（4）運動と循環器疾患死亡

目的：身体活動と循環器疾患の死亡・発症の関連は欧米諸国を中心に報告されているが、わが国での報告はほとんどない。本研究は歩行時間及びスポーツ時間とその後の循環器疾患死亡の関連を分析した。

方法：文部科学省助成大規模コホート研究（JACC study）の全国45地域の対象者に対し、1988年〜1990年に1日平均歩行時間及び1週間の平均スポーツ時間の質問に回答した者の中で、脳卒中、心筋梗塞、がんの既往者を除く73,265人（男31,023人 女42,242人）について、循環器疾患死亡（ICD10: I01-I99）との関連を分析した。年齢、循環器疾患の危険因子を調整した相対危険度をCox比例ハザードモデルにて算出した。全臨床状態の影響を除くため、歩行時間の解析では「0.5時間」、スポーツの時間の解析では「1-2時間」と、最も低い群ではなく2番目に身体活動が低い群を相対危険度の算出の基準群とした。

結果：1999年末までの平均9.7年の追跡期間中、脳卒中死亡923人（脳出血219人、くも膜下出血155人、脳梗塞327人）、虚血性心疾患死亡397人、全循環器疾患死亡1,946人を認めた。歩行1.0時間以上の群では、多変量調整相対危険度（95%CI）は、脳梗塞0.71(0.54-0.94)、全循環器疾患死亡 0.84(0.75-0.95)、スポーツ 5 時間以上の群では、虚血性心疾患0.51(0.32-0.82)、全循環器疾患死亡0.73(0.60-0.90)であった。

結論：歩行や運動が多い群では循環器疾患による死亡の相対危険度が有意に低く、歩行や運動による循環器疾患予防の可能性が示された。

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Walking and Sports Participation and Mortality From Coronary Heart Disease and Stroke

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OBJECTIVES We aimed to examine the impact of exercise on mortality from cardiovascular disease (CVD) in Asian populations.

BACKGROUND Few data have been available in Asian countries, where job-related physical activity is higher than that in Western countries.

METHODS Between 1988 and 1990, 31,023 men and 42,242 women in Japan, ages 40 to 79 years with no history of stroke, coronary heart disease (CHD), or cancer, completed a self-administered questionnaire. Systematic mortality surveillance was performed through 1999, and 1,946 cardiovascular deaths were identified. We chose the second lowest categories of walking and sports participation as the reference to reduce a potential effect of ill health.

RESULTS Men and women who reported having physical activity in the highest category (i.e., walking ≥1 h/day or doing sports ≥5 h/week) had a 20% to 60% lower age-adjusted risk of mortality from CVD, compared with those in the second lowest physical activity category (i.e., walking 0.5 h/day, or sports participation for 1 to 2 h/week). Adjustment for known risk factors, exclusion of individuals who died within two years of baseline inquiry, or gender-specific analysis did not substantially alter these associations. The multivariate-adjusted hazard ratios (95% confidence interval) for the highest versus the second lowest categories of walking or sports participation were 0.71 (0.54 to 0.94) and 0.80 (0.48 to 1.31), respectively, for ischemic stroke (IS); 0.84 (0.64 to 1.09) and 0.51 (0.32 to 0.82), respectively, for CHD; and 0.84 (0.75 to 0.95) and 0.73 (0.60 to 0.90), respectively, for CVD.

CONCLUSIONS Physical activity through walking and sports participation might reduce the risk of mortality from IS and CHD. (J Am Coll Cardiol 2005;46:1761–7) © 2005 by the American College of Cardiology Foundation

Previous prospective studies have shown an inverse association between physical activity and the risk of developing coronary heart disease (CHD) (1–4) and total or ischemic stroke (IS) (5–7) among whites and Japanese Americans. The benefits of physical activity include lowered blood pressure (8,9), increased insulin sensitivity (10,11), elevated HDL-cholesterol levels (12), and improved endothelial function (13). To our knowledge, however, no prospective study has reported these effects of exercise in Asian countries, where the prevalence of job-related physical activity has been reported to be high (14).

In the current study we examined the relationship between physical activity through walking and sports participations and the mortality due to stroke, CHD, and total cardiovascular disease (CVD) among Japanese men and women in a large cohort study.

METHODS

Study cohort and baseline questionnaire. The Japan Collaborative Cohort Study for Evaluation for Cancer Risk (JACC), sponsored by Ministry of Education, Science, Sports and Culture of Japan, was undertaken from 1988 to 1990, when 110,792 individuals (46,465 men and 64,327 women) ages 40 to 79 years and living in 45 communities across Japan participated in municipal health screening examinations and completed self-administered questionnaires about their lifestyles and medical histories of previous

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Abbreviations and Acronyms

CHD = coronary heart disease
CI = confidence interval
CVD = cardiovascular disease
HR = hazard ratio
IPH = intraparenchymal hemorrhage
IS = ischemic stroke
SAH = subarachnid hemorrhage

CVD and cancer (15). Informed consent was obtained from all subjects before completing the questionnaire. Of these subjects, 77,676 individuals (32,953 men and 44,723 women) provided a valid response to questions about the average daily time spent walking: "How long on average do you spend walking indoors or outside on a daily basis?" The list of possible answers was: "<0.5 h," "0.5 h," "0.6 to 0.9 h," and "≥1.0 h." Subjects were also questioned about the average weekly time spent in athletic and sporting events: "What is the average amount of time you spend engaging in sports on a weekly basis?" The list of possible answers were: "<1 h," "1 to 2 h," "3 to 4 h," and "≥5 h."

The validity of the estimated time spent participating in sports and leisure time physical activity was examined in a random sample of 739 men and 991 women from the baseline participants (16). The Spearman rank correlation reported that time spent participating in sports with leisure-time physical activity as reported during the previous 12 months, estimated from a structured interview on the basis of the Minnesota leisure-time physical activity questionnaire (17), was 0.53 in men and 0.58 in women. The reliability for time spent walking and engaging in sports was examined 12 months apart in a random sample of 416 men and 636 women. We obtained modest kappa coefficients: 0.32 in men and 0.31 in women for time spent walking (four categories), and 0.45 in men and 0.40 in women for time spent participating in sports (four categories).

We excluded 1,930 men and 2,481 women from the analysis because of a previous history of stroke, CHD, or cancer at the time of baseline inquiry. Therefore, a total 73,265 individuals (31,023 men and 42,242 women) were enrolled in the present study.

Mortality surveillance. To find cohort deaths, the investigators conducted a systematic review of death certificates, all of which were forwarded to the local public health center in each community. It is believed all deaths that occurred in the cohort were ascertained, except for subjects who died after they had moved from their original community, in which case the subject was treated as a censored case. Mortality data were sent centrally to the Ministry of Health and Welfare, and the underling causes of death were coded for the National Vital Statistics according to the International Classification of Disease, 10th revision. The mortality follow-up inquiry for this study was conducted until the end of 1999, and the average follow-up was 9.7 years. Only 3.4% of the subjects had moved out of the communities and were treated as censored. The Ethics Committee of the University of Tsukuba approved this study.

Statistical analysis. Statistical analysis was made on the basis of cause-specific mortality rates. Person-years of follow-up were calculated from the date of the baseline questionnaire to the date of death, moving from the community, or the end of 1999, whichever occurred first. The hazard ratio (HR) of mortality from CVD was defined as the death rate for the participants within the four categories of walking time divided by the corresponding rate among those who reported 0.5 h/day of average walking time and for the participants within the four categories of sports participation time divided by the corresponding rate among those who reported 1 to 2 h/week average time in sports.

Age-adjusted means and proportions of selected cardiovascular risk factors were presented among the categories of walking and sports participation. Differences from the second lowest category in gender-specific, age-adjusted mean values and proportions of baseline characteristics were examined with a *t* test or chi-square test. The age-adjusted and multivariate-adjusted HRs and the 95% confidence intervals (CIs) were calculated after adjustment for age, gender, and potential confounding factors with the Cox proportional hazards model. These factors included body mass index (gender-specific quintiles), history of hypertension (no versus yes), history of diabetes (no versus yes), smoking status (never, ex-smoker, and current smokers of 1 to 19 and ≥20 cigarettes/day), alcohol intake category (never, ex-drinker, and current drinker of ethanol at 1 to 22, 23 to 45, 46 to 68, and ≥69 g/day), hours of sleep (<6.0, 6.0 to 6.9, 7.0 to 7.9, 8.0 to 8.9, and ≥9.0 h/day), age of completed education (<13, 13 to 15, 16 to 18, and ≥19 years old), job style (manual worker, non-manual worker, and non-worker), perceived mental stress (low, medium, and high), and frequency of fish intake (0, <1, 1 to 2, 3 to 4, and ≥5 times/week). These factors had been known as cardiovascular risk factors and associated with walking and sports participation at baseline inquiry in this cohort. In the analysis of walking time, we also adjusted for time spent participating in sports, and in the analysis of sports participation, we adjusted for time spent walking.

Because the individuals in the lowest categories were more likely to have ill health and the goal of this study was to study physical activity in healthy subjects, we chose the second lowest categories of walking and sports participation as the reference.

