Physical Activity in Relation to Cardiovascular Disease and Total Mortality Among Men With Type 2 Diabetes

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Background—The present study was conducted to examine the relationship of physical activity with risk of cardiovascular disease (CVD) and mortality among men with type 2 diabetes. CVD risk and mortality are increased in type 2 diabetes. Few epidemiological studies have investigated the effect of physical activity on these outcomes among type 2 diabetics.

Methods and Results—Of the 3058 men who reported a diagnosis of diabetes at age 30 years or older in the Health Professionals' Follow-up Study (HPFS), we excluded 255 who reported a physical impairment. In the remaining 2803 men, physical activity was assessed every 2 years; 266 new cases of CVD and 355 deaths of all causes were identified during 14 years of follow-up. Relative risks of CVD and death were estimated from Cox proportional hazards analysis with adjustment for potential confounders. The multivariate relative risks of CVD incidence corresponding to quintiles of total physical activity were 1.0, 0.87, 0.64, 0.72, and 0.67 (P_{trend}=0.07). The corresponding multivariate relative risks for total mortality were 1.0, 0.80, 0.57, 0.58, and 0.58 (P_{trend}=0.005). Walking was associated with reduced risk of total mortality. Relative risks across quintiles of walking were 1.0, 0.97, 0.87, 0.97, and 0.57 (P_{trend}=0.002). Walking pace was inversely associated with CVD, fatal CVD, and total mortality independently of walking hours.

Conclusions—Physical activity was associated with reduced risk of CVD, cardiovascular death, and total mortality in men with type 2 diabetes. Walking and walking pace were associated with reduced total mortality. **(*Circulation*. 2003;107: 2435-2439.)**

Key Words: diabetes mellitus ■ exercise ■ heart disease

The incidence of type 2 diabetes has increased in recent decades, and it currently affects ≈8% of adults in the United States.[1] Mortality among individuals with type 2 diabetes is substantially elevated compared with nondiabetics,[2] with heart disease contributing to ≈75% of diabetic deaths.

See p 2392

The inverse association of physical activity with cardiovascular disease (CVD) and mortality in the general population is well established. High levels of physical activity are associated with substantial reductions in CVD risk,[3] and total mortality decreases by 20% to 30% for every 1000 kcal/wk of energy expenditure.[4] Clinical data show that exercise improves lipoprotein profile and reduces blood glucose in diabetic patients,[5] but data on its association with cardiovascular events and death are sparse.

In this study, we examined the relationships between levels of total physical activity and CVD and mortality among men with type 2 diabetes in the Health Professionals' Follow-up Study (HPFS). Additionally, we assessed the association of walking and walking pace with these outcomes.

Methods

The HPFS is a prospective cohort study of 51 529 male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists) aged 40 to 75 years in 1986 and living in all 50 US states. The present study included 2803 men who reported a physician's diagnosis of diabetes mellitus at the age of 30 years or older on any questionnaire from 1986 through 1998. Men who reported a diagnosis of diabetes were mailed a supplementary questionnaire that inquired about prediagnostic symptoms, clinical testing leading to diagnosis, and current treatment regimen. Cases were considered confirmed if any of the following criteria were met: 1 or more classic symptoms plus a raised fasting (≥7.8 mmol/L) or random (≥11.1 mmol/L) plasma glucose concentration; at least 2 raised plasma glucose concentrations on separate occasions (fasting, ≥7.8 mmol/L, or random, ≥11.1 mmol/L or 11.1 mmol/L after ≥2 hours on glucose tolerance testing) in the absence of symptoms; or treatment with a hypoglycemic drug (insulin or oral hypoglycemic agent). Because most cases of diabetes for the present analysis were diagnosed before 1997, we used the diagnostic criteria in place for that time period (National Diabetes Data Group [NDDG][6]) and not the more recent classifications.[7] Validity of self-reported diabetes was verified in a subsample of 71 men from the HPFS cohort. Of these, 12 had incomplete records, whereas the diagnosis of type 2 diabetes was confirmed in 57 (97%) of the remaining 59. A secondary set of analyses included only men with "definite" type 2 diabetes mellitus according to NDDG criteria.

