The duration of exercise on the treadmill was the only measure used in the group with cardiovascular disease, since many of these participants terminated the exercise test during stage 1. In that group, time on the treadmill was used as a measure of the severity of the disease.

Statistical Analysis

The association between time until death from coronary heart disease or cardiovascular disease and the fitness variables, as well as the covariables age, systolic blood pressure, high-density lipoprotein (HDL) level, low-density lipoprotein (LDL) level, glucose level, smoking, body weight or Quetelet's index, resting heart rate, and regular physical activity were investigated by means of proportional-hazards models.[18] The assumption in these models is that there is a proportional relation between the change in the value of a variable and the change in the associated hazard.

In the present study, separate analyses were performed for the healthy men and the men with cardiovascular disease, since a man's health influences his exercise performance and because a limited amount of exercise-test data was collected for the group with cardiovascular disease.

The initial models that were investigated included one fitness variable and all the potential covariables mentioned above as the independent variables. In the final models only age, smoking, HDL level, LDL level, and resting systolic blood pressure were included as covariables; the other variables were not significantly related to mortality and did not change the coefficients for the fitness variable used. The dependent variable was either time until death from coronary heart disease or time until death from cardiovascular disease. In addition, since the probability of selection for the Visit 2 sample depended to some extent on the clinic that a man attended, his age, and his plasma lipid profile, other models were constructed to assess the consistency of the effect of the fitness variable across sampling strata. The proportional-hazards assumption for each of these models was also checked with use of the partial residuals of the model. The models were computed with use of the proportional-hazards general linear model procedure in the SAS computer package.[19]

Results

There were 4276 white men 30 to 69 years of age at base line in the Lipid Research Clinics Prevalence Follow-up Study. The reasons for excluding some of those men from the analysis reported here include missing or incomplete exercise-test data (308 men) or the use of medications such as beta-blockers that may affect the heart rate (213 men). Men with symptoms

or signs of possible cardiovascular disease and those using blood-pressure medications (649 men) — the group with cardiovascular disease — were analyzed separately, since these conditions may affect heart-rate response or the ability to comply with the exercise-test protocol. The remaining 3106 men were referred to as the healthy group. There were 45 fatal cardiovascular events in the healthy group and 46 in the group with cardiovascular disease. The base-line characteristics of the two groups are shown in Table 1.

The healthy group was divided into quartiles according to heart rate at stage 2 during the exercise test. The relation of this fitness variable to selected base-line variables is shown in Table 2. Age and Quetelet's index did not differ among the quartiles. The highest fitness level (1) was associated with lower LDL cholesterol and triglyceride concentrations and a higher caloric intake per kilogram of body weight (143 kJ per kilogram for level 1 vs. 124 kJ per kilogram for level 4), but there was no difference in the proportion of smokers. Forty-nine percent in the most fit quartile according to heart rate (1) reported regular physical activity, whereas 19 percent did so in the least fit quartile (4). This finding is consistent with the increase in the mean stage 2 heart rate from 112 beats per minute for level 1 to 156 beats per minute for level 4. The highest fitness level was also associated with a systolic blood pressure that was 9 mm Hg lower than that of the men at the lowest fitness level, with a diastolic blood pressure that was 7 mm Hg lower at rest, and with a systolic blood pressure that was 24 mm Hg lower during stage 2 of the exercise test. The resting heart rate was 10 beats per minute lower in the most physically fit men than in the least fit men.

The unadjusted cumulative mortality was much higher in the quartile with the lowest level of fitness than in the most fit quartile; the rate of death from cardiovascular disease was 8.5 times higher and that of death from coronary heart disease was 6.5 times higher (Table 3). Adjustment for age did not change that relation; therefore, only the unadjusted data are presented.

The results from the proportional-hazards models for the healthy group are shown in Tables 4 and 5. The associations of both stage 2 heart rate and exercise time on the treadmill with mortality from cardiovascular disease were significant; the relative risk of death associated with an increase of 2 SD in stage 2 heart rates (35 beats per minute) was 2.7, and that associated with a decrease of 2 SD (4.4 minutes) in time on the exercise treadmill was 3.0. Similar relative risks were found for mortality from coronary heart disease (Tables 4 and 5). Exercise time on the treadmill was also associated with mortality from all causes (Table 5), and a similar relation was found for stage 2 heart rate (data not shown). The age-adjusted relative risks did not change meaningfully when the other covariables (smoking, LDL level, HDL level, and systolic blood pressure) were added to the models, indicating that the relation between physical fitness and death from cardiovascular disease and coronary heart disease is independent of these variables.

Table 1. Distribution of Risk Factors at Base Line.*

VARIABLE	HEALTHY GROUP (N = 3106)	CVD (N = 649)
	mean ±SD	
Age (yr)	43±9.3	50±9.7
Weight (kg)	83±12.1	84±12.8
LDL (mmol/liter)	3.77±1.02	3.93±1.06
HDL (mmol/liter)	1.14±0.31	1.13±0.34
Resting systolic BP (mm Hg)	124±14.9	134±18.8
Stage 2 heart rate (beats/min)	133±17.4	132±17.7
Time on treadmill (min)	10.0±2.2	8.4±2.7
	percent	
Current smoking	38.3	38.7
Physical activity	32.2	25.6

*CVD denotes cardiovascular disease, LDL low-density lipoprotein, HDL high-density lipoprotein, and BP blood pressure.

The relative risk of death from coronary heart disease for men in the group with cardiovascular disease, as compared with the healthy group, was 3.4, adjusting for the other cardiovascular risk factors; their relative risk of death from cardiovascular disease was 2.8. In addition, in the group with cardiovascular disease, exercise time on the treadmill was also associated significantly ($P \leq 0.0001$) with death from cardiovascular disease and coronary heart disease, with relative risks of 4.8 and 5.6, respective-

Table 2. Mean Values for Risk Factors in 3106 Healthy Men, According to Values for Stage 2 Heart Rate.*

VARIABLE	STAGE 2 HEART-RATE QUARTILE†			
	1	2	3	4
	mean ±SD			
Stage 2 heart rate (beats/min)	112±7.1	127±3.3	139±3.7	156±8.7
Age (yr)	43.3±8.9	43.4±9.2	43.2±9.6	43.5±9.1
Quetelet's index (kg/m^2)	26.4±3.1	26.7±3.5	26.9±3.5	26.9±3.8
Resting heart rate (beats/min)	67±9	71±10	73±10	77±12
Resting systolic BP (mm Hg)	120±14	122±14	125±14	129±15
Resting diastolic BP (mm Hg)	77±10	79±10	81±10	84±10
Stage 2 systolic BP (mm Hg)	154±20	164±22	171±23	178±24
Time on treadmill (min)	12.0±1.8	10.6±1.6	9.6±1.4	8.0±1.5
Triglycerides (mmol/liter)	1.73±1.6	2.13±2.4	2.09±1.7	2.31±2.4
LDL (mmol/liter)	3.72±1.1	3.74±1.0	3.78±1.0	3.85±1.1
HDL (mmol/liter)	1.17±0.3	1.13±0.3	1.13±0.3	1.14±0.4
	percent			
Current smoking	36.8	40.8	40.1	35.3
Physical activity	49	36	25	19

*BP denotes blood pressure, LDL low-density lipoprotein, and HDL high-density lipoprotein.

†1 represents the quartile of the men with lowest heart rates (most physically fit), and 4 the quartile with the highest heart rates (least physically fit).

Table 3. Rates of Death from Coronary Heart Disease (CHD) and Cardiovascular Disease (CVD) in Healthy Men over 8.5 Years of Follow-up, According to Quartile of Stage 2 Heart Rate.

Cause of Death	Stage 2 Heart-Rate Quartile*				Ratio of Death Rates (4:1)
	1	2	3	4	
	% (95% confidence interval)				
CHD	0.26 (0.00–0.62)	0.91 (0.24–1.58)	0.91 (0.24–1.58)	1.69 (0.77–2.61)	6.5 (1.5–28.7)
CVD	0.26 (0.00–0.62)	1.30 (0.49–2.11)	1.56 (0.68–2.44)	2.21 (1.16–3.25)	8.5 (2.0–36.7)

*1 represents the quartile of the men with the lowest heart rates (most physically fit), and 4 the quartile with the highest heart rates (least physically fit).

ly, for times that were 2 SD (5.5 minutes) shorter on the treadmill (Table 5).

Discussion

This study was designed to test the hypothesis that physical fitness, as assessed by measurements easily obtainable from a standard treadmill exercise test, is related to subsequent death from cardiovascular disease and coronary heart disease in asymptomatic men. Furthermore, we assessed this relation while controlling for other known risk factors.

As has been demonstrated in previous studies,[8-10] the highest fitness levels were associated with a better risk-factor profile (i.e., lower levels of total cholesterol, LDL cholesterol, and triglycerides and higher levels of HDL cholesterol). Also, blood pressures at rest and during exercise were lower in the most fit group. The level of physical fitness is determined by genetic factors and the degree of physical activity. Some researchers assert that genetic factors are more important and that regular physical activity adds relatively little to the level of fitness.[13] In our group of healthy men, however, the fitness level was closely related to regular physical activity as reported by the participants (Fig. 1). This finding suggests that regular physical activity is more important than genetic factors in determining the level of fitness and therefore might be an important factor in reducing the risk of death from coronary heart disease.

As shown in Figure 2, the mortality curves for fit as compared with unfit men started to diverge early and continued to diverge. This observation suggests that the difference in mortality in the various fitness quartiles was not entirely due to subclinical disease at base line that resulted in an excess of early mortality. Rather, the effect was seen consistently, over the entire follow-up period.