Cause-specific mortality was determined by the total deaths due to stroke (International Classification of Disease, 10th revision, codes I60 to 69), CHD (codes I20 to I25), and total CVD (codes I01 to I99). Stroke was further categorized as subarachnid hemorrhage (SAH) (code I60), intraparenchymal hemorrhage (IPH) (code I61), and IS (code I63). The analysis was repeated by excluding deaths within the first two years after the baseline (476 men and 267 women), to examine the potential effect of any existing pre-clinical disorders that might have interfered with participation in walking and sports.

RESULTS

A total of 73,265 individuals (31,023 men and 42,242 women) were followed up for an average of 9.7 years, and 1,946 subjects (1,081 men and 865 women) died from CVD. These deaths among men included a total of 499 from stroke (127 IPH, 57 SAH, and 186 IS) and 244 from CHD. The number of deaths among women included a total of 424 from stroke (92 IPH, 98 SAH, and 141 IS) and 153 from CHD.

Table 1 shows gender-specific, selected cardiovascular risk factors according to the four categories of walking time and sports participation time. Compared with men and women who reported 0.5 h/day of walking (second lowest category), those who reported ≥1.0 h/day of walking (highest category) were more likely to be manual workers, have a high dietary intake of fish, participate in sports, and were less educated, less likely to have perceived mental stress, and had little history of hypertension and diabetes and a lower mean of body mass index. Men who reported ≥1.0 h/day of walking smoked, drank more, and slept more, as compared with those who reported 0.5 h/day of walking. Similar associations were observed according to sports participation categories.

Compared with men and women who reported 0.5 h/day of walking, those who reported ≥1.0 h/day walking had a 17% to 33% lower age-adjusted mortality from total stroke, IS, CHD, and total CVD (Table 2). Adjustment for cardiovascular risk factors somewhat attenuated these relationships; however, the risk reduction for IS and total CVD remained statistically significant for men and women combined. The multivariate HR (95% CI) among men and women (combined) who reported a walking time of ≥1.0 versus 0.5 h/day was 0.71 (0.54 to 0.94), p = 0.02 for IS; 0.84 (0.64 to 1.09), p = 0.19 for CHD; and 0.84 (0.75 to 0.95), p = 0.006 for total CVD. These inverse associations were similarly observed for each gender, although not statistically significant in either gender.

Strong inverse associations within the sports participation categories were found for mortality from CHD and total CVD (Table 3). The multivariate HR (95% CI) among men and women who reported time spent participating in sports for ≥5 versus 1 to 2 h/week was 0.51 (0.32 to 0.82), p = 0.005 for CHD and 0.73 (0.60 to 0.90), p = 0.003 for total CVD.

We evaluated the HR of death for the lowest versus second lowest categories of time spent walking. The multivariate HR (95% CI) was 1.37 (1.10 to 1.72), p = 0.005 for total stroke mortality, and 1.35 (1.16 to 1.57), p < 0.001 for total CVD mortality.

These inverse associations for walking and sports participation time with mortality were not altered substantially when deaths occurring within two years after baseline were

Table 1. Gender-Specific Age-Adjusted Mean Values or Prevalence of Cardiovascular Risk Factors at Baseline According to Walking Time and Sports Time

	Walking Time (h/Day)								Sports Time (h/Week)							
	Men				Women				Men				Women			
	<0.5	0.5	0.6–0.9	≥1.0	<0.5	0.5	0.6–0.9	≥1.0	<1	1–2	3–4	≥5	<1	1–2	3–4	≥5
No. at risk	3,865	5,770	5,962	15,426	4,644	7,404	8,595	21,599	21,133	5,299	2,211	2,380	31,921	5,934	2,299	2,088
Percentage at risk	12.5	18.6	19.2	49.7	11.0	17.5	20.3	51.1	68.1	17.1	7.1	7.7	75.6	14.0	5.4	4.9
Age, yrs	56.1*	57.2	57.8†	57.5‡	56.7*	57.9	57.8	57.5†	56.8‡	56.5	59.2*	62.1*	57.1	57.4	59.8*	62.4*
Body mass index, kg/m²	22.9‡	22.8	22.7	22.5*	23.1†	22.9	22.9	22.8†	22.6	22.7	22.7	22.7	22.9	22.9	22.8	22.9
History of hypertension, %	19.4	19.8	20.3	17.0*	21.3	21.1	20.9	19.4†	18.1	19.2	20.0	18.6	20.2	21.1	19.8	19.1‡
History of diabetes, %	6.9	7.5	6.0*	5.0*	4.2	4.6	4.0‡	2.8*	5.6*	6.6	6.5	6.4	3.4‡	4.0	4.1	4.0
Ethanol intake, g/day	35.6*	31.8	32.9‡	35.3*	12.9*	10.3	9.4	10.4	34.9*	32.2	32.7	34.4†	10.6	9.8	9.9	10.4
Hours of sleep, h/day	7.45†	7.39	7.41	7.48*	7.14†	7.08	7.07	7.08	7.46†	7.41	7.41	7.51*	7.09	7.07	7.05	7.12
Current smoker, %	49.4	49.1	49.3	52.4*	5.5†	4.4	4.3	4.3	52.1*	48.0	47.3	49.1	4.6*	3.5	4.5‡	4.3
College or higher education, %	14.0*	20.9	19.6	12.3*	7.5*	10.6	9.7	8.6*	13.5*	20.3	21.3	16.9*	8.3*	11.9	12.0	9.8†
Office worker, %	15.4*	23.6	18.7*	7.0*	7.5*	9.0	7.4*	4.3*	11.6*	18.5	18.9*	12.8	5.7*	7.9	6.7‡	5.6*
Manual worker, %	38.1*	29.1	34.0*	47.6*	23.8*	18.4	18.0	22.9*	43.2*	34.9	30.7	36.5*	22.0*	18.5	17.4	20.8‡
High perceived mental stress, %	26.9	26.8	23.4*	20.5*	22.2	20.8	19.6	19.5†	23.2	22.9	21.1	22.7	20.6*	18.4	18.7	17.9
Frequency of fish intake, n/week	6.7†	6.5	6.8*	7.1*	6.8	6.9	7.0	7.2*	6.9	6.8	6.8	7.2*	7.0*	7.2	7.1	7.4
Sports 5 h/week and more, %	1.6*	3.6	6.1*	11.3*	1.1	1.6	3.3*	7.6*	—	—	—	—	—	—	—	—
Walking 1.0 h/day and more, %	—	—	—	—	—	—	—	—	48.6*	44.1	47.9†	73.8*	49.4	48.6	56.6*	78.7*

Test for difference from the second lowest category: *p < 0.001; †p < 0.01; ‡p < 0.05.

Table 2. Hazard Ratios (95% CI) of Mortality from Cardiovascular Disease According to Walking Time

	Walking Time (h/Day)											
	Men				Women				Men and Women			
	<0.5	0.5	0.6–0.9	≥1.0	<0.5	0.5	0.6–0.9	≥1.10	<0.5	0.5	0.6–0.9	≥1.0
Person-yrs	36,354	54,499	56,595	148,929	44,804	71,557	83,491	211,995	81,158	126,056	140,085	360,924
Total stroke												
n	70	103	89	237	72	82	76	194	142	185	165	431
Age-adjusted HR	1.24 (0.91–1.68)	1.0	0.76 (0.57–1.01)	0.81 (0.64–1.02)	1.69 (1.23–2.32)	1.0	0.81 (0.59–1.10)	0.87 (0.67–1.13)	1.44 (1.16–1.79)	1.0	0.78 (0.63–0.96)	0.83 (0.70–0.99)
Multivariate HR*	1.15 (0.84–1.57)	1.0	0.79 (0.59–1.05)	0.84 (0.67–1.07)	1.66 (1.20–2.30)	1.0	0.82 (0.60–1.12)	0.93 (0.72–1.21)	1.37 (1.10–1.72)	1.0	0.80 (0.65–0.99)	0.88 (0.74–1.05)
IPH												
n	19	29	27	52	17	17	18	40	36	46	45	92
Age-adjusted HR	1.12 (0.63–1.99)	1.0	0.84 (0.50–1.43)	0.64 (0.41–1.00)	1.87 (0.95–3.66)	1.0	0.92 (0.47–1.78)	0.85 (0.48–1.50)	1.39 (0.90–2.15)	1.0	0.87 (0.57–1.31)	0.71 (0.50–1.02)
Multivariate HR*	1.12 (0.62–2.02)	1.0	0.88 (0.52–1.49)	0.73 (0.46–1.16)	1.89 (0.95–3.76)	1.0	0.95 (0.49–1.84)	0.93 (0.52–1.66)	1.38 (0.89–2.15)	1.0	0.90 (0.60–1.37)	0.80 (0.56–1.15)
SAH												
n	6	10	7	34	11	15	20	52	17	25	27	86
Age-adjusted HR	0.93 (0.34–2.55)	1.0	0.67 (0.25–1.76)	1.24 (0.61–2.51)	1.32 (0.61–2.87)	1.0	1.14 (0.58–2.23)	1.21 (0.68–2.15)	1.15 (0.62–2.14)	1.0	0.95 (0.55–1.64)	1.21 (0.78–1.89)
Multivariate HR*	0.97 (0.35–2.73)	1.0	0.67 (0.25–1.77)	1.26 (0.61–2.60)	1.40 (0.64–3.08)	1.0	1.08 (0.55–2.11)	1.22 (0.68–2.19)	1.24 (0.66–2.31)	1.0	0.93 (0.54–1.61)	1.25 (0.80–1.97)
Ischemic stroke												
n	26	45	28	87	26	34	21	60	52	79	49	147
Age-adjusted HR	1.12 (0.69–1.81)	1.0	0.54 (0.33–0.86)	0.67 (0.47–0.96)	1.53 (0.92–2.55)	1.0	0.54 (0.32–0.94)	0.67 (0.44–1.03)	1.30 (0.92–1.85)	1.0	0.54 (0.38–0.76)	0.67 (0.51–0.88)
Multivariate HR*	1.03 (0.63–1.69)	1.0	0.56 (0.35–0.91)	0.71 (0.49–1.02)	1.38 (0.82–2.33)	1.0	0.56 (0.32–0.97)	0.73 (0.48–1.13)	1.18 (0.82–1.69)	1.0	0.56 (0.39–0.80)	0.71 (0.54–0.94)
CHD												
n	39	48	48	109	21	36	34	62	60	84	82	171
Age-adjusted HR	1.45 (0.95–2.22)	1.0	0.89 (0.60–1.33)	0.80 (0.57–1.13)	1.12 (0.66–1.93)	1.0	0.82 (0.52–1.32)	0.64 (0.42–0.97)	1.32 (0.95–1.84)	1.0	0.85 (0.63–1.16)	0.73 (0.56–0.95)
Multivariate HR*	1.56 (1.01–2.41)	1.0	0.91 (0.61–1.36)	0.93 (0.66–1.32)	1.04 (0.60–1.80)	1.0	0.82 (0.51–1.32)	0.74 (0.49–1.13)	1.34 (0.96–1.89)	1.0	0.89 (0.65–1.21)	0.84 (0.64–1.09)
Total CVD												
n	155	225	202	499	145	176	173	371	300	401	375	870
Age-adjusted HR	1.24 (1.01–1.52)	1.0	0.79 (0.66–0.96)	0.78 (0.67–0.92)	1.59 (1.28–1.99)	1.0	0.86 (0.70–1.06)	0.79 (0.66–0.94)	1.40 (1.20–1.62)	1.0	0.82 (0.71–0.94)	0.78 (0.69–0.88)
Multivariate HR*	1.21 (0.98–1.49)	1.0	0.83 (0.68–1.00)	0.85 (0.72–1.00)	1.50 (1.20–1.87)	1.0	0.87 (0.70–1.07)	0.85 (0.70–1.02)	1.35 (1.16–1.57)	1.0	0.85 (0.74–0.98)	0.84 (0.75–0.95)

