demographics, anthropometry, physical activity, medical history, diet, and other potential risk factors for cancer. Of the 100,303 eligible men, 48,850 (49%) completed the questionnaire. The investigation was approved by the Regional Ethical Committee at the Karolinska Institute in Stockholm, Sweden. For the analyses, we excluded men with incorrect or missing national registration number and men diagnosed with cancer (except nonmelanoma skin cancer) prior to baseline. This left 45,906 men eligible for the analyses.

2.2. *Assessment of physical activity*

Participants reported their level of activity at work (mostly sitting down; sitting down about half of the time; mostly standing up; mostly walking, lifts, carry little; mostly walking, lifts, carry much; heavy manual labor), home/housework (<1, 1–2, 3–4, 5–6, 7–8, or >8 h per day), walking/bicycling (almost never, <20 min per day, 20–40 min per day, 40–60 min per day, 1–1.5 h per day, or >1.5 h per day), and exercise (<1, 1, 2–3, 4–5, or >5 h per week) in the year before study enrollment. The questionnaire also included questions on inactivity (watching TV/reading (<1, 1–2, 3–4, 5–6, or >6 h per day) and hours per day of sleeping and sitting/lying down (open questions). Total leisure-time physical activity (in min per day) was calculated by adding the time spent per day on walking/bicycling and exercising. The reported time spent at each activity per day was multiplied by its typical energy expenditure requirements expressed in metabolic equivalents (METs)[10] and added together to create a MET-hours per day (24-h) score, as described by Norman and colleagues.[11]

The validity of the assessment of physical activity as used in this cohort was tested among 111 men, aged 44–78 years, from the study area by comparison with two 7-day activity records, performed 6 months apart.[11] The Spearman correlation coefficients (adjusted for within- and between-person variation in the records) between the questionnaire and activity records were 0.4 for leisure-time physical activity (combined walking/bicycling and exercise), 0.6 for home/housework, 0.4 for work/occupation, and 0.6 for total activity score.[11]

2.3. *Assessment of body size and other information*

We used the questionnaire to obtain self-reported information on weight and height at age 20, and weight and waist circumference at baseline. We estimated body mass index (BMI) from weight and height (kg/height in m^2) as a measure of overall obesity. High validity has been observed for self-reported height ($r = 0.9$) and weight ($r = 0.9$) compared with actual measurement among Swedish men.[12] Waist circumference was used as an estimate of abdominal adiposity.

Diet was assessed with a food-frequency questionnaire that determined the frequency of consumption of 96 food items during the past year; details on the validity and reproducibility of this food-frequency questionnaire have been described elsewhere.[13] Information was also collected on dietary supplement use, smoking, family history of colorectal cancer, history of diabetes, and aspirin use.

2.4. *Case ascertainment and follow-up*

Incident cases of colon and rectal cancer were identified through computerised linkage of the study cohort to the National and Regional Swedish Cancer registers, both of which have been estimated to be almost 100% complete.[14] Complementary data concerning localisation of colonic carcinomas were obtained from the regional colon cancer registry of the Uppsala–Örebro region. Only adenocarcinomas were included in this analysis. Proximal colon cancers included tumours of the caecum, appendix, ascending colon, hepatic flexure, and transverse colon (codes 153.0, 153.1, and 153.4–153.6 of the International Classification of Diseases, 9th Revision). Distal colon cancers included tumours in the splenic flexure, descending colon, and sigmoid colon (codes 153.2, 153.3, and 153.7). Cancer of the rectum included tumours occurring at the rectosigmoid junction and rectum (codes 154.0 and 154.1). Ascertainment of deaths in the cohort and dates of migration was accomplished through linkage to the Swedish Death and Population registers at Statistics Sweden.

2.5. *Statistical analysis*

Follow-up time for each man was accrued from baseline to the date of diagnosis of colon or rectal cancer, death, migration, or June 30, 2005 whichever came first. We categorised men into five groups with BMI (kg/m^2) corresponding to <23.0, 23.0–24.9, 25.0–26.9, 27.0–29.9, and ⩾30.0. The effect of weight change was assessed by subtracting the weight at age 20 from the weight at baseline. We created five categories of weight change: loss of 5 kg or more, loss or gain of less than 5 kg (reference), gain of 5–10 kg, gain of 11–20 kg, and gain of more than 20 kg. We used quintiles for weight, waist circumference, height, and total activity, and categories for specific activities.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards models[15] stratified by age in months at baseline. All multivariate models included education, family history of colorectal cancer, history of diabetes, smoking, and aspirin use. Multivariate analyses of physical activity were also adjusted for BMI, and those of BMI, waist, weight, weight changes, and height were adjusted for leisure-time physical activity. Other variables evaluated for potential confounding were multivitamin supplement use and intakes of total energy, alcohol, dietary fiber, calcium, folate, fruits, vegetables, and red meat. Inclusion of these variables had negligible effect on the associations of physical activity or anthropometric variables with colorectal cancer risk, and they were not included in the final models. We tested the proportional hazard assumption using the likelihood ratio test; there was no departure from the assumption for any covariate in the final models.

Tests of linear trends across exposure categories were assessed by fitting ordinal exposure variables as continuous terms. The Wald statistic was used to test for homogeneity of the HRs for proximal colon, distal colon, and rectal cancer.[16] We used the likelihood ratio test to assess statistical interaction. All analyses were performed using the statistical software SAS (version 9.1; SAS Institute, Cary, NC). All statistical tests were two-sided.

3. Results

The distribution of potential confounders according to leisure-time physical activity and BMI is shown in Table 1. Compared with inactive men, men with higher levels of physical activity had lower BMI and were less likely to smoke. Men with low physical activity or with greater BMI were more likely to have a history of diabetes and to use aspirin. In addition, men with high BMI were less likely to have a post-secondary education.

During a mean follow-up of 7.1 years, 496 colorectal cancers were diagnosed. Of these, 309 were located in the colon (133 proximal colon, 138 distal colon, and 38 cancers at an unknown colonic subsite) and 190 in the rectum (3 cases were

Table 1 – Baseline characteristics of study participants by categories of leisure-time physical activity and BMI[a]

Characteristic	Leisure-time physical activity (min/day)[b]			BMI (kg/m^2)		
	<10	10–59	⩾60	<23.0	23.0–29.9	⩾30
Age, mean (years)	59.7	59.5	62.5	60.4	60.1	59.7
BMI, mean (kg/m^2)	26.7	25.9	25.5	21.6	25.9	32.5
Waist, mean (cm)	99.7	96.7	94.8	87.1	96.5	110.9
Post-secondary education (%)	12.1	17.0	15.4	21.9	16.0	11.0
Family history of colorectal cancer (%)	6.7	7.2	6.9	7.1	7.2	6.5
History of diabetes (%)	9.0	6.0	5.9	4.0	5.6	12.8
Current smokers (%)	33.8	24.6	22.4	27.6	24.1	24.9
Aspirin, regular use (%)	39.1	36.8	35.0	34.0	36.5	41.1

a All variables (except age) are age-standardised to the age-distribution of the cohort. BMI = body mass index.
b Combined walking/bicycling and exercise.

Table 2 – Hazard ratios and 95% confidence intervals of colorectal cancer by physical activity in the cohort of Swedish men (1998 – June 2005)[a]

Variable	Cases[b]	Person-years[b]	Age-adjusted HR	Multivariate HR[c]
Leisure-time activity (min/day)[d]				
<10	51	23,658	1.00	1.00
10–29	100	62,006	0.73 (0.52–1.03)	0.76 (0.54–1.06)
30–59	166	117,659	0.59 (0.43–0.81)	0.64 (0.47–0.89)
⩾60	174	112,838	0.52 (0.38–0.71)	0.57 (0.41–0.79)
P for trend			<0.0001	0.001
Home/housework (h/day)[e]				
<1	187	122,569	1.00	1.00
1–2	205	138,084	0.84 (0.68–1.02)	0.90 (0.73–1.10)
⩾3	77	45,326	0.75 (0.57–0.98)	0.81 (0.62–1.07)
P for trend			0.02	0.11
Work/occupation[f]				
Light	242	165,702	1.00	1.00
Moderate	164	97,039	0.93 (0.76–1.14)	0.99 (0.81–1.22)
Heavy	76	50,214	1.08 (0.83–1.39)	1.10 (0.84–1.44)
P for trend			0.85	0.58
Total activity score (MET-h/day)				
<37.9	98	61,804	1.00	1.00
37.9–40.7	80	63,549	0.82 (0.61–1.10)	0.84 (0.62–1.13)
40.8–44.8	105	63,120	0.97 (0.73–1.28)	1.00 (0.76–1.33)
⩾44.9	82	63,505	0.79 (0.59–1.07)	0.82 (0.60–1.10)
P for trend			0.27	0.38

a CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent of energy expenditure (kcal/kg × h).
b The sum does not add up to the total owing to missing data.
c Multivariate models were stratified by age (in months) at baseline and adjusted for education (less than high school, high school graduate, or more than high school), family history of colorectal cancer (yes/no), history of diabetes (yes/no), smoking (never, past, or current smoker), aspirin use (yes/no), and body mass index (<23.0, 23.0–24.9, 25.0–29.9, or ⩾30.0 kg/m^2). Leisure-time physical activity, home/housework, and work/occupation were included simultaneously in the multivariate model.
d Combined walking/bicycling and exercise; the median MET values for the categories are 0.5, 1.4, 3.0, and 6.3 MET-h/day.
e The median MET values for the categories are 1, 3.8, and 8.8 MET-h/day.
f Light = mostly sitting down (7.4 MET-h/day) to sitting down half of the time (10.3 MET-h/day); moderate = mostly standing up (12.5 MET-h/day) to mostly walking, lifts, carry little (14.8 MET-h/day); heavy = mostly walking, lifts, carry much (17.1 MET-h/day) to heavy manual work (22.2 MET-h/day). Work/occupational activity levels were multiplied by 5.7 per day (8 h per day, 5 days per week).

diagnosed with both colon and rectal cancer). We observed an inverse association between leisure-time physical activity and risk of colorectal cancer (Table 2). Men who engaged in leisure-time physical activity for 60 min or more per day had a multivariate HR of 0.57 (95% CI 0.41–0.79) compared to men who engaged in leisure-time physical activity for less than 10 min per day. Excluding cases diagnosed during the first two years of follow-up did not change the results materially (multivariate HR = 0.56; 95% CI 0.38–0.82). The incidence rates, age-standardised to the age distribution in the cohort, were 246 and 134 per 100,000 persons per year in the lowest and highest categories of leisure-time physical activity. No significant associations were observed for home/housework, work/occupational activity, or total activity in multivariate analyses (Table 2).

Leisure-time physical activity was inversely associated with risk of both colon and rectal cancer (Table 3). Although the inverse association between leisure-time physical activity and colon cancer risk was somewhat stronger for distal than proximal colon cancer, the difference by subsite was not statistically significant (P for heterogeneity = 0.18). Home/housework was statistically significantly inversely associated with risk of colon cancer, whereas occupational and total activity was not associated with risk of any subsite (Table 3).

