Title

Passive smoking and mortality from aortic dissection or aneurysm

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Abstract

Background and aims: Evidence on the association between passive smoking and risk of aortic dissection or aneurysm is limited. This study aimed to investigate whether passive smoking increases risk of mortality from aortic dissection or aneurysm.

Methods: The Japan Collaborative Cohort (JACC) Study is a prospective community-based cohort study begun in 1988-90 and followed up to the end of 2009. We examined 48,677 individuals (mean age, 56 years; women, 46%) without history of stroke, coronary heart disease, or cancer, who provided valid responses to a lifestyle questionnaire including questions on active and passive smoking. We used 3 categories (passive smoking out of home, passive smoking at home, and passive smoking out of or at home combined) to divide never-smokers into 3 exposure groups: low, intermediate,

and high exposures, respectively. The endpoint was underlying cause of death from aortic dissection or aneurysm.

Results: During the median 19-year follow-up of 48,677 study participants, 66 died of aortic dissection, and 75, of aortic aneurysm. Multivariable hazard ratios (95% confidence intervals) for the high passive-smoking group as compared with the low passive-smoking group were 2.45 (1.02-5.88) out of home, 1.82 (0.84-3.96) at home, and 2.35 (1.09-5.09) out of or at home combined. The corresponding hazard ratios for current smokers as compared with the low passive-smoking group were 3.97 (2.14-7.39), 3.41 (1.84-6.32) and 4.09 (1.99-8.39), respectively.

Conclusions: Out-of-home passive smoking and out-of- or at-home combined passive smoking were associated with increased mortality from aortic dissection or aneurysm.

Introduction

Aortic dissection and aneurysm (aortic diseases) develop because of vascular damage to the aorta. The incidence of aortic dissection or aneurysm is much lower than those of stroke and coronary heart disease, but these aortic diseases are highly lethal.[1,2] Therefore, the prevention of aortic diseases is highly warranted.

Cigarette smoking is a major cause of cardiovascular disease, including not only coronary heart disease but also aortic dissection and aneurysm.[3] A systematic review indicated that smoking had a greater impact on risk of aortic aneurysm than on coronary heart disease: the relative risk of aortic aneurysm associated with current smoking was generally 3 to 6, while that of coronary heart disease was generally 1 to 2.[4]

Like active smoking, passive smoking is also considered to be harmful to health.[5] Many studies have examined the association between passive smoking and risk of coronary heart disease.[3,5,6] A meta-analysis of 29 studies evaluating the cardiovascular effects of passive smoking showed that the relative risk for coronary heart disease was 1.31 (95% confidence interval [CI], 1.21-1.41).[5] Similar results were obtained in earlier meta-analyses.[7-10]

However, to the best of our knowledge, no study has reported an association between passive smoking and risk of aortic dissection or aneurysm. Therefore, we

investigated the impact of passive smoking on mortality from aortic dissection or aneurysm in a large prospective study.

Materials and methods

The Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risk sponsored by the Japanese Ministry of Education, Science, Sports and Culture is a large, nationwide, community-based cohort study of Japanese men and women. It was established in 1988-1990, and 110,585 residents (46,395 men and 64,190 women, aged 40-79 years) in 45 communities around Japan were enrolled. They completed self-administered questionnaires about their lifestyles and medical histories of diseases including hypertension, diabetes mellitus, stroke, myocardial infarction, and cancer. Details of the JACC study have been described elsewhere.[11,12] Informed consent from individuals before participation in the study was obtained in 36 of the 45 communities (written consent in 35 communities and oral consent in 1 community); in the remaining 9 communities, group consent from the community leader was obtained. The JACC Study was approved by the institutional review boards of Hokkaido University, the University of Tsukuba, and Osaka University.