*Adjusted for age, gender, sports time, and cardiovascular risk factors.
CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratios; IPH = intraparenchymal hemorrhage; SAH = subarachnoid hemorrhage.

Table 3. Hazard Ratios (95% CI) of Mortality from Cardiovascular Disease According to Sports Time

	Sports Time (h/Week)											
	Men				Women				Men and Women			
	<1	1–2	3–4	≥5	<1	1–2	3–4	≥5	<1	1–2	3–4	≥5
Person-yrs	201,833	50,934	20,946	22,663	311,184	58,081	22,287	20,294	513,017	109,015	43,233	42,958
Total stroke												
n	337	70	46	46	317	61	25	21	654	131	71	67
Age-adjusted HR	1.37 (1.06–1.77)	1.0	1.17 (0.80–1.70)	0.88 (0.60–1.27)	1.04 (0.79–1.37)	1.0	0.79 (0.50–1.26)	0.60 (0.36–0.98)	1.23 (1.02–1.48)	1.0	1.00 (0.75–1.33)	0.75 (0.56–1.01)
Multivariate HR*	1.26 (0.97–1.64)	1.0	1.17 (0.81–1.71)	0.87 (0.59–1.27)	0.88 (0.67–1.17)	1.0	0.79 (0.49–1.26)	0.57 (0.35–0.95)	1.09 (0.90–1.32)	1.0	1.01 (0.76–1.35)	0.75 (0.55–1.01)
IPH												
n	91	17	12	7	72	13	4	3	163	30	16	10
Age-adjusted HR	1.42 (0.85–2.39)	1.0	1.36 (0.65–2.84)	0.61 (0.25–1.48)	1.10 (0.61–1.98)	1.0	0.63 (0.20–1.92)	0.44 (0.12–1.53)	1.29 (0.88–1.91)	1.0	1.05 (0.57–1.92)	0.53 (0.26–1.09)
Multivariate HR*	1.41 (0.83–2.40)	1.0	1.41 (0.67–2.97)	0.67 (0.27–1.64)	0.84 (0.46–1.55)	1.0	0.61 (0.20–1.87)	0.40 (0.11–1.41)	1.17 (0.78–1.74)	1.0	1.08 (0.59–1.99)	0.56 (0.27–1.16)
SAH												
n	34	14	4	5	67	17	10	4	101	31	14	9
Age-adjusted HR	0.60 (0.32–1.13)	1.0	0.66 (0.22–2.02)	0.71 (0.25–1.98)	0.78 (0.46–1.32)	1.0	1.29 (0.59–2.81)	0.49 (0.16–1.45)	0.70 (0.47–1.05)	1.0	0.99 (0.53–1.86)	0.57 (0.27–1.21)
Multivariate HR*	0.56 (0.30–1.07)	1.0	0.66 (0.22–2.03)	0.65 (0.23–1.85)	0.70 (0.41–1.21)	1.0	1.23 (0.56–2.70)	0.45 (0.15–1.36)	0.64 (0.43–0.97)	1.0	0.95 (0.51–1.80)	0.53 (0.25–1.12)
Ischemic stroke												
n	126	25	18	17	109	18	6	8	235	43	24	25
Age-adjusted HR	1.50 (0.97–2.30)	1.0	1.21 (0.66–2.22)	0.84 (0.45–1.55)	1.23 (0.75–2.03)	1.0	0.61 (0.24–1.53)	0.71 (0.31–1.62)	1.41 (1.02–1.96)	1.0	0.97 (0.59–1.60)	0.78 (0.47–1.27)
Multivariate HR*	1.34 (0.86–2.08)	1.0	1.22 (0.66–2.25)	0.84 (0.45–1.57)	1.07 (0.64–1.77)	1.0	0.62 (0.25–1.58)	0.73 (0.31–1.70)	1.26 (0.90–1.75)	1.0	1.00 (0.61–1.66)	0.80 (0.48–1.31)
CHD												
n	153	49	22	20	118	23	8	4	271	72	30	24
Age-adjusted HR	0.88 (0.64–1.21)	1.0	0.83 (0.50–1.37)	0.57 (0.34–0.96)	1.04 (0.67–1.63)	1.0	0.67 (0.30–1.49)	0.30 (0.10–0.86)	0.95 (0.73–1.23)	1.0	0.77 (0.50–1.18)	0.49 (0.31–0.78)
Multivariate HR*	0.84 (0.60–1.17)	1.0	0.86 (0.52–1.43)	0.60 (0.36–1.03)	0.91 (0.58–1.44)	1.0	0.71 (0.31–1.59)	0.30 (0.10–0.87)	0.89 (0.68–1.16)	1.0	0.80 (0.52–1.22)	0.51 (0.32–0.82)
Total CVD												
n	720	183	87	91	660	107	49	49	1380	290	136	140
Age-adjusted HR	1.11 (0.94–1.30)	1.0	0.86 (0.66–1.11)	0.68 (0.53–0.87)	1.24 (1.01–1.52)	1.0	0.88 (0.63–1.23)	0.78 (0.56–1.10)	1.18 (1.04–1.33)	1.0	0.86 (0.70–1.06)	0.71 (0.58–0.87)
Multivariate HR*	1.05 (0.89–1.24)	1.0	0.87 (0.67–1.12)	0.70 (0.54–0.90)	1.09 (0.88–1.34)	1.0	0.89 (0.63–1.25)	0.81 (0.57–1.14)	1.07 (0.94–1.22)	1.0	0.88 (0.72–1.08)	0.73 (0.60–0.90)

*Adjusted for age, gender, walking time, and cardiovascular risk factors.
Abbreviations as in Table 2.

excluded (data not shown). The multivariate HR (95% CI) among men and women (combined) for time spent walking for ≥1.0 versus 0.5 h/day was 0.73 (0.54 to 0.97), $p = 0.032$ for mortality due to IS; 0.85 (0.64 to 1.13), $p = 0.263$, for CHD; and 0.87 (0.76 to 0.99), $p = 0.028$ for total CVD. The multivariate HR (95% CI) among men and women (combined) for time spent participating in sports for ≥5 versus 1 to 2 h/week was 0.47 (0.28 to 0.78), $p = 0.004$ for mortality due to CHD and 0.78 (0.63 to 0.97), $p = 0.03$ for total CVD mortality.

DISCUSSION

In the present large prospective study of Japanese men and women, we observed approximately a 20% to 50% reduction in mortality due to IS, CHD, and total CVD associated with higher physical activity through walking and sports participation. These relationships were not substantially altered after adjustment for known risk factors or when deaths that occurred within two years were excluded from the analysis.

