therefore, these results must be confirmed in larger studies. In addition, we observed that fit individuals who were obese (such as those with BMI of 30.0-34.9, abdominal obesity, or excessive percent body fat) had a lower risk of all-cause mortality than did unfit, normal-weight, or lean individuals. Our data therefore suggest that fitness levels in older individuals influence the association of obesity to mortality.

Results concerning the relationship between mortality and obesity in older adults have been inconsistent. Some studies,[18,23,25] but not all,[19,21] have suggested a lower risk of mortality in obese individuals. We found a J-shaped association between mortality and BMI calculated from measured height and weight. The age-, sex-, and examination year–adjusted mortality rate per 1000 person-years was the lowest in the overweight group and the highest in the class II obesity group (Table 4). However, the multivariate-adjusted model (without fitness) showed a nonsignificant association (HR, 0.87; 95% CI, 0.70-1.07) with overweight compared with normal-weight persons (Table 6). The fully adjusted model (including fitness) attenuated the quadratic trend (Table 6). Our findings are consistent with the report from Gale et al,[26] who also found no evidence of increased mortality risk in mildly to moderately overweight women and men aged 65 or older after adjusting for self-reported physical activity.

Further joint analysis (Table 7) showed that in fit individuals the mortality risk was not significantly different across the 4 BMI categories, while in unfit individuals the mortality risk was J-shaped, with lower risk in those with BMI of 25.0-34.9 and higher risk in those with BMI of 18.5-24.9 and 35.0 or greater. These results support the hypothesis that moderate and higher fitness levels favorably influence mortality risk across categories of body composition. Normal-weight individuals in our study had greater longevity only if they were physically fit; furthermore, obese individuals who were fit did not have increased mortality.

The quadratic trend across BMI in the unfit individuals deserves further comment. In general, unfit individuals were inactive at baseline, whereas fit individuals were active. In elderly individuals, BMI is also a marker of other factors such as fitness and muscle mass; therefore, maintaining BMI at older age is an overall marker of health.[17] This may be attributable to competing causes of mortality that become important factors with increasing age. It also may reflect selection factors that have allowed survival to older age.

In older populations, abdominal obesity assessed by waist circumference[22-24] has been a better mortality predictor than BMI. Other indicators of adiposity, such as body fat, also have been examined for mortality associations.[26,27] However, the independent association between body fat and mortality in the older population has not been adequately demonstrated.[14,27] Re-

Table 5. Risk of All-Cause Mortality by Cardiorespiratory Fitness (Fitness) Categories—Aerobics Center Longitudinal Study, 1979-2003

	HR (95% CI) by Fitness Quintile[a]				
Model	<8.7	8.7-11.2	11.3-13.6	13.7-18.3	≥18.4
1[b]	1 [Reference]	0.53 (0.40-0.70)	0.44 (0.33-0.58)	0.43 (0.32-0.58)	0.30 (0.22-0.42)
2[c]	1 [Reference]	0.51 (0.39-0.68)	0.42 (0.31-0.56)	0.40 (0.30-0.55)	0.27 (0.19-0.39)
3[d]	1 [Reference]	0.52 (0.40-0.69)	0.43 (0.32-0.57)	0.42 (0.31-0.56)	0.29 (0.21-0.40)
4[e]	1 [Reference]	0.53 (0.40-0.71)	0.43 (0.32-0.57)	0.41 (0.31-0.56)	0.27 (0.19-0.39)
5[f]	1 [Reference]	0.54 (0.41-0.72)	0.44 (0.33-0.59)	0.44 (0.33-0.59)	0.31 (0.22-0.43)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; Fitness, cardiorespiratory fitness; HR, hazard ratio.
[a] See Table 4 footnote for definition of fitness quintiles. For all models, $P < .001$ for linear trend across quintiles.
[b] Adjusted for age, sex, examination year, smoking status, abnormal exercise electrocardiogram responses, and baseline health conditions (cardiovascular disease, hypertension, diabetes, and hypercholesterolemia, present or not for each).
[c] Adjusted for covariates listed for model 1 plus body mass index (entered as continuous variable).
[d] Adjusted for covariates listed for model 1 plus waist circumference (entered as continuous variable).
[e] Adjusted for covariates listed for model 1 plus percent body fat (entered as continuous variable).
[f] Adjusted for covariates listed for model 1 plus fat-free mass (entered as continuous variable).

Table 6. Risk of All-Cause Mortality by Adiposity Measures—Aerobics Center Longitudinal Study, 1979-2003

Adiposity Measure[a]	Model 1, HR (95% CI)[b]	*P* Value	Model 2, HR (95% CI)[c]	*P* Value
BMI[d]				
18.5-24.9	1 [Reference]	.004[e]	1 [Reference]	.005[e]
25.0-29.9	0.87 (0.70-1.07)		0.72 (0.58-0.89)	
30.0-34.9	1.11 (0.80-1.53)		0.76 (0.54-1.07)	
≥35.0	1.98 (1.09-3.61)		1.11 (0.60-2.05)	
Waist circumference				
Normal	1 [Reference]	.05[f]	1 [Reference]	.95[f]
Abdominal obesity	1.25 (1.00-1.56)		0.99 (0.79-1.25)	
Percent body fat				
Normal	1 [Reference]	.78[f]	1 [Reference]	.07[f]
Obese	1.03 (0.85-1.25)		0.83 (0.67-1.01)	
Fat-free mass quintiles				
<50.6	1 [Reference]	.36[g]	1 [Reference]	.91[g]
50.6-56.9	1.04 (0.70-1.53)		1.01 (0.69-1.49)	
57.0-61.1	0.92 (0.61-1.38)		0.86 (0.57-1.28)	
61.2-65.9	1.01 (0.66-1.54)		0.90 (0.59-1.37)	
≥66.0	1.21 (0.79-1.86)		1.02 (0.66-1.57)	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a] See "Methods" for definitions.
[b] Adjusted for age, sex, examination year, smoking status, abnormal exercise electrocardiogram responses, and baseline health conditions (cardiovascular disease, hypertension, diabetes, and hypercholesterolemia, present or not for each).
[c] Adjusted for covariates listed for model 1 plus fitness (entered as continuous variable in minutes).
[d] Calculated as weight in kilograms divided by height in meters squared.
[e] For quadratic trend.
[f] For difference.
[g] For linear trend.

searchers speculate that the controversial association between adiposity and mortality in older individuals may be attributable to selective survival, cohort effects, or unadjusted confounding.[41] We found that BMI or waist circumference, but not percent body fat, predicted overall mortality in adults at least 60 years old. From a practical perspective, these findings suggest that more complicated and expensive body fat measurement does not provide an advantage in assessing mortality risk over more readily available and less expensive obesity measures such as BMI or waist circumference. These findings also suggest that total adiposity per se may not be the factor that increases mortality risk among elderly individuals. Rather, fat distribution and some other factor intrinsic to BMI (eg, frame size) may underlie mortality risk in older adults. Further investigation of the effects of various measures of adiposity on mortality in other elderly populations, and on the potential role of confounding and modifying variables, would contribute usefully to this research area.

Our results also support the hypothesis that higher levels of fitness can reduce the risk of premature death[12,33,42,43] and expand the evidence supporting this relationship in obese older persons. In a prospective cohort of 18 750 Chinese men and 37 417 Chinese women 65 or older, Schooling et al[17] recently reported that self-reported physical activity was strongly associated with lower mortality in a dose-response manner. Our earlier report in older persons in the Aerobics Center Longitudinal Study also demonstrated that lower fitness, an objective measure of functional capacity that is related to recent physical activity habits, is associated with higher risk of all-cause mortality.[37]

However, neither our earlier report nor that by Schooling et al assessed the joint associations of physical activity, BMI, and outcomes. In the current study, we found that fitness is a strong predictor of overall death among older adults, independent of body composition and other mortality risk factors. Additional studies are needed that concurrently evaluate the joint association among objective measures of fitness or activity, body size and fatness, and longevity in the rapidly growing older population.

Increasing evidence suggests that skeletal muscle function (eg, strength, power, endurance) may contribute to improved physical functioning and longevity through biological pathways that are related to but independent of aerobic fitness.[44,45] Fat-free mass was not a significant predictor of mortality risk in the present study. However, it is possible that the quality of FFM (eg, functional phenotype), rather than the absolute amount of FFM, is the key factor in determining health risk. We were unable to include in the present study an objective measure of muscle function to examine its independent and joint relationship with adiposity, fitness, and mortality risk. More data are needed to further explore the role of muscle function in successful aging and enhanced longevity among older adults.

Our study had several strengths. We used standardized and objective measurements of fitness and adiposity and examined their associations with mortality, providing quantitative risk estimates and a lower likelihood of misclassification on the exposure variables. We are unaware of any other report in which these data are available. The extensive baseline physical examination permitted systematic evaluation of the presence or absence of baseline medical conditions. The relatively long follow-up (mean, 12 years) was sufficient to accrue enough fatal end points to allow for assessing the joint associa-

Table 7. Joint Associations of Cardiorespiratory Fitness (Fitness) and Adiposity Measures With All-Cause Mortality—Aerobics Center Longitudinal Study, 1979-2003[a]

	Fit			Unfit			
Adiposity Measure	No. of Deaths	Rate[b]	HR (95% CI)[c]	No. of Deaths	Rate[b]	HR (95% CI)[c]	*P* Value
BMI[d]							
18.5-24.9	158	1.2	1 [Reference]	34	4.9	3.63 (2.47-5.32)	<.001
25.0-29.9	152	1.2	0.88 (0.70-1.11)	44	2.7	1.74 (1.23-2.46)	<.001
30.0-34.9	32	1.6	1.12 (0.76-1.66)	18	2.5	1.68 (1.02-2.78)	.46
≥35.0	2	1.2	0.86 (0.21-3.50)	10	4.8	3.35 (1.74-6.44)	.05
Waist circumference[e]							
Normal	274	5.1	1 [Reference]	61	14.5	2.84 (2.15-3.75)	<.001
Abdominal obesity	70	6.2	1.21 (0.93-1.58)	45	13.5	2.65 (1.93-3.63)	<.001
Percent body fat[e]							
Normal	151	9.1	1 [Reference]	29	26.8	2.94 (1.97-4.38)	<.001
Obese	190	8.7	0.96 (0.78-1.19)	72	21.8	2.39 (1.81-3.16)	<.001

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a] Cross-product tests of interaction between fitness and adiposity exposures were not statistically significant: fitness-BMI ($\chi^2_1 = 0.05$, $P = .82$); fitness-waist circumference ($\chi^2_1 = 1.38$, $P = .24$); and fitness-percent body fat ($\chi^2_1 = 0.04$, $P = .84$).
[b] All-cause death rates per 1000 person-years adjusted for age, sex, and examination year.
[c] Adjusted for age, sex, examination year, smoking status, abnormal exercise electrocardiogram responses, and presence vs absence of baseline health conditions (cardiovascular disease, hypertension, diabetes, and hypercholesterolemia).
[d] Calculated as weight in kilograms divided by height in meters squared.
[e] See "Methods" for definitions.

tion among risk factors and mortality within adiposity strata.