Peters and coworkers[11] found that physical fitness, defined as the workload on a bicycle ergometer that resulted in a heart rate of 150 beats per minute, was highly predictive of nonfatal and fatal myocardial infarction during a 4.8-year follow-up in a cohort of law-enforcement officers and firefighters. The adjusted relative risk for those with below-median work capacity was 2.2. Lie and coworkers[12] measured maximal working capacity on an electrical bicycle ergometer in 2014 asymptomatic men, 40 to 59 years of age, in various occupations. They found significantly higher mortality from coronary heart disease in the least fit quartile (unadjusted relative risk, 5), as compared with the most fit. However, they did not perform multivariate analyses to assess the possible influence of other confounding factors. Sobolski and coworkers[13] measured submaximal work on a bicycle in 2363 healthy male factory workers. They found a significant relation between measured physical fitness and nonfatal and fatal myocardial infarction over a five-year follow-up period.

In our study, the crude mortality rate was much higher in the least fit quartile as compared with the most fit. Adjustment for age did not change the association between fitness and mortality. Of greater interest, however, are the results from the proportional-

Table 4. Relative Risks of Death from Cardiovascular Disease (CVD) and Coronary Heart Disease (CHD) in Healthy Men over 8.5 Years of Follow-up.*

Variable (±SD)	CVD			CHD		
	RR	95% CI	P value	RR	95% CI	P value
Age (±9.3 yr)	4.2	2.3–7.8	<0.0001	3.3	1.5–7.1	0.002
Current smoking	3.9	2.0–7.6	0.0001	4.3	1.2–9.7	0.0006
HDL (±0.31 mmol/liter)	0.44	0.85–0.23	0.017	0.35	0.81–0.15	0.014
LDL (±1.02 mmol/liter)	2.2	1.3–3.7	0.0052	2.4	1.3–4.6	0.01
Systolic BP (±14.9 mm Hg)	2.0	1.1–3.5	0.018	1.5	0.7–3.1	0.26
Stage 2 HR (±17.4 beats/min)	2.7	1.4–5.1	0.003	3.2	1.5–6.7	0.003

*RR denotes relative risk, CI confidence interval, HDL high-density lipoprotein, LDL low-density lipoprotein, BP blood pressure, and HR heart rate. The Cox regression model was used to assess the effects of all variables included in the model simultaneously. The relative risks shown are for men with a difference of +2 SD in the variables, except for smoking, in which smokers were compared with nonsmokers. P values were calculated from the standard error of the coefficients in the model.

Table 5. Relative Risks of Death from Coronary Heart Disease (CHD), Cardiovascular Disease (CVD), and All Causes in Healthy Men and Men with Cardiovascular Disease over 8.5 Years of Follow-up, According to Exercise Time on the Treadmill.*

Cause of Death and Group	Relative Risk (95% Confidence Limits)	P Value
CHD		
Healthy	2.8 (1.3–6.1)	0.007
CVD	5.6 (2.5–12.6)	<0.0001
CVD		
Healthy	3.6 (1.6–5.6)	0.0004
CVD	4.8 (2.5–9.2)	<0.0001
All causes		
Healthy	1.8 (1.2–2.6)	0.006
CVD	2.9 (1.7–4.9)	0.0001

*The Cox regression model was used, adjusting for age, smoking, HDL level, LDL level, and systolic blood pressure. The relative risks shown are for men with a decrease in time on the treadmill of 2 SD: 4.4 minutes in the healthy group and 5.5 minutes in the group with cardiovascular disease.

hazards models, which show that fitness levels as assessed by heart rate at stage 2 and treadmill time are associated significantly with death from cardiovascular disease and coronary heart disease when other major coronary risk factors are controlled for.

The covariates tested in these models included age, smoking status, systolic blood pressure, LDL level, and HDL level. Adding the covariates to the age-adjusted model decreased the relative risk by only 10 percent. Thus, most of the protective effects of a higher level of physical fitness must act by other mechanisms, at least in part, in addition to its well-known effects on blood pressure and serum lipids. At this time, other mechanisms of this effect can only be postulated.

Studies in monkeys, dogs, and rats[20-23] suggest less extensive atherogenic changes in exercising animals and an improvement in coronary collateral circulation. Noakes et al.[24] have found that physical training produced an increased threshold for ventricular fibrillation in isolated rat hearts. This effect may enable the exercising animal to have better survival as a result of increased tolerance of arrhythmias or decreased propensity to the development of life-threatening arrhythmias during an acute ischemic event.

It is well known that physical training lowers the resting heart rate, blood pressure, and "double product" (heart rate × systolic blood pressure) at a given workload and that it increases maximal oxygen uptake. The increase in maximal oxygen uptake in healthy subjects is produced by both an increase in peak cardiac output and an increased extraction of oxygen from the blood. The increase in cardiac output in trained normal persons occurs because of an increase in stroke volume; at best, physical training has a very small effect on maximal heart rate.[5,25] However, the beneficial effect of physical training in persons with coronary heart disease has been attributed primarily to peripheral mechanisms[26-28] — i.e., to changes in skeletal muscles or to an increase in arterial oxygen content.[29] Several studies in humans have shown no important effect of physical training on cardiac hemodynamic, metabolic, or angiographic measurements.[30-32] However, other reports[33-35] have shown direct cardiac effects of an intense physical training program in patients with coronary artery disease. Ehsani et al.[34] reported an increase in the double-product threshold for ischemic ST-segment depression, a decrease in the extent of ST depression at a given double product, and a reduced maximal ST depression despite an increase in the maximal double product. These data suggest that the myocardial oxygen supply is enhanced as a result of intense physical training. The differences between the results of Ehsani et al. and other negative studies may be due to the duration and intensity of the training program and also to the patient population (Ehsani et al. studied patients who were not limited by angina).

Another benefit of regular physical training that leads to a physically fit state is the positive effect on blood coagulation.[36,37] The role of thrombosis in cardiovascular mortality has not been fully described, but there is agreement that platelets are involved in the atherosclerotic process and that thrombosis of the coronary arteries acts as a mechanism of myocardial infarction and sudden cardiac death.[38] Variable changes in the activation of platelets have been observed in patients with coronary heart disease during exercise, and increased platelet aggregation has been shown in normal subjects after strenuous exercise. Recently, Rauramaa et al.[39,40] have shown that physical training lowers the aggregability of platelets in middle-aged men. These men were mildly hypertensive and overweight, and the type of exercise used was

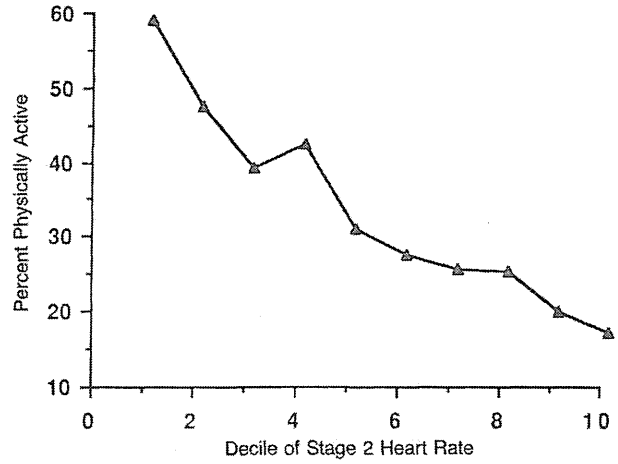

Figure 1. Percentage of Healthy Men Reporting Regular Physical Activity, According to Stage 2 Exercise Heart Rate.
Decile 1 represents the lowest heart rate, and decile 10 the highest.

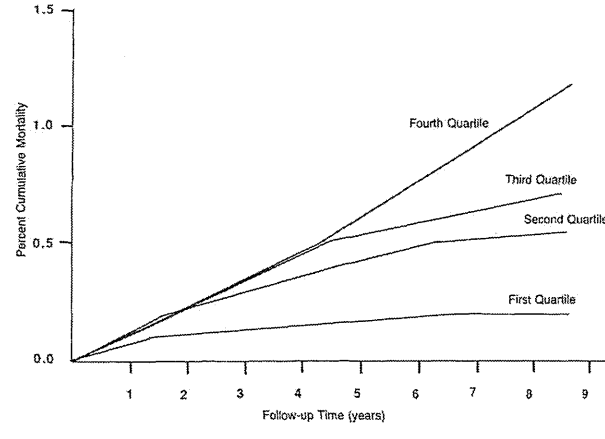

Figure 2. Cumulative Rate of Death from Cardiovascular Disease in Healthy Men, According to Quartiles of Stage 2 Exercise Heart Rate.
Life-table failure plots were computed from proportional-hazards models that included age, smoking status, HDL level, LDL level, resting systolic blood pressure, and stage 2 exercise heart rate, with continuous variables set to mean values and smoking status to zero (yes = 1, no = 0).

brisk walking to slow jogging. Thus, regular physical exercise appears to have an inhibitory effect on platelets that lasts for several days, in contrast to the acute thrombogenic effect of exercise alluded to above. These effects of regular exercise on platelet aggregability could slow the development of atherosclerotic plaques, coronary-artery thrombosis, or both.