Our findings are consistent with previous reports of Americans (1,2,5,6), Japanese-Americans (4,7), and Europeans (3) and meta-analyses (18,19). Total physical activity (>21.7 vs. 0 to 2.0 MET-h/week), physical activity through walking (≥10 vs. ≤0.5 MET-h/week), and walking pace (≥3 vs. <2 mph) were associated with 34%, 35%, and 36% respective reductions in the risk of developing CHD (1), and 48%, 40%, and 53% respective reductions in risk of IS (5) for American nurses. Similar risk reductions (approximately 30% to 50%) for CHD (3,4) and IS (7) associated with walking and leisure-time physical activity were found for Japanese-American men and European men. In previous meta-analyses, high activity and moderate activity were associated with 37% and 10% respective risk reduction of mortality from CHD (18), and high activity and moderate activity were associated with 21% and 9% respective risk reduction of incidence or mortality from IS (19), compared with low activity.

We did not find any significant inverse association between physical activity and mortality from IPH or SAH. This finding is consistent with the results of studies examining American nurses (5) but not of American male physicians (6) and Japanese-American men (7). American male physicians (6) who exercised ≥5 versus <1 time/week had a 46% lower risk for hemorrhagic stroke, but this association was observed only among subjects ages 55 to 68 years but not for those 40 to 54 years of age. Japanese-American men who were physically active had a 73% lower risk of hemorrhagic stroke mortality (7), compared with non-active men.

Furthermore, our data suggest a potential differential effect of walking versus sports participation on IS and CHD risk. We found that participation in sports was associated with a reduced mortality due to CHD, but this association did not exist with walking time. Walking time, however, was associated with a reduced risk for mortality from IS, but sports participation was not. A similar pattern of association between physical activity and CHD was observed in previous studies (2,3). In a study of American male health professionals (2), average exercise intensity was associated with reduced risk of CHD, independent of total physical activity. In European men (3), energy expenditure during engagement in leisure-time physical activity was associated with a lower risk of CHD, whereas walking or cycling to work was not. A reason for reduced mortality from IS by walking but not by sports participation in our study is uncertain. One of the potential mechanisms for the differential association might be a differential effect of physical activity intensity on insulin resistance. Reduced insulin resistance by moderate-intensity exercise was larger than by high-intensity exercise, when the amount of physical activity was not large (11). Insulin resistance raises the risk of IS more than that of CHD (20,21). Therefore, moderate intensity physical activity similar to walking (17) is more likely to improve insulin resistance and might reduce the risk of IS to a greater degree than the risk of CHD.

Common mechanisms for a reduced risk of IS and CHD associated with walking or sports participation include improved endothelial function (13), an increase in HDL-cholesterol levels (12), and the lowering of ambulatory blood pressure through decreased sympathetic nervous activity (8,9). Previous cohort studies revealed that glucose intolerance (22,23), low HDL-cholesterol levels (24,25), and high blood pressure (26, 27) raised the risk of IS and CHD, and in hypertensive patients, endothelial dysfunction raised the risk of cardiovascular events (28). In the present study, the prevalence of a history of hypertension and diabetes was lower for subjects of both genders who spent more time walking or participating in sports.

Limitations of the present study included the fact that we did not have systematic information on pre-clinical disorders that prevented the participants from walking or participating in sports. This might have lead to a bias of cause-effect reversal, even though most of the subjects were apparently healthy. To avoid the potential bias due to pre-clinical disorders and/or psychosocial distress, we chose the second lowest physical activity categories as a reference. In fact, persons with the lowest categories of physical activity were more overweight, drank more, were more mentally stressed, and less educated. This probably leads to an underestimate of HRs. We also repeated the data analysis by excluding early deaths, which would also reduce the potential confounding effect of pre-clinical disorders.

A second limitation of the current study was that we did not have incidence data. We used the death certificate and did not validate causes of death; however, previous studies have shown that death certificate diagnosis with regard to stroke subtypes is valid, owing to the high prevalence of CT scan or MRI use in hospitals in Japan (29,30).

The strength of the present study is a statistical power sufficient to detect the effects of physical activity on mortality from CVD. We found a significant inverse association between time spent walking and the risk of IS in addition to an inverse relationship between sports participation and risk of CHD in Asian countries, where job-related physical activity is generally higher than in Western countries (14).

In conclusion, the present study provides epidemiological evidence that engaging in physical activity through walking and sports participation might reduce risk of mortality from IS and CHD among Japanese men and women.

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（5）禁煙と循環器疾患死亡

背景：アジアにおいて、禁煙が循環器疾患のリスクを低下させるとする追跡研究や介入研究はない。そこで本研究では、喫煙状況及び禁煙後の期間と、その後の循環器疾患死亡との関連を分析した。

方法：文部科学省助成大規模コホート研究（JACC study）に参加した40歳から79歳の男女94,683人（男41,782人 女52,901人）について、1999年末まで約10年間追跡し、喫煙状況別（非喫煙、過去喫煙、現在喫煙（20本未満、以上））、及び過去喫煙者については禁煙期間別（0-1年、2-4年、5-9年、10-14年、15年以上）に脳卒中、虚血性心疾患、全循環器疾患死亡との関連を、年齢、循環器疾患の危険因子を調整した相対危険度をCox比例ハザードモデルにより算出した。追跡人年は941,043人年である。

結果：追跡期間中の死亡者数は、脳卒中が男性698人、女性550人、虚血性心疾患がそれぞれ348人、199人、全循環器疾患ではそれぞれ1,555人、1,155人であった。男性における非喫煙者に対する現在喫煙者の脳卒中の相対危険度は 1.39（1.13-1.70）、虚血性心疾患では2.51（1.79-3.51）、全循環器疾患では 1.60（1.39-1.84）であった。女性では脳卒中が 1.65（1.21-2.25）、虚血性心疾患で3.35（2.23-5.02）、全循環器疾患では2.06（1.69-2.51）であり、65-79の群に比べ40-64歳の群においてより大きなリスクの増大が見られた。禁煙後の虚血性心疾患及び全循環器疾患のリスクの低下は2年以内に、脳卒中のリスクの低下は 2-4年でみられた。いずれの疾患とも各年齢層（65歳未満、以上）において、禁煙後10-14年後に禁煙による効果が最大となった。

結論：本研究により、各年齢層において禁煙が循環器疾患の予防の上で重要であることが示された。

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Smoking Cessation and Mortality from Cardiovascular Disease among Japanese Men and Women

The JACC Study

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To examine the effect of smoking cessation on cardiovascular disease mortality in Asians, the authors conducted a 10-year prospective cohort study of 94,683 Japanese (41,782 men and 52,901 women) aged 40–79 years who were part of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). During 941,043 person-years of follow-up between 1989–1990 and 1999, 698 deaths from stroke, 348 from coronary heart disease, and 1,555 from total cardiovascular disease occurred in men and 550, 199, and 1,155, respectively, in women. For men, the multivariate relative risks for current smokers compared with never smokers were 1.39 (95% confidence interval (CI): 1.13, 1.70) for stroke, 2.51 (95% CI: 1.79, 3.51) for coronary heart disease, and 1.60 (95% CI: 1.39, 1.84) for total cardiovascular disease. The respective relative risks for women were 1.65 (95% CI: 1.21, 2.25), 3.35 (95% CI: 2.23, 5.02), and 2.06 (95% CI: 1.69, 2.51), with larger excess risks for persons aged 40–64 years than for older persons. The risk decline after smoking cessation occurred for coronary heart disease and total cardiovascular disease within 2 years and for total stroke after 2–4 years. For each endpoint and in both age subgroups of 40–64 and 65–79 years, most of the benefit of cessation occurred after 10–14 years following cessation. Findings imply the importance of smoking cessation at any age to prevent cardiovascular disease in Japanese.

cerebrovascular accident; coronary disease; follow-up studies; mortality; smoking cessation

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; ICD-10, *International Classification of Diseases*, Tenth Revision; JACC Study, Japan Collaborative Cohort Study for Evaluation of Cancer Risk.

Cigarette smoking is an established risk factor for coronary heart disease in both Western (1) and Asian countries (2–9), whereas the relation with risk of total stroke has been weak and inconsistent in Asian countries (2, 3, 8–15), unlike

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Western countries (16). Mortality from coronary heart disease in Japan is one third that of the United States, but stroke mortality is twofold higher in Japan (17). Therefore, the impact of cigarette smoking on cardiovascular disease should be examined carefully in Japan.

To our knowledge, there are no prospective studies or clinical trials in Asian countries showing that smoking cessation can reduce the risk of coronary heart disease and stroke, unlike Western countries (18–22). Japan has a high smoking rate among men and a low smoking rate among women (53 percent and 13 percent, respectively, in 1999), although the smoking rate has been declining among men since 1966 (23). Evidence for effects of smoking and cessation on risk of cardiovascular disease among Japanese would be not only of scientific interest but also of value for formulating public health recommendations. However, previous Japanese studies failed to examine these issues, probably because they had insufficient numbers of persons at risk or they lacked appropriate questionnaires. We examined the relation of smoking status and time since quitting smoking with mortality from cardiovascular disease in a 10-year cohort study of approximately 95,000 Japanese men and women.

