Physical Activity, Cardiovascular Risk Factors, and Mortality Among Finnish Adults With Diabetes

GANG HU, MD, PHD[1,2]
PEKKA JOUSILAHTI, MD, PHD[1,2]
NOËL C. BARENGO, MD, MPH[3]
QING QIAO, MD, PHD[1,2]
TIMO A. LAKKA, MD, PHD[4,5]
JAAKKO TUOMILEHTO, MD, PHD[1,2]

OBJECTIVE — The aim of this study was to examine both single and joint associations of physical activity and conventional cardiovascular risk factors with total and cardiovascular mortality among patients with diabetes.

RESEARCH DESIGN AND METHODS — We prospectively followed 3,708 Finnish patients with type 2 diabetes aged 25–74 years. Physical activity, smoking status, blood pressure, height, weight, and serum cholesterol level were determined at baseline. Cox proportional hazard models were used to estimate single and joint effects of physical activity and other cardiovascular risk factors on the risk of mortality.

RESULTS — During a mean follow-up of 18.7 years, 1,423 deaths were recorded, 906 of which were due to cardiovascular disease. Moderate or high levels of physical activity were associated with decreased total and cardiovascular mortality, whereas higher levels of BMI and blood pressure and current smoking were associated with increased total and cardiovascular mortality. High serum cholesterol levels also increased cardiovascular mortality. The protective effect of physical activity was consistent in diabetic patients with any levels of BMI, blood pressure, total cholesterol, and smoking.

CONCLUSIONS — A moderate or high level of physical activity was associated with a reduced risk of total and cardiovascular mortality among patients with type 2 diabetes. The favorable association of physical activity with longevity was observed regardless of the levels of BMI, blood pressure, total cholesterol, and smoking.

Diabetes Care 28:799–805, 2005

Type 2 diabetes is one of the fastest growing public health problems in both developed and developing countries. It is estimated that the number of diabetic people in the world will double from 171 million in 2000 to 366 million in 2030 (1). Cardiovascular disease (CVD) accounts for >75% of total mortality among patients with type 2 diabetes (2). Obesity, hypertension, and dyslipidemia not only are very common in patients with diabetes but also exacerbate all of the vascular complications of diabetes (3–7).

From the [1]Department of Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland; the [2]Department of Public Health, University of Helsinki, Helsinki, Finland; the [3]Department of Public Health and General Practice, University of Kuopio, Kuopio, Finland; the [4]Department of Physiology, University of Kuopio, Kuopio, Finland; and the [5]Kuopio Research Institute of Exercise Medicine, Kuopio, Finland.

Address correspondence and reprint requests to Dr. Gang Hu, Diabetes and Genetic Epidemiology Unit, Department of Epidemiology and Health Promotion, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki, Finland. E-mail: hu.gang@ktl.fi.

Received for publication 27 September 2004 and accepted in revised form 31 December 2004.

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Several studies have indicated that high leisure-time physical activity is associated with reduced total and CVD mortality among patients with diabetes or impaired glucose tolerance (8–13). However, no previous studies have examined the joint association of physical activity and all conventional CVD risk factors, including obesity, blood pressure, serum cholesterol level, and smoking, with CVD or total mortality among patients with diabetes. The aim of this study was to examine both single and joint associations of physical activity, BMI, blood pressure, serum total cholesterol level, and smoking with total and CVD mortality among Finnish patients with type 2 diabetes participating in population-based surveys.

RESEARCH DESIGN AND METHODS

Six independent cross-sectional population surveys were performed in the Kuopio and North Karelia provinces in eastern Finland in 1972, 1977, 1982, 1987, 1992, and 1997 (14). The survey was expanded to the Turku-Loimaa region in southwestern Finland in 1982, the Helsinki capital area in 1992, and the northern province of Oulu in 1997. In 1972 and 1977, a randomly selected sample (6.6%) of the population born between 1913 and 1947 was drawn. Since 1982, the sample was stratified by area, sex, and 10-year age-group according to the World Health Organization MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) protocol (15). In the six surveys, the subjects included were 25–64 years of age, and in the 1997 survey, subjects between 65 and 74 years of age were also included. Subjects who participated in more than one survey were included only in the first survey cohort. The total sample size of the six surveys was 53,166. The participation rate varied by year from 74 to 88% (14). These surveys were conducted according to the ethical rules of the National Public Health Institute, and the investigations were carried out in accordance with the Declaration of Helsinki.