Limitations of the current study include a focus on participants who were primarily white and well-educated, had middle to upper socioeconomic status, and were physically able to complete a maximal exercise test. The results may not apply to other groups of older adults. However, the homogeneity of our sample strengthens the internal validity of our findings by reducing potential confounding by unmeasured factors related to socioeconomic status, such as income, education, or prestige. Residual confounding from undetected subclinical disease at baseline may exist, although it seems unlikely that it would explain all of the observed association between fitness, adiposity, and mortality, especially given the extensive medical examination performed at baseline. The primary results were not changed meaningfully when deaths in the first 2 years of follow-up were excluded. We did not have adequate information about diet or medication use to study these factors. We focused primarily on all-cause mortality because of the relatively small number of cause-specific deaths, which prevented us from stratifying cause-specific analyses by adiposity measures.

However, some exploratory analyses were performed for associations between fitness, BMI, waist circumference, percent body fat, or FFM and cause-specific mortality (data not shown). In the current study, cardiovascular disease and cancer accounted for 74% of total deaths. After adjusting for age, sex, examination year, and current smoking, fitness was significantly associated with cardiovascular disease, coronary heart disease, and cancer mortality ($P < .05$ for linear trend, for each). However, the associations between adiposity exposures and the above cause-specific mortality outcomes were variable. Future studies should include these important exposures and extend the analysis to these and other specific causes of death with particular interest to public health, such as stroke and diabetes mellitus. Due to a limited sample of women, who contributed relatively few deaths to the analysis, we combined women and men for analyses and adjusted the analyses for sex. In our previous reports on fitness in which we have been able to perform parallel analyses in women and men, results have generally been similar for women and men.[34,46] In this cohort we had only a single baseline assessment of fitness, adiposity measurements, and other exposures; thus, we could not examine whether changes in any of these variables occurred during follow-up and whether this may have influenced the study results.

In conclusion, in this prospective study of adults 60 years or older, low fitness predicted higher risk of all-cause mortality after adjustment for potential confounding factors, including adiposity. Fit individuals had greater longevity than unfit individuals, regardless of their body composition or fat distribution. Our data provide further evidence regarding the complex long-term relationship among fitness, body size, and survival. It may be possible to reduce all-cause death rates among older adults, including those who are obese, by promoting regular physical activity, such as brisk walking for 30 minutes or more on most days of the week (about 8 kcal/kg per week), which will keep most individuals out of the low-fitness category.[43] Enhancing functional capacity also should allow older adults to achieve a healthy lifestyle and to enjoy longer life in better health.

Author Contributions: Drs Sui and Blair had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sui, LaMonte, Blair.
Acquisition of data: Sui, LaMonte, Blair.
Analysis and interpretation of data: Sui, LaMonte, Laditka, Hardin, Chase, Hooker, Blair.
Drafting of the manuscript: Sui, LaMonte, Laditka, Hardin, Chase, Hooker, Blair.
Critical revision of the manuscript for important intellectual content: Sui, LaMonte, Laditka, Hardin, Hooker, Blair.
Statistical analysis: Sui, LaMonte, Hardin.
Financial Disclosures: Dr LaMonte reported receiving book royalties (<$1000 per year) from Human Kinetics and honoraria for lectures from scientific, educational, and lay groups. Dr Blair reported receiving book royalties (<$5000 per year) from Human Kinetics; honoraria for service on the medical advisory boards of Jenny Craig, Magellan Health Services, and Matria Health Care; and honoraria for lectures from scientific, educational, and lay groups; research grants from Jenny Craig and BodyMedia Inc; and compensation as an executive lecturer for the University of North Texas. Dr Blair donates these fees to the University of South Carolina Educational Foundation or to other nonprofit groups. No other disclosures were reported.
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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	64.4(±4.8)歳			( )		前向き研究
対象数	1000～5000			( )		( )

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

Table 5. Risk of All-Cause Mortality by Cardiorespiratory Fitness (Fitness) Categories—Aerobics Center Longitudinal Study, 1979-2003

	HR (95% CI) by Fitness Quintile[a]				
Model	<8.7	8.7-11.2	11.3-13.6	13.7-18.3	≥18.4
1[b]	1 [Reference]	0.53 (0.40-0.70)	0.44 (0.33-0.56)	0.43 (0.32-0.56)	0.30 (0.22-0.42)
2[c]	1 [Reference]	0.51 (0.39-0.66)	0.42 (0.31-0.56)	0.40 (0.30-0.55)	0.27 (0.19-0.39)
3[d]	1 [Reference]	0.52 (0.40-0.69)	0.43 (0.32-0.57)	0.42 (0.31-0.56)	0.29 (0.21-0.40)
4[e]	1 [Reference]	0.53 (0.40-0.71)	0.43 (0.32-0.57)	0.41 (0.31-0.56)	0.27 (0.19-0.39)
5[f]	1 [Reference]	0.54 (0.41-0.72)	0.44 (0.33-0.59)	0.44 (0.33-0.59)	0.31 (0.22-0.43)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; Fitness, cardiorespiratory fitness; HR, hazard ratio.
[a] See Table 4 footnote for definition of fitness quintiles. For all models, $P < .001$ for linear trend across quintiles.
[b] Adjusted for age, sex, examination year, smoking status, abnormal exercise electrocardiogram responses, and baseline health conditions (cardiovascular disease, hypertension, diabetes, and hypercholesterolemia, present or not for each).
[c] Adjusted for covariates listed for model 1 plus body mass index (entered as continuous variable).
[d] Adjusted for covariates listed for model 1 plus waist circumference (entered as continuous variable).
[e] Adjusted for covariates listed for model 1 plus percent body fat (entered as continuous variable).
[f] Adjusted for covariates listed for model 1 plus fat-free mass (entered as continuous variable).

図表掲載箇所	P2513, Table5

概 要（800字まで）

本研究は、アメリカのThe Aerobics Center Longitudinal Studyに参加した男女2,603名を対象に平均12年間の追跡調査を行い、全身持久力と全死因死亡リスクとの関連を検討したものである。全身持久力は、最大トレッドミルテストにより最大酸素摂取量を測定し、測定時間により8.7分未満、8.7-11.2分、11.3-13.6分、13.7-18.3分、18.4分以上の5群に分類した。メッツ値に換算すると、それぞれ男性で7.2メッツ未満、7.2メッツ、8.5メッツ、9.5メッツ、10.8メッツ、女性で5.8メッツ未満、6.7メッツ、7.6メッツ、8.6メッツであった。測定時間が8.7分未満の集団と比較すると、それぞれ全死因死亡リスクが0.54(95%信頼区間:0.41-0.72)、0.44(0.33-0.59)、0.44(0.33-0.59)、0.31(0.22-0.43)と量反応的に有意に減少した(Ptrend<0.001)。

結 論（200字まで）

60歳以上の高齢者コホートにおいて、全身持久力と全死因死亡リスクとの間には強い負の相関がみられ、それは独立してリスクと関連していることが明らかとなった。

エキスパートによるコメント（200字まで）

全身持久力は、死亡や様々な疾患発症と強い関連を示す指標である。量反応関係も明確に認められることから、疾患発症を予防するためにも日々全身持久力を上げるような活動に取り組むことの重要性が示されている。

担当者:久保絵里子・村上晴香

BASIC SCIENCES

Influence of Cardiorespiratory Fitness on Lung Cancer Mortality

XUEMEI SUI[1], DUCK-CHUL LEE[1], CHARLES E. MATTHEWS[2], SWANN A. ADAMS[3,4], JAMES R. HÉBERT[3,4], TIMOTHY S. CHURCH[5], CHONG-DO LEE[6], and STEVEN N. BLAIR[1,3]

[1]Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC; [2]Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD; [3]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC; [4]Statewide Cancer Prevention and Control Program, University of South Carolina, Columbia, SC; [5]Pennington Biomedical Research Center, Baton Rouge, LA; and [6]Department of Exercise and Wellness, Arizona State University, Mesa, AZ

ABSTRACT

SUI, X., D. LEE, C. E. MATTHEWS, S. A. ADAMS, J. R. HÉBERT, T. S. CHURCH, C. LEE, and S. N. BLAIR. Influence of Cardiorespiratory Fitness on Lung Cancer Mortality. *Med. Sci. Sports Exerc.*, Vol. 42, No. 5, pp. 872–878, 2010. **Purpose**: Previous studies have suggested that higher levels of physical activity may lower lung cancer risk; however, few prospective studies have evaluated lung cancer mortality in relation to cardiorespiratory fitness (CRF), an objective marker of recent physical activity habits. **Methods**: Thirty-eight thousand men, aged 20–84 yr, without history of cancer, received a preventive medical examination at the Cooper Clinic in Dallas, Texas, between 1974 and 2002. CRF was quantified as maximal treadmill exercise test duration and was grouped for analysis as low (lowest 20% of exercise duration), moderate (middle 40%), and high (upper 40%). **Results**: A total of 232 lung cancer deaths occurred during follow-up (mean = 17 yr). After adjustment for age, examination year, body mass index, smoking, drinking, physical activity, and family history of cancer, hazard ratios (95% confidence intervals) for lung cancer deaths across low, moderate, and high CRF categories were 1.0, 0.48 (0.35–0.67), and 0.43 (0.28–0.65), respectively. There was an inverse association between CRF and lung cancer mortality in former (P for trend = 0.005) and current smokers (P for trend < 0.001) but not in never smokers (trend P = 0.14). Joint analysis of smoking and fitness status revealed a significant 12-fold higher risk of death in current smokers (hazard ratio = 11.9, 95% confidence interval = 6.0–23.6) with low CRF as compared with never smokers who had high CRF. **Conclusions**: Although the potential for some residual confounding by smoking could not be eliminated, these data suggest that CRF is inversely associated with lung cancer mortality in men. Continued study of CRF in relation to lung cancer, particularly among smokers, may further our understanding of disease etiology and reveal additional strategies for reducing its burden. **Key Words:** DEATH FROM LUNG CANCER, PHYSICAL ACTIVITY, SMOKING, PREVENTION, EPIDEMIOLOGY

Physical inactivity is associated with an increased overall risk of cancer mortality (17) and mortality associated with specific anatomic sites such as colon (31) and breast (14). However, there is little information regarding the association of inactivity and lung cancer, which is the most common cause of cancer death in the United States. According to the most recent report from the American Cancer Society, in 2009, an estimated 116,090 new cases of lung cancer will be diagnosed, and approximately 88,900 men are expected to die from this disease (3). Cigarette smoking is the most important cause of lung cancer. Still, many nonsmokers die of the disease, and former smokers remain at elevated risk after quitting. It is estimated that in the United States alone, about 3000 lung cancer deaths occur each year in nonsmoking adults (3). It takes up to 20 yr for a majority of former smokers' rates to drop to those of never smokers (19). Therefore, it is plausible that other factors besides smoking may play an important etiologic role. Moreover, the majority of cigarette smokers do not develop lung cancer, and this fact adds to the likelihood that there may be other factors besides smoking that modify risk. One of these other factors might be physical activity.