We also examined the relation between leisure-time physical activity at age 30 (reported retrospectively at baseline) and risk of colorectal cancer. The multivariate HR of colorectal cancer for men who engaged in leisure-time physical activity for 60 min or more per day at age 30 was 1.08 (95% CI 0.75–1.56) compared with those who engaged in such activity for less than 10 min per day at age 30.

We calculated the population attributable risk, i.e. the proportion of cases that would be avoided if the risk factor distribution of a high-risk group switched to that of a low-risk group, by using the prevalence of men who engaged in leisure-time physical activity for less than 30 min per day (27.4%; defined as high-risk group) and the multivariate HR for comparison of less than 30 min per day with 30 min per day or more (defined as low risk group). The population attributable risk was 9%.

Table 3 – Multivariate hazard ratios and 95% confidence intervals of proximal colon, distal colon, and rectal cancer by physical activity in the cohort of Swedish men (1998 – June 2005)[a]

Variable	Colon[b]		Proximal colon		Distal colon		Rectum	
	Cases[c]	HR (95% CI)[d]	Cases[c]	HR (95% CI)[d]	Cases[c]	HR (95% CI)[d]	Cases[c]	HR (95% CI)[d]
Leisure-time activity (min/day)[e]								
<10	34	1.00	12	1.00	19	1.00	17	1.00
10–29	55	0.66 (0.43–1.02)	26	0.98 (0.49–1.97)	25	0.51 (0.28–0.93)	45	0.91 (0.51–1.59)
30–59	111	0.68 (0.46–1.01)	49	0.90 (0.47–1.73)	48	0.50 (0.29–0.87)	58	0.61 (0.35–1.06)
⩾60	107	0.56 (0.37–0.83)	45	0.72 (0.37–1.40)	45	0.40 (0.22–0.70)	67	0.59 (0.34–1.02)
P for trend		0.01		0.17		0.01		0.01
Home/housework (h/day)[f]								
<1	128	1.00	55	1.00	57	1.00	61	1.00
1–2	120	0.75 (0.58–0.97)	56	0.78 (0.53–1.14)	52	0.78 (0.53–1.15)	86	1.21 (0.87–1.70)
⩾3	46	0.68 (0.48–0.96)	16	0.50 (0.29–0.89)	23	0.86 (0.52–1.41)	31	1.08 (0.69–1.69)
P for trend		0.01		0.02		0.39		0.62
Work/occupation[g]								
Light	145	1.00	62	1.00	66	1.00	99	1.00
Moderate	113	1.17 (0.91–1.52)	46	1.14 (0.76–1.69)	53	1.25 (0.85–1.82)	52	0.75 (0.53–1.06)
Heavy	41	1.03 (0.72–1.47)	21	1.26 (0.75–2.11)	14	0.79 (0.43–1.42)	35	1.16 (0.78–1.74)
P for trend		0.51		0.33		0.91		0.99
Total activity score (MET-h/day)								
<37.9	59	1.00	27	1.00	28	1.00	39	1.00
37.9–40.7	53	0.93 (0.64–1.36)	22	0.90 (0.51–1.59)	23	0.82 (0.47–1.44)	29	0.74 (0.46–1.21)
40.8–44.8	68	1.07 (0.75–1.53)	28	0.95 (0.56–1.64)	32	1.12 (0.67–1.89)	37	0.88 (0.55–1.39)
⩾44.9	47	0.79 (0.53–1.17)	30	0.71 (0.39–1.29)	19	0.70 (0.38–1.27)	35	0.86 (0.53–1.37)
P for trend		0.41		0.32		0.47		0.66

a CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent of energy expenditure (kcal/kg × h).
b Including 38 colon cancers at an unknown subsite in the colon.
c The sum does not add up to the total owing to missing data.
d Multivariate models were stratified by age (in months) at baseline and adjusted for education (less than high school, high school graduate, or more than high school), family history of colorectal cancer (yes/no), history of diabetes (yes/no), smoking (never, past, or current smoker), aspirin use (yes/no), and body mass index (<23.0, 23.0–24.9, 25.0–29.9, or ⩾30.0 kg/m^2). Leisure-time physical activity, home/housework, and work/occupation were included simultaneously in the multivariate model.
e Combined walking/bicycling and exercise; the median MET values for the categories are 0.5, 1.4, 3.0, and 6.3 MET-h/day.
f The median MET values for the categories are 1, 3.8, and 8.8 MET-h/day.
g Light = mostly sitting down (7.4 MET-h/day) to sitting down half of the time (10.3 MET-h/day); moderate = mostly standing up (12.5 MET-h/day) to mostly walking, lifts, carry little (14.8 MET-h/day); heavy = mostly walking, lifts, carry much (17.1 MET-h/day) to heavy manual work (22.2 MET-h/day). Work/occupational activity levels were multiplied by 5.7 per day (8 h per day, 5 days per week).

There were statistically significant positive associations of BMI and weight with risk of colorectal cancer (Table 4). When analysed as continuous variables, the multivariate HR of colorectal cancer for an increment of 1 BMI unit (1 kg/m^2) was 1.04 (95% CI: 1.01–1.07) and the multivariate HR for an increment of 5 kg in weight was 1.05 (95% CI 1.02–1.09). Waist circumference was weakly positively associated with the risk of colorectal cancer (Table 4). Colorectal cancer risk was not associated with height (multivariate HR = 1.03; 95% CI: 0.73–1.44, for ⩾183 versus <172 cm) or weight change over lifetime (multivariate HR = 1.16; 95% CI 0.81–1.65, for gain of more than 20 kg compared with loss or gain of less than 5 kg). The associations for BMI, weight, and waist did not differ significantly by cancer site (Table 5).

To eliminate preclinical cases that might have experienced weight loss before completing the questionnaire, we did analyses that excluded the first 2 years of follow-up. Associations of BMI and weight with risk of colorectal cancer were strengthened in these lag analyses; the multivariate HRs for the highest versus the lowest category were 1.65 (95% CI 1.09–2.51) for BMI and 1.65 (95% CI 1.15–2.38) for weight.

To evaluate the possibility of an interaction between physical activity and BMI in relation to colorectal cancer, we classified participants according to both leisure-time physical activity and BMI. The decreased risk of colorectal cancer associated with increased levels of leisure-time physical activity was observed across all categories of BMI (P for interaction = 0.33; Fig. 1). There was also no statistically significant interaction between leisure-time physical activity and age (<65 or ⩾65 years; P for interaction = 0.61), smoking status (never, past, or current; P for interaction = 0.84), or aspirin use (yes or no; P for interaction = 0.83).

4. Discussion

In this large population-based prospective cohort of Swedish men, we observed that increased amounts of leisure-time physical activity were associated with reduced risk of both colon and rectal cancer. Findings of this study also confirm direct associations of BMI and weight with colorectal cancer risk.

The reduction in colon cancer risk associated with increasing amounts of recent leisure-time physical activity in this study is consistent with the results from the majority of previous prospective and case-control studies.[3,17] A meta-analysis estimated an approximately 20–40% lower risk of colon cancer for high versus low leisure-time physical activity.[17]

Evidence suggest that the etiologic factors for cancers of the proximal and distal colon may differ.[18,19] For example, there are various molecular and clinical differences between the two subsites that may influence the susceptibility to environmental factors.[19] We found that the inverse relationship between leisure-time physical activity and risk of colon cancer was stronger for distal colon than for proximal colon,

Table 4 – Hazard ratios and 95% confidence intervals of colorectal cancer by BMI, body weight, and waist circumference in the cohort of Swedish men (1998 – June 2005)[a]

Variable	Cases[b]	Person-years[b]	Age-adjusted HR	Multivariate HR[c]
BMI (kg/m^2)				
<23.0	70	57,097	1.00	1.00
23.0–24.9	111	79,423	1.13 (0.83–1.52)	1.13 (0.84–1.53)
25.0–26.9	114	78,190	1.23 (0.91–1.65)	1.20 (0.89–1.62)
27.0–29.9	107	64,956	1.39 (1.03–1.89)	1.32 (0.97–1.80)
⩾30.0	59	30,977	1.71 (1.20–2.42)	1.54 (1.08–2.21)
P for trend			0.001	0.01
Weight (kg)[d]				
<72	81	57,221	1.00	1.00
72–76	92	58,732	1.21 (0.90–1.63)	1.18 (0.87–1.60)
77–82	104	66,406	1.31 (0.98–1.76)	1.26 (0.93–1.70)
83–89	97	61,497	1.37 (1.02–1.84)	1.28 (0.94–1.75)
⩾90	114	67,396	1.65 (1.24–2.20)	1.48 (1.09–2.03)
P for trend			0.001	0.02
Waist (cm)[d]				
<88	47	44,165	1.00	1.00
88–92	67	53,831	1.10 (0.76–1.60)	1.06 (0.73–1.55)
93–97	95	56,784	1.38 (0.97–1.96)	1.32 (0.92–1.88)
98–103	96	54,462	1.46 (1.03–2.08)	1.37 (0.96–1.96)
⩾104	102	52,928	1.44 (1.02–2.05)	1.29 (0.90–1.85)
P for trend			0.01	0.03

a BMI = body mass index; CI = confidence interval; HR = hazard ratio.
b The sum does not add up to the total owing to missing data.
c Multivariate models were stratified by age (in months) at baseline and adjusted for education (less than high school, high school graduate, or more than high school), family history of colorectal cancer (yes/no), history of diabetes (yes/no), smoking (never, past, or current smoker), aspirin use (yes/no), and leisure-time physical activity (<10, 10–29, 30–59, or ⩾60 min/day).
d Multivariate hazard ratios also adjusted for height (in quintiles).

