Physical Activity and Life Expectancy With and Without Diabetes

Life table analysis of the Framingham Heart Study

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OBJECTIVE — Physical activity is associated with a reduced risk of developing diabetes and with reduced mortality among diabetic patients. However, the effects of physical activity on the number of years lived with and without diabetes are unclear. Our aim is to calculate the differences in life expectancy with and without type 2 diabetes associated with different levels of physical activity.

RESEARCH DESIGN AND METHODS — Using data from the Framingham Heart Study, we constructed multistate life tables starting at age 50 years for men and women. Transition rates by level of physical activity were derived for three transitions: nondiabetic to death, nondiabetic to diabetes, and diabetes to death. We used hazard ratios associated with different physical activity levels after adjustment for age, sex, and potential confounders.

RESULTS — For men and women with moderate physical activity, life expectancy without diabetes at age 50 years was 2.3 (95% CI 1.2–3.4) years longer than for subjects in the low physical activity group. For men and women with high physical activity, these differences were 4.2 (2.9–5.5) and 4.0 (2.8–5.1) years, respectively. Life expectancy with diabetes was 0.5 (−1.0 to 0.0) and 0.6 (−1.1 to −0.1) years less for moderately active men and women compared with their sedentary counterparts. For high activity, these differences were 0.1 (−0.7 to 0.5) and 0.2 (−0.8 to 0.3) years, respectively.

CONCLUSIONS — Moderately and highly active people have a longer total life expectancy and live more years free of diabetes than their sedentary counterparts but do not spend more years with diabetes.

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The prevalence of diabetes is increasing dramatically worldwide. In 2000, 171 million people worldwide were affected by diabetes. This number is expected to double by 2030, mainly as a consequence of population aging and urbanization (1). Type 2 diabetes is associated with long-term complications and a high burden of morbidity (2,3). Evidence suggests an inverse association between physical activity and the risk of developing diabetes (4–11). Physical activity, through improving insulin sensitivity and glycemic control (12–14), has been associated with reduced total mortality among diabetic patients (15–20) and the general population (21).

However, the effects of physical activity on the number of years lived with and without diabetes are still unclear. Whether, for example, higher levels of physical activity would reduce the number of years lived with diabetes depends on the balance of its effect on the risks of developing diabetes and mortality. For instance, it has been shown that nonsmokers live longer with cardiovascular disease than smokers because their total life expectancy is ~8 years longer (22). As policy makers increasingly advocate modification of risk factors with the aim of decreasing population levels of disease and disability (e.g., 23), it will be important to analyze the extent to which this is actually the case. The conundrum is that modification of risk factors, such as smoking and physical activity, will at the same time decrease disease incidence and increase survival to advanced age, which is itself one of the strongest risk factors for disease.

Our aim is to quantify the differences in life expectancy without type 2 diabetes (i.e., the average number of years lived before the onset of diabetes or death) and life expectancy with type 2 diabetes (i.e., the average number of years lived with diabetes) associated with different levels of physical activity.

RESEARCH DESIGN AND METHODS

The Framingham Heart Study cohort consisted of 5,209 respondents (46% male) aged 28–62 years residing in Framingham, Massachusetts, between 1948 and 1951. The Framingham cohort is primarily white and has been followed extensively for 46 years for the occurrence of cardiovascular disease and death through surveillance of hospital admissions, death registries, and other available medical sources. Examination of participants, including an interview, a physical examination, and laboratory tests, has taken place biennially. Further description of the Framingham Heart Study can be found elsewhere (24).

To calculate transition rates by level of physical activity, we pooled three nonoverlapping follow-up periods of 12 years. Each follow-up period started with a measurement of physical activity. In the present investigation, the follow-up periods started at the original exams 4 (1956–1958), 11/12 (1969–1973), and 19/20

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Abbreviations: MSLT, multistate life table.

