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Low Cardiorespiratory Fitness and Physical Inactivity as Predictors of Mortality in Men with Type 2 Diabetes

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Background: Although physical activity is recommended as a basic treatment for patients with diabetes, its long-term association with mortality in these patients is unknown.

Objective: To evaluate the association of low cardiorespiratory fitness and physical inactivity with mortality in men with type 2 diabetes.

Design: Prospective cohort study.

Setting: Preventive medicine clinic.

Patients: 1263 men (50 ± 10 years of age) with type 2 diabetes who received a thorough medical examination between 1970 and 1993 and were followed for mortality up to 31 December 1994.

Measurements: Cardiorespiratory fitness measured by a maximal exercise test, self-reported physical inactivity at baseline, and subsequent death determined by using the National Death Index.

Results: During an average follow-up of 12 years, 180 patients died. After adjustment for age, baseline cardiovascular disease, fasting plasma glucose level, high cholesterol level, overweight, current smoking, high blood pressure, and parental history of cardiovascular disease, men in the low-fitness group had an adjusted risk for all-cause mortality of 2.1 (95% CI, 1.5 to 2.9) compared with fit men. Men who reported being physically inactive had an adjusted risk for mortality that was 1.7-fold (CI, 1.2-fold to 2.3-fold) higher than that in men who reported being physically active.

Conclusions: Low cardiorespiratory fitness and physical inactivity are independent predictors of all-cause mortality in men with type 2 diabetes. Physicians should encourage patients with type 2 diabetes to participate in regular physical activity and improve cardiorespiratory fitness.

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Exercise has become a standard therapy for patients with type 2 diabetes (1). Regular exercise improves conventional clinical risk factors, cardiorespiratory fitness, and components of the insulin resistance syndrome (2–6). However, it is unclear whether physical activity improves the prognosis of patients with diabetes. No data are available on the association of physical activity or cardiorespiratory fitness with mortality in patients with diabetes. The overall benefit of exercise for these patients is unclear, and some experts are concerned that macrovascular and microvascular complications may be worsened by an exercise program (1, 7). Some consider exercise only as a supplement to diet therapy (8). Studies have shown repeatedly that low cardiorespiratory fitness and physical inactivity are directly associated with cardiovascular disease and all-cause mortality (9–14), and our preliminary study with a small number of end points suggested that this association might persist across plasma glucose levels (15). In the current study, we evaluated the prospective association of cardiorespiratory fitness and physical inactivity with mortality in men who have type 2 diabetes.

Methods

The material presented in this report was derived from the Aerobics Center Longitudinal Study (ACLS), a prospective observational study of patients examined at The Cooper Clinic in Dallas, Texas. The study was reviewed and approved annually by the institutional review board at The Cooper Institute. Additional details of study methods and

See editorial comment on pp 669-670.

study group characteristics of this cohort have been published elsewhere (12, 13).

Patients

Participants were men with type 2 diabetes who completed a baseline medical evaluation at The Cooper Clinic in Dallas, Texas, during 1970 to 1993. These men came to The Cooper Clinic for a medical examination and health counseling. Many were sent by their employers for these services, some were referred by their personal physicians, and others were self-referred. More than 92% of the patients are white, and most are employed in executive or professional occupations; more than 75% are college graduates. Study participants come from middle and upper socioeconomic strata, but they are similar to other well-characterized study group-based cohorts in terms of blood pressure, cholesterol level, body weight, and cardiorespiratory fitness (6, 16, 17). We excluded men taking insulin and those with a history of cancer at baseline.

Clinical Examination

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

Questionnaire

Patients completed an extensive self-report of personal and family medical diseases and conditions. Each clinic physician examines only four or five patients per day and thus has time for thorough additional probing of items on the self-reported questionnaire. This complete review of the patient's medical history and the subsequent physical examination are strengths of the ACLS and provide a more thorough evaluation of baseline health status than is possible in many epidemiologic studies.

The questionnaire also featured items on health habits, including current smoking status and smoking history and whether the participant was currently dieting to lose weight or following any other special dietary plan. Physical activity pattern was ascertained by self-report on the questionnaire. An extensive list of leisure-time physical activities was presented, and participants indicated activities in which they had participated in the 3 months before the examination. In later study years, they gave additional details on the number of times per week and the duration of exercise sessions.