Patients who participated in any of

the risk factor surveys and also reported having diabetes on the questionnaire at the baseline survey, who had had a hospital discharge diagnosis of diabetes between 1968 and 2000, or who were entitled for special reimbursement for antidiabetic drugs according to the National Social Insurance Institution's Drug Register between 1964 and 2000 were considered as diabetic patients and were included in the present analysis. The National Hospital Discharge Register and Drug Register data were linked to the risk factor survey data with the unique identification numbers assigned to every resident of Finland. The Hospital Discharge Register has reported the codes for type 1 and type 2 diabetes separately since 1987. Antidiabetic drugs prescribed by a physician are free of charge in Finland and are subject to approval of the Social Insurance Institution based on a review of each case history. The physician confirms the diagnosis of diabetes applying the World Health Organization criteria: one or more classic symptoms plus fasting plasma glucose level ≥7.8 mmol/l (≥7.0 mmol/l from 1998) or result of oral glucose tolerance test ≥11.1 mmol/l; at least one increased plasma glucose concentration on a fasting plasma glucose level ≥7.8 mmol/l (≥7.0 mmol/l from 1998) or result of oral glucose tolerance test ≥11.1 mmol/l in the absence of symptoms; or treatment with a hypoglycemic drug (oral antidiabetic agents or insulin) (16,17). All approvals of patients receiving free-of-charge medication are entered into a register maintained by the Social Insurance Institution.

A total of 3,931 individuals were recognized as having diabetes. Of these, 106 subjects were excluded because they had type 1 diabetes, and 117 subjects were excluded because of incomplete data on physical activity, BMI, smoking, blood pressure, or serum cholesterol level. Therefore, 3,708 participants were included in the present study. To avoid the potential bias due to low physical activity associated with severe disease at baseline, subgroup analyses were performed after exclusion of 770 subjects who had been diagnosed with coronary heart disease (CHD), stroke, or heart failure before the baseline survey, who may have been physically inactive because of severe disease or disability at baseline, or who died during the first 2 years of follow-up.

Assessment of physical activity

Occupational, commuting, and leisure-time physical activity was assessed using a self-administered questionnaire at baseline that was mailed to the participants in advance. A detailed description of the questions is presented elsewhere (13,18–23), and these questions were similar to those used and validated in the "Seven Countries Study" (24). The subjects reported their occupational physical activity according to the following categories: *1*) light = physically very easy, sitting office work, e.g., secretarial work; *2*) moderate = work including standing and walking, e.g., store assistant, light industrial work; *3*) active = work including walking and lifting, or heavy manual labor, e.g., industrial work, farm work. The daily commuting return journey was categorized into three categories: *1*) using motorized transportation, or no work (0 min of walking or cycling); *2*) walking or bicycling 1–29 min; *3*) walking or bicycling >30 min. Self-reported leisure-time physical activity was classified into three categories: *1*) low = almost completely inactive, e.g., reading, watching television, or doing some minor physical activity but not of moderate or high level; *2*) moderate = some physical activity >4 h per week, e.g., walking, cycling, light gardening, but excluding travel to work; *3*) high = vigorous physical activity >3 h per week, e.g., running, jogging, skiing, swimming, and heavy gardening. Because our group has found that moderate and high occupational, commuting (≥1 min), or leisure-time physical activity independently and significantly reduces risk of total and CVD mortality among diabetic patients (13), physical activities were merged and regrouped into three categories: *1*) low was defined as subjects who reported light levels of occupational, commuting (<1 min), and leisure-time physical activity; *2*) moderate was defined as subjects who reported only one of the all three types of moderate to high physical activity; and *3*) high was defined as subjects who reported two or three types of moderate to high physical activity.

