tein, fruit and vegetables, and coffee or alcohol intakes did not alter the associations reported in Table 2 or Table 3.

Walking or hiking outdoors accounted for an average of 70% of the METs associated with moderate activity in each cohort. In both cohorts, we observed inverse associations between hours per week of walking or

Table 3. Relative Risk (RR) for Pancreatic Cancer in Relation to Physical Activity in the NHS and HPFS*

	Quintiles					*P* Value for Trend
	1	2	3	4	5	
	Total Physical Activity, MET, h/wk					
	≤2.8	**2.9-7.7**	**7.8-16.9**	**17.0-33.9**	**≥34.0**	
Men						
Cases/person-years	31/102 119	34/102 525	29/107 012	26/107 418	19/108 111	
Age-adjusted RR†	1.00	1.06 (0.65-1.72)	0.89 (0.54-1.48)	0.84 (0.50-1.42)	0.65 (0.37-1.14)	.07
Multivariable RR†‡	1.00	1.10 (0.68-1.80)	0.95 (0.57-1.59)	0.92 (0.54-1.55)	0.72 (0.40-1.27)	.15
	≤2.0	**2.1-4.6**	**4.7-10.4**	**10.5-21.7**	**≥21.8**	
Women						
Cases/person-years	24/143 775	27/155 886	20/150 791	21/148 463	18/151 083	
Age-adjusted RR†	1.00	1.02 (0.59-1.77)	0.79 (0.44-1.43)	0.84 (0.47-1.50)	0.70 (0.38-1.30)	.21
Multivariable RR†‡	1.00	1.00 (0.56-1.77)	0.84 (0.46-1.55)	0.84 (0.45-1.55)	0.78 (0.42-1.47)	.40
Pooled multivariable RR†‡	1.00	1.06 (0.73-1.54)	0.91 (0.61-1.34)	0.88 (0.59-1.32)	0.74 (0.49-1.14)	.10
	Vigorous Activity, MET, h/wk					
	0	**0.1-3.4**	**3.5-11.9**	**12.0-29.9**	**≥30.0**	
Men						
Cases/person-years	61/191 529	20/87 822	28/83 120	19/84 325	11/80 389	
Age-adjusted RR†	1.00	0.84 (0.51-1.39)	1.29 (0.83-2.03)	1.00 (0.59-1.67)	0.68 (0.36-1.30)	.32
Multivariable RR†‡	1.00	0.84 (0.51-1.40)	1.40 (0.89-2.20)	1.11 (0.66-1.87)	0.77 (0.40-1.48)	.59
	0	**0.2-1.6**	**1.7-6.9**	**7.0-15.9**	**≥16.0**	
Women						
Cases/person-years	62/346 628	11/102 850	10/87 299	13/115 069	14/98 151	
Age-adjusted RR†	1.00	0.67 (0.35-1.27)	0.70 (0.36-1.36)	0.68 (0.37-1.24)	0.88 (0.49-1.56)	.69
Multivariable RR†‡	1.00	0.66 (0.34-1.29)	0.64 (0.31-1.35)	0.76 (0.41-1.43)	1.06 (0.57-1.96)	.80
Pooled multivariable RR†‡	1.00	0.77 (0.51-1.15)	1.00 (0.47-2.14)	0.95 (0.64-1.43)	0.91 (0.58-1.42)	.74
	Moderate Activity, MET, h/wk					
	<0.8	**0.8-2.2**	**2.3-4.8**	**4.9-10.9**	**≥11.0**	
Men						
Cases/person-years	33/98 894	26/108 961	38/107 632	22/105 927	20/105 770	
Age-adjusted RR†	1.00	0.74 (0.44-1.24)	0.95 (0.59-1.51)	0.53 (0.31-0.90)	0.41 (0.23-0.71)	<.001
Multivariable RR†‡	1.00	0.75 (0.46-1.25)	0.95 (0.60-1.52)	0.52 (0.31-0.90)	0.41 (0.24-0.72)	<.001
	<0.9	**0.9-2.6**	**2.7-4.4**	**4.5-10.7**	**≥10.8**	
Women						
Cases/person-years	24/124 288	26/154 031	22/164 935	23/159 687	15/147 057	
Age-adjusted RR†	1.00	0.97 (0.56-1.70)	0.72 (0.40-1.28)	0.77 (0.43-1.36)	0.51 (0.27-0.97)	.03
Multivariable RR†‡	1.00	1.01 (0.56-1.81)	0.85 (0.47-1.55)	0.85 (0.46-1.57)	0.52 (0.26-1.05)	.05
Pooled multivariable RR†‡	1.00	0.85 (0.58-1.25)	0.91 (0.63-1.32)	0.65 (0.41-1.04)	0.45 (0.29-0.70)	<.001
	Walking or Hiking, per Week					
	<20 min	**20-80 min**	**1.5-3 h**	**≥4 h**		*P* Value for Trend
Men						
Age-adjusted RR†	1.00	0.93 (0.60-1.43)	0.58 (0.35-0.95)	0.43 (0.25-0.76)		<.001
Multivariable RR†‡	1.00	0.96 (0.62-1.49)	0.61 (0.37-1.00)	0.45 (0.26-0.80)		<.001
Women						
Age-adjusted RR	1.00	0.66 (0.41-1.06)	0.57 (0.34-0.96)	0.46 (0.24-0.85)		.02
Multivariable RR†‡	1.00	0.79 (0.48-1.30)	0.65 (0.38-1.13)	0.48 (0.24-0.97)		.04
Pooled multivariable RR†‡	1.00	0.88 (0.64-1.22)	0.63 (0.43-0.91)	0.46 (0.30-0.72)		<.001

*NHS indicates Nurses' Health Study; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalents; and CI, confidence interval. The NHS analyses use 1986 as baseline.
†Data presented as RR (95% CI).
‡Relative risks are from a multivariable model that included height, age in 5-year categories, pack-years of smoking (past 15 years; current and past smokers separately), history of diabetes mellitus, and history of cholecystectomy. Moderate activity was included in the vigorous activity models.

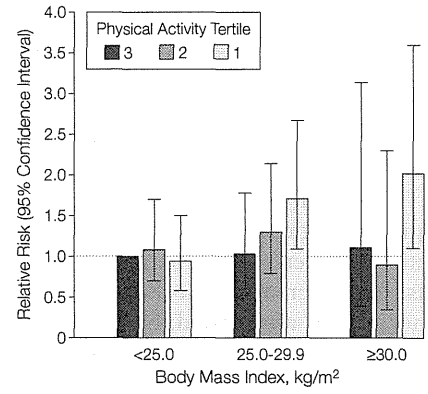
hiking and pancreatic cancer risk. Among men and women, walking or hiking 4 or more hours per week was associated with a 54% lower risk of pancreatic cancer when compared with less than 20 minutes per week.

The potential inverse association between moderate activity and pancreatic cancer risk could be the result of early symptoms associated with the disease. To address this question, we performed 2-year lag analyses in each cohort (starting follow-up time in 1988) to avoid including individuals who were diagnosed as having pancreatic cancer within 2 years of having responded to the physical activity questions. Associations in these analyses were not substantially different for total physical activity, vigorous activity, or moderate activity (pooled multivariable RR, 0.48; 95% CI, 0.25-0.92 top vs bottom quintile comparison).

To explore the possibility of an interaction between physical activity and BMI, we examined the risk of pancreatic cancer according to both total physical activity (in tertiles) and BMI (<25.0, 25.0-29.9, and ≥30.0 kg/m^2) among men and women combined. After adjusting for potential confounders, the association between total physical activity level and the pancreatic cancer risk was modified by BMI (FIGURE). Among nonoverweight participants (BMI <25 kg/m^2), total physical activity was not related to the risk of pancreatic cancer, but total physical activity was inversely associated with risk among overweight individuals (pooled multivariable RR, 0.59; 95% CI, 0.37-0.94 for top vs bottom tertile of total physical activity among individuals with BMI ≥25 kg/m^2; $P = .04$ for trend). Individuals with a BMI of 30 kg/m^2 or higher in the lowest tertile of exercise had twice the risk of pancreatic cancer compared with individuals who had a BMI of lower than 25 kg/m^2 in the highest tertile of total physical activity.

While the Figure presents data for the pooled analysis, findings were homogeneous across the 2 cohorts with the exception of a greater increase in risk in the high BMI and low physical activity category in men than women, compared with the reference (HPFS: multivariable RR, 2.43; 95% CI, 1.13-5.23; NHS: multivariable RR, 1.57; 95% CI, 0.65-3.82). The nature of the association between physical activity and BMI appears to be an example of a "joint exposure" in which elevated risk of pancreatic cancer is only apparent in individuals who have combined exposures (high BMI and low physical activity). However, the multiplicative interaction reported in the Figure was not statistically significant. Removing current smokers from these analyses resulted in similar findings.

Figure. Pancreatic Cancer According to Physical Activity and Body Mass Index From the NHS and HPFS Cohorts



NHS indicates Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

COMMENT

In 2 prospective cohort studies, we found a consistent and significant excess risk of pancreatic cancer among obese men and women (BMI ≥30 kg/m^2 compared with <23 kg/m^2). A direct association between height and the risk of pancreatic cancer was also observed in these 2 cohorts. Both cohorts demonstrated strong inverse associations for moderate physical activity, specifically for walking or hiking outdoors. Although total physical activity was not significantly related to the risk of pancreatic cancer overall, it was inversely associated with risk among overweight individuals (BMI ≥25 kg/m^2). Physical activity appeared to have no effect on risk among nonoverweight participants (<25 kg/m^2). Moreover, BMI had no apparent influence on risk among men and women who were exercising (top 2 tertiles of physical activity).

Several case-control studies have examined BMI or weight and pancreatic cancer risk, but findings have been inconsistent. A total of 4[16-18,37] of 7[14-18,37-39] case-control studies reported no association for BMI or weight and the risk of pancreatic cancer. The largest study to date,[38,39] based only on direct interviews with cases, showed a 50% to 60% increase in the risk of pancreatic cancer in obese individuals that was consistent by sex and race. Obesity was associated with increased risk of pancreatic cancer in 3 studies in which weight was determined prior to the detection of pancreatic cancer[11-13] in men, but not women, in a recent mortality cohort study.[5] A prospective cohort study of pancreatic cancer in elderly persons did not detect any association for BMI.[40]

There are several possible explanations for the discrepancies across studies on obesity and pancreatic cancer risk. Because pancreatic cancer is highly fatal, numerous case-control studies had to obtain information on cases through indirect interviews[15-18] or did not obtain weight on deceased cases.[14,38,39] These methods may have led to biased findings, if, for example, leaner individuals had higher survival rates. In retrospective studies, prediagnostic weight loss associated with pancreatic cancer may have biased weight recall. Among previous studies, cutpoints for the top categories of BMI may not have been set high enough to detect an association with BMI, as risk appears to be most elevated among men and women with a BMI of 30 or higher. In 2 studies in which no influence of BMI was observed, the cutpoints of the top categories were relatively low: 23.2 in women, 23.9 in men,[40] and 26.5 in both sexes.[16]

Previous studies have also examined the association of height and pancreatic cancer risk. Although findings have not been entirely consistent,[14-17,37] at least 2 studies reported nonsignificant positive associations for height.[16,17] In a third study conducted in the Netherlands, a sig-

nificant positive association was reported among women.[15] An association between height and cancer risk at other sites has been reported in the HPFS cohort and in other studies.[19-21] Height may serve as a proxy for net energy intake or exposure levels to growth factors such as insulin and insulin-like growth factor 1 during childhood.

To our knowledge, this was the first epidemiologic study to examine the relation between physical activity and the risk of pancreatic cancer. Thus, further studies are needed. Nonetheless, the consistency in the associations for moderate physical activity observed in 2 entirely separate cohorts argues strongly against the role of chance as an explanation for our findings.

Our findings related to BMI and physical activity may be explained, biologically, within the axis of abnormal glucose intolerance and hyperinsulinemia. In a recent prospective study, a 2-fold elevation in fatal pancreatic cancer was detected among individuals with high prediagnostic postload plasma glucose levels (>200 mg/dL [>11.1 mmol/L]) compared with low levels (<119 mg/dL [<6.6 mmol/L]).[5] Abnormal glucose metabolism and hyperinsulinemia have been proposed as underlying mechanisms that might explain the positive association between diabetes mellitus and the risk of pancreatic cancer.[4] Hyperinsulinemia has been shown to increase local blood flow and cell division within the pancreas.[41,42] By causing the downregulation of insulin-like growth factor binding protein 1, excess insulin may also result in an increase in exposure to free insulin-like growth factor 1, which has been shown to promote growth in human pancreatic cell lines.[43-45]

Physical activity has long been known to reduce glucose intolerance and an elevated BMI is associated with an increase in risk of hyperinsulinemia and diabetes. In addition, studies have demonstrated that weight loss is not necessary to benefit from the effects of physical activity on glucose tolerance and insulin clearance rates.[23,46] Our findings are consistent because we observed an inverse association between physical activity and pancreatic cancer risk, especially among those who were obese. Moreover, since the obese group is more likely to include persons with glucose abnormalities than the overweight group, evidence for a stronger inverse association with activity in the obese is consistent with a mechanism involving glucose tolerance.