MATERIALS AND METHODS

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), sponsored by the Ministry of Education, Science, Sports and Culture, began in 1988–1990 when 110,792 persons (46,465 men and 64,327 women) aged 40–79 years completed self-administered questionnaires about their lifestyles and medical histories of cardiovascular disease and cancer. They were enrolled from 45 communities across Japan, mostly when they underwent municipal health screening examinations according to the Health Law for the Aged (24, 25). Sampling methods and protocols of the JACC Study have been described elsewhere (24). Informed consent was obtained before the participants completed the questionnaires. At the baseline survey, 44,201 men and 55,592 women provided a valid response about smoking status and years since quitting smoking. We excluded 2,419 men and 2,691 women from analysis because of a previous history of stroke, coronary heart disease, or cancer at baseline. Therefore, 41,782 men and 52,901 women were followed in the present study.

Mortality surveillance

For mortality surveillance in each community, investigators systematically reviewed death certificates, all of which were filed in the public health center in the area of residency. Mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying causes of death were coded for the National Vital Statistics according to the *International Classification of Diseases*, Ninth Revision (ICD-9), from 1988 to 1994 and the *International Classification of Diseases*, Tenth Revision (ICD-10), from 1995 to 1999. Registration of death is required by the Family Registration Law in Japan and is believed to be complete across the country. Therefore, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for participants who died after they moved from their original community; these persons were treated as censored. Follow-up was conducted until the end of 1999, and the average follow-up period for the participants was 9.9 years. The present study was approved by the Ethical Committee, University of Tsukuba, Tsukuba-shi, Japan.

Statistical analysis

Statistical analyses were based on sex-specific mortality during the follow-up period from 1989 to 1999. For each participant, person-years of follow-up were calculated from the date of baseline questionnaire completion to death, emigration from the community, or the end of 1999, whichever occurred first. The sex-specific risk of mortality from cardiovascular disease was defined as the death rate among participants in categories of smoking status or years since quitting smoking. We used never smokers as the reference category for the analysis of relative risk among current smokers, and current smokers were considered the reference category for the analysis of relative risk among former smokers according to years since quitting.

Age-adjusted means and proportions of selected cardiovascular risk factors were determined according to categories of smoking status; statistical testing was not conducted because of the large sample size. The age-adjusted and multivariate-adjusted relative risks and their 95 percent confidence intervals were calculated after adjustment for age and potential confounding factors by using the Cox proportional hazards model. These confounding variables included body mass index (sex-specific quintiles), ethanol intake (never, former, current intake of 1–22, 23–45, 46–68, and ≥69 g per day), hours of walking (<0.5, 0.5, 0.6–0.9, and ≥1.0 hour per day), hours of exercise (<1, 1–2, 3–4, and ≥5 hours per week), hours of sleep (<6.0, 6.0–6.9, 7.0–7.9, 8.0–8.9, and ≥9.0 hours per day), education (<10, 10–12, 13–15, and ≥16 years), perceived mental stress (low, medium, and high), frequencies of fruit and fish intake (<1 per month, 1–3 per month, 1–2 per week, 3–4 per week, and ≥5 per week), and histories of hypertension and diabetes. Number of cigarettes smoked per day (<20, 20–29, and ≥30) and age at starting (<20, 20–24, 25–29, and ≥30 years) were also adjusted when we assessed the association of smoking cessation with mortality.

Cause-specific mortality was defined for total stroke (ICD-9 codes 430–438, ICD-10 codes I60–I69), total coronary heart disease (ICD-9 codes 410–414, ICD-10 codes I20–I25), and total cardiovascular disease (ICD-9 codes 390–459, ICD-10 codes I01–I99) separately. Total strokes were grouped further as subarachnoid hemorrhage (ICD-9 code 430, ICD-10 code I60), intraparenchymal hemorrhage (ICD-9 code 431, ICD-10 code I61), and ischemic stroke (ICD-9 codes 433–434, ICD-10 code I63). We conducted stratified analyses by sex and age (40–64 and 65–79 years) to assess effect modification, which was tested statistically by using cross-product terms of sex and age with smoking variables in the proportional hazards models. The analysis of the relation between smoking cessation and mortality was also examined by excluding early deaths within 5 years of follow-up.

TABLE 1. Sex-specific, age-adjusted mean values or prevalences of cardiovascular risk factors at baseline (1988–1990), according to smoking status, for 41,782 men and 52,901 women aged 40–79 years living in 45 communities across Japan

	Men					Women				
	Never smoker	Former smoker	Current smoker	Cigarettes smoked (no./day)*		Never smoker	Former smoker	Current smoker	Cigarettes smoked (no./day)*	
				1–19	≥20				1–19	≥20
No. at risk	8,669	10,536	22,577	7,229	15,036	49,120	861	2,920	1,949	856
Age (years)	56.6	59.5	56.0	59.1	54.5	57.1	60.0	56.1	56.8	54.2
Body mass index (kg/m²)	23.0	23.0	22.3	22.1	22.4	22.9	23.3	22.8	22.6	23.2
History of hypertension (%)	19.3	23.8	18.7	19.5	18.2	21.6	24.3	23.3	23.5	23.2
History of diabetes (%)	5.7	7.8	6.5	6.2	6.7	3.5	6.2	5.0	5.0	5.0
Ethanol intake (g/day)	28.0	32.4	37.1	33.5	38.9	9.0	15.3	20.7	16.6	31.1
Walk half an hour or more/day (%)	69.3	67.3	70.0	70.5	69.9	71.8	64.5	69.3	70.9	66 0
Exercise 5 hours or more/week (%)	7.3	7.6	6.9	7.2	6.8	4.5	3.6	4.2	4.4	3.9
Hours of sleep (no./day)	7.4	7.4	7.5	7.6	7.5	7.1	7.1	7.0	7.1	7.0
College or higher education (%)	13.4	14.9	11.6	11.3	11.8	7.8	8.9	5.8	6.5	4.4
High perceived mental stress (%)	22.1	24.2	22.8	21.5	23.5	20.0	26.1	25.4	24.0	28.4
Fruit intake (no. of days/week)	3.6	3.4	3.0	3.2	2.9	4.3	4.1	3.6	3.7	3.4
Fish intake (no. of days/week)	3.5	3.5	3.5	3.4	3.5	3.6	3.4	3.2	3.2	3.2

* Information on number of cigarettes smoked per day was missing for 312 men and for 115 women.

The population attributable risk percentage was calculated by $P \times (1 - 1/RR)$, where P represented the prevalence of smokers among cases and RR the multivariate relative risk for current smokers compared with noncurrent smokers. The formula of Greenland was used to calculate the 95 percent confidence interval (26).

RESULTS

Of 41,782 men and 52,901 women followed up for an average of 9.9 years, 1,555 men and 1,155 women died from total cardiovascular disease. These deaths among men included 698 from stroke (75 subarachnoid hemorrhages, 180 intraparenchymal hemorrhages, and 269 ischemic strokes) and 348 from coronary heart disease. The respective numbers of deaths among women were 550 (123, 120, and 189) and 199.

Table 1 shows sex-specific, selected cardiovascular risk factors according to smoking status. The proportions of current smokers and former smokers were 54 percent and 26 percent, respectively, among men; the corresponding proportions among women were 5 percent and 2 percent. Compared with men and women who never smoked, current smokers were 1 year younger, were less educated, were more often diabetic, were more mentally stressed, and had a higher mean ethanol intake. Former smokers were 3 years older, were more educated, were more often hypertensive and diabetic, were less physically active, were more mentally stressed, and had a higher mean ethanol intake.

Table 2 shows sex-specific, age-adjusted and multivariate relative risks of death from stroke, coronary heart disease, and total cardiovascular disease. Among men, current smokers had a 1.5-fold higher age-adjusted rate of mortality from total stroke, 2.4-fold higher mortality from coronary heart disease, and 1.6-fold higher mortality from total cardiovascular disease compared with never smokers. Among women, the smoking effect was somewhat stronger than that among men; the respective values were 1.8, 3.6, and 2.2. However, the interactions with sex were not statistically significant. These trends did not change materially after adjustment for potential cardiovascular risk factors. The multivariate relative risks varied by stroke subtypes: 2.98 (95 percent confidence interval (CI): 1.34, 6.63) for subarachnoid hemorrhage, 1.48 (95 percent CI: 0.97, 2.24) for intraparenchymal hemorrhage, and 1.23 (95 percent CI: 0.90, 1.69) for ischemic stroke for men and 3.25 (95 percent CI: 1.92, 5.52), 1.10 (95 percent CI: 0.51, 2.40), and 1.64 (95 percent CI: 0.97, 2.79), respectively, for women. The dose-response relations between number of cigarettes smoked daily and mortality risk were evident for women but not for men.

Former smokers generally had a risk of mortality from total cardiovascular disease intermediate between that of never smokers and that of current smokers. The multivariate relative risks of total cardiovascular disease for current smokers versus nonsmokers were 1.50 (95 percent CI: 1.36, 1.67) for men and 1.97 (95 percent CI: 1.62, 2.39) for women. On the basis of these estimates and the proportions of current smokers among cardiovascular disease cases (57 percent for men and 10 percent for women), the population attributable risk percentages for total cardiovascular disease were 19 (95 percent CI: 14, 24) percent for men and 5 (95 percent CI: 3, 7) percent for women.