Other assessments

Smoking, education, and medical history were also assessed using the self-administered questionnaire at baseline. Based on the responses, the participants were classified as never, former, and current smokers. Length of education was used as an indicator for socioeconomic status. At the study site, specially trained research nurses checked that the questionnaire was fully completed and measured blood pressure, height, and weight using a standardized protocol (15). Blood pressure was measured after 5 min of rest using a standard mercury manometer. Height was measured without shoes. Weight was measured with light clothing. BMI was calculated as weight in kilograms divided by the square of the height in meters. After measurement of blood pressure, a venous blood specimen was collected. Serum total cholesterol level was measured using the Lieberman-Burchard method in 1972 and 1977 and using an enzymatic method (CHOD-PAP; Boehringer Mannheim, Mannheim, Germany) since 1982. The enzymatic assay method gave 2.4% lower values than the Lieberman-Burchard method. The cholesterol values from 1972 and 1977 were corrected by this percentage. All samples were analyzed in the same laboratory at the National Public Health Institute.

Prospective follow-up

The study cohorts were followed until the end of 2001 through computerized register linkage. Mortality data were obtained from Statistics Finland and were linked with the survey data using the personal identification number assigned for every resident in Finland. The International Classification of Diseases, 8th, 9th, and 10th revisions, were used for coding the causes of death. CVD was defined with codes 390–459 for the 8th or 9th revisions and I00–I99 for the 10th revision.

Statistical analysis

The statistical software package SPSS for Windows (version 11.5; SPSS, Chicago, IL) was used for statistical analysis. The Cox proportional hazards model was used to estimate single and joint effects of different levels of physical activity and other risk factors at baseline with the risk of mortality. The results were reported as hazard ratios (HRs) and 95% CIs for mortality. The subjects were classified according to smoking status (never, former, or current) and physical activity (low, moderate, or high) as well as according to the sex-specific tertiles of BMI, diastolic blood pressure, systolic blood pressure, and total cholesterol level. The prospective analyses were performed using dummy variables adjusted for the follow-

Table 1—*Baseline characteristics and age-standardized total and cardiovascular mortality rate according to physical activity levels among Finnish participants with type 2 diabetes*

	Physical activity			
	Low	Moderate	High	*P*
n	709	1,247	1,752	
Age (years)	54.3 ± 9.2	51.8 ± 10.2	47.7 ± 9.9	<0.001
BMI (kg/m^2)	31.2 ± 6.0	29.8 ± 5.0	29.4 ± 4.8	<0.001
Systolic blood pressure (mmHg)	155 ± 25	155 ± 25	153 ± 23	0.048
Diastolic blood pressure (mmHg)	93 ± 14	93 ± 14	92 ± 13	0.179
Total cholesterol (mmol/l)	6.6 ± 1.5	6.5 ± 1.3	6.5 ± 1.3	0.688
Education (year)	6.9 ± 3.2	7.6 ± 3.6	7.7 ± 3.3	<0.001
Current smoking (%)	31.8	28.5	25.1	0.002
Numbers of deaths				
Total	399	472	552	
CVD	264	304	338	
Person-years	10,940	21,437	36,781	
Mortality rate/10,000 person-years*				
Total	294	179	156	
CVD	187	96	91	

Data are means ± SD unless otherwise indicated and are adjusted for age, sex, and study year. Age-standardized mortality rate was calculated using a European standard population by 10-year age intervals.

ing covariates: age, sex, study year, education, BMI, systolic blood pressure, total cholesterol level, and smoking at baseline. Because the interactions between sex and each level of physical activity, BMI, blood pressure, cholesterol, and smoking on mortality were not statistically significant, men and women were combined in the analyses. The χ^2 log-likelihood ratio test was used to compare relative abilities of the different levels of physical activity on the risk of mortality.

RESULTS — During the average follow-up of 18.7 years, 1,423 deaths were recorded; of these, 906 were coded as CVD, 605 were coded as CHD, and 202 were coded as stroke. The general characteristics of the study population at baseline are presented in Table 1. In general, physically active diabetic patients were younger, had significantly lower BMI and systolic blood pressure, and were less often smokers compared with the inactive patients. Approximately 45% of the diabetic patients were obese (BMI ≥30 kg/m^2), 78% had hypertension (diastolic blood pressure ≥90 mmHg and/or systolic blood pressure ≥140 mmHg), and 88% had hypercholesterolemia (cholesterol ≥5.0 mmol/l). The age-standardized total and CVD mortality rates showed a significant decrease from low to moderate physical activity and a small decrease from moderate to high physical activity.