An alternative mechanism for the association between BMI and pancreatic cancer may be related to DNA adduct formation.[47] Comparing pancreatic tissue from healthy individuals (organ donors) and cancer patients, DNA adduct levels were reported to be significantly higher in cancer patients. Positive correlations were found between BMI and the levels of lipid peroxidation–related DNA adducts and total adduct levels in cancer patients, which persisted after controlling for age, sex, and smoking. Thus, an increase in DNA damage to the pancreas caused by increased lipid peroxidation in individuals with elevated BMIs may be an alternative explanation for the observed association with BMI.

Our findings observed a strong association for moderate activity in both cohorts, but not for vigorous activity. One possible explanation is related to the modifying effect of obesity. Because men and women who are overweight or obese appear to benefit the most from physical activity but are less likely to participate in vigorous exercise, the effect of physical activity may be most apparent for moderate activity.

An alternative explanation for our findings is related to energy expenditure vs cardiorespiratory fitness. A recent study demonstrated that regular exercise at low intensity may be more important than cardiorespiratory fitness obtained with vigorous exercise in reducing glucose intolerance.[48] In both our cohorts, the level of vigorous activity was much lower among those with BMI of 30 kg/m^2 or higher compared with a BMI of lower than 30 (for vigorous activities: 13.0 vs 6.3 METs for BMI <30 vs BMI ≥30 in HPFS; 7.1 vs 4.5 METs for BMI <30 vs BMI ≥30 in NHS). In contrast, the difference in METs for moderate activity was substantially lower (7.8 vs 6.3 METs for BMI <30 vs BMI ≥30 in HPFS; 7.3 vs 5.5 METs for BMI <30 vs BMI ≥30 in NHS). Although the average level of METs expended in vigorous and moderate activities is similar for individuals with elevated BMIs, less time is spent exercising for those performing vigorous exercise, given that METs reflect time exercising and intensity level (intensity is higher). It is therefore possible that low activity exercising (moderate activity) is more successful at reducing risk in overweight individuals because, on average for those individuals, more time is spent exercising.

Alternatively, we cannot exclude the possibility that vigorous and moderate exercisers may have differed on other characteristics that were not considered in this article, possibly explaining the relationship reported for physical activity. However, certain dietary factors are unlikely to account for the relationships given that we observed no association for either coffee or alcohol intakes and pancreatic cancer risk,[49] and that adjusting for total fat intake did not change the associations.

The strengths of this study include a prospective design, large sample size, data from 2 completely separate cohorts, and detailed information on potential risk factors of pancreatic cancer. The prospective design precluded recall bias and the need to use next-of-kin respondents. Moreover, because exposure data were collected before the diagnosis of any cases of pancreatic cancer, any error in recall (nondifferential misclassification) would have attenuated rather than exaggerated a true association. Differential follow-up is unlikely to have made a material contribution to these findings, since follow-up was high.[50]

In summary, we observed an increased risk of pancreatic cancer among obese men and women in 2 prospective cohorts. Walking or hiking 1.5 hours or more per week was associated with a 50% reduction in pancreatic cancer risk in men and women. The inverse associa-

tion of physical activity with the risk of pancreatic cancer was most apparent among obese individuals who were more likely to have glucose abnormalities and who may thus benefit from an improved glucose response associated with exercising. While our findings require confirmation, they provide support for a role of insulin resistance and hyperinsulinemia in the pathogenesis of pancreatic cancer.

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REFERENCES

1. *Cancer Facts & Figures, 2000.* Atlanta, Ga: American Cancer Society Inc; 2000.
2. Ahlgren JD. Epidemiology and risk factors in pancreatic cancer. *Semin Oncol.* 1996;23:241-250.
3. Boyle P, Hsieh CC, Maisonneuve P, et al. Epidemiology of pancreas cancer. *Int J Pancreatol.* 1989; 5:327-346.
4. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer: a meta-analysis. *JAMA.* 1995; 273:1605-1609.
5. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA.* 2000;283:2552-2558.
6. Levine W, Dyer A, Shekelle R, Schoenberger J, Stamler J. Post-load plasma glucose and cancer mortality in middle-aged men and women: 12-year follow-up findings of the Chicago Heart Association Detection Project in Industry. *Am J Epidemiol.* 1990;131:254-262.
7. Carey VJ, Walters EE, Colditz GA, et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. *Am J Epidemiol.* 1997;145: 614-619.
8. Despres JP, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis.* 1990;10:497-511.
9. Kissebah AH, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab.* 1982;54: 254-260.
10. Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U. Impact of obesity on metabolism in men and women: importance of regional adipose tissue distribution. *J Clin Invest.* 1983;72:1150-1162.
11. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control.* 2000;11:915-923.
12. Friedman GD, Van den Eeden SK. Risk factors for pancreatic cancer: an exploratory study. *Int J Epidemiol.* 1993;22:30-37.
13. Moller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. *Eur J Cancer.* 1994;30:344-350.
14. Ji BT, Hatch MC, Chow WH, et al. Anthropometric and reproductive factors and the risk of pancreatic cancer: a case-control study in Shanghai, China. *Int J Cancer.* 1996;66:432-437.
15. Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, Walker AM. Anthropometric and reproductive variables and exocrine carcinoma of the pancreas: a population-based case-control study in the Netherlands. *Int J Cancer.* 1992;52:24-29.
16. Ghadirian P, Simard A, Baillargeon J, Maisonneuve P, Boyle P. Nutritional factors and pancreatic cancer in the francophone community in Montreal, Canada. *Int J Cancer.* 1991;47:1-6.
17. Howe GR, Ghadirian P, Bueno de Mesquita HB, et al. A collaborative case-control study of nutrient intake and pancreatic cancer within the search programme. *Int J Cancer.* 1992;51:365-372.
18. Lyon JL, Slattery ML, Mahoney AW, Robison LM. Dietary intake as a risk factor for cancer of the exocrine pancreas. *Cancer Epidemiol Biomarkers Prev.* 1993;2:513-518.
19. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med.* 1995;122:327-334.
20. Smith GD, Shipley M, Leon DA. Height and mortality from cancer among men: a prospective observational study. *BMJ.* 1998;317:1351-1352.
21. Albanes D, Jones DY, Schatzkin A, Micozzi MS, Taylor PR. Adult stature and risk of cancer. *Cancer Res.* 1988;48:1658-1662.
22. DiPietro L, Seeman T, Stachenfeld N, Katz L, Nadel E. Moderate-intensity aerobic training improves glucose tolerance in aging independent of abdominal adiposity. *J Am Geriatr Soc.* 1998;46:875-879.
23. Oshida Y, Yamanouchi K, Hayamizu S, Sato Y. Long-term mild jogging increases insulin action despite no influence on body mass index or VO2 max. *J Appl Physiol.* 1989;66:2206-2210.
24. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol.* 1994;140:1016-1019.
25. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology.* 1990;1:466-473.
26. Wolf A, Hunter D, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol.* 1994;23:991-999.
27. Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology.* 1996;7:81-86.
28. Ainsworth B, Haskell W, Leon A, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc.* 1993;25:71-80.
29. Fuchs CS, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med.* 1996;156:2255-2260.
30. Chapman D, Nam J. Asymptotic power of chi square tests for linear trends in proportions. *Biometrics.* 1968;24:315-327.
31. D'Agostino RB, Lee MLT, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: The Framingham Heart Study. *Stat Med.* 1990;9:1501-1515.
32. Silverman D, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br J Cancer.* 1999;80:1830-1837.
33. Chow WH, Johansen C, Gridley G, Mellemkjaer L, Olsen JH, Fraumeni JF Jr. Gallstones, cholecystectomy and risk of cancers of the liver, biliary tract and pancreas. *Br J Cancer.* 1999;79:640-644.
34. Baik I, Ascherio A, Rimm E, et al. Adiposity and mortality in men. *Am J Epidemiol.* 2000;152:264-271.
35. Manson JE, Stampfer MJ, Hennekens CH, Willett WC. Body weight and longevity: a reassessment. *JAMA.* 1987;257:353-358.
36. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177-188.
37. Kalapothaki V, Tzonou A, Hsieh CC, Toupadaki N, Karakatsani A, Trichopoulos D. Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. *Cancer Causes Control.* 1993;4:375-382.
38. Silverman DT, Swanson CA, Gridley G, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. *J Natl Cancer Inst.* 1998;90:1710-1719.
39. Silverman DT. Risk factors for pancreatic cancer: a case-control study based on direct interviews. *Teratog Carcinog Mutagen.* 2001;21:7-25.
40. Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE. A prospective study of pancreatic cancer in the elderly. *Int J Cancer.* 1994;58:46-49.
41. Henderson J, Daniel P, Fraser P. The pancreas as a single organ: the influence of the endocrine upon the exocrine part of the gland. *Gut.* 1981;22:158-167.
42. Fisher WE, Boros LG, Schirmer WJ. Insulin promotes pancreatic cancer: evidence for endocrine influence on exocrine pancreatic tumors. *J Surg Res.* 1996;63:310-313.
43. Takeda Y, Escribano M. Effects of insulin and somatostatin on the growth and the colony formation of two human pancreatic cancer cell lines. *J Cancer Res Clin Oncol.* 1991;117:416-420.
44. Ohmura E, Okada M, Onoda N, et al. Insulin-like growth factor I and transforming growth factor alpha as autocrine growth factors in human pancreatic cancer cell growth. *Cancer Res.* 1990;50:103-107.
45. Bergmann U, Funatomi H, Yokoyama M, Beger HG, Korc M. Insulin-like growth factor I overexpression in human pancreatic cancer: evidence for autocrine and paracrine roles. *Cancer Res.* 1995;55:2007-2011.
46. Kelley DE, Goodpaster BH. Effects of physical activity on insulin action and glucose tolerance in obesity. *Med Sci Sports Exerc.* 1999;31(suppl 11):S619-S623.
47. Wang M, Abbruzzese J, Friess H, et al. DNA adducts in human pancreatic tissues and their potential role in carcinogenesis. *Cancer Res.* 1998;58:38-41.
48. Wareham N, Wong M, Day N. Glucose intolerance and physical inactivity: the relative importance of low habitual energy expenditure and cardiorespiratory fitness. *Am J Epidemiol.* 2000;152:132-139.
49. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. *Cancer Epidemiol Biomarkers Prev.* 2001;10:429-437.
50. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. *Am J Epidemiol.* 1984; 119:837-839.

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対象の内訳		ヒト	動物	地域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		(　　)		コホート研究
	性別	男女混合	(　　)		(　　)		(　　)
	年齢	30－75歳	[redacted]		(　　)		前向き研究
	対象数	10000以上	空白		(　　)		(　　)
調査の方法	質問紙	(　　)					
アウトカム	予防	なし	なし	ガン予防	なし	(　　)	(　　)
	維持・改善	なし	なし	なし	なし	(　　)	(　　)

図表

Table 3. Relative Risk (RR) for Pancreatic Cancer in Relation to Physical Activity in the NHS and HPFS*

	Quintiles 1	2	3	4	5	P Value for Trend
Total Physical Activity, MET, h/wk						
	≤2.8	2.9-7.7	7.8-16.9	17.0-33.9	≥34.0	
Men						
Cases/person-years	31/100 149	34/102 505	39/107 012	36/107 446	19/108 111	
Age-adjusted RR†	1.00	1.05 (0.65-1.72)	0.89 (0.54-1.48)	0.84 (0.50-1.42)	0.65 (0.37-1.14)	.07
Multivariable RR†‡	1.00	1.10 (0.68-1.80)	0.95 (0.57-1.59)	0.92 (0.54-1.55)	0.72 (0.40-1.27)	.16
	≤2.0	2.1-4.6	4.7-10.4	10.5-21.7	≥21.8	
Women						
Cases/person-years	24/143 775	27/166 866	20/150 791	21/148 463	18/151 083	
Age-adjusted RR†	1.00	1.02 (0.59-1.77)	0.79 (0.44-1.43)	0.84 (0.47-1.50)	0.70 (0.38-1.30)	.21
Multivariable RR†‡	1.00	1.00 (0.58-1.77)	0.84 (0.45-1.55)	0.84 (0.45-1.55)	0.78 (0.42-1.47)	.40
Pooled multivariable RR†‡	1.00	1.06 (0.73-1.54)	0.91 (0.61-1.34)	0.86 (0.59-1.32)	0.74 (0.49-1.14)	.10
Vigorous Activity, MET, h/wk						
	0	0.1-3.4	3.5-11.9	12.0-29.9	≥30.0	
Men						
Cases/person-years	61/191 529	20/87 829	28/63 120	19/84 325	11/80 368	
Age-adjusted RR†	1.00	0.84 (0.51-1.39)	1.29 (0.83-2.03)	1.00 (0.59-1.57)	0.68 (0.35-1.30)	.32
Multivariable RR†‡	1.00	0.84 (0.51-1.40)	1.40 (0.89-2.20)	1.11 (0.66-1.87)	0.77 (0.40-1.48)	.89
	0	0.2-1.6	1.7-6.9	7.0-15.9	≥16.0	
Women						
Cases/person-years	62/246 603	11/102 880	10/87 299	13/115 069	14/98 151	
Age-adjusted RR†	1.00	0.67 (0.35-1.27)	0.70 (0.36-1.36)	0.58 (0.37-1.24)	0.88 (0.49-1.58)	.69
Multivariable RR†‡	1.00	0.66 (0.34-1.28)	0.64 (0.31-1.35)	0.76 (0.41-1.40)	1.06 (0.57-1.96)	.80
Pooled multivariable RR†‡	1.00	0.77 (0.51-1.15)	1.00 (0.47-2.14)	0.96 (0.54-1.43)	0.91 (0.56-1.43)	.74
Moderate Activity, MET, h/wk						
	<0.8	0.8-2.2	2.3-4.8	4.9-10.9	≥11.0	
Men						
Cases/person-years	33/96 894	26/108 861	38/107 632	22/105 927	20/105 770	
Age-adjusted RR†	1.00	0.74 (0.44-1.24)	0.95 (0.59-1.54)	0.53 (0.31-0.90)	0.41 (0.23-0.71)	<.001
Multivariable RR†‡	1.00	0.75 (0.45-1.25)	0.95 (0.60-1.52)	0.52 (0.31-0.90)	0.41 (0.24-0.73)	<.001
	<0.9	0.9-2.6	2.7-4.4	4.5-10.7	≥10.8	
Women						
Cases/person-years	24/124 298	25/164 001	22/164 935	23/159 687	15/147 057	
Age-adjusted RR†	1.00	0.97 (0.56-1.70)	0.72 (0.40-1.28)	0.77 (0.49-1.36)	0.51 (0.27-0.97)	.03
Multivariable RR†‡	1.00	1.01 (0.56-1.81)	0.85 (0.47-1.55)	0.85 (0.46-1.57)	0.52 (0.26-1.05)	.06
Pooled multivariable RR†‡	1.00	0.85 (0.56-1.26)	0.91 (0.63-1.33)	0.65 (0.41-1.04)	0.45 (0.29-0.70)	<.001