Table 5 – Multivariate hazard ratios and 95% confidence intervals of proximal colon, distal colon, and rectal cancer by BMI, body weight, and waist circumference in the cohort of Swedish men (1998 – June 2005)[a]

Variable	Colon[b]		Proximal colon		Distal colon		Rectum	
	Cases[c]	HR (95% CI)[d]	Cases[c]	HR (95% CI)[d]	Cases[c]	HR (95% CI)[d]	Cases[c]	HR (95% CI)[d]
BMI (kg/m²)								
<23.0	47	1.00	19	1.00	23	1.00	25	1.00
23.0–24.9	72	1.11 (0.77–1.61)	29	1.09 (0.61–1.96)	29	0.92 (0.53–1.59)	39	1.08 (0.65–1.80)
25.0–26.9	65	1.07 (0.73–1.56)	30	1.19 (0.66–2.13)	31	1.09 (0.63–1.89)	49	1.35 (0.83–2.19)
27.0–29.9	61	1.15 (0.78–1.70)	27	1.19 (0.65–2.17)	29	1.18 (0.67–2.07)	46	1.53 (0.93–2.51)
⩾30.0	39	1.60 (1.03–2.48)	15	1.43 (0.71–2.88)	17	1.49 (0.78–2.84)	21	1.44 (0.79–2.61)
P for trend		0.08		0.32		0.16		0.06
Weight (kg)[e]								
<72	49	1.00	22	1.00	21	1.00	33	1.00
72–76	70	1.50 (1.04–2.18)	22	0.98 (0.54–1.79)	38	1.99 (1.15–3.42)	23	0.71 (0.42–1.22)
77–82	61	1.22 (0.83–1.81)	29	1.20 (0.68–2.14)	23	1.11 (0.60–2.05)	43	1.29 (0.80–2.07)
83–89	54	1.19 (0.79–1.78)	22	0.94 (0.51–1.76)	27	1.51 (0.82–2.76)	43	1.40 (0.86–2.26)
⩾90	69	1.50 (1.01–2.24)	35	1.52 (0.85–2.73)	27	1.39 (0.75–2.60)	46	1.47 (0.90–2.42)
P for trend		0.23		0.20		0.71		0.02
Waist (cm)[e]								
<88	31	1.00	12	1.00	12	1.00	17	1.00
88–92	47	1.19 (0.75–1.87)	16	1.05 (0.49–2.23)	27	1.78 (0.90–3.54)	20	0.84 (0.44–1.61)
93–97	51	1.15 (0.73–1.80)	24	1.35 (0.67–2.73)	25	1.55 (0.77–3.12)	45	1.67 (0.95–2.95)
98–103	55	1.28 (0.82–2.00)	25	1.41 (0.70–2.85)	22	1.46 (0.71–2.98)	41	1.58 (0.89–2.81)
⩾104	68	1.44 (0.93–2.24)	33	1.66 (0.84–3.27)	26	1.62 (0.80–3.27)	35	1.24 (0.68–2.25)
P for trend		0.09		0.08		0.47		0.16

a BMI = body mass index; CI = confidence interval; HR = hazard ratio.
b Including 38 colon cancers at an unknown subsite in the colon.
c The sum does not add up to the total owing to missing data.
d Multivariate models were stratified by age (in months) at baseline and adjusted for education (less than high school, high school graduate, or more than high school), family history of colorectal cancer (yes/no), history of diabetes (yes/no), smoking (never, past, or current smoker), aspirin use (yes/no), and leisure-time physical activity (<10, 10–29, 30–59, or ⩾60 min/day).
e Multivariate hazard ratios also adjusted for height (in quintiles).

which is consistent with results of most of the previous prospective studies[4–6,9] but not all.[7,8]

Our finding of a lower risk of rectal cancer associated with increased amounts of leisure-time physical activity is in agreement with results of a recent large prospective cohort study.[7] In the Cancer Prevention Study II Nutrition Cohort with over 150,000 women and men, 390 individuals were diagnosed with rectal cancer during 7 years of follow-up.[7] In this cohort, a statistically significant 30% reduction in rectal cancer risk was observed for any recreational physical activity compared with none.[7] In a cohort of male Finnish smokers,[20] a statistically significant inverse association was observed between occupational activity and risk of rectal cancer; however, leisure-time physical activity was not associated with risk of either colon or rectal cancer. Other prospective studies have not observed any significant association between leisure-time or total physical activity and risk of rectal cancer,[4,8,20,21] but were limited by a small number of cases (ranging from 44 to 104). Results from case-control studies of physical activity and rectal cancer have also been inconsistent. In a meta-analysis of studies published through 2001, the summary results from case-control studies showed a nonsignificant 12–13% reduced risk of rectal cancer for high versus low physical activity (all types combined).[17] In a recent large population-based case-control study (with 952 rectal cancer cases) that was not included in the meta-analysis, high levels of leisure-time physical activity was associated with a statistically significant 30–40% lower risk of rectal cancer.[22]

Our results related to obesity and physical activity may be explained, biologically, within the axis of insulin resistance and hyperinsulinemia. Obesity is a major determinant of insulin resistance, and physical activity (independently of influencing body mass) increases insulin sensitivity and reduces insulin levels.[23] Insulin is an important growth factor of colonic epithelial cells and is a mitogen of tumour cell growth *in vitro*.[23] Supporting a role of insulin in colorectal carcinogenesis, epidemiologic studies have shown an increased risk of colorectal cancer associated with high circulating levels of insulin and C-peptide (a marker of insulin secretion)[24–27] and chronic insulin therapy.[28] In addition, a recent meta-analysis showed that diabetes was associated with a statistically significant increased risk of both colon and rectal cancer,[29] suggesting that hyperinsulinemia may be implicated in both colon and rectal cancer. Other proposed mechanisms for a protective role of physical activity on colon cancer include decreased gastrointestinal transit time, improved immune function, changes in bile acid metabolism, and altered prostaglandin levels.[30]

Findings from this study suggest that recent physical activity may be more beneficial with regard to colorectal cancer than physical activity early in adulthood (age 30).

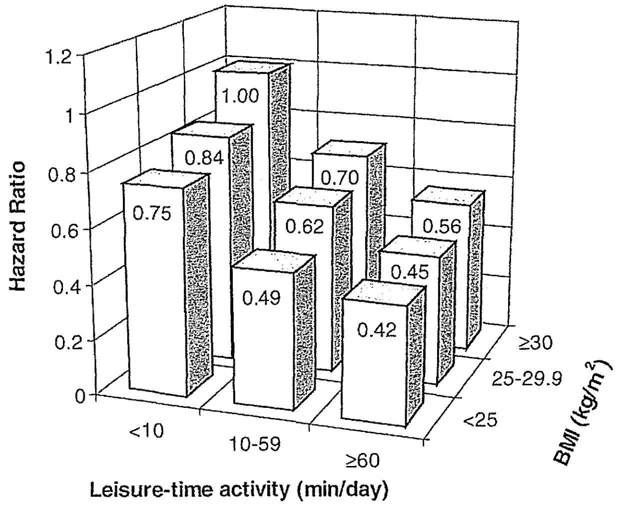

Fig. 1 – Multivariate hazard ratios of colorectal cancer by leisure-time physical activity and body mass index (BMI). Multivariate models were stratified by age (in months) at baseline and adjusted for education (less than high school, high school graduate, or more than high school), family history of colorectal cancer (yes/no), history of diabetes (yes/no), smoking (never, past, or current smoker), and aspirin use (yes/no). The nine hazard ratios with 95% confidence intervals are as follows: 1.00 (reference), 0.70 (0.36–1.38), 0.56 (0.26–1.23), 0.84 (0.42–1.66), 0.62 (0.34–1.13), 0.45 (0.24–0.84), 0.75 (0.36–1.55), 0.49 (0.26–0.90), and 0.42 (0.22–0.78).

Although one case-control study found a reduction in colon cancer risk associated with long-term vigorous activity,[31] most studies have not observed inverse associations with early adulthood activity.[7,21,32,33]

Strengths of the present study include a population-based and prospective design, a large sample size, and validated data on different types of physical activity, including leisure-time, housework, and occupational activity. Because of the large sample size, we could investigate associations by subsites in the colon and with rectal cancer with reasonable statistical power. Other strengths of the study include the virtually complete cohort follow-up and the detailed information on potential confounders. A limitation of this study is that measures of physical activity and body size were self-reported, which could lead to misclassification of exposures. However, because information on exposures was collected before the diagnosis of colorectal cancer, any misclassification would most likely have attenuated rather than exaggerated any true relationships and thus is unlikely to explain the observed associations.

In summary, results from this prospective study support the hypothesis of a protective role of leisure-time physical activity against colon cancer. Furthermore, our findings suggest that increased amounts of time spent at leisure-time physical activity may reduce the risk of rectal cancer.

Conflict of interest statement

None declared.

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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	男性	(　　)		(　　)		(　　)
年齢	45-79歳			(　　)		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	(	(　　)
アウトカム 維持・改善	なし	なし	なし	なし	(	(　　)

図　表

Table 2 – Hazard ratios and 95% confidence intervals of colorectal cancer by physical activity in the cohort of Swedish men (1998 – June 2005)[a]

Variable	Cases[b]	Person-years[b]	Age-adjusted HR	Multivariate HR[c]
Leisure-time activity (min/day)[d]				
<10	51	23,658	1.00	1.00
10–29	100	62,006	0.73 (0.52–1.03)	0.76 (0.54–1.06)
30–59	166	117,659	0.59 (0.43–0.81)	0.64 (0.47–0.89)
⩾60	174	112,838	0.52 (0.38–0.71)	0.57 (0.41–0.79)
P for trend			<0.0001	0.001
Home/housework (h/day)[e]				
<1	187	122,569	1.00	1.00
1–2	205	138,084	0.84 (0.68–1.02)	0.90 (0.73–1.10)
⩾3	77	45,326	0.75 (0.57–0.98)	0.81 (0.62–1.07)
P for trend			0.02	0.11
Work/occupation[f]				
Light	242	165,702	1.00	1.00
Moderate	164	97,039	0.93 (0.76–1.14)	0.99 (0.81–1.22)
Heavy	76	50,214	1.08 (0.83–1.39)	1.10 (0.84–1.44)
P for trend			0.85	0.58
Total activity score (MET-h/day)				
<37.9	98	61,804	1.00	1.00
37.9–40.7	80	63,549	0.82 (0.61–1.10)	0.84 (0.62–1.13)
40.8–44.8	105	63,120	0.97 (0.73–1.28)	1.00 (0.76–1.33)
⩾44.9	82	63,505	0.79 (0.59–1.07)	0.82 (0.60–1.10)
P for trend			0.27	0.38

a CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent of energy expenditure (kcal/kg × h).
b The sum does not add up to the total owing to missing data.
c Multivariate models were stratified by age (in months) at baseline and adjusted for education (less than high school, high school graduate, or more than high school), family history of colorectal cancer (yes/no), history of diabetes (yes/no), smoking (never, past, or current smoker), aspirin use (yes/no), and body mass index (<23.0, 23.0–24.9, 25.0–29.9, or ⩾30.0 kg/m²). Leisure-time physical activity, home/housework, and work/occupation were included simultaneously in the multivariate model.
d Combined walking/bicycling and exercise, the median MET values for the categories are 0.5, 1.4, 3.0, and 6.3 MET-h/day.
e The median MET values for the categories are 1, 3.8, and 8.8 MET-h/day.
f Light = mostly sitting down (7.4 MET-h/day) to sitting down half of the time (10.3 MET-h/day); moderate = mostly standing up (12.5 MET-h/day) to mostly walking, lifts, carry little (14.8 MET-h/day); heavy = mostly walking, lifts, carry much (17.1 MET-h/day) to heavy manual work (22.2 MET-h/day). Work/occupational activity levels were multiplied by 5.7 per day (8 h per day, 5 days per week).