Most previous cohort studies (2,5,9,12,20,21,26,32,34,39) have reported an inverse association between risk of lung cancer and physical activity in men; however, some have not (7,11,25,30,33,43). These inconsistent findings may be due partly to the measurement errors inherent in self-reported

Address for correspondence: Xuemei Sui, M.D., M.P.H., 921 Assembly Street, Columbia, SC 29210; E-mail: msui@mailbox.sc.edu.
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physical activity. Cardiorespiratory fitness (CRF), an objective and a more reproducible measure that reflects the functional consequences of physical activity habits, may provide a better exposure with which to evaluate associations with lung cancer risk. To the best of our knowledge, only one study (38) has been conducted on CRF and lung cancer mortality among men. However, this study examined only men with prediabetes and diabetes. To address cancer prevention strategies, it is important to investigate whether physical activity or CRF reduces cancer incidence or mortality in the general population prospectively. The objective of this report is to examine the risk of lung cancer mortality across levels of fitness, obtained by maximal exercise test on a treadmill, in a large cohort of men from the Aerobics Center Longitudinal Study (ACLS) (17).

METHODS

Study population. The ACLS is a prospective study composed of patients who received preventive medical examinations at the Cooper Clinic in Dallas, Texas. The current analysis included 38,000 men ranging in age from 20 to 84 yr who completed a clinical examination, including fitness testing, between 1974 and 2002 with mortality follow-up through December 31, 2003. Men with any physician-diagnosed cancer or those unable to complete an exercise stress test to at least 85% of their age-predicted maximal heart rate (220 minus age in years) were excluded. Women also were excluded from this analysis because of limitations in sample size and, concomitantly, lung cancer deaths. Most participants were white (>95%) and employed or previously employed in professional occupations. This study was reviewed and approved annually by the Cooper Institute institutional review board.

Baseline examination. Participants provided written informed consent to participate in the examination and follow-up study. All medical evaluations included personal and family histories, questionnaire on demographic characteristics and health habits, physical examination, anthropometry, electrocardiogram, blood chemistry analyses, blood pressure measurements, and maximal exercise test on a treadmill. The comprehensive medical evaluation is described in detail elsewhere (17,38). Briefly, body mass index (BMI) was calculated as measured weight in kilograms divided by height in meters squared. On the basis of self-reported current and past smoking behavior, participants were categorized into one of three groups: those who currently smoked cigarettes (current smokers), those who previously smoked cigarettes (former smokers), and those who never smoked cigarettes (never smokers). Number of cigarettes smoked, year started smoking, and year quitting smoking were used to calculate pack-years. To measure alcohol use, one unit of alcohol was defined as 12 oz (3.41 dL) of beer, 5 oz (1.421 dL) of wine, or 1.5 oz (0.4262 dL) of hard liquor. Physically inactive was defined as reporting no leisure-time physical activity such as walking, jogging, running, treadmill exercise, cycling, stationary cycling, swimming, racquet sports, aerobic dance, or other sports-related activities (e.g., basketball or soccer) in the 3 months before the baseline examination. Family history (from parents and siblings; first-degree relatives) of cancer was obtained from a standardized questionnaire.

Pulmonary function assessment was performed in a subset of the participants (79% of the total study sample), and forced expiratory volume in 1 s (FEV1) was obtained with a Collins 421 Survey spirometer (Collins, MA), as described elsewhere (8). All procedures were administered by trained technicians who followed standardized protocols. Hankinson et al. (13) derived predictive equations for FEV1 specific for sex, age, and height and derived from healthy participants of the Third National Health and Nutrition Examination Survey. The FEV1 was expressed both as raw values and as a percentage of the predictive values.

We determined CRF using a modified Balke maximal exercise test, as described in previous publications (6,17). The treadmill speed was 88 $m \cdot min^{-1}$ for the first 25 min. During this time, the grade was 0% for the first minute and 2% for the second minute and increased 1% each minute until 25 min had elapsed. After 25 min, the grade remained constant while the speed increased 5.4 $m \cdot min^{-1}$ each minute until test termination. Patients were encouraged to give a maximal effort during the test. The mean (SD) percentage of age-predicted maximal heart rate achieved during exercise was 101.5 (6.6). Total time of the test correlates highly ($r = 0.92$) with measured maximal oxygen uptake (23). Thus, CRF in this study is analogous to maximal aerobic power. METs (1 MET = 3.5 mL O_2 uptake per kilogram per minute) were estimated from the final treadmill speed and grade (4). We assigned men to age-specific fitness categories on the basis of their total time on the treadmill test. We classified the lowest 20% as low fit, the next 40% of the fitness distribution as moderately fit, and the upper 40% as high fit, as in our previous reports, on the basis of data from the entire cohort. The detailed cut points of treadmill duration and corresponding MET values have been reported earlier (36).

Ascertainment of lung cancer death. All participants were followed from the date of their baseline examination until their date of death or until December 31, 2003. The National Death Index was the primary data source for mortality surveillance. The underlying cause of death was determined from the National Death Index report or by a nosologist's review of official death certificates obtained from the department of vital records in the decedent's state of residence. Lung cancer mortality was defined by the *International Classification of Diseases, Ninth Revision* codes 162.2–162.9 before 1999 and *International Classification of Diseases, Tenth Revision* codes C34 during 1999–2003. We computed person-years of exposure as the sum of follow-up time among decedents and survivors.

Statistical analysis. Baseline characteristics of the study participants were calculated for the entire cohort and

by CRF groups. Differences in covariates among the three fitness groups were assessed using F-tests with two degrees of freedom. Kaplan–Meier plots were used to compare survival curves, and Cox proportional hazards models were used to compute adjusted hazard ratios (HR), associated 95% confidence intervals (CI), mortality rates (deaths per 10,000 person-years of follow-up), and linear trends of lung cancer mortality for levels of each fitness category. When calculating HR, the low-fitness group was used as the reference category. Multivariable-adjusted models controlled for the potential confounding effects of baseline age (yr), year of examination, BMI ($kg \cdot m^{-2}$), smoking status (never, former, or current smoker), alcohol intake (drinks per week), physically inactive (yes or no), and family history of cancer (present or not). Tests of linear trend across increasing categories of fitness were conducted by treating the CRF exposure as a single continuous variable. Cumulative hazard plots grouped by exposure suggested no appreciable violations of the proportional hazards assumption.

We also conducted Cox regression analyses of CRF stratified by categories of smoking status (never, former, or current smoker) and by lung function (FEV1/FVC >70% or ≤70%) to assess whether the associations were stronger in particular subgroups. Finally, we examined the joint associations of CRF and smoking status with lung cancer mortality. We assessed the interaction among exposure groups using likelihood ratio tests of nested models. Because smoking is such a strong predictor of lung cancer risk, we further controlled the pack-years smoking in a subset of men who had the information available to calculate this variable. All P values were two-tailed, and values of less than 0.05 were considered to indicate statistical significance. Analyses were done using the SAS statistical software (Version 9.1; SAS Inc., Cary, NC).

RESULTS

The baseline characteristics of participants across levels of fitness are provided in Table 1. Men in the high-fitness group were more likely to have a lower BMI, to have more favorable lipid and blood pressure profiles, to be nonsmokers, and to have higher respiratory function (all $P < 0.001$).

There were 232 deaths from lung cancer during an average 17.1 yr of follow-up (649,800 person-years of observation). The risk of lung cancer mortality is lower across incremental levels of fitness (Table 2). After adjustment for covariates (age, examination year, smoking status, alcohol intake, physical inactivity, BMI, and family history of cancer), men with moderate and high CRF had 52% and 57% lower lung cancer risk, respectively, than did men with low CRF (P for trend < 0.001). The Kaplan–Meier survival curves also indicate that men with moderate and high CRF had greater lung cancer-free time as compared with men with low CRF (Fig. 1).

Although there was no significant interaction of CRF with smoking status (P = 0.86), we were interested in examining the smoking-specific association between CRF and lung cancer mortality (Table 2, Figs. 2 and 3). The age-adjusted death rate was inversely related to CRF in former smokers (P for trend = 0.005) and current smokers (P for

TABLE 1. Baseline characteristics of the study participants across cardiorespiratory fitness (CRF) levels in men, ACLS, Dallas, Texas, 1974–2002.