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Assessment of Physical Activity

Leisure-time physical activity was assessed every 2 years between 1986 and 1998. The question was formulated as, "During the past year, what was your average time per week spent at each activity?" The average weekly time spent on walking or hiking outdoors; jogging (slower than 10 min/mile); running (10 min/mile or faster); bicycling; lap swimming; tennis, squash, or racquetball; calisthenics; or rowing was recorded beginning in 1986. Heavy outdoor work was added in 1988 and weightlifting in 1990. Walking pace, categorized as casual (≤2 mph), normal (2 to 2.9 mph), brisk (3 to 3.9 mph), or striding (≥4 mph), was also recorded. The time spent at each activity in hours per week was multiplied by its typical energy expenditure, expressed in metabolic equivalents (METS),[8] then summed over all activities to yield a MET-hour score. One MET, the energy expended by sitting quietly, is equivalent to 3.5 mL of oxygen uptake per kilogram of body weight per minute or 1 kcal per kilogram of body weight per hour.

The validity and reproducibility of the physical activity questionnaire were assessed in 1991 when 238 participants in the HPFS completed a 1-week activity diary at 4 time periods corresponding to different seasons throughout a year. The correlations between scores of physical activity from the diaries and from the questionnaire were 0.65 for total physical activity, 0.28 for nonvigorous activity, and 0.58 for vigorous activity. The correlation between questionnaire-derived vigorous activity and resting pulse was −0.45; for pulse after a self-administered step test, the correlation was −0.41.[9] In a subsample of participants in the HPFS (n=466), HDL cholesterol increased by 0.06 mmol/L (2.4 mg/dL) for each increment of 20 MET-hours/week ($P<0.01$).[10]

End Points

CVD end points consisted of fatal stroke, nonfatal stroke, fatal coronary heart disease, and nonfatal myocardial infarctions (MIs). Self-reported MIs were confirmed by review of medical records if they met World Health Organization criteria (characteristic symptoms with either typical ECG changes or elevations of cardiac enzymes). Stroke was confirmed by medical records by the criteria of the National Survey of Stroke[11] when a sum of neurological deficits with sudden or rapid onset that lasted ≥24 hours was present. Stroke events were categorized as hemorrhagic, ischemic, or of unknown cause. Physicians who reviewed the records had no knowledge of the self-reported risk factor status. Deaths were reported by next of kin, work associates, and postal authorities. In case of persistent nonresponse, the National Death Index was used to identify deceased cohort members. Cardiovascular deaths (fatal MI, fatal stroke, and coronary disease) were confirmed by review of medical records or autopsy reports with the permission of the next of kin. The cause listed on the death certificate was not sufficient alone to confirm a coronary death or a stroke. Sudden deaths (ie, death within 1 hour of symptom onset in a man without known disease that could explain death) were included in the fatal coronary heart disease category.

Data Analysis

For the analysis of CVD, person-months of follow-up accumulated starting with the date of first diabetes report until the occurrence of a cardiovascular event, death, or end of the study period, whichever came first. For the analysis of mortality, follow-up ended with occurrence of death or the end of the study period (January 31, 2000), whichever came first. We excluded men with prior diagnosis of MI, angina, coronary revascularization, transient cerebral ischemia, intermittent claudication, stroke, or cancer and those who reported difficulty in climbing stairs or walking.

We used the cumulative average of physical activity levels from all available questionnaires up to the start of each 2-year follow-up interval.[12] For example, the level of physical activity reported on the 1986 questionnaire was related to the occurrence of events from 1986 through 1988, and the level of average activity reported on the 1986 and 1988 questionnaires was related to events from 1988 through 1990.