The age-, sex-, and study year–adjusted HRs associated with low, moderate, and high physical activity were 1.00, 0.59 (95% CI 0.52–0.68), and 0.49 (0.43–0.56) for total mortality and 1.00, 0.60 (0.51–0.71), and 0.49 (0.41–0.58) for CVD mortality, respectively (Table 2). The protective effect of physical activity did not appreciably change after further adjustment for education, BMI, systolic blood pressure, cholesterol, and smoking and after additional exclusion of individuals who had been diagnosed with CHD, stroke, or heart failure before the baseline study, who may have been physically inactive because of severe disease or disability at baseline, or who died during the first 2 years of follow-up. The combined measure of occupational, commuting, and leisure-time physical activity was a better predictor of mortality than any one of three types of physical activity alone (data not shown).

The highest tertiles of BMI, diastolic and systolic blood pressure, and current smoking were each significantly associated with an increased risk of total and CVD mortality, in comparison with the lowest tertiles of BMI, diastolic and systolic blood pressure, and never smoking (Table 2). The highest level of total cholesterol also increased CVD mortality. These associations remained significant also after adjustment for education, adjustment for other CVD risk factors, and additional exclusion of individuals who had been diagnosed with CHD, stroke, or heart failure before the baseline study, who may have been physically inactive because of severe disease or disability at baseline, or who died during the first 2 years of follow-up.

The joint associations of physical activity, BMI, diastolic and systolic blood pressure, cholesterol level, and smoking on the risk of mortality are shown in Table 3. The protective effect of physical activity on total and CVD mortality was fairly consistent at different levels of other risk factors. None of the interactions between physical activity and other risk factors on mortality were statistically significant. These associations did not appreciably change after additional exclusion of individuals previously diagnosed with CHD, stroke, or heart failure before the baseline study, who may have been physically inactive because of severe disease or disability at baseline, or who died during the first 2 years of follow-up (data not shown).

CONCLUSIONS — Our analysis addressed the joint association of physical activity and CVD risk factors for total and CVD mortality among patients with type 2 diabetes. Moderate or high levels of physical activity were associated with a significantly reduced risk of total and CVD mortality, independent of age, education, BMI, blood pressure, total cholesterol, and smoking. High levels of BMI, diastolic or systolic blood pressure, and current smoking were each significantly associated with an increased risk of total and CVD mortality, and high levels of cholesterol were also significantly associated with an increased risk of CVD mortality. The protective effect of physical activity was consistent in diabetic patients at any level of BMI, blood pressure, cholesterol, and smoking.

Consistent with our findings, several other studies have shown that hypertension, elevated total and LDL cholesterol levels, decreased HDL cholesterol level, and smoking were independent predictors of CVD mortality in diabetic patients (3–7). However, the association between obesity and CVD mortality among patients with diabetes is controversial. The results from the U.K. Prospective Diabetes Study indicated that high levels of BMI and waist-to-hip ratio were not major risk factors for coronary artery disease among patients with diabetes (4). The positive association of BMI and mortality among

Table 2—*Total and cardiovascular mortality according to different levels of physical activity, BMI, blood pressure, total cholesterol level, and smoking among Finnish participants with type 2 diabetes*