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

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(1985–1989). Using the pooling of repeated observations method (25), follow-up information over three follow-up periods was pooled, yielding a total of 9,773 observation intervals. The same participant may thus be followed during three periods until the event (first onset of diabetes or death) occurs or the subject is censored. Follow-up time and physical activity status may differ in each interval. After exclusion of subjects with diabetes at exam 1 to exclude juvenile diabetes and missing information on physical activity, we studied 4,176 subjects at exam 4, 3,286 subjects at exam 11/12, and 1,660 subjects at exam 19/20, yielding a total of 9,122 follow-up observation intervals.

Diabetes assessment

Diabetes was considered present after a random blood glucose level ≥200 mg/dl or when the subject was treated with a hypoglycemic agent (insulin and/or oral hypoglycemic agent).

Assessment of physical activity

Participants were asked about their time spent resting or engaged in light, moderate, or heavy physical activity on an average day. Time spent at each activity in hours per week was multiplied by its metabolic cost (based on the oxygen consumption required for that activity) as described before by Kannel et al. (26). A weight of 1.0 was used for an activity with oxygen consumption of 0.25 l/min, for example sleep. Other weights were 1.1 for being sedentary, 1.5 for light activity, 2.4 for moderate activity, and 5 for heavy activity. The weight factor corresponds to a metabolic equivalent task. These weighted hours were added up to get a total daily physical activity score. The minimum physical activity score is 24, which is equivalent to 24 h of rest/sleep. Based on tertiles of the daily physical activity scores, we grouped the participants in three levels: low (<30), moderate (30–33), and high (>33) physical activity level.

Confounders

Potential confounders were measured at the start of each follow-up period, except for education. All analyses were adjusted for age and sex. Confounders considered were education (eighth grade or less/higher than eighth grade), smoking (never, ever, or current smoking), marital status (single, married, widowed, or separated/divorced), diseases present at baseline (any of the following: cardiovascular disease, cancer, left ventricular hypertrophy, arthritis, ankle edema, or any pulmonary disease), total cholesterol, family history of diabetes (diabetes in parents and/or siblings), and the exam of start follow-up (exam 4, 11/12, or 19/20). The exam of start follow-up was included to correct for a potential cohort and period effect. Hypertension and BMI were not considered as confounders but as intermediate factors, as physical activity may cause individuals to have lower BMI and blood pressure, which in turn reduces the risk of diabetes and mortality. Adjustment for BMI and hypertension may result in an underestimation of the true beneficial effect of physical activity. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (27). For BMI, four categories were defined: BMI <18.5 kg/m^2, $18.5 \leq$ BMI < 25 kg/m^2, $25 \leq$ BMI < 30 kg/m^2, and BMI ≥ 30 kg/m^2. Because the information on alcohol consumption was not available for all follow-up periods, alcohol was excluded from the analyses. For the final analysis, only participants who had information on all confounders, BMI, and hypertension were included (3,978, 3,067, and 1,561 subjects at exam rounds 4, 11/12, and 19/20, respectively).

Data analysis

To calculate the life expectancy with and without diabetes, we created a multistate life table (MSLT) (28). This MSLT, which combines information of people at different ages and from different birth cohorts, included three states: "free of diagnosed diabetes," "diabetes," and "death." The possible transitions were from free of diagnosed diabetes to diabetes or to death and from diabetes to death. No back flows were allowed, and only the first entry into a state was considered. Age 50 years was chosen as the starting age to include the effect of physical activity at adult ages, while avoiding unstable rates due to limited number of events below age 50 years. Another advantage is that at this age, where the prevalence of type 2 diabetes is still low, the outcomes of the MSLT for the total and diabetes-free population are virtually the same.