Table 3 shows sex- and age-specific multivariate relative risks of stroke, coronary heart disease, and total cardiovascular disease mortality. For both men and women, the excess risks of mortality associated with current smoking were more evident among middle-aged persons than among

TABLE 2. Sex-specific, age-adjusted and multivariate* relative risks and 95% confidence intervals of mortality from stroke, coronary heart disease, and total cardiovascular disease, according to smoking status, for 41,782 men and 55,592 women aged 40–79 years living in 45 communities across Japan from 1988–1990 to the end of 1999

	Men					Women				
	Never smoker	Former smoker	Current smoker	Cigarettes smoked (no./day)		Never smoker	Former smoker	Current smoker	Cigarettes (no./day)	
				1–19	≥20				1–19	≥20
No. of person-years	86,383	102,871	220,965	69,562	148,365	493,833	8,269	28,722	19,023	8,521
Total stroke										
No.	126	184	388	186	198	487	15	48	30	16
Age-adjusted RR†	1.0	1.00 (0.80, 1.25)‡	1.46 (1.19, 1.78)	1.63 (1.30, 2.04)	1.32 (1.06, 1.66)	1.0	1.27 (0.76, 2.12)	1.77 (1.31, 2.40)	1.54 (1.06, 2.22)	2.49 (1.51, 4.10)
Multivariate RR	1.0	0.95 (0.76, 1.20)	1.39 (1.13, 1.70)	1.54 (1.22, 1.93)	1.26 (1.00, 1.58)	1.0	1.20 (0.71, 2.03)	1.65 (1.21, 2.25)	1.43 (0.99, 2.08)	2.32 (1.38, 3.88)
Subarachnoid hemorrhage										
No.	7	15	53	21	32	103	2	18	12	36
Age-adjusted RR	1.0	1.75 (0.71, 4.29)	3.37 (1.53, 7.44)	3.70 (1.57, 8.73)	3.18 (1.40, 7.24)	1.0	0.94 (0.23, 3.79)	3.35 (2.03, 5.53)	3.04 (1.67, 5.53)	4.21 (1.84, 9.60)
Multivariate RR	1.0	1.67 (0.68, 4.14)	2.98 (1.34, 6.63)	3.27 (1.37, 7.79)	2.80 (1.22, 6.44)	1.0	0.90 (0.22, 3.69)	3.25 (1.92, 5.52)	3.00 (1.62, 5.55)	4.00 (1.68, 9.54)
Intraparenchymal hemorrhage										
No.	30	46	104	50	54	109	3	8	6	1
Age-adjusted RR	1.0	1.13 (0.71, 1.80)	1.61 (1.07, 2.42)	1.93 (1.22, 3.03)	1.39 (0.88, 2.18)	1.0	1.18 (0.37, 3.71)	1.20 (0.56, 2.57)	1.38 (0.61, 3.14)	0.67 (0.09, 4.80)
Multivariate RR	1.0	1.05 (0.66, 1.68)	1.48 (0.97, 2.24)	1.76 (1.11, 2.79)	1.28 (0.81, 2.02)	1.0	1.20 (0.38, 3.83)	1.10 (0.51, 2.40)	1.31 (0.57, 3.02)	0.55 (0.07, 4.05)
Ischemic stroke										
No.	54	73	142	79	60	166	6	17	9	7
Age-adjusted RR	1.0	0.87 (0.61, 1.23)	1.24 (0.91, 1.69)	1.54 (1.09, 2.17)	0.97 (0.67, 1.40)	1.0	1.39 (0.62, 3.14)	1.79 (1.07, 2.99)	1.32 (0.68, 2.59)	3.28 (1.54, 7.00)
Multivariate RR	1.0	0.84 (0.59, 1.19)	1.23 (0.90, 1.69)	1.52 (1.07, 2.15)	0.97 (0.67, 1.41)	1.0	1.24 (0.54, 2.88)	1.64 (0.97, 2.79)	1.21 (0.61, 2.39)	3.17 (1.43, 7.01)
Coronary heart disease										
No.	39	98	211	76	132	164	4	31	18	13
Age-adjusted RR	1.0	1.69 (1.18, 2.43)	2.40 (1.72, 3.36)	2.11 (1.44, 3.08)	2.63 (1.85, 3.74)	1.0	1.01 (0.37, 2.71)	3.61 (2.46, 5.30)	2.77 (1.70, 4.51)	6.19 (3.51, 10.9)
Multivariate RR	1.0	1.66 (1.15, 2.39)	2.51 (1.79, 3.51)	2.17 (1.48, 3.18)	2.77 (1.94, 3.95)	1.0	0.90 (0.33, 2.45)	3.35 (2.23, 5.02)	2.59 (1.57, 4.27)	5.95 (3.25, 10.9)
Other cardiovascular disease										
No.	86	140	283	121	157	350	16	40	28	11
Age-adjusted RR	1.0	1.09 (0.83, 1.42)	1.49 (1.17, 1.89)	1.49 (1.13, 1.96)	1.49 (1.14, 1.93)	1.0	1.82 (1.10, 3.00)	2.07 (1.49, 2.89)	1.96 (1.33, 2.88)	2.43 (1.33, 4.43)
Multivariate RR	1.0	1.04 (0.79, 1.36)	1.48 (1.16, 1.89)	1.48 (1.12, 1.95)	1.49 (1.14, 1.94)	1.0	1.70 (1.02, 2.85)	2.03 (1.45, 2.86)	1.93 (1.30, 2.86)	2.36 (1.28, 4.36)
Total cardiovascular disease										
No.	251	422	882	383	487	1,001	35	119	76	40
Age-adjusted RR	1.0	1.14 (0.98, 1.33)	1.62 (1.41, 1.86)	1.66 (1.42, 1.94)	1.59 (1.37, 1.85)	1.0	1.42 (1.01, 1.99)	2.17 (1.79, 2.64)	1.89 (1.49, 2.38)	3.07 (2.24, 4.21)
Multivariate RR	1.0	1.09 (0.94, 1.28)	1.60 (1.39, 1.84)	1.62 (1.38, 1.90)	1.58 (1.35, 1.84)	1.0	1.33 (0.94, 1.87)	2.06 (1.69, 2.51)	1.79 (1.41, 1.27)	2.91 (2.10, 4.04)

* Multivariate adjustment: age (5-year categories), body mass index (sex-specific quintiles), ethanol intake (six categories), hours of walking and exercise (four categories), hours of sleep (five categories), no. of years of education (three categories), perceived mental stress (three categories), frequencies of fruit and fish intake (five categories), and histories of hypertension and diabetes.

† RR, relative risk.

‡ Numbers in parentheses, 95% confidence interval.

TABLE 3. Multivariate* relative risks and 95% confidence intervals of mortality from stroke, coronary heart disease, and total cardiovascular disease, by age subgroup, for 41,782 men and 55,592 women aged 40–79 years living in 45 communities across Japan from 1988–1990 to the end of 1999

	Men			Women		
	Never smoker	Former smoker	Current smoker	Never smoker	Former smoker	Current smoker
			Aged 40–64 years			
No. of person-years	67,816	71,969	180,452	378,032	5,333	22,404
Total stroke						
No.	32	40	165	118	5	19
Multivariate RR†	1.0	0.93 (0.58, 1.49)‡	1.79 (1.22, 2.63)	1.0	3.00 (1.21, 7.47)	2.78 (1.65, 4.66)
Subarachnoid hemorrhage						
No.	5	8	36	43	2	10
Multivariate RR	1.0	1.40 (0.45, 4.31)	2.34 (0.91, 6.05)	1.0	3.88 (0.91, 16.5)	4.26 (2.02, 9.02)
Intraparenchymal hemorrhage						
No.	17	11	59	35	0	6
Multivariate RR	1.0	0.45 (0.21, 0.97)	1.19 (0.68, 2.06)	1.0		2.56 (0.97, 6.77)
Ischemic stroke						
No.	6	13	50	26	3	2
Multivariate RR	1.0	1.52 (0.57, 4.04)	3.10 (1.31, 7.30)	1.0	8.69 (2.45, 30.9)	1.39 (0.32, 5.97)
Coronary heart disease						
No.	9	26	99	37	1	10
Multivariate RR	1.0	2.23 (1.07, 4.65)	4.15 (2.15, 8.01)	1.0	1.86 (0.25, 13.9)	4.50 (2.09, 9.70)
Other cardiovascular disease						
No.	25	38	120	76	0	89
Multivariate RR	1.0	1.09 (0.66, 1.79)	1.56 (1.02, 2.40)	1.0		3.51 (1.89, 6.51)
Total cardiovascular disease						
No.	66	104	384	231	6	42
Multivariate RR	1.0	1.18 (0.86, 1.60)	2.03 (1.56, 2.63)	1.0	1.70 (0.75, 3.87)	3.32 (2.34, 4.71)

Table continues

elderly persons for total stroke, coronary heart disease, and total cardiovascular disease, and the interaction with age was statistically significant ($p < 0.05$) for these endpoints, except for coronary heart disease in women. We found a significant excess risk of mortality from ischemic stroke among middle-aged men (p for interaction = 0.005) but not among other sex and age subgroups. No significant association was found between smoking and mortality from intraparenchymal hemorrhage in any sex or age subgroup.