Baseline assessment

The JACC baseline questionnaire included questions about active smoking and passive smoking out of home and at home, and was completed by 77,722 study participants in 30 communities. Of these participants, we excluded 7490 who did not provide valid information on their active smoking status; 18,959 who did not provide valid information on their passive smoking status; and 2596 who had a history of stroke, myocardial infarction, and/or cancer. Finally, the study population comprised 48,677 (23,407 never-smokers, 7725 former smokers, and 17,545 current smokers), and the numbers of women were 22,377 (19,811, 556, and 2,010), respectively. We included current smokers and former smokers for comparison.

Definition of baseline passive smoking status

We classified never-smokers by frequency of passive smoking status. In the questionnaire, we asked study participants about passive smoking in 2 situations: out of home and at home. The exposure time was asked if participants reported exposure to passive smoke almost every day at home. The average exposure time was 2.4 hours (median, 2 hours; mode, 1 hour).

As for passive smoking out of home, participants were classified as high-exposure passive smokers if they reported passive-smoking exposure out of home

almost every day. If participants reported seldom passive-smoking exposure out of home, they were classified as low-exposure passive smokers. The others (exposure 3-4 days a week, 1-2 days a week, and sometimes) were classified as intermediate-exposure passive smokers. For passive smoking at home, study participants were classified as high-exposure passive smokers if they reported passive-smoking exposure at home of 2 or more hours per day almost every day. If they reported no passive-smoking exposure at home, they were classified as low-exposure passive smokers. The others (exposure of less than 2 hours per day almost every day, 3–4 days a week, 1–2 days a week, and sometimes) were classified as intermediate-exposure passive smokers.

Since low-exposure passive smokers at home may be exposed to high levels of passive smoking outside, and vice versa, we further defined the combined passive-smoking category as follows: high-exposure passive smokers as persons with high passive smoking out of home or at home; low-exposure passive smokers as those with no more than low passive smoking; and otherwise, as intermediate-exposure passive smokers. The definition of baseline passive smoking status is illustrated in Figure 1.

Mortality surveillance

We conducted a follow-up survey in each community annually and obtained information about death and moving out of the community. The date and cause of death were obtained from the official death certificate, where the underlying cause of death was coded according to the 10th Revision of the International Classification of Diseases on Mortality Statistics. We chose the endpoint as death due to aortic dissection or aortic aneurysm (codes I710-I719) for this study. If participants moved out of the communities or died of other causes, we treated them as censored participants. The follow-up continued until the end of 2009, other than for 8 areas (until 1999 in 4 areas, 2003 in 2 areas, and 2008 in 2 areas).

Statistical analysis

The sex- and age-adjusted mean values and proportions of selected cardiovascular risk factors according to smoking categories were assessed using analysis of covariance and the chi-square test. The sex- and age-adjusted and multivariable hazard ratios and 95% CIs for aortic diseases were calculated using the Cox proportional hazards model. The confounding variables were age, sex, body mass index (quintiles), history of hypertension (dichotomous), alcohol intake category (never-drinker, ex-drinker, current drinkers of ethanol at 1-45 and > 45 g/day), perceived mental stress (low, medium, and

high), walking (≤ 0.5 h versus > 0.5 h), age of completed education (at ≤ 18 versus ≥ 19 years), unemployment (persons other than regular employees or part-time workers), frequency of fresh fish intake (< 1 per month, 1–3 per month, and ≥ 1 per week), and region (Tohoku or Chubu versus others), which were correlated with passive smoking status at baseline. Person-years were defined as the time from the date of the baseline questionnaire to the date of death, moving from the community, or end of follow-up, whichever occurred first. All calculations were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA). All *P* values for the statistical tests were 2-tailed, and *P* values < 0.05 were considered significant.