	Numbers of deaths			HR (95% CI)					
				Total mortality			Cardiovascular mortality		
Variable	Total	CVD	Person-years	Model 1*	Model 2†	Model 3‡	Model 1*	Model 2†	Model 3‡
n				3,708	3,708	2,938	3,708	3,708	2,938
Physical activity									
Low	399	264	10,940	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	472	304	21,437	0.59 (0.52–0.68)	0.61 (0.53–0.70)	0.61 (0.51–0.73)	0.60 (0.51–0.71)	0.61 (0.52–0.73)	0.57 (0.46–0.72)
High	552	338	36,781	0.49 (0.43–0.56)	0.52 (0.45–0.60)	0.55 (0.47–0.66)	0.49 (0.41–0.58)	0.52 (0.44–0.62)	0.54 (0.43–0.67)
BMI§									
Tertile 1	424	249	24,358	1.00	1.00	1.00	1.00	1.00	1.00
Tertile 2	479	313	23,575	0.95 (0.84–1.09)	0.94 (0.82–1.07)	0.94 (0.80–1.10)	1.04 (0.88–1.23)	1.00 (0.84–1.18)	0.97 (0.79–1.18)
Tertile 3	520	344	21,225	1.24 (1.09–1.41)	1.14 (1.00–1.30)	1.20 (1.02–1.40)	1.38 (1.17–1.62)	1.22 (1.03–1.44)	1.25 (1.01–1.53)
Diastolic blood pressure§									
Tertile 1	364	221	20,751	1.00	1.00	1.00	1.00	1.00	1.00
Tertile 2	445	271	23,232	0.95 (0.82–1.09)	0.92 (0.80–1.06)	0.95 (0.80–1.13)	0.94 (0.78–1.12)	0.89 (0.74–1.07)	0.98 (0.78–1.23)
Tertile 3	614	414	25,175	1.23 (1.08–1.41)	1.22 (1.06–1.40)	1.26 (1.06–1.50)	1.36 (1.15–1.61)	1.29 (1.08–1.54)	1.45 (1.16–1.81)
Systolic blood pressure§									
Tertile 1	355	198	23,896	1.00	1.00	1.00	1.00	1.00	1.00
Tertile 2	430	266	22,714	1.00 (0.87–1.15)	1.00 (0.87–1.16)	1.09 (0.92–1.30)	1.07 (0.89–1.29)	1.06 (0.88–1.28)	1.29 (1.03–1.63)
Tertile 3	638	442	22,548	1.35 (1.18–1.55)	1.34 (1.17–1.53)	1.49 (1.26–1.75)	1.60 (1.35–1.90)	1.55 (1.30–1.84)	1.84 (1.48–2.29)
Total cholesterol§									
Tertile 1	370	217	20,888	1.00	1.00	1.00	1.00	1.00	1.00
Tertile 2	467	297	23,923	0.97 (0.84–1.11)	0.99 (0.86–1.13)	0.97 (0.82–1.14)	1.04 (0.87–1.24)	1.05 (0.88–1.26)	1.09 (0.87–1.35)
Tertile 3	586	392	24,347	1.07 (0.93–1.22)	1.08 (0.94–1.23)	1.09 (0.93–1.28)	1.19 (1.00–1.41)	1.20 (1.01–1.43)	1.23 (0.99–1.52)
Smoking status									
Never	750	499	39,147	1.00	1.00	1.00	1.00	1.00	1.00
Former	247	167	10,576	0.99 (0.84–1.18)	1.00 (0.84–1.19)	1.09 (0.88–1.35)	1.01 (0.81–1.25)	1.01 (0.81–1.26)	1.02 (0.78–1.34)
Current	426	240	19,434	1.52 (1.31–1.76)	1.50 (1.30–1.74)	1.53 (1.28–1.82)	1.35 (1.12–1.63)	1.34 (1.11–1.63)	1.35 (1.08–1.70)

*Model 1 was adjusted for age, sex, and study year; †model 2 included the following variables: for physical activity: age, sex, study year, education, BMI, systolic blood pressure, total cholesterol level, and smoking; for BMI: age, sex, study year, education, physical activity, systolic blood pressure, total cholesterol level, and smoking; for diastolic and systolic blood pressure: age, sex, study year, education, physical activity, BMI, total cholesterol, and smoking; for cholesterol: age, sex, study year, education, physical activity, BMI, systolic blood pressure, and smoking; for smoking: age, sex, study year, education, physical activity, BMI, systolic blood pressure, and total cholesterol; ‡model 3 represents model 2 with exclusion of 770 subjects who were diagnosed at baseline with CHD, stroke, and/or heart failure, who may have been physically inactive because of severe disease or disability at baseline, or who died during the first 2 years of follow-up; §cut points for tertiles of BMI were 27.1 and 30.4 kg/m^2 in men and 28.0 and 32.6 kg/m^2 in women, cut points for tertiles of diastolic blood pressure were 88 and 98 mmHg in men and 87 and 98 mmHg in women, cut points for tertiles of systolic blood pressure were 141 and 158 mmHg in men and 144 and 165 mmHg in women, and cut points for tertiles of total cholesterol were 5.8 and 6.9 mmol/l in men and 6.0 and 7.0 mmol/l in women.