Walking or Hiking, per Week	<20 min	20-60 min	1.5-3 h	≥4 h	P Value for Trend
Men					
Age-adjusted RR†	1.00	0.93 (0.60-1.43)	0.58 (0.35-0.96)	0.43 (0.25-0.76)	<.001
Multivariable RR†‡	1.00	0.95 (0.62-1.49)	0.61 (0.37-1.00)	0.45 (0.25-0.80)	<.001
Women					
Age-adjusted RR†	1.00	0.66 (0.41-1.06)	0.57 (0.34-0.96)	0.46 (0.24-0.85)	.02
Multivariable RR†‡	1.00	0.79 (0.48-1.30)	0.65 (0.38-1.13)	0.48 (0.24-0.97)	.04
Pooled multivariable RR†‡	1.00	0.88 (0.64-1.22)	0.63 (0.43-0.91)	0.46 (0.30-0.72)	<.001

*NHS indicates Nurses' Health Study; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalents; and CI, confidence interval. [illegible]
†Data presented as RR (95% CI).
‡Relative risks are from a multivariable model that included height, age in 5-year categories, pack-years of smoking (past 15 years; current and past smokers separately), history of diabetes mellitus, and history of cholecystectomy. Moderate activity was included in the vigorous activity models.

図表掲載箇所	P926, Table 3
概要（800字まで）	The Health Professionals Follow-up Studyとthe Nurses' Health Studyに参加している男性46648名（40－75歳）と女性117041名（30－55歳）を10～20年追跡し、身体活動や肥満や身長が、すい臓がんの発症に関与しているかを検討した論文である。身体活動は、過去1年間における8つの活動（ウォーキングやハイキング、ジョギング、ランニング、自転車、水泳、テニス、ラケットボール、健康体操、エアロビクス、ダンス）に関しての平均的な時間が尋ねられた。またウォーキングのスピードと階段の階数も尋ねられた。家事活動や職業については含まなかった。男性において、総身体活動量が2.8メッツ・時/週以下の者は、2.9－7.7, 7.8－16.9, 17.1－33.9, 34以上メッツ・時/週のものと比較して、すい臓がんのリスクが、1.10(0.68-1.8), 0.95(0.57-1.59), 0.92(0.54-1.55), 0.72(0.40-1.27)を示し、有意なリスク低下は認められなかった。女性においても、身体活動量増大に伴うリスクの低下は認められなかった。一方中強度身体活動に絞った場合、最も身体活動量が少ない群と比較して、最も多い群は0.45（0.29-0.70）のリスク低下が認められた。また、BMIで層別化し、同様の検討を行ったところ、BMI25以下の者では、身体活動量と膵臓がんのリスクと関係は認められなかったが、BMI25以上の者において、身体活動量と膵臓がん発症との関連に有意な関連が認められた。
結論（200字まで）	すい臓がんの発症における身体活動量の関連に関して、中高強度身体活動が多いことで膵臓がんの発症リスクを下げることが示された。また総身体活動に関しては、全対象者では関連が認められなったが、BMIが25以上のものでは、総身体活動量が多いものほど、膵臓がん発症リスクを低下させることが明らかとなった。
エキスパートによるコメント（200字まで）	膵臓がんと身体活動の関係については、これまであまり報告がされていなかったが、本研究のような大規模な研究によりこれらの関係が明らかにされたことは非常に意義深いと考えられる。

担当者　村上晴香

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A prospective study of lifetime physical activity and prostate cancer incidence and mortality

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BACKGROUND: The possible benefit of lifetime physical activity (PA) in reducing prostate cancer incidence and mortality is unclear.
METHODS: A prospective cohort of 45 887 men aged 45–79 years was followed up from January 1998 to December 2007 for prostate cancer incidence ($n=2735$) and to December 2006 for its subtypes and for fatal ($n=190$) prostate cancer.
RESULTS: We observed an inverse association between lifetime (average of age 30 and 50 years, and baseline age) total PA levels and prostate cancer risk. Multivariate-adjusted incidence in the top quartile of lifetime total PA decreased by 16% (95% confidence interval (CI) = 2–27%) compared with that in the bottom quartile. We also observed an inverse association between average lifetime work or occupational activity and walking or bicycling duration and prostate cancer risk. Compared with men who mostly sit during their main work or occupation, men who sit half of the time experienced a 20% lower risk (95% CI = 7–31%). The rate ratio linearly decreased by 7% (95% CI = 1–12%) for total, 8% (95% CI = 0–16%) for localised and 12% (95% CI = 2–20%) for advanced prostate cancer for every 30 min per day increment of lifetime walking or bicycling in the range of 30 to 120 min per day.
CONCLUSION: Our results suggest that not sitting for most of the time during work or occupational activity and walking or bicycling more than 30 min per day during adult life is associated with reduced incidence of prostate cancer.
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Keywords: lifetime; occupational activity; walking; cycling; physical activity; cohort; prostate cancer

An expert panel from the World Cancer Research Fund/American Institute for Cancer Research has reported that physical activity (PA) may specifically reduce the risk of advanced or aggressive prostate cancer, but no formal judgment was made regarding the strength of the evidence (WCRF/AICR, 2007). A review of 24 studies of PA and prostate cancer risk found the evidence to be inconsistent, mainly because of the heterogeneous nature of neoplasm, and urged an investigation of PA at different ages as a potentially productive approach (Friedenreich and Thune, 2001).

Two case–control studies have included a measure of lifetime PA (Friedenreich *et al*, 2004; Wiklund *et al*, 2008); one found a non-significant decrease in prostate cancer risk for lifetime recreational activity (Friedenreich *et al*, 2004), whereas the contrary was found in the other study (Wiklund *et al*, 2008). No cohort study has examined detailed measures of lifetime PA in relation to prostate cancer incidence or mortality.

To investigate lifetime total PA – and more specifically work or occupational activity and walking or bicycling, the main component of active living – in relation to incident and fatal prostate cancer, we analysed data from a population-based cohort of middle-aged and elderly men who reported their usual PA in the previous year, at age 50 and 30 years.

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MATERIALS AND METHODS

The population-based cohort of Swedish men was established in 1997–1998, when all eligible men ($n=100\,303$) aged 45–79 years residing in Västmanland and Örebro counties (central Sweden) received an invitation to participate in the study, along with a self-administered questionnaire. This covered walking or bicycling; current waist, hip and height measurements; education level; cigarette smoking; alcohol consumption; diabetes; family history of prostate cancer; and other lifestyle factors. A total of 48 645 men returned the questionnaire.

In this analysis, we excluded participants who returned an incomplete questionnaire ($n=92$), died before 1 January 1998 ($n=55$), moved out of the study area ($n=19$) or had a previous cancer diagnosis ($n=2592$); after exclusions, 45 887 men were included. This large population-based cohort is representative of Swedish males aged 45–79 years, in terms of age distribution, educational level and prevalence of overweight (Norman *et al*, 2002). Incidence rates are also comparable; for example, the incidence rate among men aged 65–69 years is 603 in the cohort and 595 per 100 000 men in entire Sweden (NBHW, 2000).

Information on usual PA levels at different ages (current, age 50 years and age 30 years) was collected using five questions relating

to occupation, housework, walking or cycling, leisure-time exercise and inactive leisure time (e.g., watching TV or reading). There were six predefined activity levels for occupational activity (from mostly sitting down to heavy manual labour) and five to six predefined categories for time spent on different activities, such as walking or bicycling (hardly ever to more than 90 min per day), home or household work (less than 1 h to more than 8 h per day), inactive leisure time (from 2 h per day or less to 5 h per day or more) and active leisure-time exercising (from less than 1 h to more than 5 h per week). There was also an open question regarding the number of sleeping hours per day.

Physical activity levels for specific activities were estimated by multiplying reported duration (hours per day) by absolute intensity. This was determined by the rate of work being performed and does not take into account the physiological capacity of the individual. The absolute intensity of activities, defined in multiples of the metabolic equivalent (MET, kcal $kg^{-1} \times h$) of sitting quietly for 1 h, was based on a compendium of PAs (Ainsworth *et al*, 2000). More details regarding the calculations and assigned intensity values used can be found elsewhere (Norman *et al*, 2001). The total PA scores at age 30 and 50 years, and at baseline age, were calculated by summing the products of duration and intensity for each PA type. The major contributor (60%) to active leisure time was walking or bicycling.

The PA questions were validated using two 7-day activity records that were maintained 6 months apart in a group of Swedish men aged 44–78 years. The 7-day activity records were shown to correlate well with the total PA questionnaire data, with a Spearman correlation coefficient of 0.6. The reproducibility of total PA, as reflected by the Spearman correlation coefficient between the first questionnaire and that obtained 6 months later, was 0.65 (Norman *et al*, 2001).

The adult lifetime average total PA (MET, h per day), work or occupational activity level and walking or bicycling (min per day) were estimated for each participant, with at least two observed values as the average of the three measures of PA at ages 30 and 50 years, and at baseline age.

Incident cases of prostate cancer were ascertained by computerised record linkage with the Swedish National Cancer Register and the Regional Cancer Register covering the study area, both of which are estimated to be almost 100% complete (Mattsson and Wallgren, 1984). From 1 January 1998 through to 31 December 2007, during 416 172 person-years, we documented 2735 newly diagnosed cases. Information on tumour–node–metastasis stage, the Gleason grade and the value of prostate-specific antigen (PSA) at prostate cancer diagnosis were available from the Swedish Prostate Cancer Quality Registry. Incident cases were classified by subtype as localised (T1–2, NX-0, MX-0 or PSA <20 or Gleason grade $\leqslant 7$) and advanced ($>$T2, NX-1, MX-1 or PSA >100 or Gleason grade >7). From 1 January 1998 through to 31 December 2006, during 377 904 person-years, we documented 1098 localised and 970 advanced cancers at diagnosis, 190 of which were fatal. Information on prostate cancer death was ascertained through linkage to the Swedish Register of Death Causes at the National Board of Health and Welfare. Classification of deaths was based on International Classification of Diseases (ICD-10, code 61 for prostate cancer).

Statistical analysis

The Cox proportional hazards model was used to estimate prostate cancer rate ratios (RRs) and 95% confidence intervals associated with lifetime average PA (total daily score, work or occupational and walking or bicycling) levels.

For incidence analyses, each participant accrued follow-up time from 1 January 1998 until the date of prostate cancer diagnosis, death from any cause or study end (31 December 2007 for total prostate cancer or 31 December 2006 for subtypes of prostate cancer), whichever came first. For fatal prostate cancer analysis, each participant accrued follow-up time from 1 January 1998 until the date of prostate cancer death, death from any cause or study end (31 December 2006), whichever came first.

In all multivariate analyses, we adjusted for baseline age, waist-to-hip ratio, height, diabetes, alcohol consumption, smoking status, years of education, total energy intake, consumption of dairy product and red meat and parental history with respect to prostate cancer.

We checked whether the proportional hazard assumption was reasonable in the multivariate models. Scaled Schoenfeld's residuals were regressed against survival time. There was no evidence of departure from the assumption. Restricted cubic splines (three knot positions corresponding to quartiles of observations) were used to flexibly model and graph the multivariate-adjusted rate ratio for lifetime average total daily PA and walking or bicycling duration in predicting prostate cancer incidence and mortality. We examined potential effect modification for the relationship between lifetime total PA and total cancer incidence according to the interval between study entry and diagnosis, baseline age ($\leqslant 60$, >60 years), educational level (post-secondary education *vs* lower) and waist–hip ratio (<0.95, $\geqslant 0.95$), and tested the statistical significance of the interactions using the Wald test.