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	対象	境界域の者	空白		( )		コホート研究
	性別	男性	( )		( )		( )
	年齢	30-69歳	[redacted]		( )		前向き研究
	対象数	1000～5000	空白		( )		( )
調査の方法	実測	( )					
アウトカム	予 防	心疾患予防	な し	ガン予防	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)	心血管疾患から体力と死亡率との関係を明らかにした研究は少ない. 我々は30～69歳の4276人の男性を対象に平均8.5年間の追跡調査をおこなった. ベースラインにおける試験は, 従来の冠状動脈の危険因子とトレッドミルテストによる評価であった. 最大下運動(ステージ2の運動負荷テスト)中における心拍数と最大運動時間を体力の指標として使用した. 不完全なデータ(n=308)を有する男性もしくは循環器系薬剤(n=213)を使用していた者については分析から除外された. ベースライン(n=649)における心血管疾患の臨床のエビデンスを持っていた者がそれぞれ別個に分析された. 心血管疾患により45名の死亡が, 生存している3106人の男性の中で起こった. 低い体力水準は, 年齢と心血管危険因子の補正後における心血管および虚血性心疾患による高い死亡のリスクとの間に関連性があった. 心血管疾患による死の相対リスクは, トレッドミルテスト中のステージ2において35拍漸増した健康な者に関しては2.7であった(95%信頼区間, 1.4～5.1; P=0.003), また, 4.4分最大運動継続時間が短い者では3.0, (95%信頼区間, 1.6～5.5; P=0.0004)であった. 虚血性心疾患による死亡に対する相対値は, それぞれ3.2 (95%信頼区間, 1.5～6.7; P=0.003), 2.8(95%信頼区間, 1.3～6.1; P=0.007)であった. 我々は, 従来の冠動脈危険因子の有無にかかわらず. 低い体力水準が, 臨床的に健康な者においても冠動脈疾患や心血管疾患による死亡との間により高いリスクで関連していると結論する.						
結 論 (200字まで)	低レベルの体力は、慢性的な冠状動脈リスクファクターに関係なく、健康な人の循環器および冠状動脈性心疾患死亡リスクを高める。						
エキスパートによるコメント (200字まで)	体力と死亡リスクについて検討された初期の研究の一つ。						

担当者　宮地 劉

The Effect of Cardiorespiratory Fitness and Obesity on Cancer Mortality in Women and Men

KELLY R. EVENSON[1], JUNE STEVENS[1,2], JIANWEN CAI[3], RATNA THOMAS[3], and OLIVIA THOMAS[2]

[1]Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC; [2]Department of Nutrition, School of Public Health, University of North Carolina, Chapel Hill, NC; and [3]Department of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, NC

ABSTRACT

EVENSON, K. R., J. STEVENS, J. CAI, R. THOMAS, and O. THOMAS. The Effect of Cardiorespiratory Fitness and Obesity on Cancer Mortality in Women and Men. *Med. Sci. Sports Exerc.*, Vol. 35, No. 2, pp. 270–277, 2003. **Purpose:** The purpose of this study was to determine the independent and combined effects of cardiorespiratory fitness and obesity on all-cause cancer mortality for women and men. **Methods:** Using the Lipids Research Clinics Prevalence Study, we examined the relationship of fitness and obesity on cancer mortality among 2585 women and 2890 men followed from 1972–1976 to 1998. Cardiorespiratory fitness was measured using a treadmill test and obesity was assessed using body mass index (BMI) calculated from measured height and weight. Gender-specific hazard ratios (HR) were calculated from proportional hazard models, which included covariates for age, education, smoking, alcohol intake, Keys score, and menopause (women only). **Results:** Adjusted cancer mortality was significantly lower in the most fit quintile relative to the other four quintiles for men (HR = 0.47; 95% CI, 0.27–0.81) but not for women (HR = 0.84; 95% CI, 0.52–1.36). Adjusted cancer mortality was significantly higher in the highest BMI quintile relative to the other four BMI quintiles for women (HR = 1.49; 95% CI, 1.06–2.09) but not for men (HR = 1.05; 95% CI, 0.77–1.43). Further adjustment for BMI on fitness and adjustment for fitness on BMI did not meaningfully change the HR. There were no significant interactions between fitness and obesity in predicting cancer mortality for either women or men. **Conclusion:** In this study, high fitness was a stronger predictor of cancer mortality in men, whereas high BMI was a stronger predictor of cancer mortality in women. **Key Words:** OBESITY, NEOPLASMS, EPIDEMIOLOGY, PHYSICAL FITNESS, LEISURE ACTIVITIES, SURVIVAL ANALYSIS

Obesity is rising at an alarming rate in the United States (24), whereas the levels of physical activity remain stable and low (12). The pattern of these health behaviors could manifest later as disease, such as cancer. From 1992 to 1998, cancer incidence rates declined in men but not women, whereas cancer death rates declined in both women and men (18). National cancer rates continue to be higher among blacks as compared with whites, with a 17% excess rate among women and a 40% excess rate among men (13). According to Friedenreich (14), some of the main biologic mechanisms by which physical activity reduces cancer risk include modifications of endogenous sex and metabolic hormone levels, and growth factors, decreased body fat, and possibly enhanced immune function.

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Only four published epidemiologic studies from two cohorts have examined the effect of fitness on all-cause cancer mortality (4,7,19,20). The association between obesity and cancer is reported from the first and second Cancer Prevention Studies (11,16,17,21). We are not aware of any epidemiologic study that has examined the interaction between cardiorespiratory fitness and obesity on all-cause cancer mortality. In a comprehensive review of physical inactivity and mortality, a need for more evidence from prospective observational cohorts on fitness or physical activity, obesity, and mortality was recommended (6). There is especially a need for studies that include women and older persons. Therefore, the purpose of this study was to determine the effect of fitness, obesity, and the interaction between fitness and obesity on all-cause cancer mortality for women and men. These associations were also explored for physical activity and its interaction with obesity on cancer mortality.

METHODS

This research used data from the Lipids Research Clinics (LRC) First Prevalence Studies and the Mortality Follow-up Studies. Participants were from eight geographically diverse centers in the United States: Cincinnati, OH; Houston, TX; Iowa City, IA; La Jolla, CA; Minneapolis, MN; Oklahoma

City, OK; Palo Alto, CA; and Seattle, WA. Recruitment used a standardized protocol in target populations defined by occupational groups, households in geographic zones, households with membership in a particular medical plan, or students and parents within school districts (22). Participants were sampled from defined groups but were not necessarily representative of the local populations. The procedures followed for this study were in accordance with the ethical standards of the Institutional Review Board and participants provided written informed consent.

The methodology and study design of the LRC Prevalence and Mortality Follow-Up Study is reported elsewhere (28,31). A two-stage procedure was used with selected participants from a brief first visit, participating in a more extensive second visit. Participants in the second visit consisted of a 15% random sample of all visit 1 participants and 100% of those with elevated plasma lipids. The response rate for both strata of the sample was 85%. It was during the second examination that fitness measures were obtained, and this examination provided the baseline measures for this study. The two examinations took place between 1972 and 1976, and the median time between an individual's two visits was 96 d.

Vital status follow-up. Deaths were obtained by annual follow-up contacts, mostly by phone, with the cohort up to the end of 1987. At the end of 1987, vital status was known on 99.6% of the cohort. After 1987, annual follow-up contacts were discontinued; follow-up was conducted by searching the National Death Index (1988–91) and the Epidemiology Research Index (1992–98). For this study, vital status information was complete through 1998. Using the Kaplan-Meier estimator, the median follow-up time was 24.9 yr. Cause of death was ascertained by nosologist's coding of the death certificates for the entire follow-up period. International Classification of Disease version 9 (ICD-9) codes 140–171 and 174–239 identified all-cause cancer deaths. We excluded skin cancer deaths from our definition (ICD-9 172–173).

Measurement of fitness and physical activity. Cardiorespiratory fitness, now called "fitness" for the remainder of this report, was assessed as the time to produce predicted maximal heart rate based on age and training during a standardized treadmill test (25). Participants were told to refrain from eating for 2 h before testing, and most tests were performed in the morning. The test was conducted according to the Bruce protocol (25). Seven, 3-min stages were used in which the speed and inclination were increased in a stepwise fashion as follows: stage 1, 1.7 miles per hour (mph) and 10% inclination; stage 2, 2.5 mph and 12% inclination; stage 3, 3.4 mph and 14% inclination; stage 4, 4.2 mph and 16% inclination; stage 5, 5.0 mph and 18% inclination; stage 6, 5.5 mph and 20% inclination; and stage 7, 6.0 mph and 22% inclination.

The ECG was monitored continuously and blood pressure was measured at the end of each stage. Heart rate was monitored continuously and was also recorded at the end of each stage, or earlier if the participant stopped during a stage. The test was stopped when participants reached 90% of their predicted maximal heart rate, based on age and physical training (9,25). In this study, physical training was determined using two questions on physical activity: (1) "Do you regularly engage in strenuous exercise or hard physical labor?" Yes or no (2). If Yes: "Do you exercise or labor at least three times a week?" Yes or no. Physical activity was categorized as: (1) very active: individuals reporting strenuous exercise or hard physical labor $\geq$ 3 times per week; (2) moderately active: individuals reporting strenuous exercise or hard physical labor $<$3 times per week; or (3) inactive: individuals reporting no strenuous exercise or hard physical labor. Physical training was determined in LRC by whether the participant was classified as very active (trained) versus moderately active or inactive (not trained).

The exercise test was terminated early if the participant was unable to continue because of chest pain, fatigue, dyspnea, or leg pain or because of abnormalities in the ECG ($\geq$1 mm horizontal ST-segment change, major arrhythmias, or conduction defects), a decrease in systolic blood pressure, technical difficulties, or if subjects were unwilling to continue. Otherwise, the test was stopped when the participant attained 90% of predicted maximal heart rate and either maintained it for 1 min, maintained it to the end of the stage, or exceeded the target heart rate by 8 bpm, whichever occurred first (25). For these analyses, fitness was quantified as the duration of the exercise test in minutes.

Other measurements. At the second visit, a detailed examination was conducted which included an interview, physical exam, graded exercise test, and collection of plasma samples. Height and weight were measured with the participant wearing light clothing and no shoes. Height was measured to the nearest 0.5 cm using a headboard and a vertical rule fixed to a wall. Weight was measured to the nearest 0.1 kg using a balance scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared ($kg \cdot m^{-2}$).

Education was categorized as less than high school graduate, high school graduate, or more than high school. Cigarette smoking was categorized as current >20 cigarettes$\cdot d^{-1}$, current ≤ 20 cigarettes$\cdot d^{-1}$, former, or never. Participants were questioned on the type and amount of different types of alcoholic beverages consumed in the past 7 d and average grams of alcohol intake per day were calculated. For statistical modeling, alcohol intake was categorized as >20, >10–20, 1–10, or 0 $g \cdot d^{-1}$. Dietary intake was assessed with a 24-h recall, and Keys score was calculated as described by Anderson et al. (3) and was treated continuously in statistical models. For women, we adjusted for self-reported menopause (yes, no).