Table 3—*Total and cardiovascular mortality according to joint levels of physical activity, BMI, blood pressure, total cholesterol level, and smoking among Finnish participants with type 2 diabetes*

	HR (95% CI)			
	Total mortality		Cardiovascular mortality	
Variable	Active*	Inactive*	Active*	Inactive*
BMI†				
Tertile 1	1.00	1.89 (1.50–2.39)	1.00	1.74 (1.28–2.37)
Tertile 2	0.97 (0.84–1.13)	1.61 (1.30–1.99)	1.01 (0.83–1.23)	1.68 (1.29–2.18)
Tertile 3	1.15 (0.99–1.35)	2.08 (1.72–2.51)	1.21 (1.00–1.46)	2.23 (1.76–2.81)
Diastolic blood pressure‡				
Tertile 1	1.00	1.99 (1.58–2.51)	1.00	2.05 (1.53–2.74)
Tertile 2	0.99 (0.83–1.17)	1.56 (1.26–1.95)	0.96 (0.78–1.20)	1.55 (1.17–2.04)
Tertile 3	1.25 (1.06–1.47)	2.34 (1.90–2.88)	1.35 (1.10–1.66)	2.45 (1.89–3.16)
Systolic blood pressure‡				
Tertile 1	1.00	2.09 (1.65–2.66)	1.00	2.36 (1.74–3.22)
Tertile 2	1.05 (0.89–1.24)	1.84 (1.46–2.31)	1.18 (0.95–1.48)	1.87 (1.38–2.52)
Tertile 3	1.44 (1.23–1.68)	2.37 (1.94–2.89)	1.72 (1.40–2.12)	2.85 (2.21–3.67)
Total cholesterol§				
Tertile 1	1.00	1.66 (1.32–2.09)	1.00	1.66 (1.24–2.23)
Tertile 2	0.92 (0.79–1.09)	1.89 (1.53–2.35)	0.99 (0.80–1.22)	1.94 (1.48–2.54)
Tertile 3	1.08 (0.92–1.26)	1.78 (1.45–2.18)	1.19 (0.97–1.46)	2.01 (1.56–2.58)
Smoking status‖				
Never	1.00	1.97 (1.68–2.30)	1.00	1.89 (1.56–2.29)
Former	1.07 (0.89–1.30)	1.62 (1.19–2.20)	1.05 (0.83–1.34)	1.75 (1.22–2.51)
Current	1.61 (1.36–1.89)	2.53 (2.01–3.19)	1.43 (1.16–1.77)	2.22 (1.65–2.99)

*Inactivity was defined as low physical activity, and active was defined as moderate or high physical activity; †adjusted for age, sex, study year, education, systolic blood pressure, total cholesterol level, and smoking; ‡adjusted for age, sex, study year, education, BMI, total cholesterol, and smoking; §adjusted for age, sex, study year, education, BMI, systolic blood pressure, and smoking; ‖adjusted for age, sex, study year, education, BMI, systolic blood pressure, and total cholesterol.

men with diabetes has been found in the Aerobics Center Longitudinal Study; however, this association became nonsignificant when fitness was included in the model (7). In the present study, high BMI at baseline was an independent predictor for both total and CVD mortality and was independent of physical activity and other risk factors. Obesity and central obesity have been found to be associated with insulin resistance and hyperinsulinemia (25).

Several previous studies, including the Aerobics Center Longitudinal Study (8), the Nurses' Health Study (9), the Whitehall Study (10), the National Health Interview Survey (11), and the Health Professionals' Follow-Up Study (12) have indicated that regular leisure-time physical activity is associated with reduced CVD and total mortality among patients with diabetes or impaired glucose tolerance. Four of these studies also indicated that walking had a similar inverse association with the risk of CVD and total mortality as vigorous leisure-time physical activity (9–12). Our previous study reported that moderate and high occupational and leisure-time physical activity as well as daily walking or cycling to and from work independently and significantly reduced risk of total and CVD mortality among patients with diabetes (13). In the Aerobics Center Longitudinal Study, a steep inverse relation between fitness and mortality was found in men with diabetes, and this association was seen in all BMI and body fatness groups (7). Regular physical activity may reduce CVD and total mortality among patients with diabetes by several mechanisms. In the general population, regular physical activity can improve insulin sensitivity, decrease blood pressure, increase HDL cholesterol levels, decrease triglyceride levels, induce weight loss and improve weight maintenance (26,27), and also reduce the risk of metabolic syndrome (28) and type 2 diabetes (18,20,29,30). Among diabetic patients, regular physical activity is also associated with improved insulin sensitivity, glycemic control, and improved levels of CVD risk factors (31,32). Nevertheless, the present study confirms previous findings that physical inactivity is an independent risk factor for CVD and total mortality in patients with diabetes. The American Diabetes Association, the National Cholesterol Education Program Export Panel, and the International Diabetes Federation (European Region) recommend physical activity for the primary and secondary prevention of CVD complications among patients with diabetes (32–34).