Of the participants, 60% had complete data on lifetime PA activity (age 30 and 50 years, and current age), 20% had one missing value (one of three time periods not reported), 10% had two missing values and only 10% had all three missing values. The proportion of incomplete data was 21% for waist–hip ratio and less than 5% for the remaining covariate data. A complete-subjects approach reduced the analytic cohort to 28 515 men, in which there were 1709 incidences of prostate cancer and 100 fatal prostate cancer cases. To evaluate a potential effect of missing values on the observed results, we used multivariate imputation by chained equations to obtain five imputed data sets of the analytic cohort including 45 887 men (van Buuren *et al*, 1999; Royston, 2004). The rate ratios estimated on imputed data sets were pooled together using Rubin's rule to obtain valid statistical inferences (Rubin and Schenker, 1986). We compared the rate ratios based on the two approaches (complete-subjects and multiple imputation) by calculating the relative difference defined as (RR complete case−RR multiple imputation)/RR multiple imputation.

All reported *P*-values are two-sided. All statistical analyses were performed with Stata, version 10 (StataCorp, College Station, TX, USA).

RESULTS

Baseline characteristics of the study population by quartiles of lifetime total PA are shown in Table 1. Compared with men in the bottom quartile of total activity, those in the higher quartiles were more likely to avoid sitting most of the time during their main work or occupation, more likely to walk or bike more than 60 min per day and less likely to have post-secondary education. Prostate cancer cases had an average age of 66 years at baseline and 72 years at diagnosis. The majority of cases (80%) were diagnosed because of clinical symptoms followed by health checkups (20%). Age and multivariate-adjusted rate ratios for prostate cancer incidence (total, localised and advanced) and mortality according to quartiles of lifetime average total PA are shown in Table 2.

Lifetime total PA was significantly inversely associated with rates of total prostate cancer incidence. The age-adjusted rate ratio for the top quartile of lifetime total PA was associated with 17% lower risk of total prostate cancer compared with the bottom quartile. Further adjustment for waist–hip ratio, height, history of diabetes, alcohol consumption, smoking status, educational level, total energy intake, consumption of dairy product and meat and parental history of prostate cancer did not substantially change the estimate; incidence in the top quartile of lifetime total PA

Table 1 Age-standardized baseline characteristics by quartiles of lifetime (age 30 and 50 years, and current age) average total physical activity in the cohort of 45 887 Swedish men aged 45–79 years followed-up from 1998 to 2007

	Quartiles of total physical activity, range (median), MET-h per day[a]				
Characteristics[b]	**Q1, <39 (37)**	**Q2, 39–42.4 (41)**	**Q3, 42.5–46 (44)**	**Q4, >46 (48)**	**Missing**
No. of individuals	9143	9143	9143	9143	9315
Not mostly sitting at work or occupation (%)	48	97	99	100	91
Walking or bicycling >60 min per day (%)	3	11	20	40	23
Age (mean, years)	57	60	60	61	64
Body mass index (kg m^{-2})	26	26	26	26	26
Height (cm)	178	178	177	177	176
Waist–hip ratio ⩾0.95 (%)	42	40	41	40	45
Prostate diagnosis by symptoms (%)	71	76	79	68	82
History of diabetes (%)	8	8	8	8	13
Family history of prostate cancer (%)	6	7	7	9	11
Alcohol consumption (never, %)	4	4	5	6	7
Smoking (never, %)	39	38	35	35	33
Education (>12 years, %)	32	21	11	5	11
Intake (mean)					
Calories per day	2609	2670	2746	2923	2611
Dairy product (times per day)[c]	5.3	5.4	5.7	6.2	5.4
Red meat (times per day)[d]	1.3	1.3	1.3	1.3	1.2

[a]All factors, except age, were directly standardized to the age distribution of the study participants. [b]Lifetime total physical activity (home or household work, work or occupation, walking or bicycling, exercise, and watching TV or reading) is the average of daily activities at age 30 and 50 years, and current (baseline) age, and it is expressed in metabolic equivalents (METs). [c]Dairy products indicates milk, cheese, yogurt, cream, and crème fraiche. [d]Red meat indicates meatballs, pork, veal, sausage, and black pudding.

Table 2 Age-adjusted and multivariate rate ratios for total, localised, advanced and fatal prostate cancer according to quartiles of lifetime (age 30 and 50 years, and current age) average total physical activity levels

	Lifetime average total physical activity, MET-hours/day				
	Q1, <39 (37)	**Q2, 39–42.4 (41)**	**Q3, 42.5–46 (44)**	**Q4, >46 (48)**	***P*-trend**
Total-incidence prostate cancer					
No. of cases	419	414	447	429	
Age-adjusted RR (95% CI)	1	0.86 (0.75–0.98)	0.91 (0.79–1.04)	0.83 (0.73–0.96)	0.030
Multivariate RR (95% CI)[a]	1	0.86 (0.75–0.99)	0.91 (0.79–1.05)	0.84 (0.73–0.98)	0.065
Localised					
No. of cases	188	162	156	182	
Age-adjusted RR (95% CI)	1	0.74 (0.60–0.91)	0.70 (0.56–0.86)	0.78 (0.64–0.96)	0.045
Multivariate RR (95% CI)[a]	1	0.75 (0.61–0.93)	0.73 (0.58–0.91)	0.82 (0.66–1.03)	0.184
Advanced					
No. of cases	133	155	172	126	
Age-adjusted RR (95% CI)	1	0.97 (0.77–1.23)	1.05 (0.84–1.32)	0.73 (0.57–0.94)	0.014
Multivariate RR (95% CI)[a]	1	0.98 (0.78–1.25)	1.07 (0.84–1.36)	0.75 (0.58–0.98)	0.035
Fatal prostate cancer					
No. of cases	20	25	27	28	
Age-adjusted RR (95% CI)	1	0.97 (0.54–1.75)	1.02 (0.57–1.82)	0.99 (0.56–1.78)	0.989
Multivariate RR (95% CI)[a]	1	0.96 (0.53–1.75)	1.02 (0.55–1.87)	0.98 (0.53–1.83)	0.999

Abbreviations: CI, confidence interval; RR, rate ratio. [a]Multivariate RRs were adjusted for age (years, continuous), waist–hip ratio (quartiles), height (continuous), diabetes (yes or no), alcohol consumption (current drinker, former drinker and never drinker), smoking status (current smoker, former smoker and never smoked), years of education (1–9 years, 9–12 years, more than 12 years), total energy intake (calories, continuous), consumption of dairy product (times per day, continuous) and red meat (times per day, continuous) and parental history with respect to prostate cancer (yes, no or not known). A complete-subjects analysis automatically discarded missing values on any covariate.

Epidemiology

decreased by 16% (95% CI = 2–27%) compared with the bottom. The inverse relationship between lifetime total PA modelled as a continuous variable and total prostate cancer risk is presented graphically in Figure 1. Excluding the first 4 years of follow-up did not change this association with PA; the multivariate-adjusted rate ratio in the top quartile of total PA significantly decreased by 17% (95% CI = 1–30%) compared with the bottom.

The magnitude and direction of the estimates based on complete subjects and multiple imputation were overall similar. The multivariate-adjusted rate ratio based on five imputed data sets in the top quartile of total PA significantly decreased by 14% (95% CI = 2–25%) compared with the bottom. The averages of the relative differences were 0.7% for the incidence of total prostate cancer, 0.2% for localised, 1.1% for advanced and 13.5% for fatal. In addition, we examined whether the influence of lifetime total PA on incidence differed according to the interval between study entry and diagnosis; no significant effect modification was observed ($P_{interaction} = 0.30$). Furthermore, there was no evidence of a

significant interaction between lifetime total PA and age ($P_{interaction} = 0.61$), educational level ($P_{interaction} = 0.28$) or waist–hip ratio ($P_{interaction} = 0.80$).

For subtypes (Table 2), the multivariate-adjusted rate ratio in the top quartile of lifetime total PA was 18% lower (95% CI = 0.66–1.03) for localised and 25% lower (95% CI = 0.58–0.98) for advanced prostate cancer compared with the bottom quartile.

We then investigated the mutually adjusted effect of lifetime work or occupational activity and leisure-time walking or bicycling – the main determinants of the total PA score – on prostate cancer risk. Compared with men who mostly sit during their main work or occupation and controlling for walking or bicycling levels, men who sit half of the time experienced a 20% lower risk (95% CI = 7–31%) of prostate cancer (Table 3). Heavy manual occupations were associated with a significantly lower risk of 28% (95% CI = 10–43%) compared with sedentary work or occupation. The multivariate-adjusted (including work or occupation activity) incidence for those men walking or bicycling a lifetime average duration of over 60 min per day was 14% (95% CI = 2–24%) lower than in those who walked or biked 20–40 min per day (Table 4). Advanced prostate cancer incidence decreased by 26% (95% CI = 8–41%) for men walking or bicycling more than 60 min per day compared with those who walked or biked 20–40 min per day.

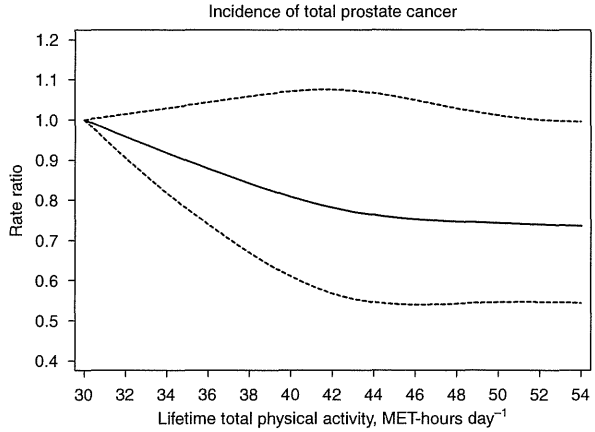

Figure 1 Multivariate rate ratio for lifetime average total physical activity (average of age 30 and 50 years, and baseline age) as predictor of total incidence of prostate cancer rates. Data were fitted using a Cox regression model with restricted cubic splines. Data were adjusted for baseline age, waist–hip ratio, height, diabetes, alcohol consumption, smoking status, years of education, total energy intake, consumption of dairy product and red meat and parental history with respect to prostate cancer. Dotted lines represent 95% confidence limits.

Examining the associations with lifetime average walking or bicycling duration as a continuous variable, and using a reference value of 30 min per day, the adjusted rate ratio for total prostate cancer decreased linearly by 7% (95% CI = 1–12%) for every 30 min per day increment in the range of 30–120 min per day. No significant trend was observed in the incidence of total prostate cancer below a lifetime average walking or bicycling of 30 min per day (Figure 2A).

Compared with men who walked or biked a lifetime average of 30 min per day, the adjusted rate ratio for localised prostate cancer linearly decreased by a marginally significant 8% (95% CI = 0–16%) for every 30 min per day increment of lifetime average walking or bicycling in the range of 30–120 min per day. The adjusted rate ratio for advanced disease linearly decreased by 12% (95% CI = 2–20%) for every 30 min per day increment in the range of 30–120 min per day (Figure 2B). For fatal prostate cancer, apart from the greater uncertainty of estimates due to the smaller number of cases, the results were similar to those for advanced disease (Figure 3). The fatality rate among those men who hardly ever walked or biked increased by about two-fold (rate ratio was 1.85; 95% CI = 0.89–3.86) compared with men in the highest average lifetime walking or bicycling of 120 min per day, although this increased rate was not significant.

Table 3 Age-adjusted and multivariate rate ratios for total, localised, advanced and fatal prostate cancer according to lifetime (age 30 and 50 years and current age) work or occupational activity levels

	Lifetime average work or occupational activity levels				
	Mostly sitting	**Sitting half of the time**	**Mostly standing**	**Heavy manual labour**	***P*-trend**
Total-incidence prostate cancer					
No. of cases	291	405	1141	111	
Age-adjusted RR (95% CI)	1	0.81 (0.69–0.94)	0.80 (0.70–0.91)	0.72 (0.58–0.89)	0.003
Multivariate RR (95% CI)[a]	1	0.80 (0.69–0.93)	0.79 (0.69–0.91)	0.72 (0.57–0.90)	0.007
Localised					
No. of cases	123	184	439	36	
Age-adjusted RR (95% CI)	1	0.86 (0.68–1.08)	0.71 (0.58–0.87)	0.55 (0.38–0.79)	<0.001
Multivariate RR (95% CI)[a]	1	0.87 (0.69–1.09)	0.72 (0.58–0.90)	0.55 (0.38–0.82)	<0.001
Advanced					
No. of cases	96	129	422	39	
Age-adjusted RR (95% CI)	1	0.75 (0.57–0.97)	0.85 (0.68–1.07)	0.75 (0.52–1.10)	0.546
Multivariate RR (95% CI)[a]	1	0.74 (0.56–0.97)	0.88 (0.69–1.12)	0.79 (0.54–1.18)	0.853
Fatal prostate cancer					
No. of cases	16	21	82	8	
Age-adjusted RR (95% CI)	1	0.65 (0.34–1.25)	0.86 (0.50–1.48)	0.84 (0.36–1.97)	0.814
Multivariate RR (95% CI)[a]	1	0.64 (0.33–1.23)	0.88 (0.49–1.58)	0.89 (0.36–2.17)	0.679

Abbreviations: CI, confidence interval; RR, rate ratio. [a]Multivariate RRs were adjusted for lifetime average walking or bicycling levels (hardly ever, <20, 20–40, 41–60 and >60 min per day), age (years, continuous), waist–hip ratio (quartiles), height (continuous), diabetes (yes or no), alcohol consumption (current drinker, former drinker and never drinker), smoking status (current smoker, former smoker and never smoked), years of education (1–9 years, 9–12 years, more than 12 years), total energy intake (calories, continuous), consumption of dairy product (times per day, continuous) and red meat (times per day, continuous) and parental history with respect to prostate cancer (yes, no or not known). A complete-subjects analysis automatically discarded missing values on any covariate.