図表掲載箇所	P2592, Table2
概　要（800字まで）	本研究は、スウェーデンのThe Cohort of Swedish Menに参加した男性45,906名を対象に平均7.1年間の追跡調査を行い、身体活動と結腸直腸がん発症リスクとの関連を検討したものである。身体活動量は、職業中の身体活動、家事活動、余暇時間活動(運動、歩行/自転車)、不活動時間を尋ね、総身体活動量はそれぞれの余暇時間活動に相当するメッツ値と実施時間を乗じ、1日当たりの活動量として算出した。余暇時間身体活動が1日当たり10分未満の集団と比較すると、30分以上、60分以上の集団でそれぞれ結腸直腸がん発症リスクが0.64(95%信頼区間:0.47-0.89)、0.57(0.41-0.79)と量反応的に減少した(Ptrend=0.001)。家事活動、職業中の身体活動、総身体活動量では、結腸直腸がん発症リスクとの有意な関連はみられなかった。部位別にみると、1日当たり60分以上の余暇時間身体活動、または1日当たり1時間以上の家事活動の実施で、結腸がん発症リスクが有意に減少した。1日当たり3時間以上の家事活動の実施で、近接結腸がん発症リスクが有意に減少した。また、1日当たり10分以上の余暇時間活動の実施で、遠位結腸がん発症リスクが有意に低下した。直腸がん発症
結　論（200字まで）	余暇時間身体活動の増加により、結腸直腸がん発症リスクを減少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）	身体活動基準の策定に用いられた研究の1つである。1日30分以上の余暇身体活動あるいは1日1時間以上の家事身体活動が低い結腸がん発症と関係することを示した。特に男性の家事活動が結腸がん発症のリスクと関連することを実証した点に意義がある。

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Exercise Intensity and Longevity in Men

The Harvard Alumni Health Study

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Objective.—To examine the independent associations of vigorous (≥6 resting metabolic rate [MET] score) and nonvigorous (<6 MET score) physical activity with longevity.

Design.—Prospective cohort study, following up men from 1962 or 1966 through 1988.

Setting/Participants.—Subjects were Harvard University alumni, without self-reported, physician-diagnosed cardiovascular disease, cancer, or chronic obstructive pulmonary disease (n=17 321). Men with a mean age of 46 years reported their physical activities on questionnaires at baseline.

Main Outcome Measure.—All-cause mortality (3728 deaths).

Results.—Total energy expenditure and energy expenditure from vigorous activities, but not energy expenditure from nonvigorous activities, related inversely to mortality. After adjustment for potential confounders, the relative risks of dying associated with increasing quintiles of total energy expenditure were 1.00 (referent), 0.94, 0.95, 0.91 and 0.91, respectively (P [trend]<.05). The relative risks of dying associated with less than 630, 630 to less than 1680, 1680 to less than 3150, 3150 to less than 6300, and 6300 or more kJ/wk expended on vigorous activities were 1.00 (referent), 0.88, 0.92, 0.87, and 0.87, respectively (P [trend]=.007). Corresponding relative risks for energy expended on nonvigorous activities were 1.00 (referent), 0.89, 1.00, 0.98, and 0.92, respectively (P [trend]=.36). Analyses of vigorous and nonvigorous activities were mutually adjusted. Among men who reported only vigorous activities (259 deaths), we observed decreasing age-standardized mortality rates with increasing activity (P=.05); among men who reported only nonvigorous activities (380 deaths), no trend was apparent (P=.99).

Conclusions.—These data demonstrate a graded inverse relationship between total physical activity and mortality. Furthermore, vigorous activities but not nonvigorous activities were associated with longevity. These findings pertain only to all-cause mortality; nonvigorous exercise has been shown to benefit other aspects of health.

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FEW PHYSICIANS, if any, would dispute that physical activity enhances health. Among other benefits, increased activity is associated with decreased incidence of coronary heart disease,[1] hypertension,[2] non–insulin-dependent diabetes mellitus,[3] and colon cancer,[4] and increased longevity.[5] What is uncertain, however, are the kinds and intensity of physical activity that should be prescribed for health. In England, Morris et al[6,7] found that to reduce coronary heart disease risk, moderately vigorous exercise is necessary. Similarly, in a recent study from Finland, Lakka et al[8] reported that only more intense, conditioning physical activity reduces the risk of myocardial infarction; less intense, nonconditioning activities have no effect. Yet others maintain that as long as total energy output—even if amassed from light or moderate exercise—is increased, risks of coronary heart disease[1,9-13] and premature mortality from any cause[5,9-11,13,14] are decreased. For example, in the Multiple Risk Factor Intervention Trial,[9] an inverse relationship between leisure time physical activity and risk of coronary heart disease and total mortality was observed among men engaged predominantly in light to moderate activities. Dutch men and women who habitually carried out light exercise (leisure-time walking, cycling, and gardening) also enjoyed decreased coronary heart disease risk.[15]

Despite this lack of consensus and the fact that few studies have compared directly the relative merits of vigorous and nonvigorous exercise, a commonly prescribed exercise regimen borrows from recommendations for developing and maintaining cardiorespiratory fitness. These regimens prescribe exercise intense enough to produce sweating or hard breathing (60% to 90% of maximum heart rate), for at least 20 minutes, three times per week.[16,17] Recently, the Centers for Disease Control and Prevention and the American College of Sports Medicine issued a new, less stringent recommendation[18]: "Every US adult should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week." This recommendation was meant to encourage more exercise among the almost 60% of US adults who engage in little or no leisure-time activity.[19]

Which is the more valid stance? To provide further information—at least, for total mortality—we investigated the relative merits of vigorous and nonvigorous exercise and their associations with premature mortality. Is, for example, 2100 kJ (500 kcal) expended in vigorous exercise associated with the same decrease in mortality risk as an equal amount expended in nonvigorous activity?

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SUBJECTS AND METHODS

Study Subjects

The Harvard Alumni Health Study is an ongoing cohort study that searches for predictors of chronic disease in men who matriculated as undergraduates at Harvard University, Boston, Mass, between 1916 and 1950. The cohort was established when 21 582 alumni (68% response) returned a mailed questionnaire on medical history and health practices in either 1962 or 1966. Eligible subjects for our study were men who reported no physician-diagnosed cardiovascular disease, cancer, or chronic obstructive pulmonary disease. Additionally, subjects had to provide data on physical activity, body weight, height, cigarette habit, physician diagnosis of hypertension and diabetes mellitus, vital status of both parents, and, if parents were deceased, age at parental death. Alumni who satisfied these criteria numbered 17321.

Assessment of Physical Activity and Other Predictors of Mortality

We assessed physical activity by asking alumni about flights of stairs climbed, city blocks walked, types of sports or recreational activities engaged in, and the time (hours per week) spent on each of these sports and recreational activities.[20] Although we did not ask specifically about occupational activity, alumni were unlikely to have expended much energy on the job apart from walking and climbing stairs. Physical activity assessment was validated by comparison of estimates of energy expenditure obtained from the questionnaire against the following: (1) other widely accepted and used physical activity questionnaires, (2) physiologic variables known to be influenced by physical activity, (3) total energy intake, (4) physical activity diaries, and (5) mechanical devices that measure bodily movement. On the basis of these criteria, this physical activity questionnaire has been shown to be reliable and valid.[21-27]

Climbing up and down one flight of stairs daily rated 118 kJ/wk, and walking 1 block daily, 235 kJ/wk. We assigned a multiple of resting metabolic rate (MET score) to every activity.[28] Since resting metabolic rate is approximately 4.2 kJ/kg of body weight per hour, we estimated the energy expended on each activity by multiplying its MET score by 4.2, body weight in kilograms and hours per week of participation. We then summed kilojoules per week from flights climbed, blocks walked, and activities performed, to provide an index of total energy expenditure per week.

We were interested in two components of total energy expenditure: that derived from vigorous activities (requiring ≥6 METs)[29] and that from nonvigorous (ie, light and moderate) activities (requiring <6 METs).[29] (Examples of vigorous activities reported by alumni include walking briskly, running or jogging, swimming laps, playing tennis, and shoveling snow.) Thus, for each alumnus, we further estimated energy expenditure from vigorous and nonvigorous activities separately.

Using alumni self-reports, we obtained information on other predictors of mortality: Quetelet's index (weight in kilograms divided by the square of height in meters), cigarette habit, physician diagnosis of hypertension or diabetes mellitus, and early parental death (defined as death occurring before age 65 years).

Ascertainment of Mortality

The Harvard Alumni Office maintains weekly rosters of deceased alumni. Their records indicate mortality follow-up data are unavailable for fewer than 1% of alumni.[30] Using information from the Alumni Office, we obtained copies of death certificates. The end point of interest for the present study was all-cause mortality occurring after return of the 1962 or 1966 questionnaire through 1988.

Statistical Analysis

We first compared age-standardized mortality rates, by means of the indirect method,[31] for increments of total, vigorous, and nonvigorous energy expenditure. To make statistical adjustment for several potential confounders simultaneously, we proceeded to use proportional hazards regression to analyze time to mortality or censoring.[32] Cumulative hazard plots disclosed no gross violation of proportional hazard assumptions. Mortality rate ratios (relative risks) were modeled as a function of physical activity. For total energy expenditure, we categorized alumni into quintiles (0 to <2524, 2524 to <4738, 4738 to <8001, 8001 to <13 142, and ≥13 142 kJ/wk). When investigating the independent associations of vigorous and nonvigorous energy expenditure with longevity, instead of using terms for total energy expenditure, we included terms for its two components. We categorized alumni according to five groups each of vigorous (<630, 630 to <1680, 1680 to <3150, 3150 to <6300, and ≥6300 kJ/wk) and nonvigorous (same cutoff points) energy expenditure. Potential confounders included in regression models were age (single years), Quetelet's index (<22.5, 22.5 to <23.5, 23.5 to <24.5, 24.5 to <26.0, or ≥26.0 kg/m^2), cigarette habit (never, former, or current smoker), and physician-diagnosed hypertension or diabetes mellitus (no vs yes). Although early parental death (neither, one, or both parents dying early) was unlikely to be related to physical activity and thus was not a confounder, it also was included since we were interested in its influence on mortality.

We tried to avoid observing an artifactual association between physical inactivity and increased mortality by excluding alumni with cardiovascular disease, cancer, and chronic obstructive pulmonary disease from the starting population. To minimize further the potential impact of this bias, we conducted additional analyses that omitted the first 5 years (arbitrarily chosen) of follow-up, because mortality among individuals with other illnesses that could limit physical activity, and also increase mortality risk, would likely occur early in follow-up.

Table 1.—Characteristics of Harvard Alumni in 1962 or 1966, According to Quintiles of Total Energy Expenditure*

Characteristic	Quintile of Total Energy Expenditure 1	2	3	4	5
Mean age, y	46.8	46.1	45.8	45.5	46.4
Mean Quetelet's index, kg/m^2	24.65	24.31	24.14	24.19	24.47
Cigarette habit, %					
Never smokers	20.1	21.9	20.9	21.1	20.2
Former smokers	32.1	30.4	32.0	31.9	33.5
Current smokers	47.8	47.7	47.1	47.0	46.3
Mean No./d of cigarettes smoked by current smokers	27	27	26	26	26
% reporting physician-diagnosed hypertension or diabetes mellitus	12.0	10.2	9.2	10.1	9.6
Early parental death (<65 y), %					
Neither parent dying early	66.9	65.4	64.6	66.3	67.6
1 parent dying early	29.0	30.7	30.6	29.6	28.0
Both parents dying early	4.1	3.9	4.8	4.1	4.4
% of total energy expenditure expended in vigorous activities†	41.7	32.1	32.2	38.9	43.5

*All characteristics (except mean age) were age standardized. Energy expenditure was estimated in kilojoules per week from climbing stairs, walking, and participating in sports or recreational activities. Quintile 1 represents the lowest energy expenditure.