TABLE 1. Distribution of Characteristics According to Physical Activity Levels Among Men With Type 2 Diabetes in 1986

	Quintiles of Physical Activity				
	1	2	3	4	5
Median physical activity, MET-hours/week	0.7	3.4	7.9	17.6	39.0
BMI, kg/m^2	27	27	27	26	25
Current smoker, %	19	10	12	11	4
Hypertension, %	50	51	45	43	40
High cholesterol, %	24	17	19	18	14
Family history of MI, %	9	9	11	13	19
Vitamin E supplement use, %	20	18	21	21	20
Total fat intake, % total kcal	35	34	33	33	32
Saturated fat intake, % total kcal	12	12	11	11	11
Dietary fiber, g/d	20	22	22	23	25
Alcohol, g/d	8	10	9	9	9
Insulin medication, %*	34	27	40	38	39

*Among definite cases according to NDDG criteria.

Participants were divided into quintiles of total volume of physical activity and walking. Tests for trend were calculated by assigning the median values to increasing categories of activity. Relative risks (RRs) were initially calculated with adjustments for age. Cox proportional hazard models were then used to estimate RRs over each 2-year follow-up interval with the cumulative average of the reported levels of physical activity on prior questionnaires, with adjustment for other potential confounders.[13,14] Multivariate models included the following covariates: alcohol intake (nondrinker or 0.1 to 4.9, 5 to 30, or >30 g/d); smoking (never-smoker, past smoker, or currently smoking 1 to 14 cigarettes/d, 15 to 24 cigarettes/d, or ≥25 cigarettes/d); family history of MI; use of vitamin E supplements; duration of diabetes (0–4.9, 5–9.9, 10–14.9, or ≥15 years); quintiles of dietary intake of energy-adjusted trans fat, saturated fat, fiber, and folate; baseline presence of hypertension and high serum cholesterol; diabetes medication (oral hypoglycemic drugs and insulin); and history of angina and CABG. In secondary analyses, we additionally controlled for body mass index (BMI; ≤25, 25 to 29.9, or ≥30 kg/m^2) to estimate how this potential intermediate factor would affect the RRs.

Results

We examined physical activity in relation to other potential risk factors for death and CVD (Table 1). Physically more active men tended to have lower BMIs, lower total fat and saturated fat intakes, higher intakes of fiber, and lower prevalence of smoking and hypertension.

During 18 894 person-years of follow-up, we documented 266 cardiovascular events, including 96 that were fatal and 170 that were nonfatal. Higher physical activity level was associated with lower CVD risk in age-adjusted and multivariate analyses (Table 2). The lowest risk was observed for the third quintile (RR 0.64, 95% CI 0.43 to 0.96), with similar RRs in the fourth and fifth quintiles. Adjustment for BMI slightly attenuated the overall RRs. Both fatal and nonfatal events were fewer among men with higher levels of physical activity, but the relationship was stronger for fatal events.

Walking was inversely associated with CVD, this association being marginally significant in multivariate analyses: 1.0, 1.01, 0.90, 1.07, and 0.66 (95% CI 0.43 to 1.02; $P_{trend}=0.05$). Walking pace was a strong predictor of total and fatal CVD. In multivariate analyses that controlled for CVD

TABLE 2. RRs (95% CIs) for CVD Associated With Physical Activity Among Men With Type 2 Diabetes (1986–2000)