Statistical analyses. From the eight LRC Prevalence Study sites mentioned earlier, participants less than 30 yr of age were excluded because mortality follow-up was not done on those participants. Starting with $N = 3880$ women and $N = 4803$ men, we excluded two participants over the age of 75 yr. Because the association between BMI and mortality is likely different in blacks compared with whites (26), we chose not to combine data from ethnic groups. The

number of minority individuals examined was too small to study them here separately (N = 532). To reduce confounding from preexisting illness (23), participants who died in the first 4 yr of follow-up (N = 165) and participants with a BMI less than 18.5 kg·m^{-2} (N = 136) were excluded.

Because heart rate response to exercise was used as an indicator of fitness, we excluded participants taking medication that may alter heart rate (N = 172) and participants with inconsistent heart rates (N = 22). We excluded 222 participants with a positive exercise test (e.g., indicating possible cardiovascular disease) and 342 participants due to contraindications for participating in the exercise test (e.g., aortic stenosis, congestive heart failure, excessive blood pressure at rest, R-on-T type premature ventricular contractions, ventricular tachycardia, parasystolic focus, atrial flutter, atrial fibrillation, and congenital heart disease) (2). If the duration of the graded exercise test was less than 1 min (N = 311), participants were excluded since a steady state for exercise was not reached. Thirty-four participants who were missing data on fitness, height, weight, smoking, Keys score, or alcohol consumption were excluded. Thus, the analysis sample included 5475 participants: 2585 women and 2890 men.

To account for the sampling scheme, the data were treated as a stratified random sample, with two strata: hyperlipidemics and normolipidemics (including borderline hyperlipidemics). Associations between fitness, BMI, and cancer mortality were examined using stratified Cox proportional hazards models, with the sampling strata (hyperlipidemics and normolipidemics) as the stratifying variable. These procedures enabled us to draw inferences to those screened at visit 1 (31). All hazard ratios (HR) were reexamined among nonsmokers (i.e., former and never smokers), in order to account for the potential of confounding by smoking. Quintile cut points for fitness and BMI were calculated using fitness and BMI results in participants who were recruited as part of the random sample. Because of the higher proportion of hyperlipidemics in the sample relative to the population, cancer mortality rates were calculated by averaging across lipid strata using the inverse of the sampling probability as the weight. SAS version 6.12 (Cary, NC) was used to conduct all analyses.

RESULTS

Descriptive statistics of study sample. Table 1 shows descriptive information on the LRC sample included for analyses. Most participants stopped the exercise test beyond 90% of predicted maximal heart rate. In women, the median percent predicted maximal heart rate achieved was 95.6% (interquartile range 92.3–99.4%) and in men the median was 96.2% (interquartile range 93.0–99.4%). The mean time on the treadmill was 7.25 min for women and 9.47 min for men. MET values were extrapolated from published exercise intensities (2,8) and yielded corresponding values for these group means of 8.44 METs for women and 10.75 METs for men. These values represent the capacity required to walk on the treadmill at the corresponding speed and grade. For the sample, 86% of women and 67% of men were in the lowest physical activity category, not reporting vigorous physical activity (e.g., inactive).

TABLE 1. Description of analysis sample at the second examination (1972–76) by gender, LRC Prevalence Study.

	Women (N = 2585)		Men (N = 2890)	
	Mean/Percentage	SD	Mean/Percentage	SD
Age (yr)	45.1	10.3	46.7	11.3
Graded exercise test (min)	7.3	2.3	9.5	2.3
BMI (kg·m^{-2})	25.0	4.5	26.8	3.5
Alcohol (g·wk^{-1})	6.3	11.0	14.7	19.6
Keys score	50.5	15.3	51.6	15.3
Menopause (%)	48.4			
Education (%)				
<High school	13.9		10.8	
High school	45.8		31.4	
>High school	40.3		57.8	
Smoking (%)				
Never	48.9		28.9	
Former	18.6		36.7	
Current ≤20 d^{-1}	23.4		18.1	
Current >20 d^{-1}	9.1		16.3	
Physical activity (%)				
Very active	10.1		26.8	
Moderately active	4.1		5.7	
Not active	85.8		67.5	

The mean BMI in this sample for women (25.0 kg·m^{-2}) and men (26.8 kg·m^{-2}) fell in the overweight range (25.0–29.9 kg·m^{-2}). Among women, 58.2% were normal weight (18.5–24.9 kg·m^{-2}), 27.4% were overweight (25.0–29.9 kg·m^{-2}), and 14.4% were obese (≥30 kg·m^{-2}). Among men, 31.1% were normal weight, 52.8% were overweight, and 16.1% were obese. The correlation between BMI and fitness was modest: r = −0.21 in women, −0.10 in men.

Cancer deaths and death rates across fitness and BMI categories. The most common cancer sites among women were lung (N = 29), breast (N = 20), colon/rectal (N = 15), and ovarian/uterine (N = 15). For men, the most common cancer sites were lung (N = 74), prostate (N = 17), and colon/rectal (N = 15). The number of cancer deaths and the age-adjusted cancer death rates for each quintile of fitness and BMI by gender are shown in Table 2, overall and among nonsmokers. In some strata, the number of deaths became small, especially in the highest quintiles of fitness. Overall at each quintile of fitness and BMI, cancer death rates were generally higher for men relative to women, except for the highest fitness quintile.

Proportional hazards modeling on fitness, obesity, and cancer mortality. A J- or U-shaped association has been found between BMI and mortality in many studies (23). Because of this, we examined the shape of the BMI and cancer mortality association, as well as the shape of the fitness and cancer mortality association. Examination of BMI and fitness with quadratic terms and quadratic spline terms (32) in separate models for women and men showed no improvement in the prediction of cancer mortality over the model with just the linear term. Therefore, only the results using BMI and fitness treated linearly are shown here.

Table 3 shows associations between fitness and cancer mortality by gender, before and after adjusting for continuous BMI. Among women, although the most fit two quin-

TABLE 2. Adjusted* cancer death rates by quintiles of fitness and BMI and by gender overall and among nonsmokers, LRC Prevalence Study.

	Fitness			BMI		
	Quintile Cut Points (min)	No. of Cancer Deaths	Age Adjusted Death Rate (per 100,000 person-yr)	Quintile Cut Points ($kg \cdot m^2$)	No. of Cancer Deaths	Age Adjusted Death Rate (per 100,000 person-yr)
Women						
Overall						
Quintile 1	1.0–5.7	53	3.6	18.5–21.1	24	3.2
Quintile 2	5.8–6.9	36	3.9	21.2–22.6	30	4.4
Quintile 3	7.0–7.9	35	3.4	22.7–24.5	30	2.6
Quintile 4	8.0–9.0	29	2.7	24.6–27.7	35	2.7
Quintile 5	9.1–14.5	20	2.8	27.8–49.3	54	4.3
Among nonsmokers						
Quintile 1	1.0–5.7	31	2.7	18.5–21.1	13	2.8
Quintile 2	5.8–6.9	19	2.9	21.2–22.6	19	3.8
Quintile 3	7.0–7.9	20	3.0	22.7–24.5	12	1.6
Quintile 4	8.0–9.0	20	2.8	24.6–27.7	24	2.5
Quintile 5	9.1–14.5	12	2.8	27.8–49.3	34	3.5
Men						
Overall						
Quintile 1	1.1–7.9	76	5.1	18.5–23.6	36	4.5
Quintile 2	8.0–9.0	33	4.3	23.7–25.2	50	4.5
Quintile 3	9.1–10.0	47	4.8	25.3–26.7	40	4.5
Quintile 4	10.1–11.4	58	3.9	26.8–28.6	48	5.2
Quintile 5	11.5–19.0	14	2.7	28.7–42.9	54	5.5
Among nonsmokers						
Quintile 1	1.1–7.9	48	4.2	18.5–23.6	17	3.5
Quintile 2	8.0–9.0	15	3.0	23.7–25.2	23	2.9
Quintile 3	9.1–10.0	27	4.2	25.3–26.7	19	3.2
Quintile 4	10.1–11.4	23	2.4	26.8–28.6	31	4.8
Quintile 5	11.5–19.0	6	4.7	28.7–42.9	29	4.6

* Adjusted for lipid strata and age using 5-yr age strata and the distribution of age in visit 1.

tiles tended to have the lowest cancer mortality risk according to the HR, especially when reducing the sample to nonsmokers, none of the relationships reached statistical significance. For men, the risk of cancer mortality tended to be lowest in the highest fitness quintile, even when reducing the sample to nonsmokers. The HR changed little for fitness when further adjusting for BMI for both women and men.

Table 3 also shows associations between BMI and cancer mortality by gender, with and without adjustment for continuous fitness. The highest risk of cancer mortality tended

TABLE 3. Adjusted* hazard ratios (95% confidence intervals; CI) for cancer mortality by quintiles of fitness and BMI and by gender overall and among nonsmokers, LRC Prevalence Study.