The present study indicated that the protective effect of physical activity on mortality appeared at different levels of weight, blood pressure, and serum total cholesterol and among smoking and nonsmoking individuals. Regular physical activity may be more important in mortality risk than many of the traditional CVD risk factors. Even though the results of an observational cohort study alone cannot prove a causal relationship, there is no doubt that physical activity should be considered an integral part of treatment among patients with type 2 diabetes.

There are several strengths and limitations in our study. First, we had a homogenous study population, and the number of participants was large. Second, the mean follow-up of 18.7 years was sufficiently long and the CVD events were ascertained without losses of follow-up. Third, in addition to leisure-time physical activity, occupational and commuting physical activities were included in the analysis. Fourth, we excluded patients with type 1 diabetes from the analysis. Finally, we performed additional analyses excluding subjects who were diagnosed with CHD, stroke, and heart failure before the baseline study, subjects who may have been physically inactive because of severe disease or disability at baseline, or subjects who had died during the first 2 years of follow-up and thus avoided the potential bias from a relative excess in early mortality and severe disease at baseline that might have resulted in low physical activity in such patients with diabetes.

The major limitation of our study is that we did not have data on the severity of diabetes, glucose control, and type of drugs used for the treatment for diabetes. Another limitation was the self-report of physical activity. Use of a questionnaire to assess habitual physical activity is always a crude and imprecise method. We had no data on possible changes in physical activity during follow-up. Misclassification, particularly overreporting of the amount of physical activity at baseline and changes in the activity during follow-up, most probably leads to an underestimation of the association between physical activity and the outcome. The results from the Aerobics Center Longitudinal Study have shown that the relative risk of total mortality for low fitness was substantially greater than that for physical inactivity (8), suggesting that self-reports probably underestimated the true association between sedentary lifestyle and mortality.

In conclusion, our study confirmed that a moderate or high level of physical activity was associated with a reduced risk of total and CVD mortality among patients with type 2 diabetes. Obesity, high blood pressure, and current smoking were independently associated with an increased risk of total and CVD mortality in patients with diabetes, and a high serum total cholesterol level was also associated with an increased risk of CVD mortality. The favorable association of physical activity with longevity was observed regardless of the levels of BMI, blood pressure, cholesterol, and smoking. Regular physical activity can be recommended to patients with diabetes whether or not they have other known CVD risk factors. However, because the results of an observational cohort study cannot be interpreted as a causal relationship, a randomized clinical trial is still warranted to test the effects of physical activity on long-term health outcomes among patients with type 2 diabetes. Such a trial is not easy to conduct.

Acknowledgments— This study was supported by grants 46558, 53585, 204274, and 205657 from the Finnish Academy.