Results

Table 1 shows sex- and age- adjusted characteristics according to smoking status. Compared with the low out-of-home passive-smoking group, the intermediate and high out-of-home passive-smoking groups were more likely to be younger; former smokers were older and current smokers were younger. The proportion of men was higher in the intermediate and high out-of-home passive-smoking groups, and almost all former and current smokers were men. The mean body mass index was higher in the intermediate out-of-home passive-smoking and former smoker groups, but lower in the current

smoker group. The mean systolic blood pressure was lower in the intermediate and high out-of-home passive-smoking groups, and the mean diastolic blood pressure was lower in the current smoker group. Former smokers were more likely to have a history of hypertension and medication use for hypertension and diabetes mellitus. Former and current smokers were more likely to have a history of diabetes mellitus. The intermediate and high out-of-home passive-smoker groups and former and current smoker groups were more likely to be current drinkers and employed and to have high perceived mental stress. The proportion of persons walking 30 minutes or more per day was lower in the former smokers. The former smokers were more educated, and the current smokers, less educated. The frequency of fresh fish intake was lower in the former and current smokers.

Similar baseline characteristics were observed for the at-home passive-smoking and combined passive-smoking groups. The several exceptions were as follows. The proportion of men was lower in the intermediate and high at-home passive-smoking groups than in the low at-home passive-smoking group, but did not differ among the low, intermediate, and high combined passive-smoking groups. The mean systolic blood pressure did not differ among the low, intermediate, and high at-home passive-smoking groups, nor among the low, intermediate, and high combined passive-smoking groups.

The proportion of current drinkers did not differ among the low, intermediate, and high at-home passive-smoking groups. The proportion of persons walking 30 minutes or more per day was higher in the intermediate and high at-home passive-smoking groups than in the low at-home passive-smoking groups. The intermediate and high at-home passive-smoking groups were less educated and less employed. The frequency of fresh fish intake was higher in the intermediate and high at-home passive-smoking groups and in the intermediate combined passive-smoking group.

The average follow-up period was 16.2 years (median, 19.2 years). During a total of 788,511 person-years' follow-up of 48,677 study participants, 66 (37 men and 29 women) died of aortic dissection, and 75 (60 men and 15 women), of aortic aneurysm. Among the aortic aneurysms, there were 23 (16 men and 7 women) thoracic, 45 (39 men and 6 women) abdominal, 2 (2 men and 0 women) thoracoabdominal, and 5 (3 men and 2 women) unclassified aneurysms. The percentage of participants who were lost to follow-up (mainly because of moving out of the communities) was 5.9% (1378/23,407) among the never-smokers, 4.8% (372/7725) among the former smokers, and 5.7% (1008/17,545) among the current smokers.

Table 2 shows the hazard ratios and 95% CIs of mortality from aortic dissection or aneurysm according to smoking status. The multivariable hazard ratios

(95% CIs) of total aortic diseases for the high passive-smoking group as compared with the low passive-smoking group were 2.45 (1.02-5.88) out of home, 1.82 (0.84-3.96) at home, and 2.35 (1.09-5.09) out of or at home combined. We also analyzed the hazard ratios of aortic dissection and aortic aneurysm separately. The multivariable hazard ratio for the high passive-smoking group as compared with the low passive-smoking group was generally 1.8 to 3.5, although it was not statistically significant owing to the small number of cases.

The multivariable hazard ratios (95% CIs) of total aortic diseases for the current smokers as compared with the low passive-smoking group were 3.97 (2.14-7.39) for the out-of-home, 3.41 (1.84-6.32) for the at-home, and 4.09 (1.99-8.39) for the out-of- or at-home combined passive-smoking groups. The multivariable hazard ratios (95% CIs) for the current smokers as compared with the low out-of-home passive-smoking group were 3.39 (1.43-8.00) for aortic dissection and 4.75 (1.87-12.06) for aortic aneurysm. The corresponding multivariable hazard ratios for the current smokers as compared with the low at-home passive-smoking group were 3.03 (1.26-7.29) and 3.91 (1.62-9.44), and those for current smokers as compared with the low combined passive-smoking group were 3.62 (1.33- 9.83) and 4.58 (1.59-13.19).