Characteristic	All (N = 38,000)	Cardiorespiratory Fitness			P for Trend
		Low CRF (n = 6245)	Moderate CRF (n = 15,024)	High CRF (n = 16,731)	
Age (yr)	43.6 ± 9.6	42.9 ± 9.1	43.9 ± 9.5	43.6 ± 9.9	<0.001
BMI ($kg \cdot m^{-2}$)	26.3 ± 3.7	29.2 ± 5.0	26.7 ± 3.3	24.9 ± 2.5	<0.001
Maximal METs	11.7 ± 2.5	8.6 ± 1.2	10.7 ± 1.1	13.7 ± 1.9	<0.001
Treadmill time duration (min)	18.0 ± 5.1	11.3 ± 2.5	16.0 ± 2.5	22.3 ± 3.5	<0.001
Lipids ($mmol \cdot L^{-1}$)					
Total cholesterol	5.45 ± 1.12	5.70 ± 1.08	5.54 ± 1.03	5.27 ± 1.18	<0.001
HDL-C	1.17 ± 0.32	1.03 ± 0.27	1.11 ± 0.28	1.25 ± 0.33	<0.001
Triglycerides	1.56 ± 1.29	2.13 ± 1.74	1.67 ± 1.21	1.23 ± 1.04	<0.001
Fasting blood glucose ($mmol \cdot L^{-1}$)	5.60 ± 2.84	5.84 ± 1.46	5.59 ± 0.93	5.50 ± 1.12	<0.001
Blood pressure (mm Hg)					
Systolic	122 ± 14	124 ± 14	121 ± 13	120 ± 13	<0.001
Diastolic	81 ± 10	84 ± 10	82 ± 10	79 ± 9	<0.001
Cigarette smoking (%)					<0.001
Never	47.6	34.6	44.7	55.1	
Former	34.4	32.8	34.5	34.9	
Current	18.0	32.6	20.8	10.0	
Alcohol intake (drinks per week)	4.7 ± 6.9	3.9 ± 7.0	4.5 ± 7.0	5.2 ± 6.8	<0.001
Physically inactive (%)	31.8	65.5	39.4	12.4	<0.001
FEV1 (L)[a]	3.8 ± 0.7	3.6 ± 0.7	3.8 ± 0.7	4.0 ± 0.6	<0.001
FEV1 predicted (L)[a]	4.2 ± 0.5	4.1 ± 0.4	4.2 ± 0.5	4.2 ± 0.5	<0.001
FEV1% predicted[a]	92.4 ± 13.7	85.9 ± 14.3	91.4 ± 13.3	96.0 ± 12.6	<0.001
FVC (L)[a]	4.9 ± 0.8	4.5 ± 0.8	4.9 ± 0.8	5.1 ± 0.8	<0.001
FEV1/FVC%[a]	78.2 ± 7.2	78.3 ± 7.9	78.2 ± 7.2	78.2 ± 7.0	0.49
Family history of cancer (%)	1.0	0.7	1.1	1.1	0.04

Data are presented as mean ± SD, unless specified otherwise.
[a] Data only available in 30,185 men.
METs = maximal metabolic equivalents achieved during the treadmill test; HDL-C, high-density lipoprotein cholesterol; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity.

TABLE 2. Event rates and hazard ratios for lung cancer mortality by cardiorespiratory fitness (CRF) groups, ACLS, Dallas, Texas, 1974–2003.

	Deaths for Lung Caner	Event Rate[a]	HR[b]	95% CI[b]	HR[c]	95% CI[c]
All men (N = 38,000)						
Low CRF	86	7.3	1.00	Referent		
Moderate CRF	86	3.1	0.48	0.35–0.67		
High CRF	60	2.3	0.43	0.28–0.65		
P linear trend		<0.001		<0.001		
Never smoker (n = 6245)						
Low CRF	7	2.0			1.00	Referent
Moderate CRF	15	1.3			0.93	0.29–2.96
High CRF	13	1.0			0.76	0.21–2.79
P linear trend		0.14				0.62
Former smoker (n = 15,024)						
Low CRF	29	7.3			1.00	Referent
Moderate CRF	35	3.4			0.44	0.26–0.74
High CRF	33	3.3			0.44	0.24–0.81
P linear trend		0.005				0.02
Current smoker (n = 16,731)						
Low CRF	50	12.1			1.00	Referent
Moderate CRF	36	6.3			0.48	0.30–0.76
High CRF	14	5.1			0.38	0.18–0.79
P linear trend		<0.001				0.001

HR, hazard ratio; CI, conference interval; CRF, cardiorespiratory fitness; BMI, body mass index.
[a] Event rate is expressed as per 10,000 person-years and adjusted for age.
[b] Adjusted for age, examination year, smoking status (never, past, or current), alcohol intake (drinks per week), physical inactivity (yes or no), BMI ($kg \cdot m^{-2}$), and family history of cancer (present or not).
[c] Adjusted for age, examination year, cigarettes per day (for former and current smoker), alcohol intake (drinks per week), physical inactivity (yes or not), BMI ($kg \cdot m^{-2}$), and family history of cancer (present or not).

trend < 0.001) but not in never smokers (P for trend = 0.14). Associations attenuated but remained significant within former and current smokers after adjustment for covariates plus cigarettes smoked per day. Excluding deaths during the first 5 yr of follow-up did not materially change the magnitude and pattern of the association. Figure 2 shows the multivariate-adjusted HR for lung cancer mortality among nine smoking–fitness combination categories. The highest relative risk was in the category of current smokers with low CRF. This group of men had an almost 12-fold higher risk of dying from lung cancer compared with those never smokers having high fitness (HR = 11.92, 95% CI = 6.03–23.58). We further assessed the effect of pack-years smoking on associations between fitness and lung cancer risk in a subset of smokers (N = 14,419) who had the data available for us to calculate pack-years smoking (Fig. 3). Additional adjustment for pack-years smoking in this subset slightly attenuated the association between CRF and lung cancer mortality, but the pattern of the associations did not materially change. Among men smoking 20 pack-years or more, a lower lung cancer mortality risk was observed among those men who were at least moderate fit (HR = 0.49, 95% CI = 0.38–0.85) compared with low-fit men.

Finally, we examined the influence of lung function on the association between fitness and lung cancer risk in a large subgroup of men (N = 30,185). There was an inverse gradient for the risk of lung cancer mortality across levels of fitness in lower (P for trend = 0.008) and higher (P for trend = 0.03) lung function groups. Among men with lower lung function, risk was lower in the moderate (HR = 0.67, 95% CI = 0.37–1.20) and high (HR = 0.38, 95% CI = 0.16–0.89) CRF groups. In individuals with higher lung function, risk was lower in both moderate

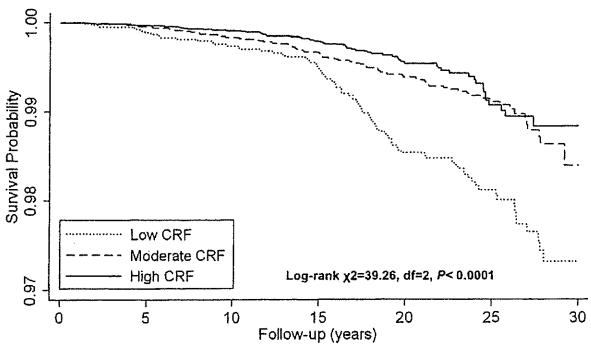

FIGURE 1—Kaplan–Meier survival curves for lung cancer mortality by cardiorespiratory fitness (CRF) levels, ACLS, Dallas, Texas, 1974–2003.

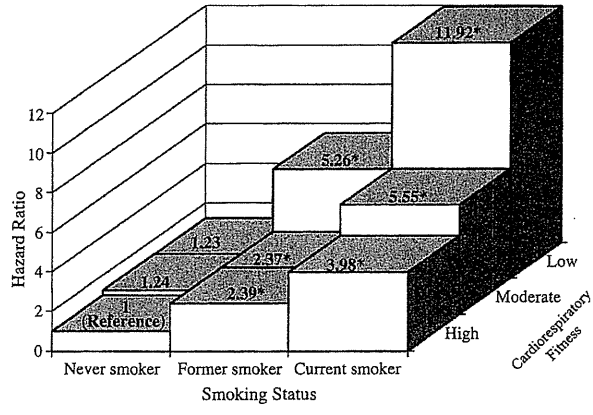

FIGURE 2—Multivariate risk for lung cancer mortality by smoking status and fitness level. The height of the bars represents hazard ratios adjusted for age, examination year, alcohol use, BMI, physical activity, and family history of cancer. *Signifies a significant difference compared to the reference (All $P < 0.05$).

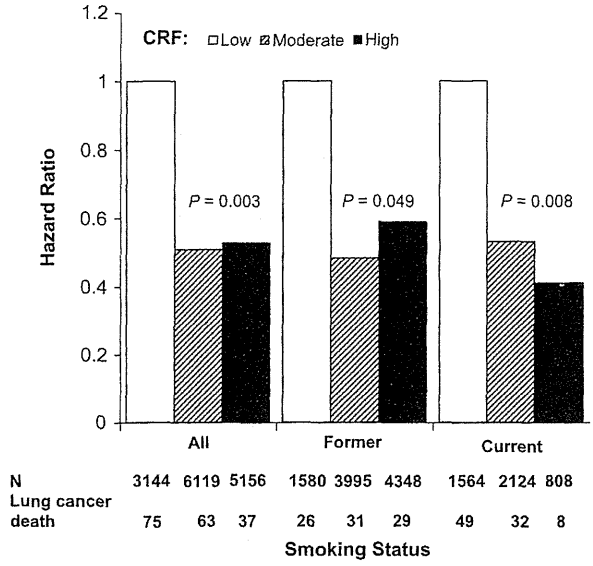

FIGURE 3—Multivariate-adjusted hazard ratios for cardiorespiratory fitness (CRF) and lung cancer mortality in a subset of men (N = 14,419) who had available data to calculate the pack-years in the ACLS. The height of the bars represents hazard ratios adjusted for age, examination year, pack-years smoking, alcohol use, BMI, physical activity, and family history of cancer.

(HR = 0.44, 95% CI = 0.28–0.68) and high (HR = 0.50, 95% CI = 0.29–0.86) CRF groups.

DISCUSSION

The primary finding of this study was that higher levels of fitness were associated with a lower risk of lung cancer mortality in men. Compared with smokers, nonsmokers had the lowest risks of lung cancer mortality regardless of their fitness levels. Our data also support the hypothesis that CRF may be protective for lung cancer mortality in current and former smoking men. These associations persisted after controlling for potential confounders. To the best of our knowledge, only one previous study has assessed the association of CRF with risk of dying of lung cancer (38). In that study, Thompson et al. (38) found that diabetic and prediabetic men who were fit, as defined by achieving at least a moderate level of fitness during a maximal exercise test, had a 57% lower risk of lung cancer mortality. In our study, we found that men with at least a moderate fitness level had a 52% lower lung cancer risk than did men with low CRF.