To obtain transition rates by levels of physical activity, we first calculated the overall sex- and age-specific transition rates for each transition (29). Next, we calculated hazard ratios of physical activity using Poisson regression. We analyzed the effect of potential confounders on the hazard ratios by first adjusting for age and sex only and next by including the following in addition: education, marital status, smoking, baseline diseases, and exam of start follow-up. Subsequently, adjustments for BMI and hypertension were added to the previous model to give information about the effect of these possible intermediates on the hazard ratios. Additionally, adjusting for BMI did not substantially change the hazard ratios. The small effect of adjusting for BMI may reflect a small risk of self-selection of heavy subjects for lower physical activity levels because physical activity includes physical activity at work. We did not adjust for total cholesterol (as continuous variable) and family history of diabetes in the final model, as these variables did not change the hazard ratios of physical activity and had a large number of missing values.

Finally, to calculate transition rates by level of physical activity, we used the overall transition rates, the prevalence of the different levels of physical activity in the population (stratified by 10-year age-group, sex, and diabetes), and the hazard ratios of physical activity adjusted for potential confounding but not for intermediates (BMI and hypertension).

Separate MSLTs were created for each level of physical activity for men and women, incorporating each of the three transitions. The MSLT started at age 50 years and was closed at age 100 years. The measures available from the MSLT include life expectancy without diagnosed diabetes (i.e., the average number of years lived free of diabetes before the onset of diabetes or death) and life expectancy with diabetes (i.e., the average number of years lived with diabetes) for populations with either low, moderate, or high physical activity and free of diabetes at age 50 years.

All statistical analyses were done using STATA version 8.2 for Windows (Stata, College Station, TX). We calculated CIs for all life expectancies and differences in life expectancies using Monte Carlo simulation (parametric bootstrapping) (30). To calculate the CIs, we used @RISK (Anonymous 2000; MathSoft) 10,000 runs.

RESULTS

Baseline characteristics

In the categories low and moderate physical activity, the proportion of women was higher than in the category with high physical activity (63 and 62%, respec-

Table 1—*Baseline characteristics by physical activity level**

	Level of physical activity (tertiles)		
	Low	Moderate	High
n	2,829 (31)	3,329 (36)	2,964 (32)
Physical activity score	28.1 ± 1.2	31.4 ± 1.0	38.0 ± 5.4
Age (years)	61.6 ± 13.1	57.6 ± 12.3	59.1 ± 11.8
Women	1,776 ± 63	2,065 ± 62	1,362 ± 46
Marital status			
Single	277 (10)	279 (8)	177 (6)
Married	1,923 (68)	2,517 (76)	2,410 (81)
Widowed	514 (18)	417 (13)	290 (10)
Divorced/separated	72 (3)	86 (3)	62 (2)
Education, eighth grade or less	696 (25)	843 (25)	738 (25)
Never smoker	1,112 (39)	1,222 (37)	868 (29)
Former smoker	662 (23)	750 (23)	864 (29)
Current smoker	1,055 (37)	1,357 (41)	1,232 (42)
Baseline diseases†	1,543 (55)	1,373 (41)	1,225 (41)
BMI (kg/m^2)	26.2 ± 4.6	25.9 ± 4.1	26.1 ± 3.9
Systolic blood pressure (mmHg)	140.2 ± 24.2	137.2 ± 22.6	136.2 ± 20.9
Diastolic blood pressure (mmHg)	89.0 ± 24.2	84.8 ± 18.0	84.3 ± 17.7
Total cholesterol (mg/100 ml)	239.0 ± 46.7	234.4 ± 43.3	230.6 ± 41.6
Family history of diabetes‡	479 (17)	560 (17)	508 (17)

Data are means ± SD or *n* (%). *After exclusion of subjects with diabetes at baseline and missing information on physical activity. †Baseline diseases: cardiovascular disease, cancer, left ventricular hypertrophy, arthritis, ankle edema, or pulmonary disease. ‡Family history of diabetes defined as diabetes diagnosed in parents and/or siblings.

tively, compared with 46%) (Table 1). Participants in the low physical activity group tended to be older (mean age 62 years) compared with the participants of the moderate and high activity groups (mean age 58 and 59 years, respectively); also, the level of baseline diseases was higher among participants with low physical activity. Blood pressure and total cholesterol showed a tendency toward an inverse relationship with physical activity (Table 1).