When we examined the relation of years since quitting smoking with risks of mortality from stroke, coronary heart disease, and total cardiovascular disease, we used current smokers as the reference category (table 4). Since the number of women former smokers was small, the data were presented by adjusting for sex as well as other confounding factors.

At 2–4 years after smoking cessation, the multivariate relative risk of total stroke was reduced 27 percent, and, at 10–14 years, most of the benefit of cessation (a 52 percent reduction) was attained and former smokers' mortality did not differ significantly from that of never smokers. A nonsignificant reduced risk of coronary heart disease and total cardiovascular disease occurred within 2 years after cessation, and most of the benefit of cessation (a 46–53 percent reduction) occurred 10–14 years after cessation, when the mortality rates did not differ from that among never smokers.

When the early deaths within 5 years of follow-up were excluded (n = 394 for stroke, n = 147 for coronary heart disease, and n = 921 for total cardiovascular disease), the results did not change substantially; the multivariate relative risks of mortality from stroke were 0.98 (95 percent CI: 0.57, 1.68) for 0–1 years since quitting smoking, 0.71 (95 percent CI: 0.45, 1.12) for 2–4 years, 0.83 (95 percent CI: 0.57, 1.20) for 5–9 years, 0.41 (95 percent CI: 0.23, 0.72) for 10–14 years, 0.66 (95 percent CI: 0.48, 0.91) for 15 or more years, and 0.47 (95 percent CI: 0.30, 0.72) for never smokers. The respective relative risks of mortality from coronary heart disease were 0.22 (95 percent CI: 0.06, 0.90), 0.89 (95 percent CI: 0.53, 1.49), 0.61 (95 percent CI: 0.36, 1.05), 0.44 (95 percent CI: 0.23, 0.87), 0.41 (95 percent CI: 0.25, 0.66), and 0.44 (95 percent CI: 0.21, 0.90). Finally, the respective relative risks of mortality from total cardiovascular disease were 0.73 (95 percent CI: 0.49, 1.11), 0.91 (95 percent CI: 0.69, 1.19), 0.70 (95 percent CI: 0.54, 0.92), 0.50 (95 percent CI: 0.36, 0.71), 0.54 (95 percent CI: 0.43, 0.67), and 0.49 (95 percent CI: 0.36, 0.67).

The risk reduction was similarly observed for persons aged 40–64 years and those aged 65–79 years. However,

TABLE 3. Continued

	Men			Women		
	Never smoker	Former smoker	Current smoker	Never smoker	Former smoker	Current smoker
			Aged 65–79 years			
No. of person-years	18,567	30,902	40,513	115,801	2,936	6,318
Total stroke						
No.	94	144	223	369	10	29
Multivariate RR	1.0	0.94 (0.73, 1.23)	1.20 (0.94, 1.53)	1.0	0.93 (0.49, 1.77)	1.28 (0.87, 1.90)
Subarachnoid hemorrhage						
No.	2	7	17	60	0	8
Multivariate RR	1.0	2.56 (0.52, 12.7)	5.11 (1.14, 22.9)	1.0		2.43 (1.12, 5.28)
Intraparenchymal hemorrhage						
No.	13	35	45	74	3	2
Multivariate RR	1.0	1.83 (0.95, 3.50)	1.81 (0.96, 3.41)	1.0	1.57 (0.48, 5.12)	0.43 (0.11, 1.79)
Ischemic stroke						
No.	48	60	92	140	3	15
Multivariate RR	1.0	0.73 (0.50, 1.07)	0.94 (0.66, 1.34)	1.0	0.65 (0.20, 2.07)	1.64 (0.92, 2.90)
Coronary heart disease						
No.	30	72	112	127	3	21
Multivariate RR	1.0	1.42 (0.93, 2.17)	1.95 (1.30, 2.92)	1.0	0.79 (0.24, 2.49)	2.97 (1.83, 4.82)
Other cardiovascular disease						
No.	61	102	163	274	16	27
Multivariate RR	1.0	1.01 (0.73, 1.39)	1.45 (1.07, 1.95)	1.0	1.93 (1.15, 3.25)	1.67 (1.10, 2.52)
Total cardiovascular disease						
No.	185	318	498	770	29	77
Multivariate RR	1.0	1.04 (0.87, 1.25)	1.41 (1.19, 1.67)	1.0	1.27 (0.87, 1.85)	1.69 (1.32, 2.15)

* Multivariate adjustment: sex, age (5-year categories), body mass index (sex-specific quintiles), ethanol intake (six categories), hours of walking and exercise (four categories), hours of sleep (five categories), no. of years of education (three categories), perceived mental stress (three categories), frequencies of fruit and fish intake (five categories), and histories of hypertension and diabetes.

† RR, relative risk.

‡ Numbers in parentheses, 95% confidence interval.

there was a nonsignificant excess risk of mortality from coronary heart disease at 2–4 years after cessation for persons aged 65–79 years.

The relations between age at starting to smoke and mortality were examined separately for current and former smokers (data not shown in table). Among both current smokers and former smokers, we found no association between age at starting to smoke and mortality, except for coronary heart disease among current smokers. Compared with that for never smokers, the multivariate relative risk of coronary heart disease mortality for current smokers was 3.68 (95 percent CI: 2.33, 5.74) for onset at less than age 20 years, 2.96 (95 percent CI: 2.06, 4.26) for age 20–24 years, 2.31 (95 percent CI: 1.41, 3.77) for age 25–29 years, and 1.80 (95 percent CI: 1.15, 2.82) for age 30 years or older.

DISCUSSION

In this large prospective study of Japanese men and women, we confirmed excess mortality from total stroke, coronary heart disease, and total cardiovascular disease associated with current smoking for both men and women and that these excess risks were more evident for those aged 40–64 years than for those aged 65–79 years (1, 16). Among stroke subtypes, we found a strong association between smoking and subarachnoid hemorrhage in both sexes and age subgroups but weak or no associations with intraparenchymal hemorrhage in either sex or age subgroup; this finding is consistent with previous Japanese studies of Japanese (27) and Caucasians (16). Excess mortality from ischemic stroke with smoking was observed among middle-aged men in the present study, whereas most of the previous studies did not show the association (3, 6, 10–12). A recent report from the Hisayama Study showed a significant association of current smoking with risk of lacunar infarction (relative risk = 2.2, 95 percent CI: 1.3, 3.9) but no association with risk of total ischemic stroke, atherothrombotic infarction, or embolic brain infarction (15). The lack of association between smoking and ischemic stroke among the elderly in the present study may be due in part to the higher proportion of embolic brain infarction in the elderly than in middle-aged persons (28, 29).

We found that smoking cessation led to a decline in risk of mortality from total stroke, coronary heart disease, and total cardiovascular disease after adjustment for number of cigarettes smoked, age at starting to smoke, and other known risk

TABLE 4. Multivariate* relative risks and 95% confidence intervals of mortality from stroke, coronary heart disease, and total cardiovascular disease, according to years since quitting smoking, for 41,782 men and 55,592 women aged 40–79 years living in 45 communities across Japan from 1988–1990 to the end of 1999

	Current smoker	No. of years since quitting smoking					Never smoker
		0–1	2–4	5–9	10–14	≥15	
No. of person-years	245,471	9,923	18,365	25,175	19,903	31,970	580,216
Total stroke							
No.	430	21	29	40	21	71	613
Multivariate RR†	1.0	1.03 (0.66, 1.60)‡	0.73 (0.50, 1.06)	0.75 (0.54, 1.04)	0.48 (0.31, 0.74)	0.71 (0.55, 0.92)	0.53 (0.37, 0.76)
Coronary heart disease							
No.	239	4	23	28	13	27	203
Multivariate RR	1.0	0.33 (0.12, 0.88)	0.91 (0.59, 1.40)	0.83 (0.56, 1.24)	0.47 (0.27, 0.83)	0.42 (0.28, 0.63)	0.43 (0.23, 0.78)
Total cardiovascular disease							
No.	986	40	86	94	58	139	1252
Multivariate RR	1.0	0.81 (0.59, 1.11)	0.88 (0.71, 1.10)	0.73 (0.59, 0.90)	0.54 (0.42, 0.71)	0.56 (0.46, 0.67)	0.47 (0.37, 0.60)
Aged 40–64 years							
No. of person-years	199,566	7,690	13,812	18,504	14,306	18,928	445,849
Total stroke							
No.	183	9	8	10	3	7	150
Multivariate RR	1.0	1.12 (0.57, 2.19)	0.50 (0.24, 1.01)	0.58 (0.31, 1.10)	0.23 (0.07, 0.71)	0.31 (0.15, 0.67)	0.30 (0.15, 0.59)
Coronary heart disease							
No.	108	2	5	9	3	7	46
Multivariate RR	1.0	0.41 (0.10, 1.65)	0.51 (0.21, 1.26)	0.77 (0.39, 1.54)	0.34 (0.11, 1.06)	0.53 (0.24, 1.15)	0.36 (0.10, 1.35)
Total cardiovascular disease							
No.	422	18	26	24	11	21	297
Multivariate RR	1.0	0.93 (0.58, 1.49)	0.70 (0.47, 1.04)	0.57 (0.38, 0.87)	0.34 (0.19, 0.62)	0.40 (0.26, 0.63)	0.36 (0.22, 0.60)
Aged 65–79 years							
No. of person-years	45,904	2,233	4,553	6,670	5,597	13,043	134,368
Total stroke							
No.	247	12	21	30	18	64	463
Multivariate RR	1.0	1.00 (0.56, 1.79)	0.87 (0.56, 1.37)	0.86 (0.59, 1.27)	0.62 (0.38, 1.00)	0.89 (0.67, 1.18)	0.67 (0.43, 1.03)
Coronary heart disease							
No.	131	2	18	19	10	20	157
Multivariate RR	1.0	0.28 (0.07, 1.13)	1.16 (0.70, 1.91)	0.91 (0.56, 1.49)	0.54 (0.28, 1.04)	0.42 (0.26, 0.68)	0.48 (0.24, 0.95)
Total cardiovascular disease							
No.	564	22	60	70	47	118	955
Multivariate RR	1.0	0.74 (0.48, 1.14)	1.00 (0.76, 1.31)	0.84 (0.65, 1.08)	0.66 (0.49, 0.89)	0.64 (0.52, 0.78)	0.53 (0.40, 0.70)