Our findings are consistent with evidence from previous cohort studies in men examining lung cancer incidence (2,5,9,12,20,21,26,32,34,39). Most of these studies combined fatal and nonfatal lung cancer end point as the outcome (5,9,20,21,26,32,34,39), and very few used only mortality data (2,12). A recent meta-analysis also concluded that higher levels of leisure-time physical activity protect against lung cancer (37). In a large study published in 1997 by Thune and Lund (39), a significant inverse relationship between activity and risk of lung cancer was found. After appropriate adjustment for potential confounders, only leisure activity was associated with a lower risk and only in men. Analysis of data in smokers considered separately showed a significant association between inactivity and lung cancer risk. However, the small number of lung cancer cases in nonsmokers and former smokers precluded separate analysis in those groups (39). The Harvard Alumni Health Study also reported a decrease in lung cancer risk in men (20). An energy expenditure of 12 600 kJ·wk^{-1} had a 39% lower risk of lung cancer compared with the reference group (<4200 kJ·wk^{-1}). These findings were significant when nonsmokers and former smokers were considered separately. The trend for smokers was similar, but the results were not statistically significant, perhaps because of small numbers. In addition, Garfinkel and Stellman (12) reported a lower incidence of lung cancer death at higher levels of leisure and occupational activity in 868,000 smokers and nonsmokers participating in the American Cancer Society's Cancer Prevention Study II. In contrast to the earlier studies, Leitzmann et al. (21) reported no association between physical activity and total lung carcinoma among never smokers but an inverse association among both former and current smokers. In agreement with this study, we found a similar pattern of the association among never, former, and current smokers. Besides the above studies, most of the other studies that found an inverse association between activity and lung cancer risk did not conduct subgroup analyses in current and former smokers (2,5,9,21,26,32,34).

The lack of association in never smokers in our study may be explained partly by the small number of lung cancer deaths. Because we noted only a slight attenuation of the relation between CRF and lung cancer mortality after controlling for pack-years of smoking, residual confounding by cigarette smoking seems unlikely. Another possible explanation might be the potential different etiology of lung cancer between never smokers and smokers (35,42). It is known, for example, that smoking is more strongly related to squamous cell than adenocarcinomas (16). Several etiologic factors have been proposed for the development of lung cancer in the never smokers, including exposure to radon, cooking fumes, asbestos, and heavy metals, environmental tobacco smokers, human papillomavirus infection, and inherited genetic susceptibility (35). The different biology of lung cancer in never smokers is apparent in differential responses to epidermal growth factor receptor inhibitors and in increased prevalence of adenocarcinoma history in never smokers (42). However, there is still the lack of a clear understanding of the factors responsible for lung cancer in never smokers. Future studies should have sufficient numbers of histopathological subtypes to allow separate analyses.

Clearly, the most important predictor of lung cancer is smoking, although it is more important in squamous cell cancers. Could the increased risk in the low-fit group be the

result of unreported smoking in that group rather than low fitness? This is unlikely for several reasons. First, the association of lower mortality across fitness groups holds for current smokers among whom, by definition, smoking would not be underreported. Second, adjustments were made carefully for current and former smoking behavior and number of cigarettes smoked daily as well as for pack-years smoking. After adjustment for cigarette smoking in the main analyses and adjustment for pack-years smoking in a subset of men, we found similar results. In addition, among men smoking 20 pack-years or more, a reduced lung cancer mortality risk was observed among those who were at least moderately fit compared with low-fit men. Therefore, it is unlikely that the results of the present study reflect confounding by cigarette smoking. The data from the Norway study provide another reason that it is unlikely that the observed inverse association between activity or fitness and decreased risk of lung cancer is due to unreported smoking in a low activity or low-fit group (39). In this study, the low activity group had fewer squamous cell cancers than the other activity groups, and squamous cell cancer is the type most closely associated with smoking. It would be unlikely for this to occur if the observed association was due to nonreported smoking rather than activity or fitness.

It is important to note that some studies have failed to report any association between physical activity and lung cancer (7,11,25,30,33,43). Leitzmann et al. (21) suggested that the inconsistent findings may be due to small sample sizes, variation in the magnitude of residual confounding by smoking, potential recall bias, or imprecise assessments of physical activity. In addition, population differences in the study cohorts, differences in lung cancer end points used (fatal, nonfatal, or combined fatal or nonfatal cases), duration of follow-up after the baseline exposure measurement, or some combination of all of the above factors may contribute to the inconsistency of results as well. Although all of the previous studies except one (38) have been based on self-reported questionnaire measures, self-reported measures of physical activity are only modestly correlated with objective measures obtained using criterion methods (1,27). The objectively measured CRF from the current study might be a more accurate and better exposure to consider. Although CRF has a genetic component (25%–40%) (15), it is clear that usual physical activity is its primary determinant.

Some plausible mechanisms exist for a protective effect of exercise and fitness against lung cancer. There are numerous studies documenting improvement in overall immune function with increasing activity through increasing the number of natural killer cells (28). Exercise is associated with reduced systemic inflammation (particularly C-reactive protein) (18), which has been proposed to promote carcinogenesis in a wide spectrum of cancers, including lung cancer (10). Physical activity may increase pulmonary ventilation, and perfusion (8,29), which accompany improved fitness (8), might decrease the interaction time of potential carcinogens in the airway and thus decrease the risk of lung cancer (40). Further, physical activity may enhance endogenous antioxidant defenses and reduce oxidative stress (24).

Strengths of the current study include its prospective design, maximal exercise testing to quantify CRF, and hard end-point of lung cancer mortality as the study outcome. We also were able to stratify the analyses by smoking status and lung function, which helped to shed light on some potential effect modifications. One weakness of our study is the lack of dietary data. However, a recent study that has adjusted for intakes of fruit, vegetables, and red meat found that these adjustments did not significantly change the conclusions (21). Another limitation of the current study is that the study population consists mainly of European American men in the middle and upper socioeconomic strata; thus, the results may not be generalizable to other adult populations. However, it should not affect the internal validity. In terms of exposure assessment, we classified men at study enrollment, but in the present analysis, we were unable to evaluate the effect of changes in physical activity or fitness over time on lung cancer mortality outcomes. It is possible that sedentary or low-fit men increased their activity or fitness levels at some point in the follow-up interval. In addition, others may have experienced decreases in these characteristics. Such misclassification of exposure would likely underestimate the magnitude of the association observed in the present study. Finally, we had insufficient information to assess the effect of CRF on lung cancer incidence. Additional studies are warranted to confirm and expand on the associations we report herein and to better understand the relationship between fitness and lung cancer risk.

In summary, our data provide evidence that low levels of fitness may play a causal role in lung cancer mortality. This finding is consistent with earlier studies on self-reported physical activity and lung cancer. In addition, we observed a greater reduction in lung cancer risk than that found in the physical activity studies. There are plausible mechanisms for a protective effect of fitness on lung cancer mortality. It is unlikely that uncontrolled and residual confounding explain the observed association. If fitness does decrease the risk of lung cancer mortality as shown in our data, then there is something more than avoiding tobacco that can be done to lower risk of the leading cause of cancer death in the United States. The lowest risk among nonsmokers and the large reduction in risk in former smokers have important, encouraging public health implications. The consensus public health guideline (41) to obtain 150 $min \cdot wk^{-1}$ of moderate-intensity physical activity such as brisk walking or jogging will move most individuals out of the low-fitness category. It may also help smokers to quit smoking (22).

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Results of the present study do not constitute endorsement by the American College of Sports Medicine.

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対象の内訳	ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	男性	( )		( )		( )
年齢	40～84歳(43.6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

TABLE 2. Event rates and hazard ratios for lung cancer mortality by cardiorespiratory fitness (CRF) groups, ACLS, Dallas, Texas, 1974–2003.

	Deaths for Lung Caner	Event Rate[a]	HR[b]	95% CI[b]	HR[c]	95% CI[c]
All men (N = 38,000)						
Low CRF	86	7.3	1.00	Referent		
Moderate CRF	86	3.1	0.48	0.35–0.67		
High CRF	60	2.3	0.43	0.28–0.65		
P linear trend		<0.001		<0.001		
Never smoker (n = 6245)						
Low CRF	7	2.0			1.00	Referent
Moderate CRF	15	1.3			0.93	0.29–2.96
High CRF	13	1.0			0.76	0.21–2.79
P linear trend		0.14				0.62
Former smoker (n = 15,024)						
Low CRF	29	7.3			1.00	Referent
Moderate CRF	35	3.4			0.44	0.26–0.74
High CRF	33	3.3			0.44	0.24–0.81
P linear trend		0.005				0.02
Current smoker (n = 16,731)						
Low CRF	50	12.1			1.00	Referent
Moderate CRF	36	6.3			0.48	0.30–0.76
High CRF	14	5.1			0.38	0.18–0.79
P linear trend		<0.001				0.001

HR, hazard ratio; CI, conference interval; CRF, cardiorespiratory fitness; BMI, body mass index.
[a] Event rate is expressed as per 10,000 person-years and adjusted for age.
[b] Adjusted for age, examination year, smoking status (never, past, or current), alcohol intake (drinks per week), physical inactivity (yes or no), BMI ($kg \cdot m^{-2}$), and family history of cancer (present or not).
[c] Adjusted for age, examination year, cigarettes per day (for former and current smoker), alcohol intake (drinks per week), physical inactivity (yes or not), BMI ($kg \cdot m^{-2}$), and family history of cancer (present or not).