Risk of diabetes and death

Higher levels of physical activity were associated with lower rates of incident diabetes (corrected for age and sex) (online appendix [available at http://care.diabetesjournals.org]). After additional correction for selected confounders, the effect slightly increased and the hazard ratio remained significant (Table 2).

The risks of mortality in subjects without diagnosed diabetes (corrected for age and sex) were inversely related to the level of physical activity (Table 2). Correcting for confounders slightly attenuated the effect, but all hazard ratios remained significant. The mortality rates in subjects with diabetes were also lower in active subjects than in sedentary subjects. After adjusting for confounders, this association was only significant for high physical activity.

Total life expectancy and life expectancy with and without diabetes

Figure 1 shows survival curves, total and free of diabetes, by level of physical activity. The area under these survival curves is total life expectancy and life expectancy without diabetes, respectively. The difference between the total and diabetes-free life expectancy is life expectancy with diabetes. At age 50 years, total life expectancy was 27.2 (men) and 33.8 (women) years, of which 25.5 and 32.1 years, respectively, were spent without diabetes and 1.7 years (both sexes) with diabetes. In contrast, life expectancy of 50-year-old individuals with diabetes is 23.8 and 24.3 years for men and women, respectively.

Life expectancy of 50-year-old men in the moderate and high activity groups was 1.8 (95% CI 0.8–2.9) and 4.1 (2.8–5.4) years longer, respectively, than of men in the lowest activity group. For women, these differences were similar: 1.7 (0.8–2.8) and 3.7 (2.6–4.9) years (Table 3). This larger total life expectancy was composed of more years lived without diabetes and fewer years lived with diabetes. Both moderately active men and women lived 2.3 (1.2–3.4) more years without diabetes than those in the lowest activity group (Table 3). In the highest activity group, men and women lived 4.2 (2.9–5.5) and 4.0 (2.8–5.1) years longer, respectively, without diabetes than their sedentary counterparts. Moderately active men and women lived ~0.5 (men: 95% CI −1.0 to 0.0, women: −1.1 to −0.1) years less with diabetes, compared with those with low physical activity. For high activity groups these differences for men and women were 0.1 and 0.2 years,

Table 2—*Hazard ratios for the different transitions*

Transition	*n*	Person-years	Physical activity	Hazard ratio (95% CI)*	Hazard ratio (95% CI)†
Incident diabetes	329	70,115	Low	1.00	1.00
			Moderate	0.63 (0.48–0.82)	0.62 (0.47–0.80)
			High	0.63 (0.49–0.83)	0.60 (0.46–0.80)
No diagnosed diabetes to death	1,598	71,856	Low	1.00	1.00
			Moderate	0.81 (0.72–0.91)	0.86 (0.76–0.96)
			High	0.61 (0.54–0.69)	0.70 (0.61–0.79)
Diabetes to death	292	4,922	Low	1.00	1.00
			Moderate	0.72 (0.55–0.95)	0.81 (0.61–1.07)
			High	0.47 (0.35–0.64)	0.53 (0.39–0.72)

*Adjusted for age and sex. †Adjusted for age; sex; education; marital status; smoking; baseline diseases, such as cardiovascular disease, cancer, left ventricular hypertrophy, arthritis, ankle edema, or pulmonary disease; and exam of start follow-up.