References

1. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047–1053, 2004
2. Muller WA: Diabetes mellitus: long time survival. *J Insur Med* 30:17–27, 1998
3. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
4. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 316:823–828, 1998
5. Sowers JR, Epstein M, Frohlich ED: Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension* 37:1053–1059, 2001
6. Folsom AR, Chambless LE, Duncan BB, Gilbert AC, Pankow JS: Prediction of coronary heart disease in middle-aged adults with diabetes. *Diabetes Care* 26:2777–2784, 2003
7. Church TS, Cheng YJ, Earnest CP, Barlow CE, Gibbons LW, Priest EL, Blair SN: Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care* 27:83–88, 2004
8. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN: Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann Intern Med* 132:605–611, 2000
9. Hu FB, Stampfer MJ, Solomon C, Liu S, Colditz GA, Speizer FE, Willett WC, Manson JE: Physical activity and risk for cardiovascular events in diabetic women. *Ann Intern Med* 134:96–105, 2001
10. Batty GD, Shipley MJ, Marmot M, Smith GD: Physical activity and cause-specific mortality in men with type 2 diabetes/impaired glucose tolerance: evidence from the Whitehall study. *Diabet Med* 19:580–588, 2002
11. Gregg EW, Gerzoff RB, Caspersen CJ, Williamson DF, Narayan KM: Relationship of walking to mortality among US adults with diabetes. *Arch Intern Med* 163:1440–1447, 2003
12. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB: Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation* 107:2435–2439, 2003
13. Hu G, Eriksson J, Barengo NC, Lakka TA, Valle TT, Nissinen A, Jousilahti P, Tuomilehto J: Occupational, commuting, and leisure-time physical activity in relation to total and cardiovascular mortality among Finnish subjects with type 2 diabetes. *Circulation* 110:666–673, 2004
14. Vartiainen E, Jousilahti P, Alfthan G, Sundvall J, Pietinen P, Puska P: Cardiovascular risk factor changes in Finland, 1972–1997. *Int J Epidemiol* 29:49–56, 2000
15. WHO MONICA Project Principal Investigators: The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. *J Clin Epidemiol* 41:105–114, 1988
16. WHO Study Group on Diabetes Mellitus: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
17. WHO Consultation: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Org., 1999
18. Hu G, Qiao Q, Silventoinen K, Eriksson JG, Jousilahti P, Lindstrom J, Valle TT, Nissinen A, Tuomilehto J: Occupational, commuting, and leisure-time physical activity in relation to risk for type 2 diabetes in middle-aged Finnish men and women. *Diabetologia* 46:322–329, 2003
19. Hu G, Barengo NC, Tuomilehto J, Lakka TA, Nissinen A, Jousilahti P: Relationship of physical activity and body mass index to the risk of hypertension: a prospective study in Finland. *Hypertension* 43:25–30, 2004
20. Hu G, Lindstrom J, Valle TT, Eriksson JG, Jousilahti P, Silventoinen K, Qiao Q, Tuomilehto J: Physical activity, body mass index, and risk of type 2 diabetes in patients with normal or impaired glucose regulation. *Arch Intern Med* 164:892–896, 2004
21. Tuomilehto J, Hu G, Bidel S, Lindstrom J, Jousilahti P: Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. *JAMA* 291:1213–1219, 2004
22. Barengo NC, Hu G, Lakka TA, Pekkarinen

H, Nissinen A, Tuomilehto J: Low physical activity as a predictor for total and cardiovascular disease mortality in middle-aged men and women in Finland. *Eur Heart J* 25:2204–2211, 2004
23. Hu G, Tuomilehto J, Silventoinen K, Barengo N, Jousilahti P: Joint effects of physical activity, body mass index, waist circumference and waist to hip ratio with the risk of cardiovascular disease among middle-aged Finnish men and women. *Eur Heart J* 25:2212–2219, 2004
24. Keys A: *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease*. Cambridge, MA, Harvard University Press, 1980
25. Després JP, Lamarche B, Mauriege P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ: Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med* 334:952–957, 1996
26. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, Haffner SM, Rewers MJ, Saad M, Bergman RN: Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA* 279:669–674, 1998
27. Wannamethee SG, Shaper AG, Alberti KG: Physical activity, metabolic factors, and the incidence of coronary heart disease and type 2 diabetes. *Arch Intern Med* 160:2108–2116, 2000
28. Laaksonen DE, Lakka HM, Salonen JT, Niskanen LK, Rauramaa R, Lakka TA: Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. *Diabetes Care* 25:1612–1618, 2002
29. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
30. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
31. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ: Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 286:1218–1227, 2001
32. American Diabetes Association: Physical activity/exercise and diabetes mellitus. *Diabetes Care* 26:S73–S77, 2003
33. National Institute of Health: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
34. Working Party of the International Diabetes Federation (European Region): Hypertension in people with type 2 diabetes: knowledge-based diabetes-specific guidelines. *Diabet Med* 20:972–987, 2003