Discussion

We observed an excess mortality from aortic dissection or aneurysm among passive smokers. To the best of our knowledge, this is the first epidemiologic study to show a positive association between passive smoking and aortic diseases. While many studies revealed active smoking as a major risk factor of aortic aneurysm,[2,3,13] few have focused on the prospective association between smoking and aortic dissection. The present study clearly showed that active smoking was strongly associated with mortality from aortic dissection, which strengthened the finding from a previous case-control study of Japanese showing that active smoking was associated with risk of aortic dissection: the odds ratio (95% confidence interval) = 3.48 (1.58-7.66).[14] Taken together, these findings indicate that passive smoking may be associated with not only aortic aneurysm but also aortic dissection.

The passive smoking-aortic diseases association was more evident for out-of-home than for at-home passive smokers. One reason for this difference could be higher exposure levels to passive smoke out of home, most likely in the workplace.[15] The concentrations of passive smoke could be higher in the workplace than at home because there are likely to be more smokers in the workplace. In addition, the times of exposure to passive smoke should be longer at work than at home because the average

exposure time of the high at-home passive-smoking group was 3.7 hours per day in the present study, and the average exposure time for workers in Japan between 1998 and 2009 was approximately 5 hours per day.[16] During that period, countermeasures against passive smoking in the workplace had not yet been put in place (that would happen in 2003, with the enactment of the Health Promotion Law). Besides, the difference between at-home and out-of-home exposures is compatible with the findings of a previous study on passive smoking and plasma fibrinogen concentrations among Japanese women: the mean fibrinogen concentrations were higher for those with out-of-home passive smoking than for those with at-home passive smoking.[17]

Compared with the above-mentioned previous meta-analysis (the summary odds ratio [95% CI] of coronary heart disease = 1.31 [1.21-1.41]),[5] the present results showed a higher hazard ratio: 2.45 (1.02-5.88), suggesting that the effect of passive smoking is stronger for aortic diseases than for coronary heart disease. The effect of active smoking is also stronger for aortic aneurysm than for coronary heart disease, as shown by a previous systematic review.[4] This finding suggests that smoking may impact on aortic diseases and coronary heart disease in different ways. Smoking induces atherosclerosis through lowering HDL-cholesterol levels and enhancing oxidation and inflammation, thereby fostering thrombotic cardiovascular events.[18] Aortic aneurysms

are thought to be a manifestation of atherosclerosis in general, but previous basic research and clinical studies have suggested that additional factors rather than atherosclerosis-related factors are probably involved in the development of aortic aneurysms.[2-4,13, 19-21] For example, elastin degradation in the vascular wall mediated by proteolytic systems is one of the additional factors.[3,4,19] Cigarette smoking has the potential to increase the expression of these proteolytic systems and attenuate the activity of their inhibitors.[3,19,22]

The limitations of the present study warrant discussion. First, the number of aortic disease cases was relatively small, although the present study has the largest epidemiologic cohort (involving 23,407 never-smokers) so far of studies examining the association between passive smoking and aortic diseases. Nevertheless, despite the limited number of cases, the associations were strong enough to be detected. Second, the information on passive smoking was obtained only at the baseline, so nondifferential changes in passive smoking status may have diluted the real association.

In conclusion, we found a strong association between passive smoking, especially that out of home, and mortality from aortic dissection or aneurysm. Our finding implies that the measures against passive smoking are important for the prevention of aortic diseases, as well as other cardiovascular diseases.

Conflict of interest

The authors declare that they do not have anything to disclose regarding conflicts of interest with respect to this manuscript.

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The entire list of JACC Study collaborators was presented previously[11].