Table 4 Age-adjusted and multivariate rate ratios for total, localised, advanced and fatal prostate cancer according to lifetime (age 30 and 50 years, and current age) walking or bicycling levels

	Lifetime average walking or bicycling, min per day					
	Hardly ever	**<20**	**20–40**	**41–60**	**>60**	***P*-trend**
Total-incidence prostate cancer						
No. of cases	55	391	706	411	403	
Age-adjusted RR (95% CI)	0.99 (0.75–1.30)	0.97 (0.86–1.10)	1	0.96 (0.85–1.09)	0.87 (0.77–0.98)	0.049
Multivariate RR (95% CI)[a]	1.03 (0.78–1.36)	0.97 (0.86–1.10)	1	0.96 (0.85–1.08)	0.86 (0.76–0.98)	0.028
Localised						
No. of cases	21	142	293	179	161	
Age-adjusted RR (95% CI)	0.92 (0.59–1.43)	0.86 (0.70–1.05)	1	1.01 (0.84–1.22)	0.84 (0.69–1.02)	0.447
Multivariate RR (95% CI)[a]	0.98 (0.63–1.53)	0.86 (0.70–1.05)	1	1.00 (0.83–1.21)	0.84 (0.69–1.02)	0.393
Advanced						
No. of cases	15	149	248	148	128	
Age-adjusted RR (95% CI)	0.85 (0.50–1.44)	1.09 (0.89–1.34)	1	0.94 (0.77–1.16)	0.74 (0.60–0.92)	0.002
Multivariate RR (95% CI)[a]	0.88 (0.52–1.49)	1.10 (0.89–1.35)	1	0.94 (0.76–1.15)	0.74 (0.59–0.92)	0.001
Fatal prostate cancer						
No. of cases	4	26	44	28	25	
Age-adjusted RR (95% CI)	1.71 (0.61–4.81)	1.19 (0.73–1.93)	1	0.93 (0.58–1.49)	0.73 (0.45–1.20)	0.062
Multivariate RR (95% CI)[a]	1.81 (0.64–5.12)	1.21 (0.74–1.97)	1	0.90 (0.56–1.46)	0.72 (0.44–1.18)	0.044

Abbreviations: CI, confidence interval; RR, rate ratio. [a]*Multivariate RRs were adjusted for lifetime work or occupational activity levels (mostly sitting, sitting half of the time, mostly standing and heavy manual labour), age (years, continuous), waist–hip ratio (quartiles), height (continuous), diabetes (yes or no), alcohol consumption (current drinker, former drinker and never drinker), smoking status (current smoker, former smoker and never smoked), years of education (1–9 years, 9–12 years, more than 12 years), total energy intake (calories, continuous), consumption of dairy product (times per day, continuous) and red meat (times per day, continuous) and parental history with respect to prostate cancer (yes, no or not known). A complete-subjects analysis automatically discarded missing values on any covariate.*

DISCUSSION

In this large population-based prospective cohort study of middle-aged and elderly men, we observed a significant inverse dose–response association between adult lifetime total PA and occupational and leisure-time walking or bicycling with prostate cancer incidence. Compared with those who mostly sit during their main work or occupation, men who sit half of the time or even less experienced a 20% lower risk of prostate cancer. Compared with men who walked or biked an average of 30 min per day, every increment of 30 min per day was associated with an incidence reduction of 7% for total, 8% for localised and 12% for advanced disease. No significant changes in incidence were observed below the lifetime walking or bicycling average duration of 30 min per day. Fatal prostate cancer rate was about two-fold higher among men who hardly ever walked or biked compared with those men who maintained the highest lifetime average of 120 min per day, although this increase was not statistically significant.

Our finding that the highest level of lifetime walking or bicycling, averaged approximately more than 40 years before diagnosis, was associated with 16% reduced risk is consistent with a previous Canadian case–control study that reported a non-significant 20% reduced risk of all prostate cancer for the top lifetime recreational level (Friedenreich *et al*, 2004). Our finding of an inverse association between lifetime walking or bicycling for 1 h per day or more and prostate cancer incidence supports the PA recommendation of the World Cancer Research Fund/American Institute for Cancer Research, which calls for a moderate activity of longer duration, namely, 60 min per day or more (WCRF/AICR, 2007). Furthermore, our finding of a strong inverse association (26% risk reduction) between lifetime walking or bicycling for an average of more than 1 h per day and advanced prostate cancer supports the findings of a previous large prospective cohort study of American men (Patel *et al*, 2005). In the American Cancer Society Cancer Prevention Study II Nutrition Cohort, baseline recreational PA (recent-past only) corresponding to 35 MET-hours per week or more (roughly corresponding to 1 h of walking or bicycling per day or more) was associated with a significant 31% risk reduction for aggressive prostate cancer (Patel *et al*, 2005).

In the Health Professional follow-up study, a strong inverse association (around 70% risk reduction) between recent-past vigorous PA and metastatic prostate cancer was observed only in men aged 65 years or older, with an evidence of effect modification by age (Giovannucci *et al*, 2005). In our analysis, we found no evidence of heterogeneity in the relationship across subgroups defined by age, educational level and waist–hip ratio.

The biological mechanisms by which PA may decrease prostate cancer risk are unknown, but PA may affect certain hormones hypothesised to be associated with prostate carcinogenesis, including insulin resistance (Goodyear and Kahn, 1998), adiponectin levels (Kelesidis *et al*, 2006; Bluher *et al*, 2007), insulin-like growth factors (Chan *et al*, 1998) and testosterone (Eaton *et al*, 1999).

Major strengths of our study include the large size of the cohort, its population-based and prospective design, the relatively large number of incident prostate cancers and the completeness of case ascertainment through the Regional and National Cancer Register. These features of the study substantially reduce the potential risk of recall and selection biases, and, importantly, increase the generalisability of the study findings. According to the National Prostate Cancer Register data, the most common cause of diagnosis in Sweden was clinical symptom (about 80% in our data), followed by health checkup (Adolfsson *et al*, 2007). Prostate-specific antigen testing may be considered to introduce bias, as this screening technique may only detect certain types of tumour. There is no official recommendation in Sweden on PSA testing as part of health checkups or for screening purposes in men without lower urinary tract symptoms (Adolfsson *et al*, 2007), hence any bias that may be introduced by PSA is of limited relevance in our data.

A potential limitation of this study is that PA was assessed through a self-administered questionnaire, which could lead to classification errors. Although our earlier validation study had indicated an overall good validity and reproducibility, there were

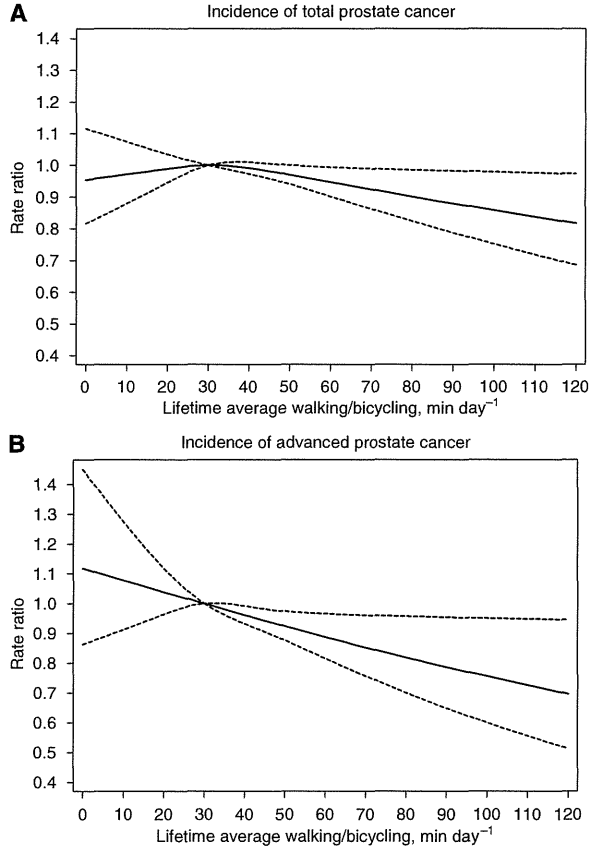

Figure 2 Multivariate rate ratio for lifetime average walking or bicycling duration (average of age 30 and 50 years, and baseline age) as predictor of total (**A**) and advanced (**B**) prostate cancer rates. Data were fitted using a Cox regression model with restricted cubic splines (reference value at 30 min per day). Data were adjusted for baseline age, lifetime work or occupational activity, waist–hip ratio, height, diabetes, alcohol consumption, smoking status, years of education, total energy intake, consumption of dairy product and red meat and parental history with respect to prostate cancer. Dotted lines represent 95% confidence limits.

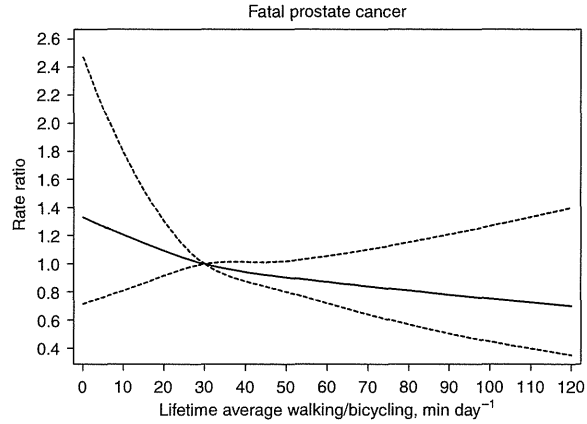

Figure 3 Multivariate rate ratios for lifetime average walking or bicycling duration (average of age 30 and 50 years, and baseline age) as predictor of fatal prostate cancer. Data were fitted using a Cox regression model with restricted cubic splines (reference value at 30 min per day). Data were adjusted for baseline age, lifetime work or occupational activity, waist–hip ratio, height, diabetes, alcohol consumption, smoking status, years of education, total energy intake, consumption of dairy product and red meat and parental history with respect to prostate cancer. Dotted lines represent 95% confidence limits.

some differences in measurement error that were dependent on individual characteristics such as body mass index (Norman *et al*, 2001). We found that the reliability of the historical PA questionnaire was relatively high (Spearman–Brown reliability were 0.7 at both age 50 and 30 years) (Orsini *et al*, 2007). Validity measures of recalled PA in the distant past were not available. However, a study on the quality of recall of PA in the distant past (32–35 years) found that about 70% of the participants (mean age 58 *vs* 60 years in our study) were good recallers, and quality was not significantly associated with age or body weight (Falkner *et al*, 2001).

As information on exposures was collected prospectively, any non-differential misclassification would probably have attenuated rather than exaggerated any true relationships, it is unlikely to explain the significant associations observed. Our study was observational, hence we cannot entirely rule out the possibility of residual confounding. Nevertheless, age-adjusted and multivariate-adjusted analyses provided overall similar results, suggesting that this is unlikely to explain our findings.

The inverse relation with PA might be the result of reverse causation if low PA was a result of an undiagnosed prostate cancer. If this were true, we might expect the effect of PA on prostate cancer risk to change after excluding the first 4 years of follow-up, but it did not.

Missing data related to prostate cancer or both PA and prostate cancer may lead to biased estimates (Demissie *et al*, 2003). However, we observed only relatively small differences when comparing complete-subject and multiple imputation approaches, suggesting that the subsample with complete data was a random subset of the entire sample.

Findings from this population-based prospective cohort study show that not sitting for most of the time during work or occupational activity and longer daily durations of the main component of active living (walking or bicycling) may be associated with reduced prostate cancer incidence. Our findings, which may have major public health implications in the prevention of prostate cancer, require confirmation by other well-designed studies.