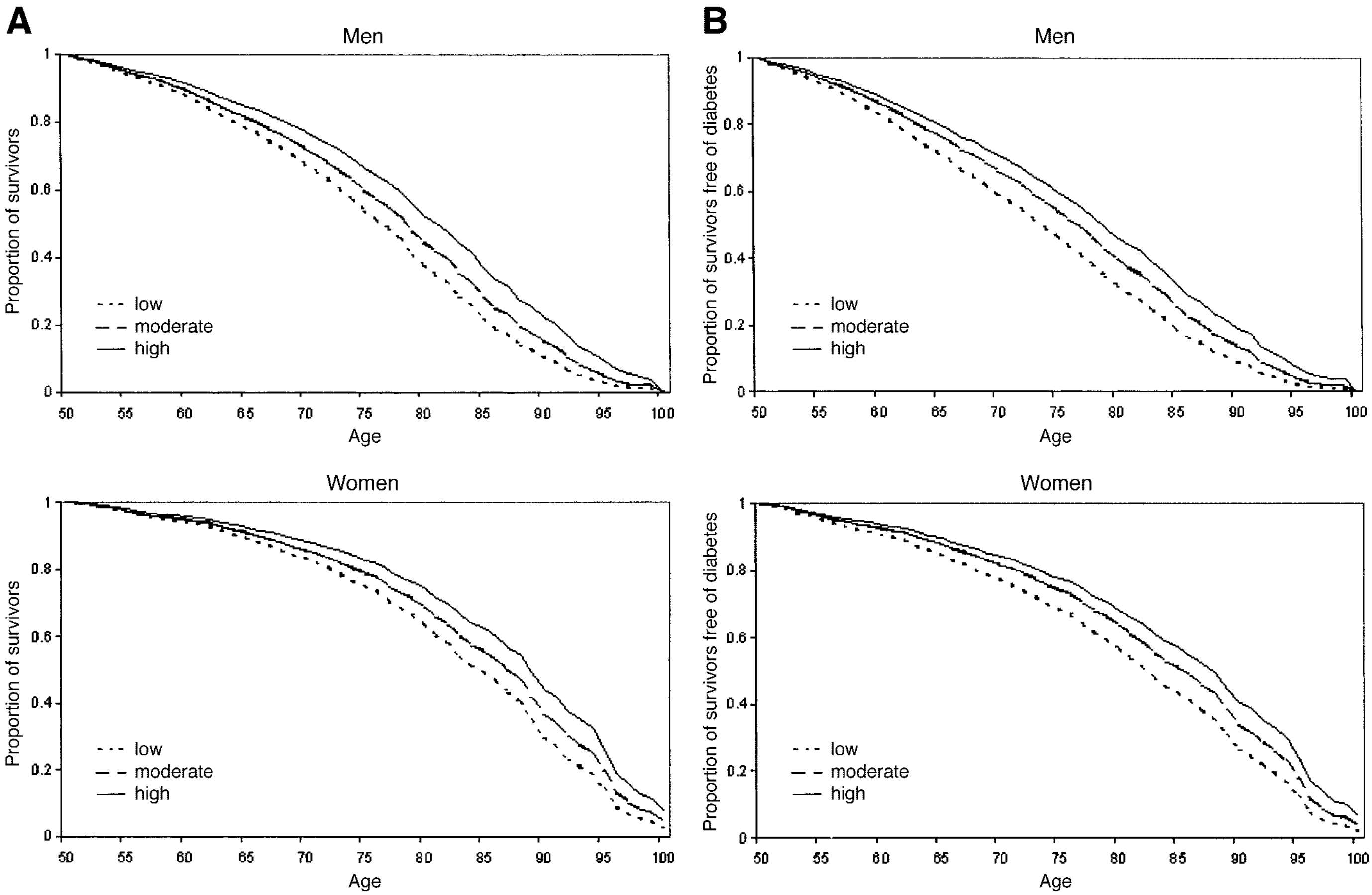

Figure 1—A: *Survival curves illustrating the probability of surviving with age by sex for different levels of physical activity (low, moderate, and high). The area under the survival curve is the total life expectancy for populations with low, moderate, or high physical activity and free of diabetes at age 50 years.* B: *Survival curves illustrating the probability of surviving free of diabetes with age by sex for different levels of physical activity (low, moderate, and high). The area under the survival curve is life expectancy without diabetes for populations with low, moderate, or high physical activity and free of diabetes at age 50 years.*

respectively, but were no longer significant (Table 3).