	Total Physical Activity, MET-Hours/Week					
	0–5.1	5.2–12.0	12.1–21.7	21.8–37.1	≥37.2	*P* for Trend
Total CVD						
Cases, n	72	61	44	47	42	
Person-years	3670	3749	3805	3829	3841	
Age adjusted	1	0.86 (0.61, 1.22)	0.63 (0.43, 0.93)	0.71 (0.49, 1.04)	0.61 (0.41, 0.91)	0.02
Multivariate*	1	0.87 (0.61, 1.25)	0.64 (0.43, 0.96)	0.72 (0.49, 1.07)	0.67 (0.44, 1.01)	0.07
Multivariate†	1	0.91 (0.63, 1.31)	0.68 (0.45, 1.02)	0.76 (0.51, 1.14)	0.72 (0.47, 1.09)	0.14
Nonfatal CVD						
Cases, n	36	40	35	32	27	
Age adjusted	1	1.18 (0.74, 1.88)	1.03 (0.63, 1.68)	1.00 (0.61, 1.64)	0.79 (0.46, 1.33)	0.19
Multivariate*	1	1.10 (0.68, 1.77)	1.02 (0.62, 1.69)	0.95 (0.57, 1.58)	0.79 (0.46, 1.36)	0.25
Multivariate†	1	1.11 (0.69, 1.80)	1.04 (0.62, 1.73)	0.97 (0.58, 1.63)	0.82 (0.47, 1.43)	0.30
Fatal CVD						
Cases, n	36	21	9	15	15	
Age adjusted	1	0.55 (0.32, 0.96)	0.26 (0.12, 0.54)	0.44 (0.24, 0.82)	0.45 (0.24, 0.84)	0.03
Multivariate*	1	0.64 (0.36, 1.13)	0.25 (0.12, 0.54)	0.48 (0.25, 0.91)	0.55 (0.28, 1.07)	0.13
Multivariate†	1	0.71 (0.40, 1.28)	0.29 (0.14, 0.63)	0.53 (0.27, 1.02)	0.62 (0.32, 1.23)	0.23

*Adjusted for alcohol intake (nondrinker, 0.1–4.9, 5–30, >30 g/d); smoking (never-smoker, past smoker, currently smoking 1–14 cigarettes/day, 15–24 cigarettes/day, ≥25 cigarettes/day); family history of MI; use of vitamin E supplements; duration of diabetes (0–4.9, 5–9.9, 10–14.9, ≥15 years); diabetes medication; quintiles of dietary intake of trans fat, saturated fat, fiber, and folate; history of angina and CABG; and baseline presence of hypertension and high serum cholesterol.

†Additionally adjusted for BMI.

risk factors, walking time, and vigorous activity, the RRs for CVD corresponding to normal pace (2 to 2.9 mph), brisk pace (3 to 3.9 mph), and very brisk pace (≥4 mph) were 0.82, 0.58, and 0.17 (95% CI 0.04 to 0.71; $P_{trend}<0.001$) compared with easy pace (<2 mph).

Physical activity was inversely associated with mortality in age-adjusted and multivariate analyses. RRs were slightly attenuated by additional adjustment for BMI (Table 3).

To address the possibility that men with severe disease reduced their amount of exercise, thereby biasing our results,

TABLE 3. RRs (95% CIs) for Total Mortality Associated With Total Physical Activity and With Walking Among Men With Type 2 Diabetes (1986–2000)

	Quintiles, MET-Hours/Week					
	1	2	3	4	5	*P* for Trend
Total physical activity, MET-hours/week	0–5.1	5.2–12.0	12.1–21.7	21.8–37.1	≥37.2	
Cases, n	96	81	57	61	60	
Person-years	3954	4116	4145	4174	4188	
Age adjusted	1	0.73 (0.54, 0.99)	0.50 (0.36, 0.70)	0.51 (0.37, 0.71)	0.49 (0.35, 0.69)	<0.001
Multivariate*	1	0.80 (0.58, 1.08)	0.57 (0.40, 0.80)	0.58 (0.41, 0.82)	0.58 (0.41, 0.83)	0.005
Multivariate†	1	0.88 (0.64, 1.21)	0.64 (0.45, 0.91)	0.64 (0.45, 0.90)	0.65 (0.45, 0.93)	0.01
Walking, MET-hours/week	0–1.4	1.5–4.1	4.2–7.9	8–16.0	≥16.1	
Cases, n	73	78	71	82	51	
Person-years	3955	4461	4001	4069	4090	
Age adjusted	1	0.91 (0.66, 1.26)	0.79 (0.56, 1.10)	0.80 (0.58, 1.11)	0.49 (0.34, 0.70)	<0.001
Multivariate*‡	1	0.97 (0.69, 1.35)	0.87 (0.61, 1.22)	0.97 (0.69, 1.37)	0.57 (0.39, 0.83)	0.002
Multivariate†‡	1	0.99 (0.71, 1.40)	0.96 (0.68, 1.36)	1.08 (0.76, 1.53)	0.60 (0.41, 0.88)	0.004