図表掲載箇所	
概 要 (800字まで)	<目的>喫煙の影響を強く受ける肺ガンによる死亡に、全身持久力がどのように関連するのか明らかにすること。<方法>コホート名:the Aerobics Center Longitudinal Study(ACLS)、対象者数:38000人、追跡期間:17.1年、因子評価方法詳細:Balkeの最大テストによる最大運動時間による推定法。Balkeの負荷試験の運動時間が最大酸素摂取量(メッツ表示)と深い関係があるので、それから最大酸素摂取量を推定し、各年代毎に20%未満、20～60%未満、60%以上で3分類した(20歳から39歳:低 10.4、中13.1 高 それ以上、40～59歳 低 9.9 中 12.2まで 高 それ以上、60歳以上 低 7．2、中9.5、高 それ以上)、因子の単位:メッツ<結果>相対リスク:分位1:1、分位2:0.48(0.35-0.67)、分位3:0.43(0.28-0.65)、喫煙歴で喫煙中、過去に喫煙歴有り、喫煙なしの3つの群に分類し分析すると、喫煙中、過去の喫煙歴有りの2群では、全被験者での分析と同様の関係が見られたが、喫煙歴なしの群では、全身持久力と肺ガン死亡リスクとの間には有意な関係は見られなかった。
結 論 (200字まで)	アメリカ人男性の肺がんに対する全身持久力(最大酸素摂取量)の予防効果。全体での効果あり。しかし、左に示した現在喫煙者に対する強い効果と、前喫煙者にも効果有り、しかし 非喫煙者(一回もすったことはない)には効果なし
エキスパートによるコメント (200字まで)	喫煙は肺ガンの最も強力なリスクファクターである。喫煙と低い全身持久力が肺ガンによる死亡に及ぼす相互作用をはじめて示した研究で、極めて意義深い。

担当者 宮地元彦

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The Association between Cardiorespiratory Fitness and Impaired Fasting Glucose and Type 2 Diabetes Mellitus in Men

Ming Wei, MD; Larry W. Gibbons, MD; Tedd L. Mitchell, MD; James B. Kampert, PhD; Chong D. Lee, EdD; and Steven N. Blair, PED

Background: Several studies show an inverse association between self-reported physical activity and type 2 diabetes. It is not known whether physical activity or cardiorespiratory fitness is associated with the onset of objectively determined impaired fasting glucose and type 2 diabetes.

Objective: To determine whether cardiorespiratory fitness, an objective marker of physical activity, is associated with risk for impaired fasting glucose and type 2 diabetes.

Design: Population-based prospective study.

Setting: Preventive medicine clinic.

Patients: 8633 nondiabetic men (of whom 7511 did not have impaired fasting glucose) who were examined at least twice.

Measurements: Cardiorespiratory fitness (determined by a maximal exercise test on a treadmill), fasting plasma glucose level, and other clinical and personal characteristics and incidence of impaired fasting glucose and type 2 diabetes.

Results: During an average follow-up of 6 years, 149 patients developed type 2 diabetes and 593 patients developed impaired fasting glucose. After age, cigarette smoking, alcohol consumption, and parental diabetes were considered, men in the low-fitness group (the least fit 20% of the cohort) at baseline had a 1.9-fold risk (95% CI, 1.5- to 2.4-fold) for impaired fasting glucose and a 3.7-fold risk (CI, 2.4- to 5.8-fold) for diabetes compared with those in the high-fitness group (the most fit 40% of the cohort). The risk for impaired fasting glucose was elevated in older men and those with a higher body mass index. Age, body mass index, blood pressure, triglyceride level, and a history of parental diabetes were also directly related to risk for type 2 diabetes.

Conclusions: Low cardiorespiratory fitness was associated with increased risk for impaired fasting glucose and type 2 diabetes. A sedentary lifestyle may contribute to the progression from normal fasting glucose to impaired fasting glucose and diabetes. Risk for type 2 diabetes was elevated in older persons and those with higher body mass index, blood pressure, and triglyceride levels and a parental history of diabetes.

This paper is also available at http://www.acponline.org.

Ann Intern Med. 1999;130:89-96.

Type 2 diabetes is a common disease in industrialized countries. It is a major cause of cardiovascular disease and all-cause mortality (1–6), and its prevalence has increased continuously over the past few decades (1). The American Diabetes Association currently defines impaired fasting glucose as a fasting plasma glucose level from 6.1 to 6.9 mmol/L (110 to 125 mg/dL) and type 2 diabetes as a fasting plasma glucose level of 7.0 mmol/L (126 mg/dL) or more (1).

Data from several prospective studies show an inverse association between physical activity and diabetes (7–13). However, these studies are limited by the use of self-reporting of physical activity and presence of type 2 diabetes (7–12). Self-reporting of physical activity tends to be imprecise, and type 2 diabetes is undiagnosed in about 50% of the prevalent cases (14). This leads to misclassification on both exposure and outcome measures (15). These limitations may result in underestimation of the true association between sedentary habits and risk for type 2 diabetes. Impaired fasting glucose is a strong predictor of type 2 diabetes, cardiovascular disease, and other diabetic complications (6, 16–18). The underlying cause of impaired fasting glucose is unknown, and no prospective study of the association between physical activity and impaired fasting glucose has been published.

We examined the relation of cardiorespiratory fitness, objectively determined by a maximal exercise test on a treadmill, to the incidence of impaired fasting glucose and type 2 diabetes. Cases of impaired fasting glucose and diabetes at baseline and follow-up were determined by using the American Diabetes Association's current guidelines (1).

Methods

Patients

In our population-based prospective study, we included 8633 men 30 to 79 years of age at baseline

(mean, 43.5 years) who completed at least two medical evaluations at the Cooper Clinic in Dallas, Texas, from 1970 to 1995. Patients come to the Cooper Clinic for preventive medical examinations and health promotion counseling. Many are sent by their employers for these services, some are referred by their personal physicians, and others are self-referred. More than 97% of the patients are white, and most are employed in executive or professional occupations. More than 75% are college graduates. Although study participants came from middle and upper socioeconomic strata, they were similar to other well-characterized population-based cohorts in terms of blood pressure, cholesterol level, body weight, and cardiorespiratory fitness (19).

The study was reviewed and approved annually by the institutional review board at the Cooper Institute for Aerobics Research. Additional details of the study methods and population characteristics of the cohort have been published elsewhere (20, 21). Because clinical or subclinical heart disease and other conditions associated with type 2 diabetes may alter the level of physical activity and thus cardiorespiratory fitness, we excluded men with an abnormal resting or exercise electrocardiogram or a history of heart attack, stroke, or cancer at the baseline clinical examination ($n = 2350$).

The baseline evaluation was performed after participants gave written informed consent for the initial medical examination and registration in the follow-up study. Examinations were done after patients had fasted for at least 12 hours and included personal and family health histories, a questionnaire on demographic characteristics and health habits, a physical examination, an exercise test, anthropometric measurement, electrocardiography, blood chemistry analyses, and blood pressure measurement. Technicians who followed a standard manual of operations administered all procedures.

Impaired fasting glucose and type 2 diabetes were diagnosed according to American Diabetes Association criteria that define impaired fasting glucose as a fasting plasma glucose level of 6.1 to 6.9 mmol/L (110 mg/dL to 125 mg/dL) and diabetes as a fasting plasma glucose level of 7.0 mmol/L (126 mg/dL) or more (1). Patients who did not meet these criteria but who reported a history of diabetes or current therapy with oral antidiabetic agents or insulin were also considered to have diabetes. We excluded patients who had diabetes at baseline according to any of these criteria ($n = 377$).

Cardiorespiratory fitness was assessed with a maximal exercise test that followed a modified Balke protocol (22). Details of treadmill speed and elevation have been described elsewhere (20, 21). Briefly, the test began with the patient walking on a horizontal treadmill at 88 m/min. After the first minute, the elevation increased to 2%; the elevation then increased 1% each minute up to 25 minutes. For the few patients who were still able to continue, the elevation was held constant after 25 minutes and the speed was increased by 5.4 m/min until the patient reached volitional fatigue. Use of this protocol for the exercise test correlates highly ($r = 0.92$) with measured maximal oxygen uptake (23). All patients in our study achieved at least 85% of their age-predicted maximal heart rate; average maximal heart rates ($\pm$ SD) in each age group were 186 ± 11 beats/min for patients 30 to 39 years of age, 179 ± 12 beats/min for those 40 to 49 years of age, 172 ± 13 beats/min for those 50 to 59 years of age, and 162 ± 17 beats/min for those 60 years of age or older. Average maximal heart rates in each age group exceeded the age-predicted rate (220 beats/min − age in years), which indicates that the exercise test can be considered maximal performance.

We defined level of fitness by total time on the treadmill at the baseline examination, as in our previous studies (20, 21). Treadmill times were placed in frequency distributions for specific age groups (30 to 39, 40 to 49, 50 to 59, or 60 or more years of age). The least fit 20% of the participants in each age group were classified as low fitness, the next 40% as moderate fitness, and the remaining 40% as high fitness. The respective cut-points for total treadmill time in the low-, moderate-, and high-fitness groups were 945 seconds or less, 946 to 1259 seconds, and 1260 seconds or more for patients 30 to 39 years of age; 849 seconds or less, 850 to 1020 seconds, and 1021 seconds or more for patients 40 to 49 years of age; 750 seconds or less, 751 to 1035 seconds, and 1036 seconds or more for patients 50 to 59 years of age; and 644 seconds or less, 645 to 953 seconds, and 954 seconds or more for patients 60 years of age or older. These cut-points at the 20th and 60th percentiles to define fitness levels were used in previous studies (20, 21) and were selected before analysis for our investigation. However, we calculated these cut-points with patients in the current study, from which unhealthy persons were excluded. Therefore, they differ somewhat from the cut-points derived from the entire cohort of the Aerobics Center Longitudinal Study (21).

For some analyses, such as the models that included change in fitness from baseline to follow-up, cardiorespiratory fitness was expressed as maximal metabolic units (metabolic equivalents [METs], calculated as the working metabolic rate/resting metabolic rate; 1 MET is equivalent to an oxygen uptake of $3.5 \cdot mL^{-1} \cdot kg^{-1}$) achieved on the exercise test. In other analyses, time on the treadmill was used as a continuous variable.

Serum samples were analyzed by using automated techniques in a laboratory that participates in

Table 1. Baseline Characteristics of 8633 Men According to Cardiorespiratory Fitness Level

Characteristic	Cardiorespiratory Fitness Level*		
	Low	Moderate	High
Participants, *n*	1665	3425	3543
Mean age, *y*	43.9 ± 8.1	43.6 ± 10.9	43.2 ± 8.1
Mean exercise tolerance, *metabolic equivalents*	9.3 ± 0.9	11.3 ± 0.8	13.7 ± 1.2
Mean body mass index, kg/m^2	28.3 ± 3.9	26.4 ± 2.9	25.0 ± 2.3
Mean waist circumference, *cm*†	99.8 ± 10.5	93.0 ± 16.0	85.6 ± 17.6
Mean total cholesterol level, *mmol/L*	5.67 ± 1.01	5.54 ± 1.00	5.33 ± 1.18
Mean high-density lipoprotein cholesterol level, *mmol/L*	1.06 ± 0.27	1.13 ± 0.28	1.27 ± 0.32
Mean triglyceride level, *mmol/L*	1.92 ± 1.28	1.58 ± 1.13	1.17 ± 0.79
Mean diastolic blood pressure, *mm Hg*	82.6 ± 9.9	80.7 ± 9.2	78.8 ± 8.7
Mean systolic blood pressure, *mm Hg*	122.3 ± 13.7	120.0 ± 12.4	119.5 ± 12.8
Mean alcohol use, *g/wk*	185.9 ± 264.4	176.0 ± 281.3	172.2 ± 297.2
Current smoker, %	31	19	10
Parental diabetes, %	28	26	26

* All *P* values for trend across fitness groups were less than 0.05 except for parental diabetes.
† Data from 5759 men.

the Centers for Disease Control and Prevention Lipid Standardization Program. Blood pressure was measured by using auscultatory methods with a mercury sphygmomanometer. We defined high blood pressure as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or a history of hypertension. Height and weight were measured with a standard physician's scale and stadiometer, and body mass index was calculated as weight in kg/height in m^2. Waist circumference was measured with a standard anthropometric tape.