CONCLUSIONS— Moderately and highly active people live longer and spend more years without diabetes than subjects with low physical activity levels. At age 50 years, life expectancy free of diabetes is 2.3 years longer for moderately active men and women and at least 4 years longer for highly active men and women. The effect of physical activity on life expectancy without diabetes reflects both the lower incidence of diabetes and the lower mortality of nondiabetic individu-

Table 3—*Life expectancy in years at age 50 years for three levels of physical activity**

	Total life expectancy*	Differences in total life expectancy†	Life expectancy free of diagnosed diabetes	Differences in life expectancy free of diagnosed diabetes†	Life expectancy with diabetes	Differences in life expectancy with diabetes†
Men						
Low activity	25.3 (24.4–26.3)	ref	23.3 (22.4–24.2)	ref	2.0 (1.6–2.6)	ref
Moderate activity	27.1 (26.0–28.0)	1.8 (0.8–2.9)	25.6 (24.4–26.8)	2.3 (1.2–3.4)	1.5 (1.1–2.1)	−0.5 (−1.0 to 0.0)
High activity	29.4 (28.3–30.5)	4.1 (2.8–5.4)	27.5 (26.3–28.7)	4.2 (2.9–5.5)	1.9 (1.5–2.5)	−0.1 (−0.7 to 0.5)
Women						
Low activity	32.3 (31.5–33.1)	ref	30.3 (29.4–31.2)	ref	2.0 (1.7–2.5)	ref
Moderate activity	34.0 (33.0–35.0)	1.7 (0.8–2.8)	32.6 (31.6–33.6)	2.3 (1.2–3.4)	1.5 (1.1–2.0)	−0.6 (−1.1 to −0.1)
High activity	36.0 (34.9–37.2)	3.7 (2.6–4.9)	34.2 (33.1–35.4)	4.0 (2.8–5.1)	1.8 (1.3–2.4)	−0.2 (−0.8 to 0.3)

Data are years (95% CI). *Life expectancy free of diagnosed diabetes is the average number of years lived free of diabetes prior to the onset of diabetes or death and life expectancy with diabetes is the average number of years lived with diabetes. These life expectancies refer to a population alive and free of diabetes at age 50 years. All life expectancies have been calculated with hazard ratios adjusted for age; sex; education; marital status; smoking; baseline diseases, such as cardiovascular disease, cancer, left ventricular hypertrophy, arthritis, ankle edema, or pulmonary disease; and exam of start follow-up. †Differences are calculated using the low physical activity group as reference: moderate vs. low and high vs. low. ref, reference.

als associated with increasing physical activity levels. Life expectancy with diabetes is at least 0.5 and 0.1 years less for moderate and highly active people, respectively, compared with those with low physical activity. This reflects two opposing effects: *1*) lower incidence of diabetes in the active group reducing the time spent with diabetes and *2*) lower mortality in diabetic subjects, increasing the time spent with diabetes. The net result is that while moderate and highly active people live longer, they do not spend more years with diabetes.

The reported hazard ratios found in our study fall well within the range of the published measures of the effect of physical activity on incident diabetes (4–6,8, 9,31–33) and mortality of diabetic subjects (15,16,19,20). However, comparison with prior studies is difficult because the measurement scales and definitions of physical activity used differ. Most studies published on the subject (4,6,8,9,31,32) have found dose-response relations between physical activity and the incidence of diabetes. We similarly found a dose-response relation between physical activity and the mortality rates among nondiabetic and diabetic subjects. However, similar to a few other studies (5,33,34), we found that the degree of protection against diabetes was virtually the same in those with either vigorous or moderate physical activity levels. Additional analyses (data not shown) suggest that, in particular, the oldest subjects are responsible for this lack of a clear dose-response relation. Our data suggested that the effect of physical activity could be different in those aged >80 years. A possible explanation is that at this age, the lower physical activity group still at risk for diabetes is more selected due to higher risks of diabetes and mortality earlier in their life than those with higher levels of physical activity. However, the study was underpowered to detect any true difference in effect, and it is unlikely that such a difference would have affected our conclusions. Similar to Gregg et al. (20), the effect of moderate physical activity on the transition of diabetes to death did not reach statistical significance after full adjustment. Additional analyses showed that using a hazard ratio of 1.00 for this transition in the moderate active group would only strengthen our results.