Laboratory Evaluations

Cardiorespiratory fitness was assessed by using a maximal exercise test that followed a modified version of Balke and Ware's protocol (18). Briefly, the test began with the participant walking on a horizontal treadmill at 88 m/min. After the first minute, the elevation increased to 2%, and it further 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 increased to 5.4 m/min until the participant reached volitional fatigue. Exercise test performance with this protocol correlates highly with measured maximal oxygen uptake ($r = 0.92$) (19).

Serum samples were analyzed by using automated techniques in a laboratory that participates in and meets the quality control standards of the Centers for Disease Control and Prevention Lipid Standardization Program. Blood pressure was measured by auscultatory methods with a mercury sphygmomanometer according to American Heart Association guidelines (20). The lowest of three blood pressure measurements at the clinic examination was recorded as the baseline blood pressure. Height and weight were measured by using a standard beam-balance scale and stadiometer, and body mass index was calculated.

Type 2 Diabetes

Diabetes was defined according to criteria of the American Diabetes Association: fasting plasma glucose level of 7.0 mmol/L or greater (≥126 mg/dL) (21). Three hundred seventy patients who did not meet this criterion but who gave a history of physician-diagnosed diabetes were considered to have diabetes. Patients were classified as having known diabetes or unknown diabetes according to their diabetes status before the baseline Cooper Clinic examination.

Definition of Exposure Variables

The principal exposure variables used in our analyses were cardiorespiratory fitness and self-reported physical activity. These exposures were determined at the baseline examination.

Cardiorespiratory Fitness

We categorized total time from the maximal exercise test into frequency distributions for specific age groups (30 to 39, 40 to 49, 50 to 59, and ≥60 years). The least fit 20% of the participants in each age group were classified as low fit, the next 40% of the distribution as moderately fit, and the highest 40% as high fit. We have used these cut-points to define fitness in previous studies (12, 13), and they are based on our entire cohort rather than on diabetic patients only. We selected these cut-points before undertaking the current analysis. Cardiorespiratory fitness is expressed as maximal metabolic units (METs) attained during the exercise test. The METs are calculated as the working metabolic rate divided by the resting metabolic rate, and 1 MET is equivalent to an oxygen uptake of $3.5 \cdot mL^{-1} \cdot kg^{-1}$.

Physical Activity

Patients who reported walking, jogging, or participating in aerobic exercise programs in the 3 months before the examination were classified as active, regardless of the frequency and duration of exercise. Otherwise, patients were classified as inactive. In our cohort, more than 76% of men who reported being active at baseline still reported being active at the second visit after more than 1 year. In comparison, only 34% of men who reported being inactive at baseline reported being active at the second examination ($P < 0.001$). Self-reported physical activity status in our cohort is correlated with maximal exercise test performance (6, 22).

Baseline or Parental Cardiovascular Disease

We defined baseline cardiovascular disease as a personal history of heart attack, stroke, or a revascularization procedure; an abnormal resting or exercise electrocardiogram; or the highest heart rate during exercise testing that was less than 85% of the age-predicted maximal heart rate ([220 − age in years] × 0.85). Men who reported a history of cardiovascular disease in either parent were classified as having parental cardiovascular disease.

Conventional Cardiovascular Disease Risk Factors

We assigned men to risk strata for conventional cardiovascular disease risk factors on the basis of recent recommendations (23). We defined high blood pressure as systolic blood pressure of 140 mm Hg or more, diastolic blood pressure of 90 mm Hg or more, or a history of physician-diagnosed hypertension. We classified participants with a total cholesterol level of 6.2 mmol/L (240 mg/dL) or more as having high cholesterol, those with self-reported current smoking as current smokers, those with a self-reported parental history of myocardial infarction or stroke as having a history of parental cardiovascular disease, those with a body mass index less than 25.0 kg/m^2 as normal weight, and those with a body mass index of 25.0 kg/m^2 or more as overweight.

Statistical Analysis

Our primary outcome measure was all-cause mortality. We used the National Death Index to identify decedents in the ACLS. The National Death Index has been shown to be an effective, accurate means of ascertaining deaths in the general population, with a sensitivity of about 96% and a specificity of 100% (24). We obtained official death certificates from states in which there were ACLS decedents, and we had the certificates coded by a nosologist according to the *International Classification of Diseases, Ninth Revision*. Only the underlying cause of death was used in analyses for this report.