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This study was supported by the Swedish Research Council/Longitudinal studies, by the Swedish Cancer Society and by the Swedish Foundation for International Cooperation in Research and Higher Education (STINT). NO analysed the data and drafted the paper incorporating critical inputs from all authors. AW is a principal investigator of the cohort; she conceived the study and participated in its design and coordination. RB, MB, MP, SA, JJ, EG and AW provided critical revision of the paper and assisted with the analysis and interpretation. All authors have read and approved the final paper. We have obtained approval from the Ethical Committees at Karolinska Institutet to study diet and different lifestyle factors (physical activity) in relation to prostate cancer (KI Dnr 03-645) in the Cohort of Swedish men.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

Adolfsson J, Garmo H, Varenhorst E, Ahlgren G, Ahlstrand C, Andren O, Bill-Axelson A, Bratt O, Damber JE, Hellstrom K, Hellstrom M, Holmberg E, Holmberg L, Hugosson J, Johansson JE, Petterson B, Tornblom M, Widmark A, Stattin P (2007) Clinical characteristics and primary treatment of prostate cancer in Sweden between 1996 and 2005. *Scand J Urol Nephrol* **41:** 456–477

Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS (2000) Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* **32:** S498–S504

Bluher M, Brennan AM, Kelesidis T, Kratzsch J, Fasshauer M, Kralisch S, Williams CJ, Mantzoros CS (2007) Total and high-molecular weight adiponectin in relation to metabolic variables at baseline and in response to an exercise treatment program: comparative evaluation of three assays. *Diabetes Care* **30:** 280–285

Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, Hennekens CH, Pollak M (1998) Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* **279:** 563–566

Demissie S, LaValley MP, Horton NJ, Glynn RJ, Cupples LA (2003) Bias due to missing exposure data using complete-case analysis in the proportional hazards regression model. *Stat Med* **22:** 545–557

Eaton NE, Reeves GK, Appleby PN, Key TJ (1999) Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. *Br J Cancer* **80:** 930–934

Falkner KL, McCann SE, Trevisan M (2001) Participant characteristics and quality of recall of physical activity in the distant past. *Am J Epidemiol* **154:** 865–872

Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, Elliott FG (2004) Case–control study of lifetime total physical activity and prostate cancer risk. *Am J Epidemiol* **159:** 740–749

Friedenreich CM, Thune I (2001) A review of physical activity and prostate cancer risk. *Cancer Causes Control* **12:** 461–475

Giovannucci EL, Liu Y, Leitzmann MF, Stampfer MJ, Willett WC (2005) A prospective study of physical activity and incident and fatal prostate cancer. *Arch Intern Med* **165:** 1005–1010

Goodyear LJ, Kahn BB (1998) Exercise, glucose transport, and insulin sensitivity. *Annu Rev Med* **49:** 235–261

Kelesidis I, Kelesidis T, Mantzoros CS (2006) Adiponectin and cancer: a systematic review. *Br J Cancer* **94:** 1221–1225

Mattsson B, Wallgren A (1984) Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* **23:** 305–313

NBHW (2000) *Cancer Incidence In Sweden 1998.* The National Board of Health and Welfare, Centre of Epidemiology: Stockholm. Report no. 91-7201-450-4

Norman A, Bellocco R, Bergstrom A, Wolk A (2001) Validity and reproducibility of self-reported total physical activity–differences by relative weight. *Int J Obes Relat Metab Disord* **25:** 682–688

Norman A, Bellocco R, Vaida F, Wolk A (2002) Total physical activity in relation to age, body mass, health and other factors in a cohort of Swedish men. *Int J Obes Relat Metab Disord* **26:** 670–675

Orsini N, Bellocco R, Bottai M, Pagano M, Wolk A (2007) Reproducibility of the past year and historical self-administered total physical activity questionnaire among older women. *Eur J Epidemiol* **22:** 363–368

Patel AV, Rodriguez C, Jacobs EJ, Solomon L, Thun MJ, Calle EE (2005) Recreational physical activity and risk of prostate cancer in a large cohort of US men. *Cancer Epidemiol Biomarkers Prev* **14:** 275–279

Royston P (2004) Multiple imputation of missing values. *Stata J* **4:** 227–241

Rubin DB, Schenker N (1986) Multiple imputation for interval estimation from simple random samples with ignorable nonresponse. *J Am Stat Assoc* **81:** 366–374

van Buuren S, Boshuizen HC, Knook DL (1999) Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* **18:** 681–694

WCRF/AICR (2007) *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective.* World Cancer Research Fund/American Institute for Cancer Research: Washington DC

Wiklund F, Lageros YT, Chang E, Balter K, Johansson JE, Adami HO, Gronberg H (2008) Lifetime total physical activity and prostate cancer risk: a population-based case-control study in Sweden. *Eur J Epidemiol* **23:** 739–746

論文名	A prospective study of lifetime physical activity and prostate cancer incidence and mortality
著 者	Orsini N, Bellocco R, Bottai M, Pagano M, Andersson SO, Johansson JE, Giovannucci E, Wolk A
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発行年	2009
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/19861965

対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		(　　)		コホート研究
	性別	男性	(　　)		(　　)		(　　)
	年齢	62歳	[redacted]		(　　)		前向き研究
	対象数	10000以上			(　　)		(　　)
調査の方法	質問紙	(　　)					
アウトカム	予 防	なし	なし	ガン予防	なし	(　　)	(　　)
	維持・改善	なし	なし	なし	なし	(　　)	(　　)

図 表

Table 2 Age-adjusted and multivariate rate ratios for total, localised, advanced and fatal prostate cancer according to quartiles of lifetime (age 30 and 50 years, and current age) average total physical activity levels

	Lifetime average total physical activity, MET-hours/day				
	Q1, <39 (37)	Q2, 39–42.4 (41)	Q3, 42.5–46 (44)	Q4, >46 (48)	P-trend
Total incidence prostate cancer					
No. of cases	419	414	447	429	
Age-adjusted RR (95% CI)	1	0.86 (0.75–0.99)	0.91 (0.79–1.04)	0.83 (0.73–0.96)	0.030
Multivariate RR (95% CI)[a]	1	0.86 (0.75–0.99)	0.91 (0.79–1.05)	0.84 (0.73–0.98)	0.068
Localised					
No. of cases	188	162	156	182	
Age-adjusted RR (95% CI)	1	0.74 (0.60–0.91)	0.70 (0.56–0.86)	0.78 (0.64–0.96)	0.045
Multivariate RR (95% CI)[a]	1	0.75 (0.61–0.93)	0.72 (0.58–0.91)	0.80 (0.66–1.03)	0.184
Advanced					
No. of cases	133	155	172	126	
Age-adjusted RR (95% CI)	1	0.97 (0.77–1.23)	1.06 (0.84–1.32)	0.73 (0.57–0.94)	0.014
Multivariate RR (95% CI)[a]	1	0.98 (0.78–1.25)	1.07 (0.84–1.36)	0.75 (0.58–0.98)	0.038
Fatal prostate cancer					
No. of cases	20	22	27	28	
Age-adjusted RR (95% CI)	1	0.97 (0.54–1.75)	1.02 (0.57–1.82)	0.99 (0.56–1.78)	0.989
Multivariate RR (95% CI)[a]	1	0.96 (0.53–1.75)	1.02 (0.56–1.87)	0.96 (0.52–1.83)	0.995

Abbreviations: CI, confidence interval; RR, rate ratio. [illegible]

Table 4 Age-adjusted and multivariate rate ratios for total, localised, advanced and fatal prostate cancer according to lifetime (age 30 and 50 years, and current age) walking or bicycling levels

	Lifetime average walking or bicycling, min per day					
	Hardly ever	<20	20–40	41–60	>60	P-trend
Total incidence prostate cancer						
No. of cases	53	391	906	411	403	
Age-adjusted RR (95% CI)	0.99 (0.75–1.30)	0.97 (0.86–1.10)	1	0.96 (0.85–1.09)	0.87 (0.77–0.98)	0.049
Multivariate RR (95% CI)[a]	1.03 (0.78–1.36)	0.97 (0.86–1.10)	1	0.96 (0.85–1.08)	0.86 (0.76–0.98)	0.026
Localised						
No. of cases	21	142	333	179	161	
Age-adjusted RR (95% CI)	0.92 (0.59–1.43)	0.86 (0.70–1.05)	1	1.01 (0.84–1.22)	0.84 (0.69–1.02)	0.447
Multivariate RR (95% CI)[a]	0.98 (0.63–1.53)	0.86 (0.70–1.05)	1	1.00 (0.83–1.21)	0.84 (0.69–1.02)	0.395
Advanced						
No. of cases	15	149	348	145	128	
Age-adjusted RR (95% CI)	0.85 (0.50–1.44)	1.09 (0.89–1.34)	1	0.94 (0.77–1.15)	0.74 (0.60–0.92)	0.002
Multivariate RR (95% CI)[a]	0.88 (0.52–1.49)	1.10 (0.89–1.35)	1	0.94 (0.76–1.15)	0.74 (0.59–0.92)	0.001
Fatal prostate cancer						
No. of cases	4	26	44	26	25	
Age-adjusted RR (95% CI)	1.71 (0.61–4.81)	1.19 (0.73–1.93)	1	0.93 (0.58–1.49)	0.73 (0.45–1.20)	0.062
Multivariate RR (95% CI)[a]	1.81 (0.64–5.12)	1.21 (0.74–1.97)	1	0.90 (0.56–1.46)	0.72 (0.44–1.18)	0.044

Abbreviations: CI, confidence interval; RR, rate ratio. [illegible]

図表掲載箇所	P1934, Table2 P1436, Table4
概 要 (800字まで)	本研究は、スウェーデン人を対象にした国民調査に参加した45,887名の中高年男性を対象に約10年の追跡調査を行い、生涯の総身体活動量と前立腺がん発症/死亡との関連を検討したものである。研究参加当時、30歳時、50歳時の身体活動量を5つの質問(職業時、家事、移動(歩行または自転車)、余暇時間の身体活動時間、および、不活動時間)によって尋ね、メッツ時/日に換算し合計した。生涯の総身体活動量を39メッツ時/日未満、39-42.4メッツ時/日、42.5-46メッツ時/日、46メッツ時/日以上の4群に分類した。総身体活動量が39メッツ時/日未満の集団と比較すると、39-42.4メッツ時/週の集団と、46メッツ時/日以上の集団では、それぞれ、前立腺がんの全発症のリスクが0.86(95%信頼区間:0.75-0.99)、0.84(0.73-0.98)と有意に減少した。進行性前立腺がんでは、46メッツ時/日以上の集団で0.75(0.58-0.98)とリスクが減少した。身体活動分類別にみると、歩行または自転車の生涯総身体活動量が20-40分/日の集団と比較すると、60分/日以上の集団では、前立腺がんの全発症のリスクが0.86(0.76-0.98)と有意に減少し、進行性前立腺がんにおいても0.74(0.59-0.92)と減少した。限局性前立腺がんや致死性前立腺がんにおいては有意な差はみられなかった。また、職業中の身体活動についても、座位中心の仕事と比較すると、座位・立位半々、ほぼ立位、肉体労働の分類でそれぞれ、前立腺がんの全発症のリスクが0.80(0.69-0.93)、0.79(0.69-0.91)、0.72(0.57-0.90)と量反応的にリスクの減少がみられた。
結 論 (200字まで)	中高年男性において、身体活動量が多いことは前立腺がん発症に予防効果があることが明らかとなった。特に、生涯の週当たりの総身体活動量が39メッツ時/週、もしくは、歩行や自転車を60分/日以上行うことによるリスク減少が明らかで、職業中も座位時間がより少ない方が有意に発症が低くなることが明らかとなった。
エキスパートによるコメント (200字まで)	身体活動基準の策定に用いられた研究の1つである。約4万6千名を10年間追跡した大規模な調査であり、前立腺がんが身体活動量を増加させることで予防可能であることを示唆した重要な研究である。リスクの低下と関連が認められた60分以上の歩行や自転車の身体活動は、現在の身体活動基準と照らし合わせて同等量の身体活動である。

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Original Contribution

Leisure Time Spent Sitting in Relation to Total Mortality in a Prospective Cohort of US Adults

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The obesity epidemic is attributed in part to reduced physical activity. Evidence supports that reducing time spent sitting, regardless of activity, may improve the metabolic consequences of obesity. Analyses were conducted in a large prospective study of US adults enrolled by the American Cancer Society to examine leisure time spent sitting and physical activity in relation to mortality. Time spent sitting and physical activity were queried by questionnaire on 53,440 men and 69,776 women who were disease free at enrollment. The authors identified 11,307 deaths in men and 7,923 deaths in women during the 14-year follow-up. After adjustment for smoking, body mass index, and other factors, time spent sitting (≥6 vs. <3 hours/day) was associated with mortality in both women (relative risk = 1.34, 95% confidence interval (CI): 1.25, 1.44) and men (relative risk = 1.17, 95% CI: 1.11, 1.24). Relative risks for sitting (≥6 hours/day) and physical activity (<24.5 metabolic equivalent (MET)-hours/week) combined were 1.94 (95% CI: 1.70, 2.20) for women and 1.48 (95% CI: 1.33, 1.65) for men, compared with those with the least time sitting and most activity. Associations were strongest for cardiovascular disease mortality. The time spent sitting was independently associated with total mortality, regardless of physical activity level. Public health messages should include both being physically active and reducing time spent sitting.

mortality; motor activity; prospective studies; sedentary lifestyle

Abbreviations: CI, confidence interval; CPS-II, Cancer Prevention Study II; ICD, *International Classification of Diseases*; MET, metabolic equivalent.

It is now well established that the US obesity epidemic will have major public health consequences. This epidemic is attributed, at least in part, to reduced overall physical activity expenditure. It has long been recognized that physical activity has a beneficial impact on the incidence and mortality of many chronic diseases, including cardiovascular disease, diabetes, stroke, and various types of cancer including colon and postmenopausal breast cancer (1–5). Dose-response relations between physical activity and improved health outcomes have been reported, and substantial evidence supports health benefits even with physical activity below recommended levels (1, 3, 6, 7).

There is a growing body of evidence showing that reducing the amount of time spent sitting, regardless of the amount of physical activity, may improve the metabolic consequences of obesity (8–11). However, current public health guidelines focus largely on increasing physical activity with little or no reference to reducing time spent sitting (12–15). Numerous studies support an association with sitting time and endpoints such as obesity, type 2 diabetes, cardiovascular disease (11, 16, 17), and unhealthy dietary patterns in children and adults (18–20). However, to our knowledge, few studies have examined time spent sitting in relation to total mortality (21–23), but they were limited by sample size (21, 22) or qualitatively assessed time spent sitting (21).

To better assess the relation between time spent sitting and total mortality, both independent of and in combination with physical activity, we conducted a detailed analysis in the American Cancer Society's Cancer Prevention Study II

(CPS-II) Nutrition Cohort. This cohort has the advantage of being very large with approximately 184,000 US adults and over 19,000 deaths for whom detailed information on time spent sitting and physical activity was collected at baseline.