*Adjusted for alcohol intake (nondrinker, 0.1–4.9, 5–30, >30 g/d); smoking (never-smoker, past smoker, currently smoking 1–14 cigarettes/day, 15–24 cigarettes/day, ≥25 cigarettes/day); family history of MI; use of vitamin E supplements; duration of diabetes (0–4.9, 5–9.9, 10–14.9, ≥15 years); diabetes medication; quintiles of dietary intake of trans fat, saturated fat, fiber, and folate; history of angina and CABG; and baseline presence of hypertension and high serum cholesterol.

†Additionally adjusted for BMI.

‡Additionally adjusted for vigorous activity.

we excluded 422 men (61 cases) who reduced their levels of activity by >20 MET-hours/week from one questionnaire to the next. The RRs across quintiles of physical activity, adjusted for the same covariates, were 1.0, 0.85, 0.66, 0.56, and 0.62 (95% CI 0.42 to 0.92; $P_{trend}=0.01$). When analyses were performed with simple updated physical activity, physical activity was inversely associated with CVD risk and mortality. The inverse association was also observed in analyses restricted to men with definite type 2 diabetes mellitus according to NDDG criteria.

We further assessed the effect of walking on mortality. Total walking volume was associated with a reduced mortality rate in age-adjusted and multivariate analyses (Table 3). Walking pace was inversely associated with risk of all-cause mortality independently of walking hours. When analyzed in the same multivariate model with walking hours, the RRs corresponding to normal, brisk, and very brisk pace were 0.59, 0.62, and 0.42 (95% CI 0.19 to 0.97; $P_{trend}=0.07$) compared with walking at easy pace.

Discussion

Physical activity was associated with a lower risk of CVD and total mortality in men with type 2 diabetes. Walking was inversely associated with total mortality, and faster walking pace was inversely associated with CVD and total mortality independently of the time spent walking. These inverse associations were not explained by other CVD risk factors.

The prospective design of the present study eliminated selection or recall bias, which could occur in case-control studies. Also, having measured physical activity and covariates repeatedly during follow-up, we incorporated lifestyle changes into the analysis. Other strengths of the present study include the long follow-up, the relative homogeneity of socioeconomic status among subjects, and the detailed information on walking, walking pace, and potential confounders. Men with cancer at baseline, with previous CVD, and with physical impairment were excluded from analyses. These exclusions are likely to have minimized potential reverse causality. We were also able to control for severity of diabetes by adjusting for duration of diabetes and use of oral hypoglycemic drugs. Furthermore, when we excluded men who greatly reduced their levels of physical activity in the previous 2 years, we obtained similar results.

One limitation of the present study was self-report of physical activity. Even though our questionnaire was validated against diary and biomarker values, some misclassification is inevitable. Any misclassification is likely to be random and to bias results toward the null. As an indirect measure of validity, previously we have reported that physical activity assessed by these same questions in the HPFS is associated with a reduced risk of gallstones, diabetes, and prostate cancer.[15–17] The results did not change in analyses restricted to men with definite type 2 diabetes mellitus according to NDDG criteria, which suggests the validity of self-reported diabetes in this cohort.

We found that physical activity was a strong predictor of fatal CVD events, but the relationship with nonfatal events was nonsignificant. This difference may reflect a true effect of physical activity on case fatality. Previously, in a study of 7735 men from the British regional heart study, physical activity was the strongest behavioral factor associated with case fatality of first-occurrence MI.[18] On the other hand, the difference may reflect residual confounding in the assessment of nonfatal events.

