

Long-Term Exposure to Particulate Matter and Mortality from Cardiovascular Diseases in Japan: The Ibaraki Prefectural Health Study (IPHS)

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Aim: To examine the association between long-term exposure to suspended particulate matter (SPM) and cardiovascular mortality in Japan after controlling for known major confounding factors among a large middle and elderly cohort study in Ibaraki Prefecture, Japan.

Methods: We followed 91,808 residents (men 34%) who undertook a national health check-up at age 40–79 years for 17 years (1993–2010). Two different exposure indices were adopted: baseline SPM concentration (in the year 1990) and average SPM concentration for the first (average of 1990 and 1995) and the second half (average of 2005 to 2009) of the study period. Sex-specific adjusted risk ratios (RRs) for cardiovascular mortality were calculated using general mixed Poisson regression models after adjusting the age, BMI, history of diabetes mellitus and hypertension, creatinine, glutamic pyruvic transaminase, total cholesterol, high-density lipoprotein cholesterol, smoking, alcohol, and temperature. The variation between seven medical administration areas was also taken into account as a random effect.

Results: Baseline SPM concentration was associated with an increased risk of mortality from all cardiovascular diseases, coronary artery disease, and stroke. The adjusted RRs (95% confidence interval [CI]) per 10 $\mu\text{g}/\text{m}^3$ increase in SPM concentration for all cardiovascular mortality were 1.147 (1.014–1.300) for men and 1.097 (0.985–1.222) for women. The point estimate of RR was highest for non-hemorrhagic stroke in men (1.248 [0.991–1.571]), although CI overlapped the unity. The RRs seemed slightly lower in the second half than in the first half, though the CIs widened in the second half.

Conclusion: Our results suggest that long-term exposure to SPM is associated with an increased risk of all cardiovascular mortality for men in Ibaraki, Japan.

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Key words: Cardiovascular disease, Stroke, Cohort study, Particulate matter

Introduction

The Global Burden of Disease Study revealed that diseases caused by pollution were responsible for an estimated 9 million premature deaths worldwide in 2015, representing 16% of the total global mortality^{1,2}.

Of these deaths, 6.5 million were caused by air pollution, so continued measures to combat air pollution clearly need to be pursued vigorously.

Particulate matter (PM) is one of the most frequently studied forms of air pollution, and it is known to be linked to various diseases. The role of short-term

Methods

Study Population

Ibaraki Prefecture is located adjacent to the Tokyo Metropolitan Area; it covers more than 6,000 km² (representing 1.6% of Japan's total land area), about 65% of which is relatively flat and habitable, and it has a population of about 28 million people. The southern part of the prefecture is urban and within 1 hour's commuting distance of Tokyo: the residential areas are spread around rather than being concentrated in large conurbations. The central and northern parts are rural and predominantly agricultural. Thus, the mean annual PM concentrations in the prefecture are high in the south and low in the north.

The detailed protocol of the IPHS community-based prospective cohort study launched by the Ibaraki prefectural government and selection procedures have been published previously¹⁶⁻²². Briefly, our study population comprised 98,196 individuals (33,414 men and 64,782 women) aged 40–79 years who underwent health check-ups in Ibaraki Prefecture in 1993 and who were followed up until the end of 2010. These health check-ups were conducted by local municipalities in accordance with Japan's Health Service Law for the Aged.

Our final study population of 91,808 subjects excluded 5,458 individuals (2,211 men and 3,247 women) with a self-reported history of cardiovascular disease, and 930 individuals (192 men and 738 women) with incomplete information on variables required for statistical analysis. The study subject selection flow is shown in [Fig. 1](#). The protocol for this cohort study was approved by the Ibaraki Epidemiology Study Union Ethics Review Committee.