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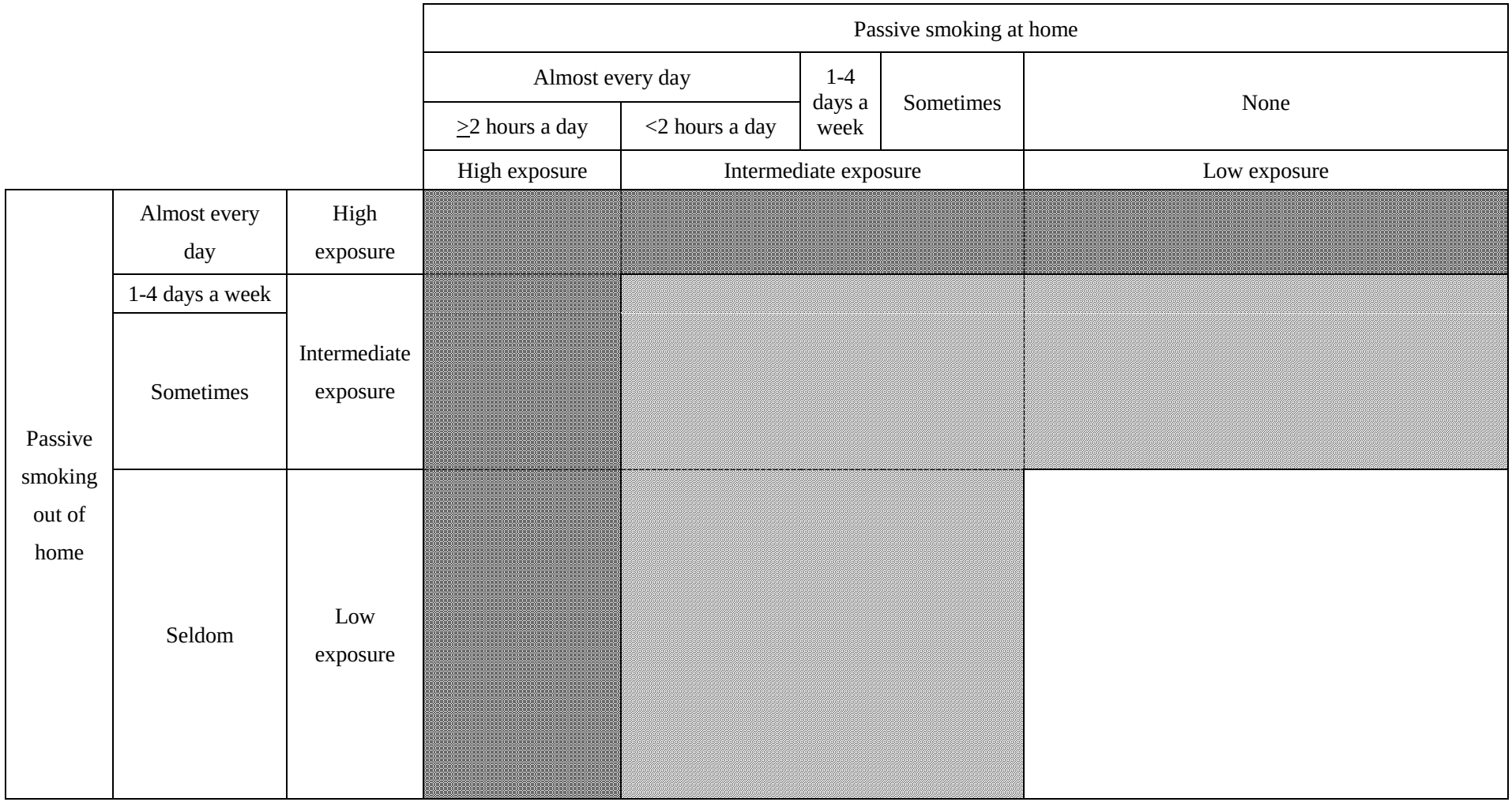
- No study has reported an association between passive smoking and risk of aortic dissection or aneurysm.
- This is the first epidemiologic study to show that passive smoking is associated with mortality from aortic diseases.
- Preventive measures against passive smoking would be effective to prevent aortic diseases.