Data were analyzed by using the SAS statistical package (SAS Institute, Inc., Cary, North Carolina). The analyses assumed that physical activity and fitness were essentially unchanged during the study period. We used survival curves to estimate survival function against time and log [−log (survival time)] to check the proportional hazards model assumption. Log [−log (survival function)] estimates were approximately parallel across exposure groups (low fitness or physical inactivity) and nonexposure groups. Cox proportional hazard models were used to determine the association between mortality and estimated exposures after adjustment for potential confounders (25, 26). Interaction terms between estimated exposures and other independent variables were entered into the initial models to evaluate possible interactions; however, no significant interactions were found. For adjusted relative risks, all results were from models that included all listed variables without interaction terms. All P values provided are for two-sided tests, and P values less than 0.05 were considered statistically significant.

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Results

The study group comprised 1263 men identified at the baseline examination as having type 2 diabetes. We followed these men for an average of 11.7 years; minimum follow-up was 1 year. There were 180 deaths during 14 777 person-years of follow-up. Using our definition of low cardiorespiratory fitness as the least fit 20% of men in our entire cohort, we identified 534 (42%) patients as low fit and 729 (58%) as fit. The prevalence of self-reported physical inactivity was 50% in men with diabetes and 33% in men without diabetes. Baseline characteristics of the study participants by fitness category are presented in **Table 1**. Men in the two fitness groups were similar in age, history of parental cardiovascular disease, prevalence of dieting, and whether they

Table 1. Baseline Characteristics of 1263 Men with Diabetes, according to Cardiorespiratory Fitness Group

Characteristic*	Cardiorespiratory Fitness Level		*P* Value
	Fit	Unfit	
Participants, *n*	729	534	
Mean age, *y*	50.5 ± 10.0	49.9 ± 9.8	>0.2
Mean exercise tolerance, *mEq*	10.9 ± 1.7	8.0 ± 1.3	<0.001
Mean body mass index, *kg/m²*	26.8 ± 0.3	29.9 ± 5.4	<0.001
Mean fasting glucose level, *mmol/L (mg/dL)*	7.5 ± 2.4 (135.1 ± 42.8)	8.6 ± 3.6 (154.7 ± 64.1)	<0.001
Mean total cholesterol level, *mmol/L (mg/dL)*	5.9 ± 1.1 (227.3 ± 41.4)	6.1 ± 1.4 (235.5 ± 54.9)	0.005
Mean uric acid level, *mmol/L*	0.38 ± 0.08	0.39 ± 0.09	0.017
Mean triglyceride level, *mmol/L (mg/dL)*	2.0 ± 1.6 (176.9 ± 141.6)	3.2 ± 5.4 (283.2 ± 477.9)	<0.001
Mean diastolic blood pressure, *mm Hg*	83.4 ± 9.8	85.7 ± 10.7	<0.001
Mean systolic blood pressure, *mm Hg*	127.7 ± 15.8	130.1 ± 16.4	0.008
Mean alcohol consumption, *g/wk*	196.0 ± 319.0	191.1 ± 335.5	>0.2
Current smoker, %	20	32	<0.001
Self-reported activity, %	65	29	<0.001
Known diabetes before evaluation, %	49	48	>0.2
Baseline cardiovascular disease, %	19	37	<0.001
Parental cardiovascular disease, %	37	37	>0.2
On a diet, %†	49	43	>0.2
Non-Hispanic white ethnicity, %‡	93	91	>0.2

* Mean values are expressed with SDs.
† Data were collected starting in 1986; only 389 patients provided data for this variable.
‡ Data were collected starting in 1987; only 207 patients provided data for this variable.

had known diabetes at baseline. Unfit men were more likely than fit men to have baseline cardiovascular disease, smoke cigarettes, and be physically inactive. Unfit men also had relatively high levels of fasting plasma glucose, total cholesterol, uric acid, and triglyceride and high blood pressure.

Survival curves for all-cause mortality by fitness category are presented in the **Figure**. The survival curves began to separate in the first few years of follow-up, and the difference between fitness groups remained over time.

To evaluate the independent association of fitness or activity with mortality in patients with diabetes, relative risks with 95% CIs were adjusted for age and examination year and were stratified by other mortality predictors (**Table 2**). The association between low fitness and mortality was present in men with known or unknown diabetes; men who were normal weight or overweight; and men with or without a parental history of cardiovascular disease, baseline cardiovascular disease, high blood pressure, high cholesterol levels, and current smoking.