†Among alumni who did expend energy in climbing stairs, walking, or participating in sports or recreational activities (17 090 of 17 321 alumni). Vigorous activities were defined as those that required 6 or more units of resting metabolic rate (METs).

Ninety-five percent confidence intervals were calculated for estimated relative risks, and all *P* values were from two-tailed tests. To assess whether vigorous and nonvigorous energy expenditure differed significantly in their independent associations with longevity, we used the covariance matrix to estimate variance for the difference between the two parameter estimates.[33]

RESULTS

Table 1 describes alumni characteristics at study entry by quintiles of total energy expenditure. The mean age of alumni was 46 years, with little variation across quintiles. The mean Quetelet's index decreased as energy expenditure increased from the lowest to the third category, then increased beyond that. Almost half of the alumni smoked cigarettes in 1962 or 1966; the proportion who smoked declined steadily with increasing energy expenditure. Approximately 10% of alumni declared a physician diagnosis of hypertension or diabetes mellitus, while approximately 30% reported that one or both parents had died early. Table 1 also presents, for alumni who declared some form of physical activity (n=17 090), the proportion of total energy expenditure derived from vigorous activities.

We then examined age-standardized mortality rates by level of energy expenditure (Table 2). Between 1962 or 1966 and 1988, a total of 3728 deaths occurred in 384 681 person-years of observation. Mortality generally declined with increasing total energy expenditure (*P*=.001). At about 14 700 kJ/wk of total energy expenditure, mortality appeared to stabilize. Mortality also declined with higher levels of vigorous energy expenditure, regardless of the level of nonvigorous activity, up to 12 600 kJ/wk. Beyond this level of vigorous energy expenditure, mortality increased slightly. However, the overall inverse association was significant (*P*<.001). On the other hand, nonvigorous energy expenditure, regardless of the level of vigorous activity, was not associated with mortality (*P*=.87).

To consider other potential confounders, we proceeded to multivariate analyses, adjusting additionally for Quetelet's index, smoking, hypertension, diabetes mellitus, and early parental death. Total energy expenditure, in quintiles, continued to relate significantly and inversely to mortality. The adjusted relative risks were 1.00 (referent), 0.94 (95% confidence interval, 0.86 to 1.04), 0.95 (0.86 to 1.05), 0.91 (0.83 to 1.01), and 0.91 (0.82 to 1.00), respectively (*P* for trend<.046).

With the findings in Table 2, we could not determine whether vigorous physical activity, nonvigorous physical activity, or both was responsible for the inverse relationship with mortality. We thus conducted multivariate analyses to adjust mutually for vigorous and nonvigorous energy expenditure, while simultaneously adjusting for potential confounders (Table 3). Vigorous energy expenditure again was significantly and inversely related to mortality (*P*=.007), whereas the trend for nonvigorous energy expenditure again was not significant (*P*=.36). However, relative risk estimates for vigorous energy expenditure did not differ significantly from corresponding estimates for nonvigorous energy expenditure.

To minimize potential bias from ill health in the starting population, we conducted additional analyses that omitted the first 5 years after physical activity assessment (see "Statistical Analysis" section). We analyzed 3297 deaths (Table 4). Vigorous energy expenditure remained significantly and inversely related to mortality (*P*=.007), but we again observed no significant trend with nonvigorous energy expenditure (*P*=.32). Relative risk estimates for the two kinds of energy expenditure differed significantly at 1680 kJ/wk and higher. Trends for the two types of energy expenditure also differed significantly (*P*=.02).

We next tried to account for changes in physical activity over time. In 1977, we had sent another questionnaire to surviving alumni that requested updated information on medical history and health habits, including physical activity. Seventy-six percent of surviving alumni responded. We conducted further analyses that updated physical activity in 1977 for alumni who returned a questionnaire that year and who continued to be free of self-reported, physician-diagnosed cardiovascular disease, cancer, or chronic obstructive pulmonary disease. We also built in a 5-year lag after either physical activity assessment. Relative risks of mortality for the same five categories of vigorous energy expenditure were 1.00 (referent), 0.89 (95% confidence interval, 0.79 to 1.00), 0.83 (0.71 to 0.97), 0.76 (0.63 to 0.91), and 0.75 (0.64 to 0.89), respectively (*P* for trend=.001). Corresponding relative

Table 2.—Age-Standardized Mortality Rates Among Harvard Alumni, 1962 or 1966 Through 1988, According to Energy Expended on All, Vigorous, and Nonvigorous Activities in 1962 or 1966*

Physical Activity in 1962 or 1966, kJ/wk	No. of Deaths	Person-Years	Age-Standardized Mortality Rate/10 000
Energy expended on all activities			
<2100	700	65 241	103.78
2100-<4200	850	82 859	102.55
4200-<6300	553	55 670	99.79
6300-<8400	360	41 005	92.30
8400-<10 500	292	32 665	92.88
10 500-<12 600	222	26 347	88.35
12 600-<14 700	182	20 421	88.05
≥14 700	569	60 473	90.76
P for trend	...	...	<.001
Energy expended on vigorous activities			
<2100	2730	250 181	102.25
2100-<4200	401	44 373	95.90
4200-<6300	158	24 590	74.26
6300-<8400	107	17 098	76.94
8400-<10 500	104	14 222	89.97
10 500-<12 600	50	9389	62.00
12 600-<14 700	43	6564	79.29
≥14 700	135	18 264	86.23
P for trend	...	...	<.001
Energy expended on nonvigorous activities			
<2100	1276	135 930	97.81
2100-<4200	855	94 574	94.92
4200-<6300	590	59 321	101.63
6300-<8400	245	27 100	90.40
8400-<10 500	203	19 620	96.98
10 500-<12 600	152	14 779	90.33
12 600-<14 700	101	9842	89.43
≥14 700	306	23 515	102.22
P for trend	...	...	.87

*Energy expenditure was estimated from climbing stairs, walking, and participating in sports or recreational activities. Vigorous activities were defined as those that required 6 or more units of resting metabolic rate (METs); nonvigorous activities, those that required less than 6 METs.

Table 3.—Relative Risks of All-Cause Mortality Among Harvard Alumni, 1962 or 1966 Through 1988, According to Vigorous and Nonvigorous Physical Activity in 1962 or 1966*

	Energy Expenditure, kJ/wk				
Kind of Activity	<630	630-<1680	1680-<3150	3150-<6300	≥6300
Vigorous activity					
No. of deaths	1459	1123	428	279	439
Relative risk (B1)	1.00	0.88	0.92	0.87	0.87
95% confidence interval	Referent	0.82-0.96	0.82-1.02	0.77-0.99	0.78-0.97
Nonvigorous activity					
No. of deaths	481	652	784	804	1007
Relative risk (B2)	1.00	0.89	1.00	0.98	0.92
95% confidence interval	Referent	0.79-1.01	0.89-1.12	0.88-1.12	0.82-1.02
P (B1−B2)	...	.88	.29	.18	.53

*Relative risks are adjusted for age, Quetelet's index, cigarette habit, physician-diagnosed hypertension or diabetes mellitus, and early (<65 years) parental death. Relative risks for vigorous and nonvigorous energy expenditure are mutually adjusted. Vigorous activities were defined as those that required 6 or more units of resting metabolic rate (MET); nonvigorous activities, those that required less than 6 METs. *P* of trend across categories of vigorous energy expenditure is .007. *P* of trend across categories of nonvigorous energy expenditure is .36.

Table 4.—Relative Risks of All-Cause Mortality Among Harvard Alumni, 1967 or 1971 Through 1988, According to Vigorous and Nonvigorous Physical Activity in 1962 or 1966*

	Energy Expenditure, kJ/wk				
Kind of Activity	<630	630-<1680	1680-<3150	3150-<6300	6300+
Vigorous activity					
No. of deaths	1282	998	379	250	388
Relative risk (B1)	1.00	0.88	0.91	0.87	0.86
95% confidence interval	Referent	0.81-0.96	0.81-1.02	0.76-1.00	0.76-0.96
Nonvigorous activity					
No. of deaths	386	579	691	713	928
Relative risk (B2)	1.00	0.98	1.09	1.08	1.05
95% confidence interval	Referent	0.86-1.11	0.96-1.23	0.96-1.23	0.93-1.18
P (B1−B2)	...	.19	<.044	.02	.02

*Relative risks are adjusted for age, Quetelet's index, cigarette habit, physician-diagnosed hypertension or diabetes mellitus, and early (<65 years) parental death. Relative risks for vigorous and nonvigorous energy expenditure are mutually adjusted. Vigorous activities were defined as those that required 6 or more units of resting metabolic rate (METs); nonvigorous activities, those that required less than 6 METs. *P* of trend across categories of vigorous energy expenditure is .001. *P* of trend across categories of nonvigorous energy expenditure is .32. Analyses exclude first five years after physical activity assessment.

risks for nonvigorous energy expenditure were 1.00 (referent), 0.94 (0.79 to 1.12), 0.97 (0.82 to 1.15), 0.96 (0.81 to 1.14), and 0.89 (0.75 to 1.04), respectively (*P* for trend=.18). The trend across categories of vigorous energy expenditure differed significantly from that across categories of nonvigorous energy expenditure (*P*=.001).

We observed similar findings among men younger than 55 years and among older men. There also was no interaction by Quetelet's index; findings did not differ between leaner (<24.5 kg/m^2) and heavier (≥24.5) men.

In a final effort to disentangle the independent associations of the two kinds of energy expenditure with mortality, we examined alumni who reported only one kind of activity in 1962 or 1966. Alumni who performed only vigorous activities (and no nonvigorous exercise) numbered 919; of these, 259 died during follow-up. On the basis of this small number, we observed a marginally significant trend (*P*=.05) of decreasing age-standardized mortality with increasing vigorous energy expenditure (data not shown, but available from the authors on request). Among 1195 alumni who reported only nonvigorous activity (and no vigorous exercise) in 1962 or 1966, 380 died during follow-up. In age-standardized analysis, we found nonvigorous energy expenditure and mortality to be unrelated (*P*=.99) (data not shown, but available from the authors on request).

COMMENT

These prospective data demonstrate a graded, inverse relationship between an index of total physical activity and mortality in middle-aged men, concurring with most other investigations.[9-11,13,14] Of the components of total physical activity, we found vigorous (activities at ≥6 METs) but not nonvigorous (<6 METs) exercise to be associated with decreased mortality. Men who expended 6300 kJ/wk or more in vigorous exercise had 0.75 to 0.87 times the risk of dying during follow-up, compared with those who expended less than 630 kJ/wk. This difference in mortality risk is of approximately the same magnitude as that between alumni 20% or more overweight[34] and those of ideal weight,[5] or that between alumni who smoked one pack of cigarettes or less daily and nonsmokers.[5]

These data also suggest that the decrease in mortality associated with higher levels of energy expenditure may taper off after approximately 14 700 kJ/wk of total energy expenditure or 12 600 kJ/wk of vigorous energy expenditure (Table 2). In a British study, investigators noted a similar finding among younger men, ie, declining rates of coronary heart disease with increasing physical activity levels until the most active category ("very frequent sporting exercise or frequent sporting exercise plus other recreational activities"), in which rates began to increase. Some investigators have postulated that this phenomenon may be explained by the increased oxidative stress associated with prolonged physical exertion.[35] However, when we classified alumni according to their total energy expenditure in 1977 (instead of 1962 or 1966, as in the present analyses), we observed that mortality continued to decline at 14 700 kJ/wk.[5]

It is unclear to us why vigorous, but not nonvigorous, physical activity is associated with greater longevity. A recent report suggested that for favorable changes in high-density lipoprotein cholesterol and triglyceride levels, a threshold intensity of 5 to 6 METs of conditioning exercise is needed.[36] However, exercise intensity appears unrelated to the magnitude of decrease in blood pressure levels.[2] Perhaps the inverse association between physical activity and mortality is related not so much to exercise itself, but to the improved cardiorespiratory fitness that is induced.[37,38] Vigorous exercise is more effective than nonvigorous activity for cardiorespiratory conditioning. The kind of vigorous activity also may be relevant; for example, jogging, which is sustained and dynamic, is effective for such conditioning, whereas heavy yardwork is unlikely to be as sustained and thus would be less effective in conditioning.