Even though exercise is considered a cornerstone in the treatment of diabetes, only 3 cohort studies have previously investigated its relationship with CVD risk and mortality in diabetic patients. Two of these used crude measures of activity. In a sample of 492 diabetic men and women from the National Health and Nutrition Examination Survey followed up for 2 years, Ford and DeStefano[19] found that inactivity in nonleisure time was significantly associated with coronary heart disease death. In that study, activity was assessed through self-rating on leisure-type activity and non–leisure-type activity. In a sample of 1263 diabetic men followed up for 12 years in the Aerobics Center Longitudinal Study, participants who reported being physically inactive had an adjusted risk for mortality of 1.7 (95% CI 1.2 to 2.3) compared with those reporting being physically active.[20] In the same study, the low-fitness group had a multivariate adjusted risk for all-cause mortality of 2.1 (95% CI 1.5 to 2.9) compared with the fit group.

In a study of 5125 diabetic women in the Nurses' Health Study, using a similar set of questions to those in the present analysis, Hu et al[21] found a 45% reduction in CVD risk with moderate to vigorous activity in the highest quintile. Among women who did not exercise vigorously, the multivariate RRs for CVD across quartiles of MET-hours of walking were 1.0, 0.85, 0.63, and 0.56 ($P=0.03$ for trend). Also, faster usual walking pace was independently associated with lower risk.

Exercise intervention studies show that physical activity can improve insulin sensitivity, glycemic control, and lipoprotein profile among individuals with type 2 diabetes. Most metabolic studies find a significant effect of exercise on glucose control[22–24] and on triglycerides.[25,26] A meta-analysis of clinical trials on the effect of exercise on glucose control found that interventions longer than 8 weeks reduced HbA1c from 8.31% to 7.65% (weighted mean difference 0.66%, $P<0.001$) independently of body mass. This effect is clinically important and is likely to reduce diabetic complications in a significant manner.[5]

The mechanisms responsible for the effect of exercise include both non–insulin-mediated and insulin-mediated glucose disposal.[27,28] Similarly to insulin, a single bout of exercise increases the rate of glucose uptake into the skeletal muscles, the process being regulated by the translocation of GLUT4 glucose transporters to the plasma membrane and transverse tubules. Also, exercise and training increase insulin-stimulated glucose uptake. Other mechanisms that are likely to explain the effect of physical activity on cardiovascular risk are direct action on the heart (increased myocardial oxygen supply, improved myocardial contraction, and electrical stability), increased HDL cholesterol, decreased LDL cholesterol, lowered blood pressure at rest, and decreased blood coagulability.[29] Moderate-intensity activities like brisk walking can also be associated with improvements in lipoprotein profile[30] and glucose control.[3]

When we compared rates of CVD in men with type 2 diabetes with the rates of CVD in nondiabetic men in the HPFS within each level of activity, the age-adjusted CVD risk was approximately 2.7 to 3.9 times higher in type 2 diabetics. In multivariate analyses among nondiabetic men, physical activity was associated with a CVD risk reduction of up to 18% in a dose-response manner (data not shown). Among men with type 2 diabetes, we found a maximum risk reduction for both CVD and mortality in the third quintile of total physical activity (12 to 21.7 MET-hours/week, which corresponds to ≈3 to 5 hours of brisk walking, 2 to 3 hours of jogging, or 1 to 2 hours of running), which indicates an L-shaped relationship. The L shape may be an artifact caused by the relatively smaller number of cases among men with type 2 diabetes or may suggest a more important effect of moderate activity in this group. Thus, exercise levels that are safe for the diabetic patient and are easily attainable may be enough to achieve clinically important risk reductions. Some diabetic complications limit activity levels or prohibit certain types of activity. For example, prolonged walking and step exercises should be avoided in overt peripheral neuropathy, high-intensity activity is contraindicated in overt nephropathy, and weightlifting or high-impact aerobics are contraindicated in retinopathy. Hence, early initiation of a moderate exercise program may be the best strategy for reducing risk of later macrovascular complications. Nonetheless, at any time in the progression of diabetes, moderate exercise is likely to reduce the occurrence of CVD and death.

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