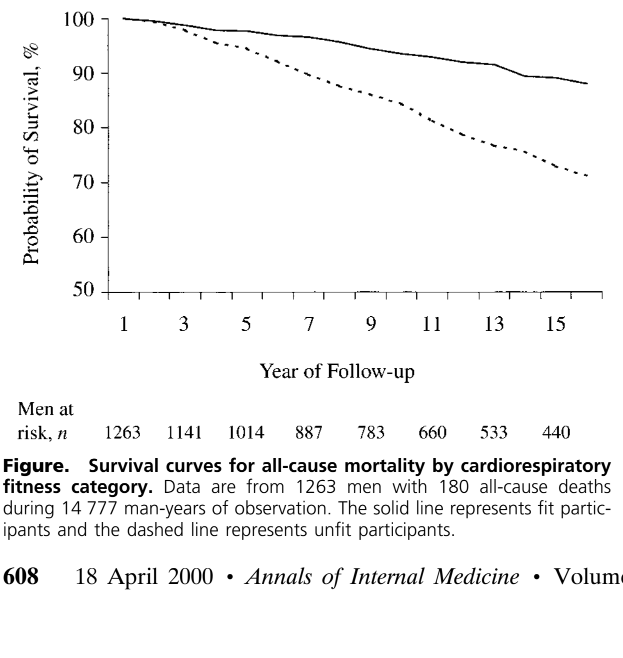

Figure. Survival curves for all-cause mortality by cardiorespiratory fitness category. Data are from 1263 men with 180 all-cause deaths during 14 777 man-years of observation. The solid line represents fit participants and the dashed line represents unfit participants.

Next, we evaluated the association between cardiorespiratory fitness or activity status and mortality in the overall study group (**Table 3**). After adjustment for age, examination year, current smoking, alcohol intake, history of parental cardiovascular disease, baseline cardiovascular disease, high total cholesterol level, high triglyceride level, elevated body mass index, high blood pressure, and baseline fasting glucose level, unfit men had a 2.1-fold (95% CI, 1.5-fold to 2.9-fold) higher risk for death than men who were fit at baseline. Each 1-MET increment of cardiorespiratory fitness was associated with a 25% (CI, 17% to 32%) lower risk for all-cause mortality in multivariate analysis ($P < 0.001$). The results were similar in patients who met fasting plasma glucose level criteria at the baseline examination and those in whom diabetes was diagnosed by a history of diabetes only. We found an excess number of deaths in unfit men with diabetes from the underlying causes of cardiovascular disease, cancer, diabetes, gastric disease, and injury (**Table 4**).

Some men failed to achieve 85% of the age-predicted maximal heart rate during the exercise test. Sometimes this was because they were unable to continue the exercise test to exhaustion. In other cases, the supervising physician may have stopped the exercise test early because of untoward signs or symptoms. Patients in whom the test was terminated early for either of these reasons would have their cardiorespiratory fitness underestimated and would be more likely than other patients to be classified as having low fitness. Both of these situations were probably more likely to occur in men with underlying disease. For this reason, we excluded patients who failed to achieve an appropriate maximal heart rate during the exercise test (127 men with 40 deaths during follow-up) and reanalyzed the data. The results were similar to those obtained in the analysis of the entire study group. After adjustment for age, examination year, baseline cardiovascular disease, high total cholesterol level, high triglyceride level, elevated body mass index, high blood pressure, parental cardiovascular disease, current smoking, and baseline fasting glucose levels, unfit men had a higher risk for death than men who were fit at baseline (odds ratio, 2.2 [CI, 1.6 to 3.2]). Relative risks adjusted for age and examination year that were stratified by other mortality predictors were also similar to the overall results (data not shown).

We examined the association between self-reported physical activity and mortality. A similar pattern was evident in analyses of physical activity, although overall the relative risks for deaths were lower in the activity analyses than in the fitness analyses.

Measurements of high-density lipoprotein cholesterol were added to the clinic examination in 1978, and such measurements were available only for 663 men in the current analyses. In multivariate analysis of the subgroup of men for whom data on high-density lipoprotein cholesterol were available, including both high-density lipoprotein cholesterol and low-density lipoprotein cholesterol data in the model had little effect on the association among low fitness, physical inactivity, and mortality.