Several previous studies also have examined the association of vigorous and nonvigorous exercise with health. Morris et al[6,7] found an inverse relationship between physical activity and coronary heart disease incidence only among British men who reported vigorous sports. A similar observation was made among Finnish men by Lakka et al.[8] However, Shaper et al[12] reported that even among British men with little vigorous ("sporting") exercise, myocardial infarction rates apparently decreased (not formally tested) with increasing physical activity. Slattery et al[11] also observed apparent decreases in age-adjusted death rates (not formally tested) with increasing light to moderate activity among US railroad workers who reported no vigorous activity. Among men who reported some vigorous activity, the trend with increasing light to moderate activity was unclear. In multivariate analyses adjusting for age, smoking, blood pressure, and serum cholesterol level, the estimated coefficient for vigorous activity was significant, and that for light to moderate activity, nonsignificant. However, investigators did not examine whether the coefficients for the two kinds of activity differed significantly.

In investigating the independent, relative merits of vigorous and nonvigorous activity, the issues involved are analogous to those in epidemiologic studies of diet. We wished to investigate the independent associations of vigorous and nonvigorous physical activity with mortality, apart from their contributions to total energy expenditure, and their relative merits. In studies of dietary fat and coronary heart disease, investigators are interested in the effect of fat that is independent of other nutrients, and of total energy intake.[39] To separate this effect, various analytic strategies have been proposed.[39-42] We have adapted one of these strategies[40] to achieve our end. As noted by Willett[39] and restated recently by Wacholder et al,[43] it is not adequate merely to note that the coefficient of one kind of energy expenditure (nutrient) is significant, and the coefficient of the other, nonsignificant. The appropriate focus should be the *difference* in coefficients (ie, [B1−B2] in Tables 3 and 4).

The most plausible alternate explanation for our findings is that alumni reported light and moderate activities with greater imprecision than vigorous activities, resulting in greater misclassification of the former. We had no data to test this hypothesis. In a separate validation study of our physical activity questionnaire, Ainsworth et al[27] reported that in men aged 21 to 59 years, the correlation between energy expenditure estimated from the questionnaire and that estimated from physical activity diaries was .69 for activities of 6 METs or more. For lower-intensity activities, the correlations were less than .35. However, among healthy alumni in the present study, the correlation between nonvigorous energy expenditure in 1962 or 1966 and 1977 was comparable with that for vigorous energy expenditure (r=.35 and .40, respectively). These low correlations imply that during the long follow-up, patterns of physical activity had changed. In further analyses that did account for changes in physical activity in 1977, we arrived at similar conclusions.

We could not determine whether our findings resulted from differences in diet, blood pressure levels, glucose tolerance, or serum lipid levels. We were unable to make statistical adjustment for dietary differences because we did not have detailed dietary information for alumni before 1988. According to the dietary data of 1988, estimated total energy consumed increased with increasing total, vigorous, and nonvigorous energy expenditure. However, the proportion of total energy consumed as fat or saturated fat did not vary across activity categories. Thus, confounding by fat intake was unlikely, with the caveat that diet in 1988 may not reflect earlier diet adequately. Some investigators argue that differences in blood pressure levels, glucose tolerance, and serum lipid levels should not be controlled for. Physical training lowers blood pressure levels,[2] increases insulin sensitivity,[44] and favorably influences lipid profiles.[45] Therefore, these variables may represent some of the mechanisms through which physical activity modifies mortality risk. Rather than being true confounders, then, they may represent events in the causal pathway and thus should not be controlled for.[31] We did not have data on serum lipid levels, but we took into account physician-diagnosed hypertension and diabetes mellitus. Self-reported physician-diagnosed disease among these alumni is believed to be valid.[4,20,30] Not adjusting for these diseases did not materially alter findings.

Although these observational data preclude a conclusion of causality,[46] several highly plausible mechanisms exist that link increased physical activity to decreased mortality. In addition to those described previously, physical training also improves cardiac mechanical and metabolic function,[47] reduces platelet aggregation, and increases fibrinolytic activity.[48] Our findings indicate that sedentary individuals should increase their activity level to enhance longevity. Specifically, vigorous activities were associated with greater longevity. However, we strongly believe that even nonvigorous exercise is preferable to sedentariness. Our findings pertain only to all-cause mortality; meanwhile, even modest exercise has been shown to improve, for example, lipid and glucose profiles.[49,50]

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エキスパートレビューのフォーマット

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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	男性	( )		( )		( )
	年齢	46歳			( )		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	な し	な し	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )
図 表							
図表掲載箇所							
概 要 (800字まで)	目的:活発な運動(6 METsもしくはそれ以上)と低中強度(6 METs以下)運動が死亡リスクに及ぼす効果とその独立した関連性を長期間にわたり調査すること。デザイン:1962もしくは1966年から1988年までの調査によるコホート研究。対象者および設定:対象者は、医師によって心血管疾患、ガン、または慢性閉塞性肺疾患と診断されていない、自己記入式質問紙調査に回答したハーバード大学同窓生(n=17321)であった。対象者(平均年齢46歳)においては、ベースラインにおける質問紙調査に基づいて身体活動が報告された。主な測定結果:すべての原因による死亡(3728名)。結果:低中強度活動のエネルギー消費量ではなく、活発な活動のエネルギー消費量および総エネルギー消費量と死亡率との間に負の相関関係がみられた。潜在的交絡因子補正後、死亡の相対リスクは総エネルギー消費量が増加する5段階において、それぞれ1.00(referent)、0.94、0.95、0.91. 0.91(P <.005)の関係性を示した。相対リスクを630、630～1679、1680～3149、3150～6299、6300 kJ/week以上の活発な活動の各消費量からみてみると、それぞれ1.00(referent) 0.88、0.92、0.87、0.87(P <.007)の関係性を示した。これを低中強度活動での消費量で一致させると、相対リスクは、1.00(referent)、0.89、1.00、0.98、0.92 (P =0.36)の関係性を示した。活発な活動および低中強度活動を相互に調整した場合、活発な活動(259名が死亡)のみの間では、活動量の増加に伴う年齢標準化による死亡率の低下が観察された(P=0.05)が、低中強度の活動(380名が死亡)のみでは、同様の傾向はみられなかった(P=0.99)。結論:これらのデータは、総身体活動量と死亡率との間で、等級ごとに負の相関関係を示すことを立証するものである。さらに、活発な活動の量は寿命との関連性がみられた。これらの知見は、すべての死亡原因に対してのみ適用される。						
結 論 (200字まで)	高い強度の運動(6メッツ以上)であれば週当たり1680KJ以上行えば総死亡リスクを減らせる。						
エキスパートによるコメント (200字まで)	単に身体活動量のみでなく、活動の強度にフォーカスを当てて検討した貴重なデータである。比較的高い強度の運動を行えば、身体活動が多いことに加えてさらに利益があるかもしれない。						

担当者 宮地 劉

Physical Activity Recommendations and Decreased Risk of Mortality

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Background: Whether national physical activity recommendations are related to mortality benefit is incompletely understood.

Methods: We prospectively examined physical activity guidelines in relation to mortality among 252 925 women and men aged 50 to 71 years in the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health Study. Physical activity was assessed using 2 self-administered baseline questionnaires.

Results: During 1 265 347 person-years of follow-up, 7900 participants died. Compared with being inactive, achievement of activity levels that approximate the recommendations for moderate activity (at least 30 minutes on most days of the week) or vigorous exercise (at least 20 minutes 3 times per week) was associated with a 27% (relative risk [RR], 0.73; 95% confidence interval [CI], 0.68-0.78) and 32% (RR, 0.68; 95% CI, 0.64-0.73) decreased mortality risk, respectively. Physical activity reflective of meeting both recommendations was related to substantially decreased mortality risk overall (RR, 0.50; 95% CI, 0.46-0.54) and in subgroups, including smokers (RR, 0.48; 95% CI, 0.44-0.53) and nonsmokers (RR, 0.54; 95% CI, 0.45-0.64), normal weight (RR, 0.45; 95% CI, 0.39-0.52) and overweight or obese individuals (RR, 0.48; 95% CI, 0.44-0.54), and those with 2 h/d (RR, 0.53; 95% CI, 0.44-0.63) and more than 2 h/d of television or video watching (RR, 0.50; 95% CI, 0.45-0.55). Engaging in physical activity at less than recommended levels was also related to reduced mortality risk (RR, 0.81; 95% CI, 0.76-0.86).

Conclusions: Following physical activity guidelines is associated with lower risk of death. Mortality benefit may also be achieved by engaging in less than recommended activity levels.

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PHYSICAL ACTIVITY PROMOTES health and longevity,[1,2] and increasing participation in regular exercise has been a major public health goal in the United States for decades.[3] The Office of the US Surgeon General (OSG), the Centers for Disease Control and Prevention (CDC), and the American College of Sports Medicine (ACSM) all endorse a minimum of 30 minutes of moderate activity on most days of the week, an amount and intensity of activity that is feasible for most Americans.[4,5] Recent nationally representative survey data[6] indicate that more than 50% of the adult US population do not meet the lower bound of the physical activity recommendations,[4,5] a proportion that has remained essentially unchanged throughout the last decade.[7] Commonly reported barriers to activity participation include lack of time and the perceived effort of exercise.[8]

Given the potential mortality benefit from achieving the physical activity guidelines, surprisingly little is known about current physical activity recommendations as they relate to mortality. The sparse epidemiologic data available suggest a 20% to 30% decreased mortality risk for subjects expending approximately 1000 kcal/wk—the equivalent of minimal adherence to the recommendations.[9] Moreover, the specific role of activity of at least moderate intensity is poorly understood.[10-12] Several investigations found an inverse association only for vigorous activity[13-18] or noted strong inverse relations with fitness,[19-21] whereas other studies[22-28] reported that moderate activity was also sufficient to decrease mortality risk.