MATERIALS AND METHODS

Study population

Men and women in this analysis were drawn from the 184,190 participants in the CPS-II Nutrition Cohort (hereafter referred to as the "Nutrition Cohort"), a prospective study of cancer incidence and mortality begun by the American Cancer Society in 1992 (24). The Nutrition Cohort is a subgroup of approximately 1.2 million participants in the baseline CPS-II cohort, a prospective mortality study established by the American Cancer Society in 1982 (25). Members of the CPS-II cohort who resided in 21 states with population-based state cancer registries and were 50–74 years of age in 1992 were invited to participate by completing a mailed questionnaire. The 10-page mailed questionnaire included questions on demographic, reproductive, medical, behavioral, and lifestyle factors. The recruitment and characteristics of the Nutrition Cohort are described in detail elsewhere (24).

We excluded sequentially from this analysis men and women who reported a personal history of cancer (n = 21,785), heart attack (n = 11,560), stroke (n = 2,513), or emphysema/other lung disease (n = 9,321) at the time of enrollment. We also excluded individuals with missing data on physical activity (n = 4,240), missing sitting time (n = 2,954), missing or extreme (top and bottom 0.1%) values of body mass index (n = 2,121), or missing smoking status (n = 1,347) at baseline. Finally, to reduce the possibility of undiagnosed serious illness at baseline that would preclude or interfere with physical activity, we excluded individuals who reported both no daily life activities and no light housekeeping (n = 4,730), as well as those who died from any cause within the first year of follow-up (n = 403). After exclusions, the analytical cohort consisted of 123,216 individuals (53,440 men and 69,776 women) with a mean age of 63.6 (standard deviation, 6.0) years in men and 61.9 (standard deviation, 6.5) years in women when enrolled in the study in 1992.

Mortality endpoints

The primary endpoint was death from any cause occurring between 1 year after the time of enrollment and December 31, 2006. Deaths were identified through biennial automated linkage of the entire cohort with the National Death Index (26). Death certificates or codes for cause of death have been obtained for 98.7% of all known deaths. Causes of death were classified by using the *International Classification of Diseases* (ICD), Ninth Revision (27), for deaths occurring from 1992 to 1998 and the Tenth Revision (28) for deaths from 1999 to 2006. Specific causes of death were grouped into 3 broad categories: cardiovascular disease (ICD, Ninth Revision, codes 390–459 and ICD, Tenth Revision, codes I00–I99); cancer (ICD, Ninth Revision, codes 140–195 and 199–208 and ICD, Tenth Revision, codes C00–C76 and C80–C97); and all other causes.

Measures of time spent sitting and physical activity

Time spent sitting was assessed by using the question, "During the past year, on an average day (not counting time spent at your job), how many hours per day did you spend sitting (watching television, reading, etc.)?" Responses included "none, <3, 3–5, 6–8, >8 hours per day." Time spent sitting was categorized as 0–<3, 3–5, or ≥6 hours/day.

Information on recreational physical activity was collected by using the question, "During the past year, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics, and dancing?" Responses to each individual activity included "none," "1–3 hours/week," "4–6 hours/week," or "≥7 hours/week." The summary metabolic equivalent of energy expenditure (MET)-hours/week was calculated for each participant. A MET is estimated by dividing the energy cost of a given activity by resting energy expenditure (29). The summary MET score for each participant was calculated by multiplying the lowest number of hours within each category by the general MET level of each activity according to the Compendium of Physical Activities (29) to provide conservatively estimated summary measures because of the likelihood of overreporting physical activity and the older age of study participants. MET scores assigned for various activities include the following: 3.5 for walking, 7.0 for jogging/running, 7.0 for lap swimming, 6.0 for tennis or racquetball, 4.0 for bicycling/stationary biking, 4.5 for aerobics/calisthenics, and 3.5 for dancing.

We also assessed daily life physical activities with the question, "During the past year, what was the average time per week you spent at the following kinds of activities: gardening/mowing/planting, heavy housework/vacuuming, heavy home repair/painting, and shopping?" We calculated MET-hours/week from these activities using the following values (29): 3.0 for gardening/mowing/planting, 2.5 for heavy housework/vacuuming, 3.0 for heavy home repair/painting, and 2.5 for shopping.

The primary purpose in this analysis was to examine the relation of leisure-time sitting to all-cause death rates. Therefore, we combined recreational and daily life activity into total leisure-time physical activity at baseline, because the relation between regular physical activity and all-cause mortality has been well documented. Total leisure-time activity was categorized in MET-hours/week as <17.5, 17.5–<24.5, 24.5–<31.5, 31.5–<42.0, 42.0–<52.5, 52.5–<63.0, or ≥63.0. The lowest cutpoint corresponds with approximately the 10th percentile of activity level in our population, and each subsequent category increases by the metabolic equivalent of approximately 3 hours of light-intensity daily life activities per week.

Statistical analysis

Cox proportional hazards modeling (30) was used to compute relative risk, with follow-up time in days as the time axis. All Cox models were stratified on exact year of age. For each exposure variable, we assessed risk in 3 models: 1) adjusted only for age, 2) adjusted for age and

other potential confounding factors, and 3) mutually adjusting for both physical activity and time spent sitting in addition to all potential confounders. The potential confounders included were race (white, black, other), smoking status (never, current, former), duration (≤35, >35 years) and frequency (<20, ≥20 cigarettes/day) of smoking among current smokers, years since quitting among former smokers (≤5, 6–10, 11–15, 16–20, 21–25, >25 years), body mass index (weight (kg)/height $(m)^2$) (<18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, ≥30.0), marital status (married, widowed, divorced, separated, never married), education (less than high school, high school graduate, some college, college graduate, graduate school or higher), alcohol consumption (0, <1, 1, >1 drink/day), total caloric intake (quartiles), and comorbidity score (0, 1, ≥2). Dietary intake was assessed by using a 68-item modified brief food frequency questionnaire by Block et al. (31) and validated in a subset of cohort members (32). The comorbidities score included high blood pressure, diabetes, and high cholesterol. Other potential confounders assessed were fruit and vegetable intake, fat intake, red meat intake, and occupational status (employed, retired, homemaker), but these factors were not included in the model as they had no impact on any risk estimates for physical activity or time spent sitting.

Tests of linear trend for sitting time and physical activity measures were calculated by assigning the median value within each category to that category. We also examined the combined effects of physical activity and time spent sitting. For these models, the number of categories of total daily physical activity was reduced from 7 to 5 (<24.5, 24.5–<31.5, 31.5–<42.0, 42.0–<52.5, ≥52.5 MET-hours/week). Men and women who were most physically active and spent the least time sitting (≥52.5 MET-hours/week and <3 hours/day sitting) served as the referent group.

Secondary analyses also examined the associations between body mass index and mortality from all cardiovascular diseases, all cancers, and all other causes of death among men and women separately. We also tested for effect modification by gender, body mass index, smoking status, attained age, and follow-up time. Because there was no statistically significant effect modification by gender, all other factors were tested for effect modification in both sexes combined to maximize statistical power.

We also conducted a sensitivity analysis to further examine whether the amount of time spent sitting at baseline was a result of undiagnosed illness that was not accounted for through exclusions for prevalent disease or excluding the first year of follow-up. Using data on physical activity and time spent sitting in 1992, as well as our first follow-up survey in 1997, we examined long-term (5-year) sitting time and physical activity in relation to subsequent mortality rates. Finally, we conducted a sensitivity analysis among men and women who were either retired or homemakers to eliminate the potential impact of occupational time spent sitting or in physical activity.

RESULTS

We observed 11,307 deaths in men and 7,923 in women over the 1,610,728 person-years of follow-up. Men and women who spent the least leisure time sitting were leaner, more likely to have never smoked cigarettes, more likely to be employed, and had lower total energy intake (Table 1). Leisure time spent sitting was not associated with physical activity ($r = -0.03$). Study participants generally engaged in light- to moderate-intensity activities, such as walking for exercise, gardening, shopping, and housework. Moderate- to vigorous-intensity activities were relatively uncommon in this older population; 83% of men and 87% of women reported walking for exercise, and 37% of men and 36% of women listed walking as their only form of recreational physical activity.

Associations of leisure time spent sitting, physical activity, and their combined effects with mortality are shown in Table 2. After multivariate adjustment, leisure time spent sitting was positively associated with all-cause mortality rates in both women and men; however, associations appeared stronger in women (for ≥6 vs. <3 hours/day, relative risk = 1.37, 95% confidence interval (CI): 1.27, 1.47) than men (relative risk = 1.18, 95% CI: 1.12, 1.25) ($P_{heterogeneity} = 0.003$). After further adjustment for physical activity, these associations remained virtually unchanged. There was a dose-related, inverse relation between physical activity and mortality rates in women and in men beginning at relatively low levels of activity (Table 2). Risk estimates for physical activity similarly were virtually unchanged after further adjustment for time spent sitting.

When examining the combined effects of time spent sitting and physical activity on all-cause death rates, time spent sitting was associated with increased risk regardless of level of physical activity (Figures 1 and 2). The relative risks for the joint effects of sitting and physical activity (≥6 hours/day sitting and <24.5 MET-hours/week activity) were 1.94 (95% CI: 1.70, 2.20) and 1.48 (95% CI: 1.33, 1.65), for women and men respectively, compared with women and men who reported both sitting the least (<3 hours/day) and being the most physically active (≥52.5 MET-hours/week).

We examined the association between time spent sitting and total mortality in men and women combined, stratified by body mass index (Table 3). Although time spent sitting and physical activity were more strongly associated with mortality among lean persons (for time spent sitting, $P_{interaction} = 0.06$; for physical activity, $P_{interaction} = 0.002$), both measures were significantly associated with risk of total mortality regardless of body mass index. No other factors examined, including smoking status or attained age, appeared to modify the associations between time spent sitting and physical activity in relation to total mortality (data not shown). Results from the sensitivity analysis among participants who are retired or homemakers also did not differ from those in the overall cohort (data not shown).

Although we excluded the first year of follow-up and prevalent disease, we further examined whether observed associations were a result of unidentified prevalent illness in 2 ways. First, we examined the associations between baseline exposures stratified by follow-up time. Although associations were slightly attenuated, they persisted and remained statistically significant over the 14-year follow-up (data not shown). Second, we conducted a sensitivity analysis combining questions about sitting time and physical

Table 1. Age-adjusted Percentages and Means of Selected Baseline Characteristics in 1992, by Hours of Leisure Time Spent Sitting for Women and Men, Cancer Prevention Study II Nutrition Cohort

	Sitting in 1992											
	Women						Men					
	<3 hours/day (n = 34,075)		3–5 hours/day (n = 29,335)		≥6 hours/day (n = 6,366)		<3 hours/day (n = 22,876)		3–5 hours/day (n = 23,723)		≥6 hours/day (n = 6,841)	
	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%
Age at baseline, years	60.7 (0.04)		62.8 (0.04)		63.4 (0.08)		62.6 (0.04)		64.1 (0.04)		64.8 (0.07)	
Body mass index in 1992, kg/m^2	24.9 (0.02)		25.9 (0.03)		26.8 (0.06)		26.1 (0.02)		26.6 (0.02)		27.0 (0.04)	
Total MET-hours/week	42.8 (0.12)		40.7 (0.13)		39.9 (0.29)		46.1 (0.16)		44.4 (0.16)		44.5 (0.29)	
Retired/homemaker		61.6		69.9		73.1		50.0		61.0		64.7
Race												
White		97.4		97.4		96.9		97.3		97.4		97.5
Black		1.4		1.5		1.6		1.2		1.3		1.2
Other		1.2		1.1		1.5		1.4		1.4		1.3
Educational level												
Less than high school		4.7		4.7		5.5		7.8		7.2		7.2
High school graduate		30.5		33.9		33.0		18.8		19.5		16.9
Some college		31.1		31.3		31.1		24.3		27.3		25.1
College graduate		19.9		18.2		17.3		22.2		21.7		22.5
Graduate school		13.2		11.2		12.3		26.3		23.7		27.8
Smoking status												
Never		60.1		53.8		48.7		39.5		31.7		30.8
Current		6.7		9.9		13.4		7.1		9.7		12.7
Former		32.4		35.7		37.0		52.1		57.4		55.1
Alcohol use												
Never		45.3		44.5		47.7		32.5		31.3		31.8
<1 drink/day		38.8		39.2		35.2		39.2		39.5		38.1
1 drink/day		7.7		7.9		7.4		12.9		13.1		12.1
>1 drink/day		4.3		5.0		5.7		11.3		12.9		14.4
Caloric intake, kcal/day	1,326.69 (2.7)		1,383.78 (2.9)		1,455.24 (6.2)		1,770.64 (4.3)		1,839.98 (4.1)		1,923.58 (7.8)	

Abbreviations: MET, metabolic equivalent; SE, standard error.