	Fitness				BMI			
	Hazard Ratio	95% CI	Hazard Ratio Adjusted for BMI	95% CI	Hazard Ratio	95% CI	Hazard Ratio Adjusted for Fitness	95% CI
Women								
Overall								
Quintile 1	1	—	1	—	0.74	0.45–1.22	0.77	0.46–1.27
Quintile 2	1.09	0.71–1.68	1.10	0.71–1.69	0.83	0.52–1.32	0.86	0.54–1.37
Quintile 3	1.04	0.67–1.62	1.06	0.68–1.66	0.61	0.38–0.96	0.62	0.39–0.98
Quintile 4	0.89	0.55–1.43	0.91	0.56–1.49	0.61	0.39–0.94	0.61	0.40–0.95
Quintile 5	0.82	0.47–1.43	0.86	0.49–1.50	1	—	1	—
Among nonsmokers								
Quintile 1	1	—	1		0.79	0.37–1.69	0.87	0.40–1.89
Quintile 2	1.29	0.68–2.44	1.30	0.69–2.47	0.83	0.40–1.75	0.93	0.43–1.97
Quintile 3	1.00	0.52–1.94	1.02	0.52–2.01	0.96	0.50–1.82	1.04	0.54–1.99
Quintile 4	0.53	0.23–1.20	0.54	0.23–1.23	0.48	0.23–1.03	0.52	0.24–1.11
Quintile 5	0.67	0.28–1.61	0.70	0.29–1.70	1	—	1	—
Men								
Overall								
Quintile 1	1	—	1	—	1.00	0.65–1.55	1.06	0.69–1.64
Quintile 2	1.02	0.67–1.54	1.01	0.66–1.54	1.09	0.74–1.61	1.15	0.78–1.71
Quintile 3	0.90	0.61–1.32	0.89	0.61–1.31	0.93	0.61–1.40	0.99	0.65–1.50
Quintile 4	0.91	0.63–1.33	0.91	0.62–1.32	0.98	0.66–1.44	0.99	0.67–1.47
Quintile 5	0.41	0.23–0.75	0.41	0.22–0.74	1	—	1	—
Among nonsmokers								
Quintile 1	1	—	1	—	1.40	0.76–2.59	1.46	0.79–2.71
Quintile 2	1.31	0.74–2.34	1.29	0.72–2.30	1.45	0.84–2.51	1.52	0.87–2.64
Quintile 3	0.81	0.45–1.46	0.79	0.45–1.42	1.26	0.72–2.23	1.34	0.75–2.38
Quintile 4	1.43	0.84–2.45	1.36	0.79–2.34	1.04	0.57–1.91	1.08	0.59–1.99
Quintile 5	0.57	0.26–1.25	0.53	0.24–1.17	1	—	1	—

* Adjusted for age, smoking (overall only), education, alcohol, Keys score, and menopause (women only).

TABLE 4. Adjusted* hazard ratios (95% confidence intervals; CI) for cancer mortality by gender overall and among nonsmokers, LRC Prevalence Study.

	Fitness				BMI			
	Hazard Ratio	95% CI	Hazard Ratio Adjusted for BMI	95% CI	Hazard Ratio	95% CI	Hazard Ratio Adjusted for Fitness	95% CI
Women								
Overall (n = 2585)								
Quintile 1	1.01	0.71–1.43	0.98	0.69–1.40	0.97	0.62–1.50	0.99	0.64–1.54
Quintiles 2–5	1	—	1	—	1	—	1	—
Nonsmokers (N = 839)								
Quintile 1	1.08	0.63–1.85	1.05	0.61–1.82	0.97	0.50–1.86	1.00	0.52–1.93
Quintiles 2–5	1	—	1	—	1	—	1	—
Overall (N = 2585)								
Quintile 5	0.84	0.52–1.36	0.87	0.53–1.41	1.49	1.06–2.09	1.45	1.03–2.04
Quintiles 1–4	1	—	1	—	1	—	1	—
Nonsmokers (N = 839)								
Quintile 5	0.75	0.35–1.59	0.77	0.36–1.65	1.34	0.78–2.30	1.24	0.72–2.16
Quintiles 1–4	1	—	1	—	1	—	1	—
Men								
Overall (N = 2890)								
Quintile 1	1.11	0.82–1.51	1.11	0.81–1.51	0.95	0.66–1.37	0.96	0.66–1.38
Quintiles 2–5	1	—	1	—	1		1	
Nonsmokers (N = 992)								
Quintile 1	0.95	0.60–1.50	0.98	0.62–1.55	1.17	0.72–1.93	1.18	0.72–1.94
Quintiles 2–5	1	—	1	—	1	—	1	—
Overall (N = 2890)								
Quintile 5	0.47	0.27–0.81	0.47	0.27–0.81	1.05	0.77–1.43	1.00	0.73–1.38
Quintiles 1–4	1	—	1	—	1		1	—
Nonsmokers (N = 992)								
Quintile 5	0.50	0.25–1.00	0.48	0.24–0.96	0.78	0.49–1.23	0.75	0.47–1.18
Quintiles 1–4	1	—	1	—	1	—	1	—

* Adjusted for age, smoking (overall only), education, alcohol, Keys score, and menopause (women only).

to occur in the highest BMI quintile among women. Among men, BMI quintiles were not related to cancer mortality overall. The HR for BMI changed little when further adjusting for fitness for both women and men.

Based on our findings in Table 3, we collapsed across quintiles and compared the lowest quintile versus the other four quintiles and the highest quintile versus the other four quintiles for both fitness and BMI (Table 4). For both women and men being in the lowest quintile of fitness (hypothesized highest risk) relative to the other four quintiles did not meaningfully change the hazard for cancer mortality overall or among nonsmokers. However, cancer mortality was generally reduced for men in the highest quintile of fitness (hypothesized lowest risk) relative to the other four quintiles.

For women, being in the highest quintile (hypothesized highest risk) relative to the other four quintiles of BMI significantly increased cancer mortality risk overall, which was attenuated among nonsmokers only. For men, being in the highest quintile of BMI relative to the other four quintiles was not related to cancer mortality risk overall. The estimate in nonsmokers was below one; however, the confidence intervals were wide. Additionally, there appeared to be no relationship for women or men with cancer mortality when comparing the lowest quintile (hypothesized lowest risk) to the other four quintiles of BMI, overall and among nonsmokers. Further adjustment of BMI by fitness and further adjustment of fitness by BMI did not meaningfully change these results.

Interactions between fitness and obesity were tested keeping both measures continuous in the proportional hazard models. There were no significant interactions between fitness and obesity predicting cancer mortality overall (P = 0.37 women, P = 0.46 men) or among nonsmokers (P = 0.65 women, P = 0.26 men). Table 5 displays the interactions between fitness and BMI, using quintile categories from Table 4. We hypothesized that individuals in both the first BMI quintile and the fifth fitness quintile would be at lowest risk, and those in the fifth BMI quintile and first fitness quintile would be at the highest risk. There was some support for the former of the two hypotheses.

Physical activity and cancer mortality. We also explored whether physical activity predicted cancer mortality, adjusting for obesity, age, education, smoking, alcohol, Keys score, and menopause (women only). Among women, when compared with those who were not active, being classified as very active (HR = 1.32; 95% CI, 0.50–3.47) or moderately active (HR = 1.18; 95% CI, 0.67–2.10) was not significantly related to cancer mortality. Similarly among men, when compared with those who were not active, being classified as very active (HR = 1.33; 95% CI, 0.74–2.37) or moderately active (HR = 0.97; 95% CI, 0.70–1.35) was not significantly related to cancer mortality. There were no significant interactions between physical activity categories and continuous BMI predicting cancer mortality in either women (P = 0.34 very active, P = 0.57 moderately active) or men (P = 0.49 very active, P = 0.10 moderately active). The results were similar when restricting to only nonsmokers.

DISCUSSION

Fitness and physical activity and risk of cancer mortality. Using the LRC Prevalence Study cohort, we found that the risk of cancer mortality was lower in the most fit quintile relative to the other four quintiles of fitness for

TABLE 5. Adjusted* hazard ratios (95% confidence intervals; CI) on the interaction between fitness and BMI for cancer mortality by gender, LRC Prevalence Study.

	Fitness				Fitness			
	Hazard Ratio Quintile 1	95% CI	Hazard Ratio Quintiles 2–5	95% CI	Hazard Ratio Quintile 5	95% CI	Hazard Ratio Quintiles 1–4	95% CI
Women								
Overall (N = 2585)								
BMI quintile 1	1.72	0.84–3.56	0.84	0.45–1.56	0.94	0.34–2.61	1.16	0.59–2.32
BMI quintiles 2–5	1	—	1.11	0.76–1.62	1	—	1.17	0.68–2.03
Overall (N = 2585)								
BMI quintile 5	1.33	0.75–2.37	1.54	0.93–2.56	1.04	0.30–3.60	1.61	0.91–2.86
BMI quintiles 1–4	1	—	0.97	0.64–1.49	1	—	1.06	0.63–1.81
Men								
Overall (N = 2890)								
BMI quintile 1	0.86	0.46–1.61	0.87	0.53–1.43	0.33	0.04–2.54	1.89	0.99–3.62
BMI quintiles 2–5	1	—	0.88	0.63–1.22	1	—	1.87	1.06–3.32
Overall (N = 2890)								
BMI quintile 5	1.01	0.59–1.71	0.94	0.60–1.49	1.48	0.41–5.34	2.30	1.19–4.45
BMI quintiles 1–4	1	—	0.89	0.63–1.26	1	—	2.30	1.24–4.29

* Adjusted for age, smoking, education, alcohol, Keys score, and menopause (women only).

men (HR 0.47; 95% CI, 0.27–0.81), adjusting for multiple confounders including BMI. The reduction in risk remained when reducing the sample to nonsmokers (i.e., former and never smokers), although some risk estimates included the null value. The reduction in risk also remained when further adjusting for BMI. However, cancer mortality was not significantly reduced for women comparing the most fit quintile relative to the other four quintiles of fitness (HR 0.87; 95% CI, 0.53–1.41).

The size of the associations of fitness with cancer mortality was generally similar in LRC women and men compared with those observed in other studies. In this study, the relative hazard comparing the highest quintile to the lowest quintile of fitness for cancer mortality was 0.86 (95% CI, 0.49–1.50) for women and 0.41 (95% CI, 0.22–0.74) for men, controlling for multiple covariates including BMI. The relationship between fitness and cancer mortality was reported from the Aerobics Center Longitudinal study in an earlier study (7) and later updated (19,20). Based on 44 female (N = 7080) and 179 male (N = 25,341) cancer deaths, the risk of cancer mortality was 0.47 (95% CI, 0.18–1.22) for women and 0.36 (95% CI, 0.21–0.61) for men comparing the highest quintile of fitness to the lowest quintile, adjusted for age, exam year, smoking, chronic illness, and ECG abnormalities (19). In the Canada Health Survey Mortality Follow-up Survey, fitness was assessed at home by using a submaximal step test (4). The risk of cancer mortality increased across three levels of decreasing fitness levels, adjusting for age, gender, smoking, and alcohol consumption. However, the estimates included the null value, based on only 32 cancer deaths for women and men.