Statistical Analysis

We used SAS statistical software for data analyses (24). The incidence of impaired fasting glucose was calculated for men with normal fasting glucose at baseline, and the incidence of diabetes was based on data from all 8633 patients. For analyses with impaired fasting glucose as the outcome, we excluded 1122 men who had impaired fasting glucose at baseline and an additional 69 men who had normal fasting plasma glucose at baseline but developed diabetes during follow-up. Rates of impaired fasting glucose or diabetes were calculated by dividing the number of incident cases during the study period by the number of person-years over the same period. We defined the study period as the interval between the baseline examination and the last follow-up visit. We used logistic regression to estimate the association between dependent variables and independent variables after adjustment for possible confounding factors. We used general linear models to study the cross-sectional association of fitness level and parental history of diabetes (24, 25). To account for the possible cohort effect of baseline year, we examined the relation between incident cases and baseline year and found no association. We used tests for ordinal linear trend to evaluate the possible relation of higher treadmill time with risk for impaired fasting glucose or diabetes after dividing the sample into the three fitness groups. All *P* values are two-sided, and those less than 0.05 were considered statistically significant.

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Results

During an average follow-up of 6.1 ± 4.8 years (range, 1 to 24.8 years) that included 52 588 person-years, 593 men developed impaired fasting glucose and 149 developed diabetes. Of the men with incident diabetes, 139 (93%) were not aware of their diabetes at the follow-up examination; disease was identified on the basis of fasting plasma glucose levels alone. The respective incidence rates per 1000 person-years among patients 30 to 44 years of age, 45 to 59 years of age, and 60 years of age or older were 10.2, 17.2, and 23.4 for impaired fasting glucose and 1.9, 3.8, and 8.9 for type 2 diabetes.

Table 1 shows baseline characteristics of participants in each fitness level for selected variables. In general, men in the high-fitness group had the lowest levels of total cholesterol and triglycerides, body mass index, waist circumference, diastolic blood pressure, and systolic blood pressure; the lowest prevalence of current cigarette smoking; and the highest levels of high-density lipoprotein cholesterol at baseline.

The relation between fitness level and incidence of impaired fasting glucose or type 2 diabetes is shown in **Table 2**. We limited the analyses of cardiorespiratory fitness and impaired fasting plasma glucose to incident cases during follow-up. Of the

Table 2. Incidence of Impaired Fasting Glucose in 7442 Men with Normal Baseline Fasting Plasma Glucose Levels and Type 2 Diabetes among 8633 Men

Condition	Cardiorespiratory Fitness Level*		
	Low	Moderate	High
Impaired fasting glucose			
Participants, *n*	1339	2938	3165
Total person-years	7719	18 017	19 238
Participants who developed impaired fasting plasma glucose, *n*	147	254	192
Incidence of impaired fasting glucose per 1000 person-years	19.0	14.1	10.0
Odds ratio (95% CI)†	2.0 (1.6–2.5)	1.5 (1.2–1.8)	1.0
Odds ratio (95% CI)‡	1.9 (1.5–2.4)	1.5 (1.2–1.8)	1.0
Type 2 diabetes			
Participants, *n*	1665	3425	3543
Total person-years, *n*	9752	21 075	21 761
Participants who developed diabetes, *n*	58	57	34
Incidence of diabetes per 1000 person-years	5.9	2.7	1.6
Odds ratio (95% CI)†	3.7 (2.4–5.7)	1.7 (1.1–2.6)	1.0
Odds ratio (95% CI)‡	3.7 (2.4–5.8)	1.7 (1.1–2.7)	1.0

* Tests for trend in incidences of impaired fasting glucose and diabetes across fitness levels were significant ($P < 0.01$).
† Adjusted for age and years of follow-up.
‡ Adjusted for age, parental diabetes, alcohol consumption, current smoking, and years of follow-up.

8633 men in the study, 1122 had impaired fasting glucose at baseline and an additional 69 men with normal baseline glucose values developed diabetes during follow-up, leaving 7442 men in the impaired fasting glucose analyses. Impaired fasting glucose developed in 593 of the 7442 men during follow-up. After adjustment for age, parental diabetes, current smoking, and alcohol use, men in the low-fitness group had a 1.9-fold higher risk for impaired fasting glucose than men in the high-fitness group. We observed a dose–response gradient across the three fitness levels (test for trend, $P < 0.001$). When we repeated this analysis including the 69 men with normal baseline fasting plasma glucose who developed type 2 diabetes during follow-up, results were similar to the data shown in **Table 2.**

We then examined the association between baseline fitness and incidence of type 2 diabetes in all 8633 men. Because men with impaired fasting glucose at baseline were eight times more likely than men with normal fasting glucose values at baseline to develop diabetes, we examined the relation of fitness to diabetes separately in these two groups. After finding that the association between fitness and diabetes in these two groups was similar, we combined the groups in further analyses. Men in the low-fitness group had a 3.7-fold greater risk for diabetes than men in the high-fitness group after adjustment for age, parental diabetes, current smoking, and alcohol use. In addition, we found a dose–response gradient between fitness level (in both categorical and continuous variables) and incidence of impaired fasting glucose and diabetes (test for trend, $P < 0.001$).

We evaluated the association between cardiorespiratory fitness level and impaired fasting glucose and type 2 diabetes after additional adjustment for high levels of high-density lipoprotein cholesterol and triglycerides, elevated body mass index, high blood pressure, and parental diabetes. Men in the low-fitness group had a greater adjusted risk for impaired fasting glucose and diabetes at baseline than did men in the high-fitness group (**Table 3**). Significant trends ($P < 0.001$) were seen across fitness groups for both outcome measures. In addition, older age and high body mass index had significant direct associations with impaired fasting glucose. Likewise, older age, high body mass index, high blood pressure, high triglycerides, and parental diabetes were significantly (P values ranged from 0.045 to 0.001) and directly associated with diabetes.

We measured waist circumference in a subgroup of 5759 study participants. The age-adjusted odds ratio for diabetes was 2.7 (95% CI, 1.6 to 4.8) in men with a waist circumference of 90 cm or more compared with those with a waist circumference less than 90 cm. However, after fitness level, waist circumference, and other covariables were included in the same model, waist circumference, body mass index, and parental diabetes became nonsignificant

Table 3. Adjusted Odds Ratios for Incidence of Impaired Fasting Glucose and Type 2 Diabetes by Cardiorespiratory Fitness Level and Other Potential Risk Factors Estimated by Multiple Logistic Regression

Variable	Odds Ratio (95% CI)	*P* Value
Impaired fasting glucose*		
Cardiorespiratory fitness levels†		
High	1.0	
Moderate	1.4 (1.1–1.7)	0.002
Low	1.7 (1.3–2.1)	<0.001
Age (every 10 years)	1.5 (1.3–1.7)	<0.001
Body mass index ≥ 27 kg/m^2	1.5 (1.2–1.8)	0.002
High blood pressure (>140/90 mm Hg or history of hypertension)	1.1 (0.9–1.4)	>0.2
Triglyceride level ≥ 1.69 mmol/L	1.2 (0.9–1.8)	0.16
Parental diabetes	1.2 (1.0–1.4)	0.12
Type 2 diabetes*		
Cardiorespiratory fitness level†		
High	1.0	
Moderate	1.4 (0.9–2.2)	0.11
Low	2.6 (1.6–4.2)	<0.001
Age (per 10 years)	1.6 (1.3–2.0)	<0.001
Body mass index ≥ 27 kg/m^2	2.0 (1.4–2.9)	<0.001
High blood pressure (>140/90 mm Hg or history of hypertension)	1.5 (1.0–2.2)	0.045
Triglyceride level ≥ 1.69 mmol/L	2.0 (1.4–2.7)	<0.001
Parental diabetes	1.9 (1.4–2.7)	<0.001

* Model included baseline age; fitness level; high body mass index; high blood pressure; high levels of high-density lipoprotein cholesterol, total cholesterol, and triglyceride; parental diabetes; current smoking; alcohol consumption; and years of follow-up.
† Tests for trend across fitness groups for both impaired fasting glucose and type 2 diabetes were significant ($P < 0.001$).

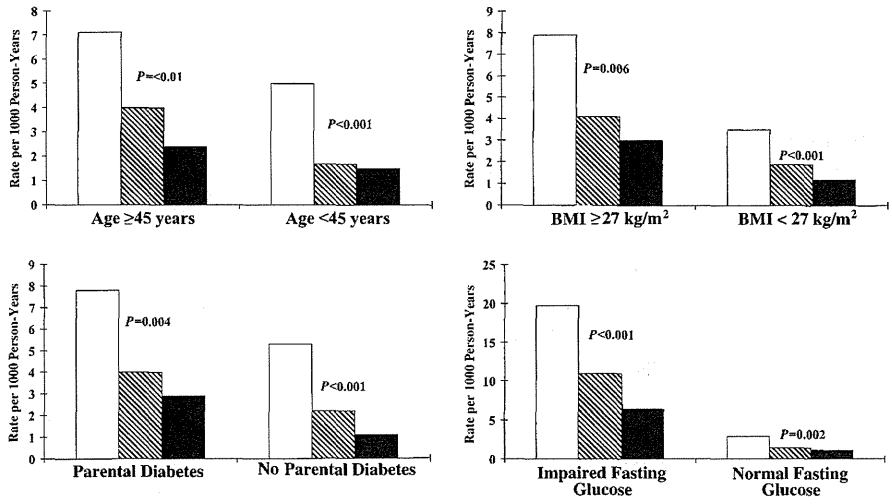

Figure. Incidence of type 2 diabetes per 1000 persons-years by cardiorespiratory fitness levels according to age group (*top left*), body mass index (*BMI*) (*top right*), history of parental diabetes (*bottom left*), and impaired fasting glucose (*bottom right*). White bars represent the low-fitness group, striped bars represent the moderate-fitness group, and black bars represent the high-fitness group.