* Multivariate adjustment: sex, age (5-year categories), body mass index (sex-specific quintiles), ethanol intake (six categories), hours of walking and exercise (four categories), hours of sleep (five categories), no. of years of education (three categories), perceived mental stress (three categories), frequencies of fruit and fish intake (five categories), histories of hypertension and diabetes, daily number of cigarettes smoked (three categories), and age at starting to smoke (four categories).

† RR, relative risk.

‡ Numbers in parentheses, 95% confidence interval.

factors. Following cessation, risk began to decline within 2 years for coronary heart disease and total cardiovascular disease and after 2–4 years for total stroke, and these findings were similar for middle-aged and older participants. For total stroke, coronary heart disease, and total cardiovascular disease mortality, most of the benefit of cessation occurred 10–14 years following cessation, and these trends were similar for both age subgroups. The Nurses' Health Study of US women aged 30–55 years reported that most of the smoking cessation benefit occurred after 2–4 years for total and ischemic stroke (19) and after 10–14 years for coronary heart disease (18). Other cohort studies of US and British men showed that the reduction in risk of stroke occurred at less than 2 years (30) or less than 5 years (19) after smoking cessation, and the excess risk of stroke was eliminated after 5 years (19, 31). Two clinical trials of 5 years' and 10 years' duration showed that smoking cessation led to a reduction in coronary heart disease among middle-aged men (21, 22).

Limitations of the present study warrant discussion. First, it is possible that persons who quit smoking many years before baseline were more likely to have died or to have been diagnosed with stroke, coronary heart disease, or cancer, and these persons were not included in the analysis. This scenario would lead to a bias in examining the relation between years since smoking cessation and mortality risk. However, no essential change in the relations after excluding the early deaths within 5 years of follow-up, or no increase in the histories of these chronic diseases with years since quitting (sex- and age-adjusted prevalence: 11 percent for 0–1 years, 11 percent for 2–4 years, 11 percent for 5–9 years, 9 percent for 10–14 years, and 7 percent for 15 or more years since quitting), suggests that the survival bias may be small. Furthermore, a subsample study of 8,944 current smokers at baseline who also responded to the 5-year follow-up included 915 quitters and 8,029 continuing smokers who were followed for another 5 years to ascertain mortality. The multivariate relative risks for quitters compared with continuing smokers were 1.00 (95 percent CI: 0.55, 1.81) for total stroke, 0.81 (95 percent CI: 0.34, 1.91) for coronary heart disease, and 1.08 (95 percent CI: 0.75, 1.60) for total cardiovascular disease. This subsample study suggests a possible decline in mortality from coronary heart disease among quitters. However, the sample size was too small to reach a definite conclusion.

Second, we used mortality as the endpoint, which may lead to misclassification in the diagnosis of stroke subtypes in particular. However, widespread use of computed tomography in local Japanese hospitals since the 1980s has probably made death certificate diagnosis of stroke subtypes sufficiently accurate (28, 32).

Third, use of mortality data also requires caution when interpreting the association between smoking cessation and disease risk. The nonsignificant excess risk of mortality from coronary heart disease after 2–4 years of quitting among those aged 65–79 years could be a chance or an "ill-quitter" effect; namely, persons who developed coronary heart disease may have quit smoking because of the illness (33). Furthermore, the effect of smoking cessation on mortality from cardiovascular disease may be observed later than that for incidence because of the time lag from incidence to death.

Fourth, data on the history of dyslipidemia (high total or low density lipoprotein cholesterol and low high density lipoprotein cholesterol levels), an established coronary risk factor, were not available in the present study. Smoking has no effect on blood total and low density lipoprotein cholesterol levels and raises high density lipoprotein cholesterol levels (34). Thus, history of dyslipidemia could be a mediator but was probably not a confounder for the association between smoking and mortality.

Fifth, it is possible that smoking cessation during follow-up led to underestimation of the association between current smoking and mortality from cardiovascular disease. However, we could not update the smoking information because we had 5-year follow-up data for only 38 percent of the subjects. However, those limited follow-up data suggested that the proportions of current smokers who quit smoking were 16 percent for men and 3 percent for women, and the proportions of never smokers who started smoking were 3 percent for men and 0.5 percent for women. Therefore, the relative risk of mortality for current smoking may have been underestimated slightly. Furthermore, it is difficult to eliminate totally the residual confounding and unknown health-related factors associated with smoking cessation because of the observational design of the study. Compared with continuous smokers, former smokers may be more health conscious and of a higher socioeconomic status, while some of them quit smoking because of illness; the net effect of these factors is uncertain (22).

The strength of the present study is the high statistical power to detect sex- or age-specific associations of smoking and smoking cessation with mortality from cardiovascular disease among Japanese men and women.

The mechanisms by which smoking causes coronary heart disease and ischemic stroke include short-term effects of accelerated thrombus formation through increased plasma fibrinogen (35), increased platelet aggregability (36), increased hematocrit (37) and decreased fibrinolytic activity (38), reduced blood flow in the myocardium and brain due to vasoconstriction (39, 40), and cardiac arrhythmia (41). A longer-term effect is atheroma formation through direct injury of endothelial cells (42) and low high density lipoprotein cholesterol levels (34). The mechanism for smoking being linked to subarachnoid hemorrhage is not clear, but some evidence suggests that smoking increases the release of proteinases from activated pulmonary macrophages, which enhances the fragility of cerebral aneurysms (43), and that smoking increases hemodynamic stress on the Circle of Willis (44) through the enhanced atherosclerosis in basal cerebral and carotid arteries.

We estimated that 17 percent of male deaths and 5 percent of female deaths from total cardiovascular disease were attributable to current smoking. In 1999, the numbers of annual deaths from cardiovascular disease were 149,937 for men and 159,444 for women (23). Therefore, approximately 36,000 cardiovascular deaths (28,000 men and 8,000 women) could be avoidable by smoking cessation in Japan.

In conclusion, the present study confirmed a relation between smoking and mortality from cardiovascular disease, and it also provides empirical evidence that smoking cessation leads to a reduction in mortality risk for Japanese men and women. In our study, the risk reduction for coronary heart disease and total cardiovascular disease began to appear within 2 years of quitting, and that for stroke after 2–4 years of quitting. The full effect of risk reduction was achieved at 10–14 years for persons aged both 40–64 and 65–79 years. These findings imply that smoking cessation is important at any age to prevent cardiovascular disease among Japanese.

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(6) 乳製品、カルシウムの摂取と循環器疾患死亡との関連

目的：乳製品の摂取と循環器疾患による死亡状況との関連を分析した。

方法：文部科学省の助成による大規模コホート（JACC study）の対象者に対し、1988 年～1990 年に質問紙による調査を行った。そのうち、栄養に関する質問について回答を得られた者の中で、脳卒中、心筋梗塞、がんの既往者を除いた 40～79 歳の 53,387 人（男性 21,068 人、女性 32,319 人）について、乳製品（牛乳、ヨーグルト、チーズ）の摂取頻度と循環器疾患死亡との関連を調べた。乳製品の摂取頻度（週あたりの頻度）の合計により乳製品によるカルシウム摂取量を算出し、20%タイルで 5 分割した後、年齢、性、body mass index（BMI）等を調整した相対危険度を算出した。

結果：9.6 年間の平均追跡期間中、脳卒中による死亡者は 566 人（脳梗塞 273 人、脳出血 140 人、くも膜下出血 101 人）、虚血性心疾患 182 人であった。全循環器疾患死亡者は 1,329 人であった。乳製品の摂取が週平均 0.5 回未満の群に対する、男性で平均週 7.8 回以上摂っている群、女性で平均 8.5 回以上摂っている群の脳卒中による死亡リスクは、男性で 0.53（0.34-0.81）、女性で 0.57（0.38-0.86）であった。また、脳梗塞については、男性で 0.53（0.29-0.99）、女性で 0.50（0.27-0.95）であった。出血性脳卒中（脳出血およびくも膜下出血）については、男性で 0.46（0.23-0.91）、女性で 0.51（0.28-0.94）であった。虚血性心疾患については、乳製品の摂取と死亡リスクの低下との有意な関連は見られなかった。

結論：乳製品からのカルシウム摂取が脳卒中特に脳梗塞の死亡リスクを低下させる可能性が示された。