We did not observe a relationship between our measure of physical activity and cancer mortality, despite the apparent relationship with fitness. This could be due to our crude estimate of physical activity, based on a two-item assessment. It is possible that in this case cardiorespiratory fitness may have been a better marker of long-term physical activity. In the Aerobics Center Longitudinal Study (19), a reduction in cancer mortality risk was observed with higher levels of physical activity among men but not women, although the confidence intervals were large and imprecise. In the Canada Health Survey, the risk of cancer mortality was not related to physical activity levels (4), but their estimates were also imprecise. Based on a comprehensive review by Thune and Furberg (27) (which included the two studies just mentioned), of 17 observational studies of physical activity and all-cause cancer mortality, 10 studies indicated a significant reduced effect of leisure or occupational activity, whereas 6 studies suggested a reduced effect and 1 study showed an increased risk. A weaker effect on this association was generally found in women as compared with men. Since then, an update was published for the British Regional Heart study showing a reduced risk for cancer in the most active compared to the least active group of men (29).

Differences across studies may be due to the timing of measurement (15). There may be periods in life when attaining certain levels of physical activity or fitness are more important in preventing cancer than in other time periods. The time periods in life when physical activity may result in decreased endogenous sex hormones have not been established (14). Unfortunately, in the LRC Prevalence Study, fitness and physical activity were only measured once. Studies documenting the changing course of physical activity and fitness over time can further our understanding of these associations.

Obesity and risk of cancer mortality. In this study, when controlling for multiple confounders, the risk of cancer mortality was generally lower for women but not for men, comparing the lowest BMI quintile with the highest quintile. These results were not meaningfully changed when further adjusting for fitness. Our results can be compared to several studies from the Cancer Prevention Studies. In the first Cancer Prevention Study of approximately 750,000 women and men enrolled during 1959–72, cancer mortality was higher among those 40% or more overweight (16,21). The cancer mortality ratios were consistently higher in overweight women than overweight men. In the second Cancer Prevention Study of approximately 1.5 million women and men enrolled in 1982, the relationship between BMI and the

risk of death from cancer was fairly linear, showing no elevation in risk among women and men in the lowest BMI category (11,17). Similar to our results and to the results from the first cohort, risk of cancer mortality was higher at a given category of BMI for women as compared with men.

Interactions between fitness and obesity on cancer mortality. We investigated, but did not find, significant interactions between fitness and obesity for cancer mortality among women or men. This null finding remained when examining the interaction between physical activity and obesity on cancer mortality across gender. No other epidemiologic reports provide information on the interaction between fitness and obesity, but one study does provide estimates for the interaction between physical activity and obesity on cancer mortality. For women and men in the National Health and Nutrition Examination I cohort, the risk of all-cause cancer mortality increased as physical activity declined (3 levels) within BMI strata < 22.0 and 22.0–26.0 $kg \cdot m^{-2}$ (1). However, at higher levels of BMI (>26.0 $kg \cdot m^{-2}$), physical activity was not related to cancer mortality in women or men.

Limitations. The LRC cohort was not a representative sample of the U.S. population, but nevertheless, the cohort was drawn from diverse groups and represents the clinics, work sites, geographic locations, school districts, or membership within a medical plan from which they were sampled. Our measure of fitness measure was excellent for an epidemiologic study, whereas the measures of adiposity and physical activity were less precise. The correlation between BMI and percent body fat is approximately 0.7 in adults (30). An additional limitation of this work was the statistical power, because many of the risks and interactions documented here were assessed with relatively large confidence intervals. The cut points we chose to form categories of fitness and BMI could have a large effect on the magnitude of the risks observed. We *a priori* chose our quintile cut-points based on the random sample strata chosen for LRC. Also, we did not have an adequate number of cancer cases to examine deaths from certain types of cancer separately. Furthermore, prevalent cancer was not collected at baseline. To account for this limitation, we excluded cancer mortality events that occurred during the first 4 yr of follow-up.

CONCLUSIONS

In conclusion, these data indicate that higher fitness levels may reduce the risk of cancer mortality for men. Additionally, not being obese may reduce the risk of cancer mortality among women. Interactions between fitness and obesity on cancer mortality were not identified. A working group for the International Agency for Research on Cancer of the World Health Organization recently published a summary on physical activity and weight control in the context of cancer prevention (5). They recommended that prevention of overweight and obesity should begin early and individuals should be encouraged to perform regular physical activity. The American Cancer Society also recently updated their guidelines on physical activity and nutrition (10), supporting a physically active lifestyle. Taking these steps will reduce the risk of cancer, as well as cardiovascular disease, diabetes, and total mortality (5).

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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	男女混合	( )		( )		( )
年齢	女性45.1±10.3歳、男性46.7±11.3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	ガン予防	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)	目的：本研究の目的は、ガンによる全死亡原因における体力と肥満の単独もしくは結合された影響について決定することであった。方法：我々は、Lipids Research Clinics Prevalence Studyを用いて、2585名の女性および2890名の男性の中で、ガンによる死亡における体力と肥満の関係を1972-1976年より1998年まで調査した。全身持久性体力は、トレッドミルテストによる結果を用い、肥満は、身長と体重から算出されたBMI値(BMI)を用いて評価した。性特有の危険比(HR)は比例ハザードモデルから算出され、それらは年齢、教育、喫煙、アルコール摂取量、キーズ点、および閉経(女性のみ)を共変量として含まれた。結果：補正されたガンの死亡率は、男性の最も適合した5段階は他の5段階に対して有意に低かった(HR=0.84[0.52-1.36]95%信頼区間)。しかし、女性では低くはなかった(HR=0.47[0.27-0.81] 95%信頼区間)。また、補正されたガンの死亡率は、女性において、最も高いBMIは他の4つの5段階に対して有意に高かった(HR=1.49[1.06-2.09]95%信頼区間)が、男性では高くなかった(HR=1.05[0.77-1.43]95%信頼区間)。さらに、体力におけるBMIおよびBMIにおける体力補正では、HRに意味のある変化はなかった。女性および男性いずれのガン死亡予測においても、体力と肥満との間に有意な交互作用はみられなかった。結論：本研究では、高い体力が男性のガンによる死亡のより強い予測因子であったが、女性では高いBMIがガンによる死亡のより強い予測因子であった。
結　論 (200字まで)	男性の場合、高い体力(最大酸素摂取量37.6ml/kg/分以上)が癌による死亡リスクを約半分にするために必要。女性の場合、BMI27.7以下にすることで癌死亡リスクを半分にできる。
エキスパートによるコメント (200字まで)	男性と女性でガンにかかる部位の違いなどもこの研究の結果に関係しているであろう。

担当者　宮地 劉

The Relation of Body Mass Index, Cardiorespiratory Fitness, and All-Cause Mortality in Women

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Abstract

FARRELL, STEPHEN W., LEEANN BRAUN, CAROLYN E. BARLOW, YILING J. CHENG, AND STEVEN N. BLAIR. The relation of body mass index, cardiorespiratory fitness, and all-cause mortality in women. *Obes Res.* 2002;10:417–423.

Objective: To examine the relation of body mass index (BMI), cardiorespiratory fitness (CRF), and all-cause mortality in women.

Research Methods and Procedures: A cohort of women (42.9 ± 10.4 years) was assessed for CRF, height, and weight. Participants were divided into three BMI categories (normal, overweight, and obese) and three CRF categories (low, moderate, and high). After adjustment for age, smoking, and baseline health status, the relative risk (RR) of all-cause mortality was determined for each group. Further multivariate analyses were performed to examine the contribution of each predictor (e.g., age, BMI, CRF, smoking status, and baseline health status) on all-cause mortality while controlling for all other predictors.

Results: During follow-up (113,145 woman-years), 195 deaths from all causes occurred. Compared with normal weight (RR = 1.0), overweight (RR = 0.92) and obesity (RR = 1.58) did not significantly increase all-cause mortality risk. Compared with low CRF (RR = 1.0), moderate (RR = 0.48) and high (RR = 0.57) CRF were associated significantly with lower mortality risk (p = 0.002). In multivariate analyses, moderate (RR = 0.49) and high (RR = 0.57) CRF were strongly associated with decreased mortality relative to low CRF (p = 0.003). Compared with normal weight (RR = 1.0), overweight (RR = 0.84) and obesity (RR = 1.21) were not significantly associated with all-cause mortality.

Discussion: Low CRF in women was an important predictor of all-cause mortality. BMI, as a predictor of all-cause mortality risk in women, may be misleading unless CRF is also considered.

Key words: cardiovascular fitness, women's health, exercise testing, aerobic power, metabolic equivalent

Introduction

Overweight is a common disorder in the United States and other industrialized countries. According to body mass index (BMI) data from the third National Health and Nutrition Examination Survey, the prevalence of overweight (BMI, >25 kg/m^2) for adults in the United States is now estimated to be 55% (1,2).

Using the criteria of BMI, waist-to-hip ratio, or waist circumference, overweight has been associated with increases in both all-cause (3,4) and cardiovascular (5,6) mortality for women in several prospective studies. Whereas this association persists after adjusting for potential confounding variables such as cigarette smoking, these studies did not measure cardiorespiratory fitness (CRF) level. A low CRF level is an important independent predictor of all-cause mortality in both men and women (7,8). Failure to measure and consider CRF may confound the relationship between BMI and mortality. The failure to measure CRF in studies examining the relationship of BMI and mortality may be attributable to logistical constraints, but may also be attributable, in part, to an underlying assumption that all overweight and obese individuals are sedentary and unfit, an assumption that is not valid. Our group has shown that moderately to highly fit overweight or obese men have significantly lower rates of all-cause mortality than normal-weight or overweight men with low levels of CRF (9,10). Additionally, the health benefits of normal weight in men are limited to those who have moderate

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or high levels of CRF (11). Our primary goal in the current study was to extend these observations to women. Thus, the purpose of our study was to quantify the association between BMI, CRF, and all-cause mortality in adult women.