(odds ratios of about 1.4 to 1.6), whereas the odds ratio was 2.8-fold (CI, 1.5- to 5.3-fold) higher in men in the low-fitness group than in men in the high-fitness group. No significant interactions were found between fitness level and covariables.

As shown in **Tables 2** and **3**, cardiorespiratory fitness had an independent inverse association with impaired fasting glucose and diabetes. To further illustrate the independent association of fitness with diabetes, incidence rates in the low-, moderate-, and high-fitness groups are shown in the **Figure** in strata of other correlates of diabetes risk. The inverse gradient of rates across fitness groups is present in younger and older men, those with high or low body mass index, those with and those without a parental history of diabetes, those with impaired fasting glucose at baseline, and those with normal baseline glucose levels. We saw similar gradients for diabetes across fitness groups in strata of systolic blood pressure, high-density lipoprotein cholesterol level, triglyceride level, and smoking status (data not shown).

We also evaluated the relation of change in fitness from the first to the second examination to risk for impaired fasting glucose and type 2 diabetes in additional models with adjustment for baseline levels of high-density lipoprotein cholesterol and triglycerides, body mass index, blood pressure, and history of parental diabetes. An increase in fitness of 1 MET was associated with a 20% (CI, 10% to 30%) increase in risk for impaired fasting glucose and a 28% (CI, 12% to 47%) increase in risk for type 2 diabetes.

To address the possibility that fitness may vary according to genetic predisposition to diabetes, we compared the baseline fitness levels of patients with a history of parental diabetes with those of patients without such a history. Age-adjusted mean maximal METs were only 1% lower in the former group than in the latter group (11.9 compared with 11.8 METs; $P = 0.02$); this small difference was not significant after additional adjustment for body mass index ($P > 0.2$).

Discussion

The most novel finding in our study was the steep inverse gradient for incidence of impaired fasting glucose across cardiorespiratory fitness categories. To our knowledge, this is the first prospective study to evaluate the relation of fitness or physical activity to the onset of impaired fasting glucose. Our most important finding is the strong inverse association between baseline cardiorespiratory fitness and development of type 2 diabetes determined objectively by using American Diabetes Association criteria for the fasting plasma glucose level (1). This association is clinically significant; the risk for diabetes is 3.7-fold higher in men in the low-fitness group than in men in the high-fitness group. The inverse associations between fitness and impaired fasting glucose and diabetes persisted after adjustment for age, parental history of diabetes, alcohol consumption, and cigarette smoking. Because body mass index, waist circumference, high levels of high-density lipoprotein cholesterol and triglycerides, and high blood pressure may be mediators linking physical inactivity to higher risk for impaired fasting glucose and diabetes (26–29), we further adjusted for these variables. After this adjustment, the associations between cardiorespiratory fitness and study outcomes were diminished somewhat but remained statistically significant (**Table 3**). Age and body mass index were also significantly

associated with impaired fasting glucose and type 2 diabetes. In addition, blood pressure, triglyceride level, and a history of parental diabetes were associated with type 2 diabetes in these analyses. These data support the hypothesis that the effect of physical activity on impaired fasting glucose and diabetes may be mediated, at least in part, by some of these variables, but physical activity also has an independent effect on these outcomes. The hypothesis that inactivity and low fitness are causally related to diabetes risk is strengthened further by our observation that an improvement in fitness from the first to the follow-up examinations was independently associated with risk for diabetes.

Several investigators report a prospective association between physical activity and type 2 diabetes (7–13). In most (7–10, 12) but not all (11, 13) studies, a significant inverse association is seen between physical activity and risk for diabetes. In these studies, risk for diabetes was typically 30% to 125% higher among sedentary patients than among physically active patients. This may be an underestimate of the true risk associated with an inactive lifestyle. Some studies included self-reported physical activity as the exposure and self-reported type 2 diabetes as the outcome. A misclassification of exposure in these studies is probably the result of relatively imprecise assessment of self-reported physical activity, especially in obese persons, who tend to overestimate their activity level (30). Diabetes was also self-reported in these studies (7–12). This leads to misclassification on the outcome variable because type 2 diabetes is undiagnosed in about 50% of the prevalent cases (14), and this problem may be even more severe for new cases. In our study, 93% of the men with incident diabetes diagnosed by objective fasting plasma glucose criteria did not report diabetes on the follow-up medical history questionnaire. Therefore, an important strength of our study is the objective measurement of cardiorespiratory fitness as the exposure and fasting plasma glucose measurements at baseline and follow-up to detect incident impaired fasting plasma glucose and diabetes. We should have had many fewer misclassifications of both the exposure and outcome variables than did previous prospective studies on this topic. In addition, waist circumference has been proposed as an important predictor of type 2 diabetes (29), and none of the previous studies between physical activity and diabetes considered the effect of this variable. When we adjusted for waist circumference in a subgroup of men, the strong inverse association between fitness and diabetes remained.

Our study is the first large prospective investigation to examine the relation of cardiorespiratory fitness to incident diabetes as determined by American Diabetes Association criteria. Cardiorespiratory fitness was associated with type 2 diabetes in a recent small study (31). An oral glucose tolerance test was used to identify incident cases of diabetes, but these data were not available to exclude prevalent diabetes cases at baseline. In one report, vital capacity was used as a surrogate of physical fitness; only a weak correlation ($r = 0.17$) was seen between estimated maximal oxygen uptake and vital capacity (32). Nevertheless, their results are consistent with our findings.

We considered whether a genetic predisposition for diabetes among unfit persons might partially explain our findings. We found a twofold increased risk for diabetes in men with diabetic parents compared with those whose parents did not have diabetes, which is consistent with results from many epidemiologic studies (33). Numerous reports have suggested genes or loci that may underlie type 2 diabetes, but few of these findings have been replicated (33, 34). In a small case–control study, Nyholm and colleagues (35) found that maximal oxygen intake was 14% lower in 21 diabetic relatives than in 22 nondiabetic relatives. However, the investigators did not account for differences in age or sex between case-patients and controls. The ratio between men and women was 34% lower in diabetic relatives, and the diabetic relatives were an average of 2.2 years older than the controls. Because men and younger persons tend to have higher fitness levels (20), the lower maximal oxygen uptakes seen in diabetic relatives may have been due to confounding by age and sex. After adjusting for age and body mass index, we found no difference in cardiorespiratory fitness for the men in our study by strata of parental history of diabetes. Furthermore, we saw a similar inverse gradient for diabetes risk across fitness categories in men with and those without a parental history of diabetes. Thus, although genetic factors may influence diabetes risk, our data do not support the hypothesis that these factors are determinants of cardiorespiratory fitness. Cardiorespiratory fitness has a genetic component, but it is determined primarily by exercise habits (36, 37).

The limitations of our study must be considered. We assessed cardiorespiratory fitness by using a maximal exercise test that followed a standard protocol (22), but maximal oxygen uptake was not measured directly. However, exercise test performance measured with this protocol correlates highly ($r = 0.92$) with measured maximal oxygen uptake (23). The high maximal exercise heart rates indicate that study participants achieved maximal effort.

In addition, although we determined the presence of diabetes by using objective criteria, we were unable to identify patients with type 1 diabetes and specific types of diabetes (1). However, according to

the estimated annual incidence of type 1 diabetes in the United States (9.2 in 100 000 years for adults) (38), type 1 diabetes should constitute only about 3% of our cases. This does not create a serious misclassification problem. Finally, our study participants were all men and more than 97% were white; whether our results also apply to women or minority ethnic groups remains to be determined.

Many studies have evaluated insulin resistance and diabetes and the effect of physical activity on insulin resistance (39–44). Although exceptions exist, overall these studies support a favorable effect of physical activity on insulin resistance (44). Skeletal muscle is the predominant site of insulin resistance in impaired fasting glucose and diabetes, and increased glucose transport, phosphorylation, and muscle glycogen synthesis after exercise training is similar in normal persons and in those with insulin resistance (40). These phenomena, along with increased delivery of insulin to active muscle caused by increased blood flow during exercise, may be some of the mechanisms by which physical activity improves insulin sensitivity (41). In addition, physical activity may reduce insulin resistance by its favorable effect on body fat (29). We do not have baseline data on insulin resistance and do not know whether the men in the low-fitness group were insulin resistant. However, Eriksson and Lindgarde (32) found that both baseline insulin response and fitness estimated crudely by vital capacity were independent predictors of diabetes.

We did not use oral glucose tolerance tests, but this should not be a serious limitation. The American Diabetes Association recommends that diabetes prevalence and incidence in epidemiologic studies be determined by using fasting plasma glucose levels (1). Use of the American Diabetes Association criteria avoids the discrepancy between cut-point values for fasting plasma glucose level and plasma glucose level as measured by the oral glucose tolerance test (1, 17, 18). The overall incidence of diabetes and the eightfold increased risk for diabetes among men with impaired fasting glucose in our study were similar to results of other studies of white populations in which the incidence and prevalence of type 2 diabetes were estimated by the World Health Organization (16). Advantages of using the fasting plasma glucose level are that it is more reproducible, simpler, less costly, and easier to obtain than the plasma glucose level following an oral glucose tolerance test (1, 18).

In conclusion, we found strong evidence that high cardiorespiratory fitness is associated with reduced risk for impaired fasting glucose and type 2 diabetes. Public health recommendations for physical activity (45) should be implemented and may contribute to reducing the incidence of impaired fasting glucose and type 2 diabetes.

From the Cooper Institute for Aerobics Research and the Cooper Clinic, Dallas, Texas.

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Requests for Reprints: Ming Wei, MD, Cooper Institute for Aerobics Research, 12330 Preston Road, Dallas, TX 75230; e-mail, mwei@cooperinst.org.

Current Author Addresses: Drs. Wei, Kampert, Lee, and Blair: Cooper Institute for Aerobics Research, 12330 Preston Road, Dallas, TX 75230.
Drs. Gibbons and Mitchell: Cooper Clinic, 12200 Preston Road, Dallas, TX 75230.

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