We examined physical activity recommendations in relation to mortality in a large prospective cohort with comprehensive physical activity data. Our study differs from most previous investigations[2,9] in quantifying the dose-response associations in a manner that facilitates an application to the current guidelines.[4,5]

METHODS

STUDY POPULATION

The National Institutes of Health–AARP (formerly known as the American Association of Retired Persons) (NIH-AARP) Diet and Health Study was established in 1995-1996, when 566 407 AARP members 50 to 71 years old who were residing in one of 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) responded to a baseline questionnaire requesting information on medical history, diet, and structured exercise.[29] Within 6 months of the baseline questionnaire, subjects were asked to complete a second questionnaire that collected additional exposure information, including lifestyle activity. Eligible subjects for the present study were participants who responded to both questionnaires and who were alive and had not moved out of the study area before returning the second questionnaire (n=334 905). Of these, we excluded individuals who reported a previous diagnosis of cancer (n=19 479), cardiovascular disease (n=45 621), or emphysema (n=8123) and individuals with missing information on physical activity (n=8757). After these exclusions, the analytic cohort comprised 252 925 subjects (142 828 men and 110 097 women). The study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute. Completion of the self-administered baseline questionnaire was considered to imply informed consent.

COHORT FOLLOW-UP AND END POINT ASCERTAINMENT

Cohort members were followed up by annual linkage of the cohort to the National Change of Address database maintained by the US Postal Service, through processing undeliverable mail, by using other address change update services, and directly from cohort members' notifications. For matching purposes, we have virtually complete data on first and last name, address history, sex, and date of birth. Social security numbers are available for 85% of our cohort. Follow-up for vital status is performed by annual linkage of the cohort to the Social Security Administration Death Master File.[30] Verification of vital status and cause of death is provided by searches of the National Death Index (NDI) Plus.[31] We estimate that follow-up for deaths in our cohort is more than 93% complete.[30,31] Maintenance of the cohort also involves periodic linkage to the 8 state cancer registries serving our cohort.[32] The primary end point in the present analysis was mortality from any cause. We also investigated the 2 main causes of death: mortality from cardiovascular disease (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 390.0-448.9) and mortality from cancer (*ICD-9* codes 140.0-208.9). In further analyses, we considered mortality from stroke and from a combination of cancers considered a priori to be associated with physical activity (ie, cancers of the colon, breast, prostate, lung, and endometrium).[33]

ASSESSMENT OF PHYSICAL ACTIVITY

The baseline questionnaire inquired about structured vigorous exercise during the previous year, defined as the frequency each week spent at activities such as exercise and sports that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat. There were 6 possible response options: never; rarely; 1 to 3 times per month; 1 to 2 times per week; 3 to 4 times per week; and 5 or more times per week. We used that assessment to examine the ACSM physical activity guidelines that recommend at least 20 minutes of continuous vigorous exercise 3 times per week[34] as a means of improving cardiorespiratory fitness.

The second questionnaire requested information on the average time spent each week at activities of at least moderate intensity using categories of never; rarely; weekly, but less than 1 h/wk; 1 to 3 h/wk; 4 to 7 h/wk; and more than 7 h/wk. Specific examples included brisk walking/fast dancing, walking during golf, hiking/mountain climbing, cheerleading/drill team, tennis, biking, swimming, aerobics, jogging/running, rowing, basketball/baseball, football/soccer, handball/racquetball, weight lifting, heavy gardening, and heavy housework. We used 3 hours of activity of at least moderate intensity per week as a cut point to approximate the current OSG/CDC/ACSM physical activity recommendations[4,5] that emphasize the overall health benefits of 30 minutes of activity of moderate intensity on most days of the week.

Our physical activity assessment contains important elements of the Physical Activity Scale for the Elderly (PASE), which showed an intraclass correlation coefficient of 0.84 for 2 administrations of the questionnaire mailed 3 to 7 weeks apart[35] and a correlation coefficient of 0.58 comparing activity energy expenditure as assessed by the questionnaire with that using the doubly labeled water method.[36]

STATISTICAL ANALYSIS

Cox proportional hazards regression[37] with age as the time scale was used to estimate relative risks (RRs) and 95% confidence intervals (CIs) of mortality. Follow-up time was calculated from the scan date of the second questionnaire until death from any cause or the end of study on December 31, 2001. Terms for activity of at least moderate intensity and vigorous exercise were entered into the models simultaneously to assess their independent effects. The models were adjusted for age, sex, race/ethnicity, marital status, family history of cancer, education, smoking status, menopausal hormone therapy, aspirin, and intakes of multivitamins, vegetables, fruit, red meat, and alcohol. Information on family history of cardiovascular disease was unavailable. Because body mass index (BMI) and smoking[38] could be intermediate steps in the causal pathways linking physical activity to decreased mortality, we analyzed the data with and without inclusion of those variables in the model.

RESULTS

During 1 265 347 person-years of follow-up, we documented 7900 deaths. At baseline, half of the cohort (50.4%) reported engaging in activity of at least moderate intensity for more than 3 h/wk, and slightly less than half (47.8%) reported engaging in a minimum of 20 minutes of vigorous exercise 3 times per week. Subjects with increased levels of activity of at least moderate intensity or vigorous exercise tended to have a higher education level and, as expected, were leaner, showed less adulthood weight gain, and had greater intakes of total energy compared with less active subjects (**Table 1**).

Increased physical activity was associated with a clear decrease in risk of mortality from any cause (**Table 2**). Compared with the lowest category of no activity of at least moderate intensity, participants in the highest category of more than 7 h/wk had a multivariate RR of 0.68 (95% CI, 0.63-0.74). For vigorous exercise, any level above the inactive category was related to decreased mortality risk. Compared with no vigorous exercise, the multivariate RR was 0.71 (95% CI, 0.66-0.77) for the highest cat-

Table 1. Baseline Characteristics According to Activity of at Least Moderate Intensity and Vigorous Exercise

	Activity of at Least Moderate Intensity,[b] h/wk					Vigorous Exercise,[c] Times per Week				
Characteristic[a]	Inactive	<1	1-3	4-7	>7	Inactive	<1	1-2	3-4	≥5
Participants, No.	34 426	26 685	64 289	65 717	61 808	40 856	34 843	56 233	70 282	50 711
Age, y	62.3	62.0	62.2	62.5	62.9	62.5	61.7	62.1	62.7	62.9
Sex, %										
Women	44	44	44	43	44	54	45	42	41	38
Men	56	56	56	57	56	56	55	58	59	62
Race/ethnicity, %										
White	91	92	94	94	94	92	94	94	94	94
Black	5	4	3	3	3	5	3	3	3	3
Hispanic	2	2	2	2	2	2	2	2	2	2
Asian/Pacific Islander/Native American	2	2	1	1	1	2	1.	1	2	2
College education, %	70	76	78	79	76	66	75	78	80	79
Married or living as married, %	64	67	68	70	70	60	67	70	71	72
Family history of cancer, %	51	52	52	52	52	51	52	52	52	52
Current smoker, %	15	13	12	10	10	18	15	12	8	8
Past smoker, %	47	47	49	50	50	44	48	48	51	52
BMI	28.5	27.9	27.1	26.4	25.9	28.3	27.6	27.0	26.3	25.8
Weight gain since age 18 y, kg	21.1	19.8	17.7	15.5	13.9	20.8	19.2	17.7	15.4	13.3
Television or video watching, h/d	4	3	3	3	3	4	3	3	3	3
Current menopausal hormone therapy, %[d]	42	45	46	49	46	40	45	46	50	48
Past menopausal hormone therapy, %[d]	9	9	9	9	8	9	9	9	9	8
Regular aspirin use, %[e]	36	37	37	37	37	34	36	37	38	38
Total energy intake, kcal/d	1860	1809	1809	1829	1944	1835	1786	1838	1838	1960
Vegetable intake, servings/1000 kcal/d	1.6	1.7	1.8	1.9	1.9	1.6	1.7	1.8	1.9	2.0
Fruit intake, servings/1000 kcal/d	1.5	1.6	1.7	1.8	1.9	1.5	1.5	1.6	1.8	1.9
Red meat intake, g/1000 kcal/d	37	37	35	33	32	37	37	36	32	30
Alcohol intake, g/d	14	13	13	13	14	13	13	13	13	14
Multivitamin use, %	52	55	57	58	58	51	54	57	59	59

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] All values (except age) were directly standardized to the age distribution of the cohort.
[b] Activity of at least moderate intensity is defined as activities with an estimated energy expenditure of greater than 3 metabolic equivalents (METs). The MET is defined as the ratio of work to resting energy expenditure (1 MET = 1 kcal/kg/h or 3.5-mL oxygen uptake/kg/min). Resting energy expenditure is assumed to be 1 MET.
[c] Vigorous exercise is defined as activities that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat.
[d] Among postmenopausal women.
[e] Regular aspirin use is defined as use of aspirin or aspirin products once per week or more.

egory of at least 20 continuous minutes of vigorous exercise 5 or more times per week.

Adjustment for BMI had no appreciable effect on the risk estimates (Table 2). However, adjustment for smoking accounted for a considerable difference between the age- and sex-adjusted and multivariate findings for vigorous exercise. Inclusion of biological intermediary covariates that may mediate the effect of physical activity (hypertension, high cholesterol level, and diabetes) had no impact (data not shown).

To determine whether undiagnosed chronic disease may have caused a decrease in physical activity levels, thereby biasing our results, we excluded all deaths that occurred during the first 1, 2, and 3 years of follow-up and limited our analysis to subjects who reported undergoing regular cancer screening examinations at entry. Results were virtually unchanged (data not shown).

Much of the strong inverse association between physical activity and mortality was because of mortality from cardiovascular disease (Table 2). In contrast, physical activity was less strongly related to cancer mortality, but the decrease in risk was statistically significant. Compared with the lowest category of no activity of at least moderate intensity, amounts of more than 7 h/wk were related to significantly decreased risk of cancer mortality (RR, 0.83; 95% CI, 0.74-0.93). Compared with no vigorous exercise, the multivariate RR of cancer mortality for at least 20 minutes of vigorous exercise 3 to 4 times per week was 0.82 (95% CI, 0.74-0.92), and 5 or more times per week of vigorous exercise provided no additional benefit.

We next investigated the effects of activity of at least moderate intensity at levels that approximate the OSG/CDC/ACSM consensus guidelines for moderate activity (30 minutes on most days of the week)[4,5] and vigorous exercise as encouraged by the ACSM (20 minutes 3 or more times per week).[34] Activity levels reflective of meeting the recommendations of moderate activity and vigorous exercise both showed significant benefits for mortality (**Table 3**). Associations for mortality from cardiovascular disease were of comparable magnitude as those seen for mortality from any cause. Relations were weaker but evident for mortality from cancer.