Figure 1 Definitions of baseline passive smoking status.



The combination of passive smoking: High exposure, Intermediate exposure, Low exposure.

The vertical and horizontal lengths of responses to the questionnaire were proportional to the proportion of the responses.

Table 1

Sex- and age-adjusted mean values and proportions of cardiovascular risk factors and other characteristics according to smoking status

	Passive smoking among never-smokers					Former smokers		Current smokers	
	Low	Intermediate	*p* value	High	*p* value		*p* value		*p* value
Passive smoking out of home									
Number of study participants	12,936	7123		3348		7725		17,545	
Age, y	57.5	55.0	<0.001	50.7	<0.001	59.2	<0.001	55.6	<0.001
Men, %	9.6	20.7	<0.001	26.5	<0.001	92.6	<0.001	88.6	<0.001
Body mass index, kg/m^2	22.8	23.0	0.004	22.8	1.00	23.0	<0.001	22.5	<0.001
Systolic blood pressure, mmHg	131.8	131.1	0.04	130.7	0.008	131.7	1.00	131.8	1.00
Diastolic blood pressure, mmHg	79.2	79.0	0.35	78.7	0.07	79.0	0.73	78.5	<0.001
History of hypertension, %	18.2	18.6	0.84	18.4	0.99	24.2	<0.001	19.6	0.07
Medication use for hypertension, %	13.1	13.8	0.53	13.6	0.92	17.0	<0.001	14.1	0.22
History of diabetes mellitus, %	4.1	3.6	0.37	4.2	1.00	7.0	<0.001	5.5	<0.001
Medication use for diabetes mellitus, %	2.6	2.3	0.78	2.5	1.00	3.8	<0.001	3.2	0.10
Current drinkers, %	41.4	47.8	<0.001	52.0	<0.001	59.0	<0.001	59.5	<0.001
High perceived mental stress, %	18.5	21.6	<0.001	29.7	<0.001	24.4	<0.001	23.9	<0.001
Walking ≥30 min/day, %	69.7	71.5	0.05	68.3	0.37	67.1	0.01	70.0	0.98
Exercise ≥5 h/week, %	5.9	6.5	0.30	6.3	0.91	6.9	0.14	5.9	1.00
College or higher education, %	15.3	15.8	0.75	16.4	0.34	17.6	0.003	12.5	<0.001
Unemployed, %	70.8	65.1	<0.001	34.6	<0.001	62.3	<0.001	61.2	<0.001
Fresh fish intake, times/week	3.5	3.5	0.85	3.4	0.06	3.4	<0.001	3.3	<0.001

Table 1 continued.

Passive smoking at home									
Number of study participants	10,799	8215		4393		7725		17,545	
Age, y	56.2	55.2	<0.001	53.8	<0.001	59.6	<0.001	56.0	0.25
Men, %	22.7	11.5	<0.001	4.4	<0.001	93.0	<0.001	88.5	<0.001
Body mass index, kg/m^2	22.7	23.0	<0.001	23.0	<0.001	23.0	<0.001	22.5	<0.001
Systolic blood pressure, mmHg	131.2	131.5	0.43	131.8	0.13	131.7	0.29	131.8	0.08
Diastolic blood pressure, mmHg	78.9	79.2	0.46	79.3	0.19	79.0	0.98	78.5	0.13
History of hypertension, %	17.5	19.1	0.02	19.5	0.02	24.1	<0.001	19.5	0.004
Medication use for hypertension, %	13.2	13.9	0.47	13.3	1.00	17.0	<0.001	14.1	0.26
History of diabetes mellitus, %	4.2	3.6	0.24	3.8	0.72	7.0	<0.001	5.5	<0.001
Medication use for diabetes mellitus, %	2.8	2.1	0.05	2.1	0.15	3.8	0.003	3.2	0.30
Current drinkers, %	44.8	45.7	0.41	45.9	0.46	58.5	<0.001	59.0	<0.001
High perceived mental stress, %	21.4	20.4	0.34	23.5	0.03	24.1	0.003	23.5	0.009
Walking ≥30 min/day, %	68.3	71.6	<0.001	72.5	<0.001	66.9	0.27	69.8	0.12
Exercise ≥5 h/week, %	6.2	6.1	0.98	6.4	0.98	6.8	0.44	5.9	0.78
College or higher education, %	17.1	14.0	<0.001	14.2	<0.001	17.7	0.82	12.6	<0.001
Unemployed, %	60.8	65.6	<0.001	63.0	0.03	62.8	0.05	62.1	0.18
Fresh fish intake, times/week	3.4	3.6	<0.001	3.6	<0.001	3.3	0.72	3.3	0.30