Table 2. Association between Low Cardiorespiratory Fitness and Mortality in Various Subgroups, Adjusted for Age and Examination Year

Category	Men	Deaths	Relative Risk (95% CI)*
	n		
Known diabetes status at baseline			
Yes	613	96	2.5 (1.7–3.8)
No	650	84	3.1 (2.0–5.0)
Parental cardiovascular disease			
Yes	468	83	2.0 (1.3–3.1)
No	795	97	3.7 (2.4–5.7)
Baseline cardiovascular disease			
Yes	336	96	2.0 (1.3–3.1)
No	927	84	2.9 (1.9–4.5)
High blood pressure			
Yes	525	96	2.2 (1.5–3.4)
No	738	84	3.5 (2.2–5.6)
Cholesterol level			
≥6.2 mmol/L (≥240 mg/dL)	436	77	3.2 (2.0–5.3)
<6.2 mmol/L (<240 mg/dL)	827	103	2.5 (1.7–3.8)
Body mass index			
≥25 kg/m^2	867	127	2.8 (1.9–4.1)
<25 kg/m^2	396	53	2.9 (1.7–4.9)
Current smoker			
Yes	281	42	1.9 (1.0–3.7)
No	982	138	3.2 (2.2–4.5)

* Relative risk for death in low-fit men compared with fit men in each stratum of the other exposure.

Table 3. All-Cause Mortality by Low Fitness or Inactivity in Men with Type 2 Diabetes

Category	Adjustment	Relative Risk (95% CI)	*P* Value
Low fitness*	Age and examination year	2.9 (2.1–3.6)	<0.001
	Age, examination year, smoking, alcohol intake, and parental cardiovascular disease	2.8 (2.0–3.8)	<0.001
	Age, examination year, and conventional risk factors†	2.1 (1.5–2.9)	<0.001
Inactivity‡	Age and examination year	1.8 (1.3–2.5)	<0.001
	Age, examination year, smoking, alcohol intake, and parental cardiovascular disease	1.8 (1.3–2.5)	<0.001
	Age, examination year, and conventional risk factors†	1.7 (1.2–2.3)	0.002

* Compared with fit men.
† Conventional risk factors were baseline cardiovascular disease, parental cardiovascular disease, high cholesterol level, current smoking, diabetes status, glucose level, alcohol intake, high blood pressure, and overweight. Based on data from 1188 men.
‡ Compared with active men.

Discussion

The main finding in our study of men with type 2 diabetes is that patients who had a low fitness level and were physically inactive had higher mortality rates during follow-up than did men who were active and fit. Our study examined the associations between cardiorespiratory fitness or physical activity and mortality in diabetic patients. The association between low fitness or inactivity and mortality is strong, with adjusted relative risks for death of 2.1 for low fitness and 1.7 for self-reported inactivity. These associations persisted after adjustment for age, parental history of cardiovascular disease, alcohol consumption, cigarette smoking, high cholesterol level, high blood pressure, high glucose level, overweight, and baseline cardiovascular disease (**Table 3**).

Physical activity is typically recommended to improve risk factor profiles for patients with type 2 diabetes (1). Physical activity may contribute to weight loss; glycemic control; and improvement of insulin sensitivity, blood pressure, and lipid profile (1, 4, 27–31). The possible effect of physical activity on reducing the risk for death in diabetic patients may be mediated, at least in part, by some of these mechanisms, but it also seems to have an independent effect on mortality rates. Our data suggest that the beneficial effect of physical activity for patients with type 2 diabetes extends beyond its effect on intermediate risk factors. For example, some experts consider physical activity as a supplement to weight control. However, one third of the diabetic men reflected in our data, as well as in national data (32), had normal weight. Our study showed that fitness had the same protective effect in normal-weight diabetic men as in overweight diabetic men.