Research Methods and Procedures

Study Participants and Measurements

The Aerobics Center Longitudinal Study (ACLS) is a prospective epidemiological follow-up of patients who underwent an examination at the Cooper Clinic (Dallas, TX). Participants for this study included 9925 female patients (mean age, 42.9 ± 10.4 years) who completed a comprehensive medical examination during the interval between December 6, 1970 and December 31, 1996. All participants were United States citizens, and nearly all (98%) were white.

After receiving written informed consent from each participant, a clinical evaluation was performed. Examinations included fasting blood chemistry, personal and family health history, anthropometry, resting blood pressure, electrocardiogram, and a maximal graded exercise test on a motor-driven treadmill. Height and weight were measured by a stadiometer and a standard physician's scale. BMI was calculated as weight in kilograms per square meter. On the basis of NIH guidelines, three categories of BMI were used in this study: normal weight (BMI, 18.5 to 24.99), overweight (BMI, 25 to 29.99), and obese (BMI, ≥30). All procedures were administered by trained technicians who followed standardized protocols.

CRF was measured on a treadmill with the modified Balke protocol. 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%, whereas speed was increased by 5.4 m after each minute until volitional fatigue. Treadmill time has been shown to correlate highly (r = 0.94) with directly measured maximal oxygen uptake in women (12). Patients were encouraged to give a maximal effort during the test, and those who did not achieve at least 85% of age-predicted maximal heart rate were excluded from the analyses.

Treadmill time was used to group study participants into CRF categories on the basis of age-specific cutoffs. The age groups were as follows: 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and 70 to 79 years. Because there are several different treadmill protocols used in laboratories, and METs are a standard measure well understood in the field, we then calculated maximal MET levels of participants from treadmill time using the following formula (13): maximal MET level = (treadmill time in minutes × 1.750) + 10.5/3.5. Based on previous mortality findings in this population (7), three categories of CRF were created. The least fit 20% in each age group were classified as low fit, the next 40% as moderately fit, and the top 40% as highly fit.

Participants were classified as apparently healthy unless they reported chronic illnesses (e.g., myocardial infarction, stroke, hypertension, diabetes, cancer) at the time of their baseline examination or had an abnormal resting or exercise electrocardiogram. Women with at least one of these conditions were classified as unhealthy.

Mortality Surveillance

We followed study participants for mortality from the date of their initial examination to either the date of death or, for survivors, to December 31, 1996. The National Death Index was used to identify possible deaths, and official death certificates were retrieved for these individuals. Information on the death certificate was compared with the participant's clinical record to confirm a match. The mean length of follow-up was 11.4 ± 6.2 years.

Statistical Analyses

Our initial analysis compared the relative risk (RR) with 95% CIs of all-cause mortality among normal-weight (n = 7801), overweight (n = 1527), and obese (n = 597) women after adjusting for age, smoking status, and baseline health status. After adjustment for age, smoking status, and baseline health status, RR with 95% CIs was determined for low-fit, moderately fit, and highly fit women. We then performed a multivariate analysis using BMI, CRF, age, smoking status, and baseline health status to determine the independent contribution of each to all-cause mortality. We also performed a separate multivariate analysis using these variables to determine whether there was a significant interaction between CRF and BMI.

Results

Demographic characteristics of subjects are shown in Tables 1 and 2. Overall, the CRF level and risk profile of the normal-weight group was more favorable than that of the overweight and obese groups (Table 1). Similarly, the risk profile of the highly fit group was more favorable than the moderately and low-fit groups (Table 2). There were 195 deaths during follow-up (during 113,145 woman-years of follow-up). Cancer (118 deaths) and cardiovascular disease (44 deaths) were the leading causes of mortality in the cohort, accounting for 83% of all deaths. RR of all-cause mortality across different levels of BMI adjusted for age, smoking status, and baseline health status are presented in Figure 1. There were no significant differences in all-cause mortality among the normal-weight (RR = 1.0), overweight (RR = 0.92; 95% CI, 0.61 to 1.37), or obese (RR = 1.58; 95% CI, 0.95 to 2.63) groups. However, the RR of the obese group did approach statistical significance (p = 0.08).

Figure 2 shows a comparison of all-cause mortality among low-fit, moderately fit, and highly fit women after adjustment for age, smoking status, and baseline health

Table 1. Descriptive characteristics for 9925 women by BMI category (Aerobics Center Longitudinal Study, 1970 to 1996)

	Normal (n = 7801), BMI 18.5 to 24.99	Overweight (n = 1527), BMI 25 to 29.99	Obese (n = 597), BMI ≥ 30	p value for trend
Age (years)	42.2 ± 10.4	46.0 ± 10.6	44.2 ± 10.5	0.0001
Height (cm)	164.6 ± 5.9	163.8 ± 6.7	163.4 ± 8.5	0.0001
Weight (kg)	58.2 ± 6.0	72.3 ± 7.0	91.0 ± 13.6	0.0001
BMI (kg/m^2)	21.5 ± 1.7	26.9 ± 1.4	34.1 ± 4.9	0.0001
Cholesterol (mM)	5.1 ± 1.1	5.5 ± 1.1	5.5 ± 1.1	0.0001
Glucose (mM)	5.2 ± 6.1	5.4 ± 1.0	5.7 ± 1.4	0.0486
Triglycerides (mM)	0.9 ± 0.8	1.3 ± 0.9	1.6 ± 1.1	0.0001
Treadmill performance (maximal METs)	9.9 ± 2.3	8.4 ± 1.9	7.1 ± 1.6	0.0001
Resting SBP (mm Hg)	110.7 ± 13.8	115.8 ± 13.8	121.8 ± 15.2	0.0001
Resting DBP (mm Hg)	74.3 ± 9.2	77.4 ± 9.0	82.0 ± 9.6	0.0001
Present smoker (%)	928 (11.9)	141 (9.2)	62 (10.4)	0.0117
Apparently healthy (%)	6629 (85.0)	1150 (75.3)	407 (68.2)	0.0001
Number of deaths (%)	149 (1.9)	29 (1.9)	17 (2.9)	0.2221

With the exception of the last three variables, all data are means ± SD.
BMI, body mass index; MET, metabolic equivalent; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Descriptive characteristics for 9925 women by CRF category (Aerobics Center Longitudinal Study, 1970 to 1996)

	Low CRF (n = 1657)	Moderate CRF (n = 3747)	High CRF (n = 4521)	p for trend
Age (years)	43.2 ± 10.1	43.0 ± 10.3	42.7 ± 10.8	0.0001
Height (cm)	163.7 ± 6.0	164.2 ± 6.2	164.8 ± 6.3	0.0001
Weight (kg)	69.3 ± 16.1	62.8 ± 10.4	59.5 ± 8.0	0.0001
BMI (kg/m^2)	25.9 ± 5.8	23.3 ± 3.7	21.9 ± 2.5	0.0001
Cholesterol (mM)	5.3 ± 1.0	5.3 ± 1.1	5.1 ± 1.2	0.0001
Glucose (mM)	5.4 ± 1.1	5.2 ± 0.7	5.3 ± 8.0	0.0982
Triglycerides (mM)	1.3 ± 0.9	1.1 ± 0.8	0.9 ± 1.0	0.0001
Treadmill performance (maximal METs)	6.5 ± 1.0	8.6 ± 1.1	11.4 ± 1.9	0.0001
Resting SBP (mm Hg)	116.0 ± 15.7	112.1 ± 14.0	110.8 ± 13.6	0.0001
Resting DBP (mm Hg)	77.6 ± 10.3	75.4 ± 9.4	74.3 ± 9.0	0.0001
Smoker (%)	299 (18.0)	495 (13.2)	337 (7.5)	0.0001
Apparently healthy (%)	1225 (73.9)	3113 (83.1)	3848 (85.1)	0.0001
Number of deaths (%)	75 (4.5)	63 (1.7)	57 (1.3)	0.0001

With the exception of the final three variables, data are means ± SD.
CRF, cardiorespiratory fitness; BMI, body mass index; MET, metabolic equivalent; SBP, systolic blood pressure; DBP, diastolic blood pressure.

status. Compared with low-fit women (RR = 1.0), moderately fit (RR = 0.48; 95% CI 0.34 to 0.68) and highly fit women (RR = 0.57; 95% CI, 0.40 to 0.82) had a significantly lower risk of mortality (p = 0.002).

Figure 3 shows the proportion of women who were classified as having moderate or high CRF within several different strata of BMI. With increasing BMI, the proportion of fit women decreased linearly. For example, 90.5% of women with a BMI between 18.5 and 21 kg/m^2 were classified as having moderate or high CRF, compared with 20.5% of women with a BMI >37.1 kg/m^2.

Table 3 summarizes a multivariate analysis using CRF, BMI, smoking status, and baseline health status as categorical independent variables and age as a continuous independent variable. The RR of each variable was adjusted for all other variables in the model to examine the independent contribution of each on all-cause mortality. We determined that there was no significant interaction between CRF and BMI; therefore, no interaction terms were included in the model. Compared with women with low CRF (RR = 1.0), women with moderate (RR = 0.49; 95% CI, 0.35 to 0.69) and high (RR = 0.57; 95% CI, 0.40 to 0.83) CRF were significantly less likely to die during follow-up (p = 0.003). Overweight (RR = 0.84; 95% CI, 0.56 to 1.26) and obese (RR = 1.21; 95% CI, 0.71 to 2.05) women were no more likely to die than normal-weight women in this model.