Table 1 continued.

Combination of passive smoking									
Number of study participants	6863	9831		6713		7725		17,545	
Age, y	58.2	55.6	<0.001	52.6	<0.001	59.5	<0.001	55.9	<0.001
Men, %	15.1	16.0	0.23	14.7	0.90	92.9	<0.001	88.5	<0.001
Body mass index, kg/m^2	22.7	22.9	<0.001	22.9	0.003	23.0	<0.001	22.5	<0.001
Systolic blood pressure, mmHg	131.5	131.4	1.00	131.3	0.93	131.7	0.86	131.8	0.62
Diastolic blood pressure, mmHg	79.0	79.1	1.00	79.0	1.00	79.0	1.00	78.6	0.07
History of hypertension, %	17.5	18.4	0.38	19.1	0.08	24.2	<0.001	19.6	0.009
Medication use for hypertension, %	13.3	13.4	1.00	13.5	1.00	17.0	<0.001	14.1	0.52
History of diabetes mellitus, %	4.4	3.6	0.07	4.0	0.56	7.0	<0.001	5.5	0.02
Medication use for diabetes mellitus, %	2.9	2.3	0.11	2.3	0.21	3.8	0.03	3.2	0.68
Current drinkers, %	42.0	45.7	<0.001	48.1	<0.001	58.5	<0.001	59.0	<0.001
High perceived mental stress, %	18.9	20.3	0.11	25.5	<0.001	24.1	<0.001	23.5	<0.001
Walking ≥30 min/day, %	68.6	70.7	0.02	70.6	0.05	67.1	0.30	70.0	0.23
Exercise ≥5 h/week, %	6.2	6.1	1.00	6.4	0.93	6.8	0.42	5.9	0.88
College or higher education, %	16.5	15.3	0.13	15.3	0.16	17.5	0.39	12.4	<0.001
Unemployed, %	67.9	67.2	0.78	50.9	<0.001	63.3	<0.001	62.3	<0.001
Fresh fish intake, times/week	3.4	3.6	<0.001	3.5	0.15	3.4	0.53	3.3	0.19

p values for difference from the category of low passive smoking.

Table 2

Hazard ratios (95% CIs) of mortality from aortic dissection or aneurysm according to smoking status