Table 2. Relative Risk of Death From All Causes According to Leisure Time Sitting and Physical Activity Among Women and Men, Cancer Prevention Study II Nutrition Cohort, 1993–2006

	Women						Men					
	No. of Deaths	Person-Years	Relative Risk[a]	95% CI	Relative Risk[b]	95% CI	No. of Deaths	Person-Years	Relative Risk[a]	95% CI	Relative Risk[b]	95% CI
Sitting in 1992, hours/day												
0–<3	3,038	456,987	1.00	Referent	1.00	Referent	4,030	298,227	1.00	Referent	1.00	Referent
3–5	3,781	386,736	1.14	1.08, 1.19	1.13	1.07, 1.18	5,413	301,973	1.08	1.03, 1.12	1.07	1.03, 1.12
≥6	1,104	81,963	1.37	1.27, 1.47	1.34	1.25, 1.44	1,864	84,842	1.18	1.12, 1.25	1.17	1.11, 1.24
P_{trend}			<0.0001		<0.0001				<0.0001		<0.0001	
Total physical activity in 1992, MET-hours/week												
<17.5	1,157	107,418	1.00	Referent	1.00	Referent	1,186	63,336	1.00	Referent	1.00	Referent
17.5–<24.5	699	63,751	0.98	0.89, 1.07	0.98	0.89, 1.07	991	59,365	0.89	0.82, 0.97	0.90	0.82, 0.97
24.5–<31.5	1,382	159,718	0.81	0.75, 0.88	0.82	0.75, 0.88	1,397	86,898	0.84	0.78, 0.91	0.85	0.78, 0.92
31.5–<42	1,588	195,423	0.78	0.72, 0.84	0.78	0.73, 0.85	2,284	133,341	0.88	0.82, 0.94	0.88	0.82, 0.95
42–<52.5	1,255	157,978	0.76	0.70, 0.82	0.76	0.70, 0.83	1,857	115,894	0.81	0.75, 0.87	0.81	0.75, 0.87
52.5–<63	772	99,477	0.75	0.68, 0.82	0.76	0.69, 0.83	1,453	88,468	0.79	0.73, 0.85	0.79	0.74, 0.86
≥63	1,070	141,921	0.73	0.67, 0.80	0.74	0.68, 0.81	2,139	137,740	0.79	0.74, 0.85	0.80	0.74, 0.86
P_{trend}			<0.0001		<0.0001				<0.0001		<0.0001	
Physical activity, MET-hours/week, and sitting, sitting-hours/day, in 1992												
≥52.5, <3	788	126,961	1.00	Referent			1,401	100,780	1.00	Referent		
≥52.5, 3–5	831	94,582	1.12	1.02, 1.24			1,640	96,805	1.02	0.95, 1.09		
≥52.5, ≥6	223	19,854	1.25	1.07, 1.45			551	26,623	1.07	0.97, 1.18		
42–<52.5, <3	490	77,704	1.01	0.90, 1.13			656	50,122	0.98	0.89, 1.07		
42–<52.5, 3–5	596	66,885	1.14	1.03, 1.27			903	52,499	1.04	0.95, 1.13		
42–<52.5, ≥6	169	13,389	1.31	1.10, 1.54			298	13,274	1.20	1.06, 1.36		
31.5–<42, <3	603	96,191	1.00	0.90, 1.11			806	57,814	1.08	0.99, 1.18		
31.5–<42, 3–5	797	83,531	1.20	1.09, 1.33			1,131	59,678	1.13	1.05, 1.23		
31.5–<42, ≥6	188	15,701	1.35	1.15, 1.58			347	15,849	1.23	1.09, 1.38		
24.5–<31.5, <3	525	76,992	1.10	0.98, 1.23			467	38,048	0.96	0.86, 1.06		
24.5–<31.5, 3–5	682	68,555	1.20	1.09, 1.34			699	37,945	1.18	1.07, 1.29		
24.5–<31.5, ≥6	175	14,171	1.39	1.18, 1.64			231	10,905	1.13	0.99, 1.31		
<24.5, <3	632	79,138	1.30	1.17, 1.44			700	51,464	1.09	0.99, 1.19		
<24.5, 3–5	875	73,184	1.42	1.29, 1.57			1,040	55,045	1.23	1.13, 1.33		
<24.5, ≥6	349	18,847	1.94	1.70, 2.20			437	16,192	1.48	1.33, 1.65		

Abbreviations: CI, confidence interval; MET, metabolic equivalent.

[a] Adjusted for age at interview, race, marital status, education, smoking status, body mass index in 1992, alcohol use, total caloric intake, and comorbidities score.

[b] Adjusted for all of the above plus total physical activity (for sitting) and hours sitting (for total physical activity).

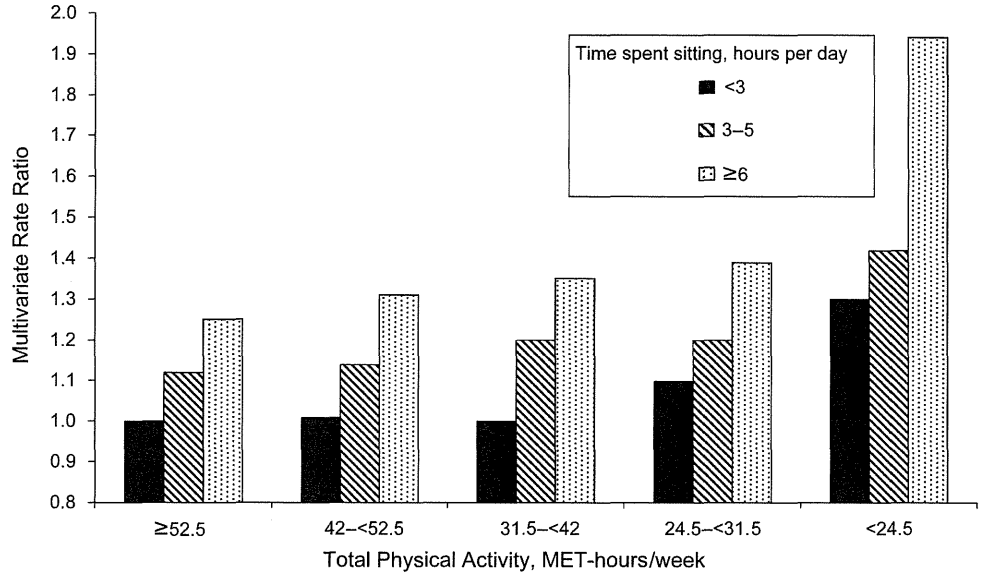

Figure 1. Combined multivariate-adjusted rate ratios ($P < 0.05$) for leisure time spent sitting and physical activity in relation to all-cause mortality, women only, in the Cancer Prevention Study II Nutrition Cohort, 1993–2006. MET, metabolic equivalent.

activity at baseline with those from our first follow-up survey in 1997 to examine sustained (5-year) measures. Results from these analyses did not differ from those presented for baseline alone (data not shown).

Associations between time spent sitting and physical activity were stronger for cardiovascular disease mortality than for cancer (Table 4). Time spent sitting was associated with an increased risk of cardiovascular disease mortality in both men and women, whereas it was associated with increased cancer mortality only among women. There was a statistically significant inverse relation between physical activity and cardiovascular disease mortality beginning at relatively low levels of activity in both men ($P_{trend} = 0.0001$) and women ($P_{trend} < 0.0001$). In contrast, total physical activity was not significantly associated with lower cancer mortality among men and only modestly associated with lower cancer mortality in women. Longer time spent sitting was associated with higher death rates from all other causes, and physical activity was inversely associated with death rates from other causes. The most common conditions in this category were respiratory diseases (22.7% in men, 20.4% in women), central nervous system diseases (20.3%

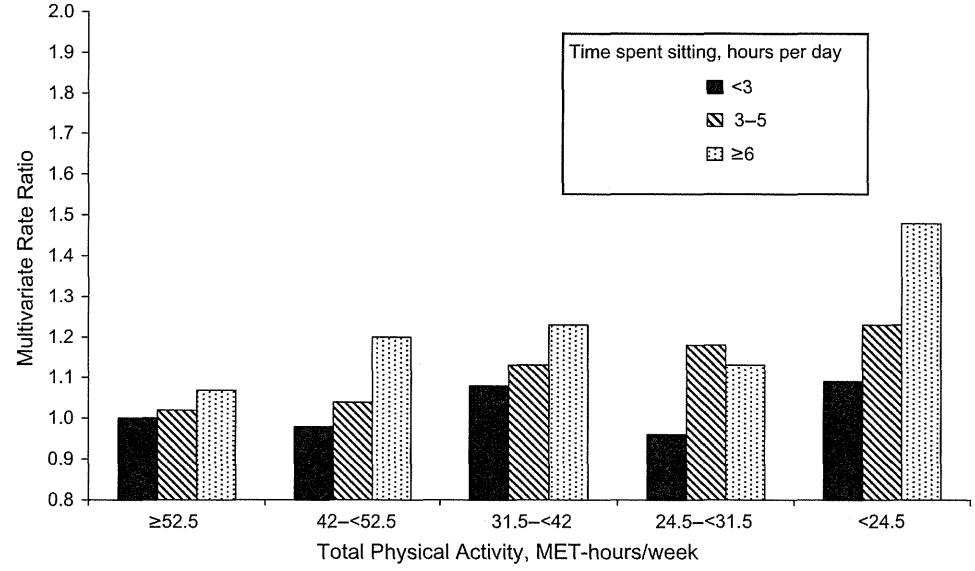

Figure 2. Combined multivariate-adjusted rate ratios ($P < 0.05$) for leisure time spent sitting and physical activity in relation to all-cause mortality, men only, in the Cancer Prevention Study II Nutrition Cohort, 1993–2006. MET, metabolic equivalent.

Table 3. Relative Risk of Death From All Causes According to Leisure Time Spent Sitting and Physical Activity, Stratified by Body Mass Index, Among Women and Men, Cancer Prevention Study II Nutrition Cohort, 1993–2006

	Body Mass Index, kg/m^2								
	<25.0			25.0–<30.0			≥30.0		
	No. of Deaths	Relative Risk[a]	95% CI	No. of Deaths	Relative Risk[a]	95% CI	No. of Deaths	Relative Risk[a]	95% CI
Sitting in 1992, hours/day									
0–<3	3,278	1.00	Referent	2,768	1.00	Referent	1,022	1.00	Referent
3–5	3,768	1.10	1.05, 1.15	3,852	1.11	1.05, 1.16	1,574	1.05	0.97, 1.14
≥6	1,119	1.28	1.20, 1.37	1,220	1.21	1.12, 1.29	629	1.19	1.08, 1.32
P_{trend}		<0.0001			<0.0001			0.001	
				$P_{interaction} = 0.06$					
Total physical activity in 1992, MET-hours/week									
<17.5	866	1.00	Referent	935	1.00	Referent	542	1.00	Referent
17.5–<24.5	669	0.94	0.85, 1.04	668	0.90	0.81, 0.99	353	0.94	0.82, 1.08
24.5–<31.5	1,202	0.86	0.79, 0.94	1,054	0.79	0.72, 0.86	523	0.86	0.76, 0.97
31.5–<42	1,605	0.80	0.73, 0.87	1,622	0.86	0.80, 0.94	645	0.86	0.76, 0.96
42–<52.5	1,380	0.77	0.70, 0.83	1,250	0.78	0.72, 0.85	482	0.86	0.76, 0.98
52.5–<63	996	0.76	0.69, 0.83	937	0.79	0.72, 0.87	292	0.79	0.69, 0.92
≥63	1,447	0.72	0.66, 0.79	1,374	0.82	0.76, 0.89	388	0.78	0.69, 0.89
P_{trend}		<0.0001			0.0003			0.0001	
				$P_{interaction} = 0.002$					

Abbreviations: CI, confidence interval; MET, metabolic equivalent.

[a] Adjusted for age at interview, race, marital status, education, smoking status, body mass index in 1992, alcohol use, total caloric intake, comorbidities score, and total physical activity (for sitting) and hours sitting (for total physical activity).

in men, 19.8% in women), digestive diseases (9.6% in men, 10.4% in women), and diabetes (7.8% in men, 6.3% in women).

DISCUSSION

In this large prospective cohort, women who reported sitting for more than 6 hours during their leisure time versus less than 3 hours a day had an approximately 40% higher all-cause death rate, and men had an approximately 20% higher death rate. This association was independent of the amount of physical activity. The combination of both sitting more and being less physically active (>6 hours/day sitting and <24.5 MET-hours/week physical activity) was associated with a 94% and a 48% increase in all-cause death rates in women and men, respectively, compared with those who reported sitting the least and being most active (<3 hours/day sitting and ≥52 MET-hours/week physical activity).

Our findings for time spent sitting are consistent with those from the 3 other studies that have previously examined the association between time spent sitting and mortality (21–23). One study included approximately 17,000 Canadian adults with 1,832 deaths, and the authors reported a significant dose-response relation between a qualitative measure of time spent sitting (almost none of the time, one fourth of the time, half of the time, three fourths of the time, almost all of the time) and total mortality (21). The second study, which included 8,800 Australian adults and 284 deaths, found an almost 50% increase in total mortality with 4 or more hours of television viewing compared with less than 2 hours per day (22). In both of these studies, associations were strongest for cardiovascular disease mortality (21, 22). The third study included approximately 83,000 Japanese adults and reported a positive association with sedentary behavior and total mortality among men, but not women (23).

Our physical activity findings were similar to those reported from the majority of other studies (1, 2, 33). Mortality rates were approximately 25% lower among men and women who reported the most versus the least daily physical activity. Although optimal health benefits are achieved at a much higher level of physical activity, death rates were substantially lower even in the second lowest category compared with the lowest category, suggesting a benefit from even relatively light levels of physical activity. As mentioned, the participants in our study were older and engaged in primarily light-intensity activities, such as walking for exercise and gardening. It should be noted that no previous study has examined the combined effects of sitting time and physical activity.

Several factors could explain the positive association between time spent sitting and higher all-cause death rates.