Self-reported physical activity is known to be imprecise and is influenced by several factors. Obese

Table 4. Cause-Specific Mortality in 1188 Men with Diabetes*

ICD-9 Code	Disease	Deaths, *n*	Adjusted Relative Risk (95% CI)†
250	Diabetes	10	7.4 (1.4–39.6)
390–449	Cardiovascular disease	92	2.0 (1.2–3.0)
140–208	Cancer	39	2.4 (1.2–4.8)
520–579	Digestive disease	8	4.7 (0.9–24.9)
800–959	Injury	13	3.3 (1.0–11.7)

* ICD-9 = International Classification of Diseases, Ninth Revision.
† Adjusted for age, examination year, and conventional risk factors (baseline cardiovascular disease, parental cardiovascular disease, high cholesterol level, current smoking, diabetes status, glucose level, alcohol intake, high blood pressure, and overweight). Fit men served as the reference category.

patients tend to overreport their physical activity, leading to misclassification (33). Poorly designed questionnaires and faulty memory are other common problems. These limitations may underestimate the true association between sedentary habits and outcomes. In contrast, cardiorespiratory fitness in our study was measured objectively. Although cardiorespiratory fitness has a genetic component, many studies show that regular physical activity improves cardiorespiratory fitness (1, 22, 28). Patients with diabetes who are in exercise programs have also been reported to experience an increase in cardiorespiratory fitness (28). Using cardiorespiratory fitness to document the dose of habitual physical activity is a better measure of sedentary lifestyle than are self-reported questionnaire data.

Despite the problem of misclassification with self-reported activity, we found that inactive men with diabetes had higher mortality rates than active men with diabetes. However, the association was weaker than when cardiorespiratory fitness was used as the mortality predictor.

In the current study, the risk for death due to diabetes seemed substantially higher in low-fit men than in fit men. Because many deaths attributed to diabetes were due to other underlying causes, the number of deaths due to diabetes was small. However, these data could indicate that low fitness was associated with a worsening metabolic profile. Several investigators have shown that participation in exercise improves glycemic control and insulin resistance (27, 28, 31), which has an important impact on cardiovascular disease (21, 34). We found that low fitness was associated with higher rates of death from cardiovascular disease and cancer in men with diabetes; this finding is consistent with our earlier results in healthy men (35). In addition, we found that fitness was inversely associated with deaths due to digestive diseases and injuries. Cardiorespiratory fitness may not only improve cardiac performance, metabolism, and lipid profiles but also may enhance immune function (1, 36), bone mineral density (37), or other characteristics that lead to lower mortality risk from various causes.

The specific exercise prescription necessary for good health in diabetic patients is unknown. However, the current consensus public health recommendation of 30 minutes of moderate-intensity exercise (for example, a brisk walk) on most days of the week would probably be sufficient to develop or maintain the fitness level that was associated with lower mortality rates in our study (12, 22).

Our study has limitations. Patients taking insulin were excluded because only a small number of our patients were receiving this therapy. Therefore, our focus was on patients with type 2 diabetes who retained at least some capacity for endogenous insulin secretion. Studies have reported that hyperglycemia is associated with mortality (21). We did not have glycosylated hemoglobin data at baseline, but we were able to adjust for fasting plasma glucose level. However, many studies have found that physical activity improves levels of fasting plasma glucose, glycosylated hemoglobin, blood pressure, and serum lipids (1, 4, 27–31); our analyses adjusted for these intermediate risk factors, which may underestimate the true effect of fitness and physical activity on mortality. As with most prospective epidemiologic studies, we used baseline values as predictor variables. Underestimation of risk associations because of regression dilution during follow-up has been documented in these types of studies. Although it is clear that moderate-intensity exercise could be performed by most patients with diabetes, we suggest that patients with type 2 diabetes who plan to begin an exercise program consult their physicians, especially patients with severe metabolic disorders and other complications (1, 7). In addition, our study participants were all men, and more than 92% were white. The population was well educated and of middle to upper socioeconomic status. Results from this population for conventional risk factors of cardiovascular disease and diabetes are consistent with those from other populations (4, 12, 13, 38–40). The homogeneity of our study sample on socioeconomic characteristics may be considered a strength of the study because it reduces the likelihood of confounding by these variables. Nonetheless, whether our results apply to women, members of other ethnic groups, or persons of low socioeconomic status remains to be determined.

Type 2 diabetes is common in many countries and is a major cause of morbidity and death (41). In 1998, treatment of diabetes accounted for 25% of all spending under the U.S. Medicare program (42). Despite medical advances in the treatment of diabetes and extensive use of these therapies, differences in mortality between patients with diabetes and the general population have actually widened in recent decades (43). In the current study, we observed large differences in mortality between physically fit patients and unfit patients. This study does not prove a causal pathway between exercise and mortality; only randomized and controlled clinical trials can provide definitive evidence on this important clinical topic. Nonetheless, our data suggest that patients with diabetes may benefit from a regular physical activity program.

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