

Annals of Internal Medicine

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

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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 $3.5 \cdot \text{mL}^{-1} \cdot \text{kg}^{-1}$) 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, <i>n</i>	1665	3425	3543
Mean age, <i>y</i>	43.9 ± 8.1	43.6 ± 10.9	43.2 ± 8.1
Mean exercise tolerance, <i>metabolic equivalents</i>	9.3 ± 0.9	11.3 ± 0.8	13.7 ± 1.2
Mean body mass index, <i>kg/m²</i>	28.3 ± 3.9	26.4 ± 2.9	25.0 ± 2.3
Mean waist circumference, <i>cm</i> †	99.8 ± 10.5	93.0 ± 16.0	85.6 ± 17.6
Mean total cholesterol level, <i>mmol/L</i>	5.67 ± 1.01	5.54 ± 1.00	5.33 ± 1.18
Mean high-density lipoprotein cholesterol level, <i>mmol/L</i>	1.06 ± 0.27	1.13 ± 0.28	1.27 ± 0.32
Mean triglyceride level, <i>mmol/L</i>	1.92 ± 1.28	1.58 ± 1.13	1.17 ± 0.79
Mean diastolic blood pressure, <i>mm Hg</i>	82.6 ± 9.9	80.7 ± 9.2	78.8 ± 8.7
Mean systolic blood pressure, <i>mm Hg</i>	122.3 ± 13.7	120.0 ± 12.4	119.5 ± 12.8
Mean alcohol use, <i>g/wk</i>	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 m². 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.

Role of the Funding Source

The funding agencies did not participate in the collection, analysis, or interpretation of data presented in this report or in the decision to submit the manuscript for publication.

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, <i>n</i>	1339	2938	3165
Total person-years	7719	18 017	19 238
Participants who developed impaired fasting plasma glucose, <i>n</i>	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, <i>n</i>	1665	3425	3543
Total person-years, <i>n</i>	9752	21 075	21 761
Participants who developed diabetes, <i>n</i>	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)	<i>P</i> Value
Impaired fasting glucose*		
Cardiorespiratory fitness level†		
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 ($P < 0.001$).

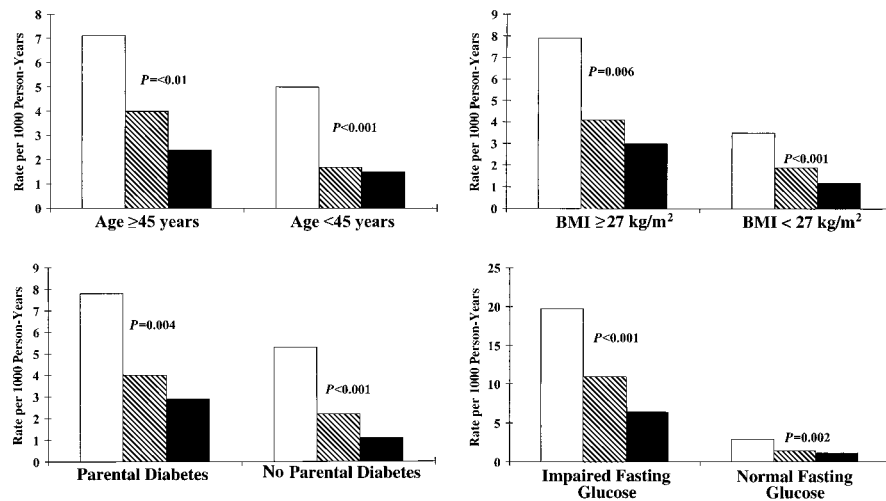


Figure. Incidence of type 2 diabetes per 1000 persons-years by cardiorespiratory fitness levels according to age group (top left), body mass index (BMI) (top right), history of parental diabetes (bottom left), and impaired fasting glucose (bottom right). White bars represent the low-fitness group, striped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

ican 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.

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Acknowledgments: The authors thank the patients, physicians, and technicians at the Cooper Clinic for their participation, Dr. Kenneth H. Cooper for establishing the Aerobics Center Longitudinal Study, Carolyn E. Barlow for data management, and Melba Morrow for editorial assistance.

Grant Support: In part by a grant from the National Institutes of Health National Institute on Aging (AG06945) and by several private contributions.

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