We evaluated higher levels of physical activity by examining the effects of activity reflective of meeting both

Table 2. Relative Risk (RR) of Mortality From Any Cause and Mortality From Specific Causes According to Activity of at Least Moderate Intensity and Vigorous Exercise

Type of Activity[a]						*P* Value for Trend
Mortality From Any Cause						
Activity of at least moderate intensity, h/wk	Inactive	<1	1-3	4-7	>7	
No. of deaths	1683	937	1940	1794	1546	
Person-years	170 907	133 217	321 719	329 352	310 151	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.80 (0.74-0.87)	0.72 (0.68-0.77)	0.68 (0.63-0.73)	0.61 (0.57-0.66)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.81 (0.75-0.88)	0.74 (0.69-0.79)	0.70 (0.65-0.75)	0.63 (0.59-0.69)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.82 (0.75-0.89)	0.74 (0.70-0.80)	0.70 (0.65-0.75)	0.63 (0.59-0.68)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.85 (0.79-0.93)	0.79 (0.74-0.85)	0.76 (0.71-0.82)	0.68 (0.63-0.74)	<.001
Vigorous exercise, times per week	Inactive	<1	1-2	3-4	≥5	
No. of deaths	2000	1109	1682	1775	1334	
Person-years	202 815	174 174	281 371	352 635	254 352	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.70 (0.65-0.75)	0.66 (0.62-0.71)	0.55 (0.51-0.59)	0.58 (0.53-0.62)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.71 (0.66-0.77)	0.68 (0.63-0.73)	0.57 (0.53-0.61)	0.59 (0.55-0.64)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.72 (0.67-0.78)	0.71 (0.66-0.76)	0.61 (0.57-0.66)	0.65 (0.60-0.70)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.77 (0.71-0.83)	0.77 (0.72-0.82)	0.68 (0.63-0.73)	0.71 (0.66-0.77)	<.001
Mortality From Cardiovascular Disease						
Activity of at least moderate intensity, h/wk	Inactive	<1	1-3	4-7	>7	
No. of deaths	511	303	574	516	432	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.86 (0.75-1.00)	0.71 (0.63-0.81)	0.64 (0.56-0.73)	0.56 (0.49-0.65)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.88 (0.76-1.02)	0.74 (0.66-0.84)	0.68 (0.60-0.78)	0.60 (0.52-0.69)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.88 (0.76-1.02)	0.73 (0.65-0.83)	0.67 (0.58-0.76)	0.58 (0.50-0.67)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.94 (0.81-1.08)	0.80 (0.71-0.91)	0.75 (0.66-0.86)	0.65 (0.57-0.75)	<.001
Vigorous exercise, times per week	Inactive	<1	1-2	3-4	≥5	
No. of deaths	611	316	491	521	397	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.65 (0.56-0.74)	0.63 (0.56-0.71)	0.53 (0.47-0.60)	0.57 (0.50-0.65)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.66 (0.58-0.76)	0.65 (0.58-0.74)	0.56 (0.50-0.64)	0.61 (0.53-0.70)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.67 (0.58-0.77)	0.67 (0.59-0.76)	0.59 (0.52-0.67)	0.64 (0.56-0.74)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.72 (0.63-0.82)	0.74 (0.66-0.84)	0.66 (0.59-0.76)	0.71 (0.62-0.82)	<.001
Mortality From Cancer						
Activity of at least moderate intensity, h/wk	Inactive	<1	1-3	4-7	>7	
No. of deaths	645	392	884	894	818	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.84 (0.74-0.95)	0.80 (0.72-0.89)	0.81 (0.72-0.90)	0.77 (0.68-0.86)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.84 (0.74-0.96)	0.81 (0.73-0.90)	0.82 (0.73-0.91)	0.79 (0.69-0.87)	.002
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.86 (0.76-0.98)	0.83 (0.75-0.93)	0.84 (0.75-0.93)	0.79 (0.71-0.89)	.003
Full multivariate RR (95% CI)[b]	1 [Reference]	0.88 (0.78-1.00)	0.86 (0.78-0.96)	0.88 (0.79-0.98)	0.83 (0.74-0.93)	.02
Vigorous exercise, times per week	Inactive	<1	1-2	3-4	≥5	
No. of deaths	754	508	811	854	706	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.84 (0.75-0.94)	0.82 (0.74-0.91)	0.66 (0.60-0.74)	0.75 (0.67-0.84)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.85 (0.76-0.95)	0.83 (0.75-0.92)	0.67 (0.61-0.75)	0.76 (0.68-0.86)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.87 (0.78-0.98)	0.89 (0.80-0.99)	0.76 (0.69-0.85)	0.88 (0.78-0.98)	.008
Full multivariate RR (95% CI)[b]	1 [Reference]	0.91 (0.81-1.02)	0.94 (0.85-1.04)	0.82 (0.74-0.92)	0.95 (0.85-1.07)	.23

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval.

[a] Activity of at least moderate intensity is defined as activities with an estimated energy expenditure of greater than 3 metabolic equivalents (METs). The MET is defined as the ratio of work to resting energy expenditure (1 MET = 1 kcal/kg/h or 3.5-mL oxygen uptake/kg/min). Resting energy expenditure is assumed to be 1 MET. Vigorous exercise is defined as activities that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat.

[b] The multivariate models used age as the underlying time metric and included the following covariates: sex (women; men), body mass index (<18.5; 18.5-24.9; 25.0-29.9; 30.0-34.9; 35.0-39.9; and ≥40.0), smoking (never smoking; past smoking of 1-19 cigarettes per day; past smoking of ≥20 cigarettes per day; current smoking of 1-19 cigarettes per day; and current smoking of ≥20 cigarettes per day), race/ethnicity (white; black; Hispanic; and Asian/Pacific Islander/Native American combined), education (<high school; high school; vocational school or some college; and college graduate), marital status (married or living as married; and divorced, separated, widowed, or never married), family history of cancer (yes; no), menopausal hormone therapy (never; current or former user of estrogen only; current user of estrogen and progestin combined; former user of estrogen and progestin combined; and not applicable), aspirin use (yes; no), multivitamin use (yes; no), intakes of vegetables (quintiles), fruit (quintiles), red meat (quintiles), and alcohol (0; 0.01-4.9; 5.0-14.9; 15.0-29.9; 30.0-49.9; and ≥50.0 g/d). The multivariate analyses of activity of at least moderate intensity and vigorous exercise were mutually adjusted.

recommendations for moderate activity and vigorous exercise (**Table 4**). Compared with subjects who were physically inactive, those with activity levels equivalent to meeting both recommendations showed a strong reduction in risk for mortality from any cause (multivariate RR, 0.50; 95% CI, 0.46-0.54). A similarly strong inverse association was noted for mortality from cardiovascular disease (multivariate RR, 0.48; 95% CI, 0.41-0.55) and mortality from stroke (multivariate RR, 0.40; 95% CI, 0.26-0.61), and a weaker relation was seen for mortality from cancer (multivariate RR, 0.74; 95% CI, 0.65-0.85) and mortality from physical activity–related cancers (multivariate RR, 0.73; 95% CI, 0.60-0.89). Those who reported doing some activity at less than recom-

Table 3. Relative Risk (RR) of Mortality From Any Cause and Mortality From Specific Causes According to Achievement of Physical Activity Recommendations

	Recommendation for MPA[a]			Recommendation for VPA[b]		
Variable	Inactive	No	Yes	Inactive	No	Yes
Mortality from any cause						
No. of deaths	1683	2877	3340	2000	2791	3109
Person-years	170 907	454 937	639 504	202 815	455 545	606 988
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.74 (0.70-0.79)	0.65 (0.61-0.69)	1 [Reference]	0.67 (0.63-0.71)	0.55 (0.52-0.59)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.81 (0.76-0.86)	0.73 (0.68-0.78)	1 [Reference]	0.77 (0.72-0.81)	0.68 (0.64-0.73)
Mortality from cardiovascular disease						
No. of deaths	511	871	948	611	807	918
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.76 (0.68-0.85)	0.61 (0.54-0.69)	1 [Reference]	0.63 (0.57-0.70)	0.53 (0.48-0.60)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.85 (0.75-0.95)	0.71 (0.63-0.80)	1 [Reference]	0.73 (0.66-0.82)	0.67 (0.60-0.75)
Mortality from cancer						
No. of deaths	645	1276	1712	754	1319	1560
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.81 (0.74-0.89)	0.79 (0.72-0.87)	1 [Reference]	0.82 (0.75-0.90)	0.69 (0.63-0.76)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.87 (0.79-0.96)	0.87 (0.78-0.96)	1 [Reference]	0.92 (0.84-1.01)	0.87 (0.79-0.96)

Abbreviation: CI, confidence interval; MPA, moderate physical activity; VPA, vigorous physical activity.
[a] Recommendation for MPA: more than 3 hours of activity per week of at least moderate intensity corresponding to 30 minutes of activity of moderate intensity on most days of the week.
[b] Recommendation for VPA: 20 minutes of continuous vigorous exercise 3 or more times per week.
[c] Adjusted for the covariates listed in a footnote in Table 2. The multivariate analyses of recommendation for MPA and recommendation for VPA were mutually adjusted.

Table 4. Relative Risk (RR) of Mortality From Any Cause and Mortality From Specific Causes According to Joint Categories of Physical Activity Recommendations

Variable	Inactive	Neither Recommendation	Recommendation for MPA Only[a]	Recommendation for VPA Only[b]	Recommendation for Both MPA and VPA
Mortality from any cause					
No. of deaths	879	2520	1392	1161	1948
Person-years	74 139	361 407	222 814	190 298	416 690
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.59 (0.55-0.64)	0.51 (0.47-0.56)	0.47 (0.43-0.51)	0.36 (0.33-0.39)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.70 (0.65-0.75)	0.62 (0.57-0.68)	0.61 (0.55-0.66)	0.50 (0.46-0.54)
Mortality from cardiovascular disease					
No. of deaths	278	761	379	349	569
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.56 (0.49-0.65)	0.44 (0.38-0.51)	0.44 (0.37-0.51)	0.32 (0.28-0.37)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.68 (0.59-0.78)	0.56 (0.48-0.65)	0.58 (0.49-0.68)	0.48 (0.41-0.55)
Mortality from cancer					
No. of deaths	308	1082	683	531	1029
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.73 (0.64-0.83)	0.72 (0.63-0.82)	0.62 (0.54-0.72)	0.55 (0.48-0.62)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.83 (0.73-0.94)	0.83 (0.72-0.95)	0.79 (0.68-0.91)	0.74 (0.65-0.85)

Abbreviations: CI, confidence interval; MPA, moderate physical activity; VPA, vigorous physical activity.
[a] Recommendation for MPA: more than 3 hours of activity of at least moderate intensity per week corresponding to 30 minutes of activity of moderate intensity on most days of the week.
[b] Recommendation for VPA: 20 minutes of continuous vigorous exercise 3 times per week.
[c] Adjusted for the covariates listed in a footnote in Table 2.

mended levels showed modest but significantly decreased risk of mortality from any cause, cardiovascular disease, and cancer.

Achievement of activity levels corresponding to the guidelines for either moderate activity or vigorous exercise or the combination of guidelines for moderate activity and vigorous exercise was inversely associated with mortality in subgroups defined by sex, age, race/ethnicity, education, smoking status, BMI, and television or video watching (**Table 5**), indicating no important effect modification (*P* value for interaction, >.05 for all). Vigorous exercise showed a particularly strong reduction in mortality risk among individuals with high (>2 h/d) television or video watching.

COMMENT

In this large prospective study, engaging in physical activity of at least moderate intensity for more than 3 h/wk was associated with a 27% decreased risk of mortality. Following the recommendation for vigorous exercise of 20 minutes 3 or more times per week was related to a 32% reduction in mortality risk. These data lend strong