Discussion

The purpose of the current study was to examine the relation of BMI, CRF, and all-cause mortality in women. To the best of our knowledge, ours is the first study to explore this topic in women. We have demonstrated in this study that low CRF is a stronger predictor than BMI of all-cause mortality in women.

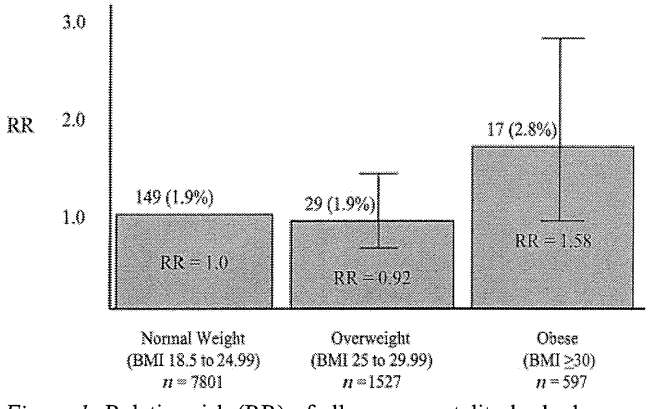

Figure 1: Relative risk (RR) of all-cause mortality by body mass index (BMI) category. RRs have been adjusted for age, smoking, and baseline health status. ACLS women from 1970 to 1996. Numbers on top of bars represent number of deaths and percentage of group members who died.

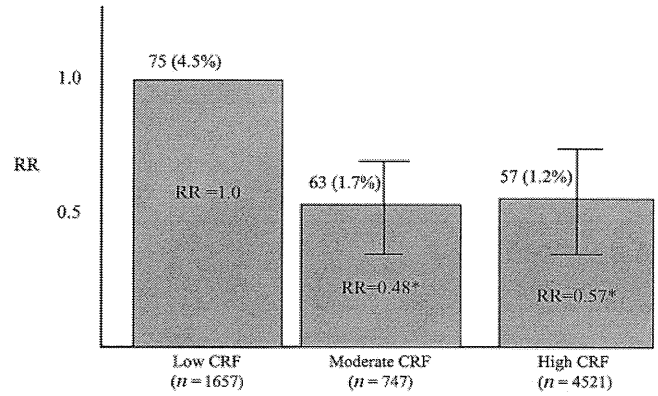

Figure 2: Relative risk (RR) of all-cause mortality by cardiorespiratory fitness (CRF) category. RRs have been adjusted for age, smoking, and baseline health status. ACLS women from 1970 to 1996. Numbers on top of bars represent number of deaths and percentage of group members who died. *, significantly different than low CRF group (p = 0.002).

In the current study, obese women had a RR of 1.58 compared with normal-weight women (Figure 1), and this value approached statistical significance (p = 0.08). One possible reason we did not see a greater RR for obese women is that we adjusted for baseline health status as well as age and smoking in our model. Because conditions such as hypertension and Type 2 diabetes are to some extent a consequence of obesity, adjusting for baseline health status lessens the effect of obesity on mortality because some of its consequences are removed. In a separate analysis where we adjusted for only age and smoking status, the RR of the obese group (RR = 1.70) was significantly different (p = 0.04) from the normal-weight group.

Obesity is an important public health problem; prevalence of obesity and overweight in the United States are currently estimated to be 22% and 55%, respectively. This study was not intended to minimize or trivialize the importance of these conditions. However, we strongly believe it is important to consider CRF levels when examining the impact of overweight status and obesity on mortality. It is also important not to make the assumption that all overweight and obese individuals are sedentary and unfit. Our group has shown previously that some overweight and obese men possess moderate or even high levels of CRF (9,10). Furthermore, fit overweight and obese men have significantly lower rates of all-cause mortality than normal-weight men who are unfit, even after controlling for confounding variables such as cigarette smoking (9).

Whereas most health professionals assume that intentional weight loss in overweight and obese individuals is beneficial, it is interesting to note that the scientific evidence that intentional weight loss decreases all-cause mortality is limited to one study (14). Virtually all other studies on weight loss and mortality failed to differentiate between

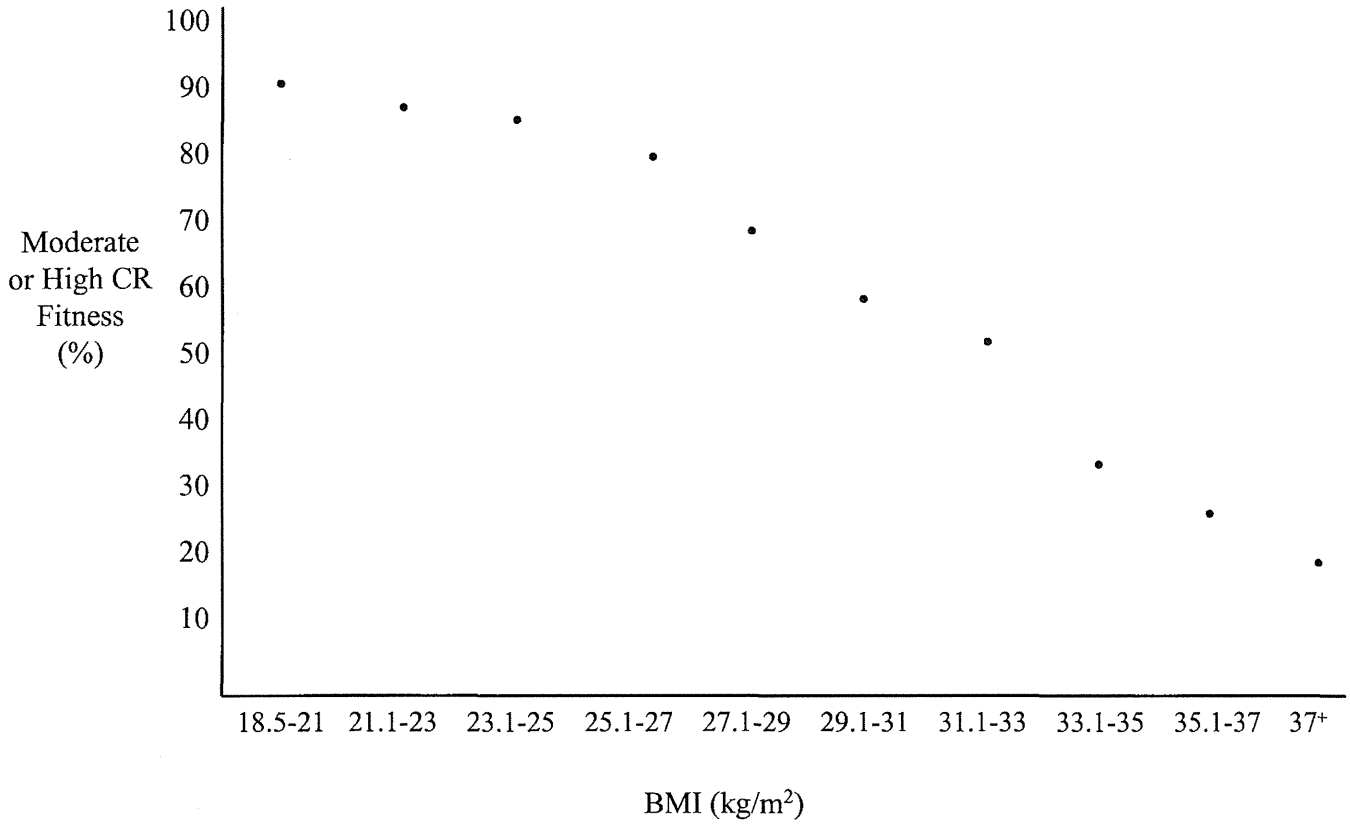

Figure 3: Percentage of women with moderate or high cardiorespiratory fitness (CRF) by body mass index (BMI). ACLS women from 1970 to 1996.

intentional and unintentional weight loss (15), making the results largely noninterpretable. Until we know for certain that intentional weight loss significantly decreases all-cause mortality, it is worth considering that perhaps our time as health professionals would be better spent striving to help sedentary and unfit individuals increase levels of CRF, and encouraging healthy diets and smoking cessation in the population, rather than focusing specifically on weight loss. For example, Project Active (16) compared the effects of a lifestyle physical activity program with a traditional structured exercise program in previously sedentary men and women over a 24-month period. Although body weight did not change in either group, significant improvement in physical activity levels, CRF, systolic and diastolic blood pressure, and percentage of body fat was achieved by both groups. Project Active also demonstrated that exercise prescription and programs need not necessarily be structured, nor is a state-of-the-art fitness center needed for individuals to improve activity levels, CRF levels, and risk factors. In an early study, Tremblay et al. (17) showed that the metabolic profile of obese women could be normalized by exercise and a low-fat diet, even when significant weight loss did not occur.

CRF is primarily a function of the heart's maximal ability to pump blood (maximal cardiac output) and the ability of skeletal muscle to extract and use oxygen (maximal arteriovenous O_2 difference). These two variables have both genetic and environmental influences. For example, the contribution of genetics to heart size, structure, and cardiac function variance in the population is estimated to be between 30% to 70% (18). Similarly, a genetic component is thought to account for 40% to 50% of the population variation in the proportion of type 1 (slow-twitch) skeletal muscle fibers in humans (18). Thus, it is clear there are genetic factors that limit the extent to which CRF can be developed. However, environment (the frequency, intensity, and duration of aerobic training) has a significant effect on CRF as well and appears to account for more of the variation in CRF than do genetic factors.

It should be emphasized that the criterion for the fit category in this study was any value above the 20th percentile for each age group. For example, a 40- to 49-year old woman would require a maximal oxygen uptake of at least 28.0 mL/kg per minute (8 METs) to be classified as fit. This modest goal is attainable for most women, as has been shown by aerobic-training studies where as much as a mean