A strength of this study is the use of data from a prospective, well-organized study, with long-term follow-up. Another advantage is that the glucose levels as well as other risk factors are measured at regular, biannual intervals. In our study, diagnosis of diabetes was based on glucose tests or the use of hypoglycaemic agents instead of self-report. In studies based on self-reported diabetes, many subjects with diabetes remain undiagnosed. In this study, there could be underdiagnosis only if subjects were not present at one or more exams (or had a false-negative test). As most subjects only missed one or a few subsequent exams, it becomes more a matter of delayed diagnosis than underdiagnosis.

Some limitations should be mentioned. The present study is an observational study and not a randomized trial. Consequently, bias may occur if diseases at baseline are responsible for inactivity (reverse causation) and if other factors confound the association between physical activity and the transition rates. There are two approaches to avoid reverse causation: exclusion of subjects with known diseases at baseline or adjustment for baseline diseases in the analysis. We used the second option, since we considered that by excluding subjects with diseases at baseline, there would be a selection of healthy people, and therefore the results would not be applicable to the whole population.

Residual confounding cannot entirely be ruled out, but as we examined the potential effect of a large set of confounders (age, sex, education, presence of diseases, marital status, smoking, exam of start follow-up, cholesterol, and family history of diabetes) and included those that affected the association between physical activity and the transitions, we do not expect that this would have biased our results.

Another limitation of our study is that in the Framingham Heart Study, physical activity levels were evaluated by self-report, which may introduce misclassification of exposure. However, this misclassification is likely to be nondifferential, which can only attenuate our results and fade a stronger association. We maximized the power of our study by using 12 years of follow-up. As a long period of follow-up reduces the effect of selection, but increases the risk of misclassification of exposure, the optimal follow-up time is unknown. Since it has been reported that levels and effects of physical activity change with time (35), we evaluated the effect of length of follow-up on the relation between physical activity and the transitions. These sensitivity analyses showed that with a follow-up period of 8 or 10 years instead of 12 years, our main conclusions did not change (data not shown).

The added value of this study is the combination of the observed effects of physical activity on incidence of diabetes and mortality in a large prospective study and the translation into the population health measures (life expectancy with and without diabetes). This study shows that physically inactive people have shorter lives, and, moreover, they live fewer years without diabetes and more or an equivalent number of years with diabetes compared with people with higher levels of physical activity. These results underline the public health importance of increasing physical activity levels in the population. Moreover, as Reunanen et al. (2) found that total costs of medications for people with diabetes were 3.5 times greater than those for nondiabetic control subjects, our findings are also important for the health care sector. When people live longer, but do not spend more years with diabetes, they do not put an extra demand on diabetes-related health care.

As far as the associations reflect causal relationships, our study suggests that if sedentary people could be stimulated to be at least moderately active, they could extend their lives and increase their lifetime spent without diabetes without spending more years with diabetes.