	Passive smoking among never-smokers			Former smokers	Current smokers
	Low	Intermediate	High		
Passive smoking out of home					
Person-years	218,384	121,686	59,391	116,188	272,862
Total aortic diseases					
No. of events	22	12	7	20	80
Sex- and age-adjusted HR, 95% CI	Reference	1.25 (0.62-2.53)	2.50 (1.05-5.94)	1.53 (0.73-3.20)	3.67 (1.98-6.81)
Multivariable HR, 95% CI	Reference	1.24 (0.61-2.52)	2.45 (1.02-5.88)	1.58 (0.75-3.33)	3.97 (2.14-7.39)
Aortic dissection					
No. of events	14	8	4	8	32
Sex- and age-adjusted HR, 95% CI	Reference	1.27 (0.53-3.03)	1.82 (0.59-5.65)	1.50 (0.52-4.29)	3.12 (1.35-7.20)
Multivariable HR, 95% CI	Reference	1.31 (0.55-3.15)	1.78 (0.56-5.61)	1.66 (0.57-4.87)	3.39 (1.43-8.00)
Aortic aneurysm					
No. of events	8	4	3	12	48
Sex- and age-adjusted HR, 95% CI	Reference	1.15 (0.34-3.83)	3.56 (0.92-13.7)	1.61 (0.55-4.74)	4.39 (1.71-11.28)
Multivariable HR, 95% CI	Reference	1.10 (0.33-3.67)	3.45 (0.88-13.43)	1.58 (0.54-4.61)	4.75 (1.87-12.06)

Table 2 continued.

Passive smoking at home					
Person-years	183,619	141,628	74,213	116,188	272,862
Total aortic diseases					
No. of events	19	12	10	20	80
Sex- and age-adjusted HR, 95% CI	Reference	0.95 (0.46-1.95)	1.85 (0.85-4.01)	1.34 (0.64-2.80)	3.22 (1.74-5.96)
Multivariable HR, 95% CI	Reference	0.89 (0.43-1.83)	1.82 (0.84-3.96)	1.36 (0.65-2.85)	3.41 (1.84-6.32)
Aortic dissection					
No. of events	11	6	9	8	32
Sex- and age-adjusted HR, 95% CI	Reference	0.74 (0.27-2.01)	2.37 (0.97-5.77)	1.38 (0.47-4.03)	2.90 (1.23-6.83)
Multivariable HR, 95% CI	Reference	0.69 (0.25-1.87)	2.33 (0.95-5.70)	1.48 (0.50-4.39)	3.03 (1.26-7.29)
Aortic aneurysm					
No. of events	8	6	1	12	48
Sex- and age-adjusted HR, 95% CI	Reference	1.25 (0.43-3.61)	—	1.34 (0.48-3.75)	3.61 (1.48-8.83)
Multivariable HR, 95% CI	Reference	1.18 (0.41-3.43)	—	1.31 (0.47-3.64)	3.91 (1.62-9.44)

Table 2 continued.

Combination of passive smoking					
Person-years	115,088	168,642	115,730	116,188	272,862
Total aortic diseases					
No. of events	12	14	15	20	80
Sex- and age-adjusted HR, 95% CI	Reference	1.04 (0.48-2.26)	2.38 (1.10-5.13)	1.58 (0.70-3.60)	3.82 (1.86-7.83)
Multivariable HR, 95% CI	Reference	1.01 (0.47-2.20)	2.35 (1.09-5.09)	1.62 (0.71-3.70)	4.09 (1.99-8.39)
Aortic dissection					
No. of events	7	8	11	8	32
Sex- and age-adjusted HR, 95% CI	Reference	0.94 (0.34-2.59)	2.39 (0.92-6.26)	1.61 (0.50-5.18)	3.39 (1.27-9.03)
Multivariable HR, 95% CI	Reference	0.92 (0.33-2.55)	2.38 (0.90-6.25)	1.76 (0.54-5.77)	3.62 (1.33-9.83)
Aortic aneurysm					
No. of events	5	6	4	12	48
Sex- and age-adjusted HR, 95% CI	Reference	1.16 (0.35-3.81)	1.92 (0.51-7.22)	1.56 (0.48-5.09)	4.24 (1.46-12.31)
Multivariable HR, 95% CI	Reference	1.12 (0.34-3.67)	1.89 (0.50-7.17)	1.52 (0.47-4.95)	4.58 (1.59-13.19)

HR = hazard ratio; CI = confidence interval.

Multivariable HR: adjusted for sex, age, body mass index, history of hypertension, alcohol intake category, perceived mental stress, walking, age of completed education, job status, and region.