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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. Reunanen A, Kangas T, Martikainen J, Klaukka T: Nationwide survey of comorbidity, use, and costs of all medications in Finnish diabetic individuals. *Diabetes Care* 23:1265–1271, 2000
3. Zimmet P, Alberti KGMM, Shaw J: Global and societal implications of the diabetes epidemic (Review). *Nature* 414:782–787, 2001
4. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH: A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 268:63–67, 1992
5. Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Hennekens CH, Speizer FE, Rimm EB, Krolewski AS: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774–778, 1991
6. Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE, Manson JE: Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *JAMA* 282:1433–1439, 1999
7. Helmrich S, Ragland D, Leung R, Paffenbarger R: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325:147–152, 1991
8. Haapanen N, Miilunpalo S, Vuori I, Oja P, Pasanen M: Association of leisure time physical activity with the risk of coronary heart disease, hypertension and diabetes in middle-aged men and women. *Int. J Epidemiol.* 26:739–747, 1997
9. 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
10. Choi BCK, Shi F: Risk factors for diabetes mellitus by age and sex: results of the National Population Health Survey. *Diabetologia* 44:1221–1231, 2001
11. 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
12. Boule NG, Kenny GP, Haddad E, Wells GA, Sigal RJ: Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia* 46:1071–1081, 2003
13. Ellis SE, Elasy TA, Sigal RJ, Boule NG, Kenny G: Exercise and glycemic control in diabetes. *JAMA* 286:2941–2942, 2001
14. Borghouts LB, Keizer HA: Exercise and insulin sensitivity: a review. *Int J Sports Med* 21:1–12, 2000
15. 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
16. 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
17. Ford E, DeStefano F: Risk factors for mortality from all causes and from coronary heart disease among persons with diabetes: findings from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Am J Epidemiol* 133:1220–1230, 1991
18. Kohl H, Gordon N, Villegas J, Blair S: Cardiorespiratory fitness, glycemic status, and mortality risk in men. *Diabetes Care* 15:184–192, 1992
19. 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
20. Gregg EW, Gerzoff RB, Caspersen CJ, Williamson DF, Narayan KMV: Relationship of walking to mortality among US adults with diabetes. *Arch Intern Med* 163:1440–1447, 2003
21. Paffenbarger R, Hyde R, Wing A, Hsieh C: Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med* 314:605–613, 1986
22. Mamun AA, Peeters A, Barendregt J, Willekens F, Nusselder W, Bonneux L: Smoking decreases the duration of life lived with and without cardiovascular disease: a life course analysis of the Framingham Heart Study. *Eur Heart J* 25:409–415, 2004
23. World Health Organization: *Active Ageing: A Policy Framework*. Geneva, World Health Org., 2002
24. Study FH: Design, rationale, and objectves [article online]. Available at http://www.nhlbi.nih.gov/about/framingham/design.htm. Accessed 15 August 2005
25. Cupples LA, D'Agostino RB, Anderson K, Kannel WB: Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. *Stat Med* 7:205–222, 1988
26. Kannel WB, Sorlie P: Some health benefits of physical activity: the Framingham Study. *Arch Intern Med* 139:857–861, 1979
27. Cifkova R, Erdine S, Fagard R, Farsang C, Heagerty AM, Kiowski W, Kjeldsen S, Luscher T, Mallion JM, Mancia G, Poulter N, Rahn KH, Rodicio JL, Ruilope LM, van Zwieten P, Waeber B, Williams B, Zanchetti A: Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J Hypertens* 21:1779–1786, 2003
28. Schoen R: *Modelling Multigroup Populations.* New York, Plenum Press, 1988
29. Nusselder WJ, Looman CWN, de Mheen PJM-v, van de Mheen H, Mackenbach JP: Smoking and the compression of morbidity. *J Epidemiol Community Health* 54:566–574, 2000
30. Efron B, Tibshrani RJ: *An Introduction to the Bootstrap.* Cox DR, Hintley DV, Reid N, Rubin DB, Silverman RW, Eds. New York, Chapman and Hall, 1993
31. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB: Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med* 161:1542–1548, 2001
32. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE: Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA* 289:1785–1791, 2003
33. Gurwitz JH, Field TS, Glynn RJ, Manson JE, Avorn J, Taylor JO, Hennekens CH: Risk factors for non-insulin-dependent diabetes mellitus requiring treatment in the elderly. *J Am Geriatr Soc* 42:1235–1240, 1994
34. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG: Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *BMJ* 310:560–564, 1995
35. Andersen LB: Relative risk of mortality in the physically inactive is underestimated because of real changes in exposure level during follow-up. *Am J Epidemiol* 160:189–195, 2004