Exposure Assessment

The Ministry of the Environment and local governments have been operating ambient air monitoring stations around Japan since the 1970s. Under the Japanese Air Quality Standard, suspended particulate matter (SPM) is defined as particles that can pass through samplers that remove 100% of particles with an aerodynamic diameter of over 10 μm. Therefore, SPM, as monitored in Japan, is considered to consist of particles of less than 6.5–7 μm in aerodynamic diameter, with a 50% cut-off level. Exposure to SPM was measured by a nationwide background SPM con-

exposure to air pollution in cardiovascular disease has been widely studied since the 1990s^{3, 4}), and the high proportion of hospital admissions due to cardiovascular disease is also well documented⁵). In addition, studies carried out in Europe and the United States have established clear links between long-term exposure to PM and adverse effects on the cardiovascular system^{6, 7}). On the other hand, research results on the effects of long-term exposure to PM on mortality due to cardiovascular disease in Asia, including Japan, have been inconsistent⁸⁻¹¹). Profiles of cardiovascular death and risk factors differ between Asian and Western countries: Asia has greater mortality from stroke than from coronary heart disease, whereas the opposite is true in Western countries¹²). However, considering the fact that 60% of the world's population lives in Asia, more evidence is needed from the region about associations between PM and cardiovascular death in Asia.

In Japan, three studies have been conducted to assess the effects of long-term PM exposure on cardiovascular mortality, which provided inconclusive evidence. In fact, an inverse association between PM exposure and stroke mortality was observed: the incidence of and mortality from stroke were found to be high in rural areas of northern Japan, where PM concentrations are low, and low in urban areas of western Japan, where PM concentrations are high^{13, 14}). As is well known, stroke is responsible for more deaths in Japan than coronary heart disease¹⁵).

To address the issues raised in these previous studies, we decided to focus on a cohort study conducted within a single Japanese prefecture rather than on a nationwide study covering different regions. Accordingly, we selected the Ibaraki Prefectural Health Study (IPHS), a large cohort study conducted in Ibaraki Prefecture near Tokyo. With information on individual cardiovascular risk factors from this study, which was conducted in one prefecture, we assessed the effects of long-term exposure to PM on cardiovascular mortality.

Aim

This study aimed to examine the association between long-term exposure to PM and cardiovascular mortality in Japan, with fine adjustment for clinical status and comorbidity.

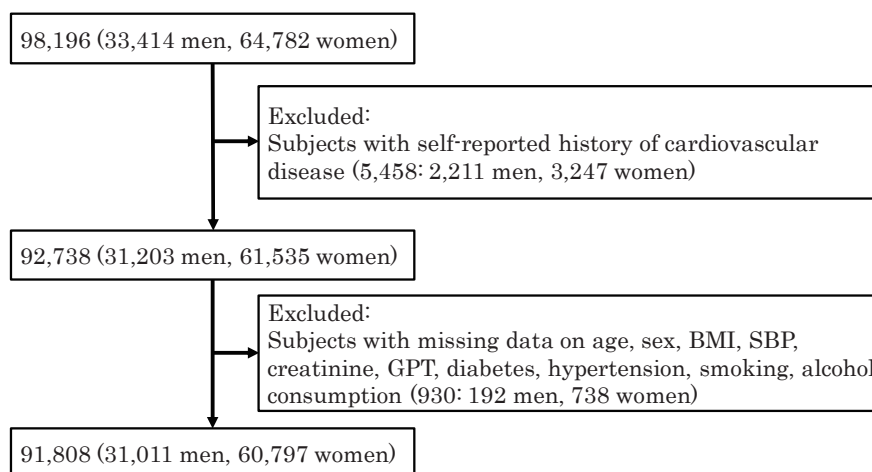


Fig. 1. Study subject selection flow

centration model, which interpolates the neighborhood (within the radius of 20 km) fixed monitoring data to a 1 x 1 km grid surface, using inverse distance weighting methods. For this study, the background SPM concentration model in 1990, 1995, 2000, 2005, and 2009 were used, and the concentrations in all grids within each municipality (average population 2,440 in a municipality; range 2–26 grids and 7 grids in a municipality on average) were averaged.

As an index of SPM exposure, we assigned the averaged SPM concentration in the municipality which the study subjects resided in at the time of the baseline of the IPHS. The SPM concentration in 1990 was used as a baseline exposure index. **Fig. 2** shows the averaged SPM concentrations in the municipalities of Ibaraki Prefecture in 1990, where a clear north–south gradient in SPM level was seen; whereas, there was no clear gradient in the standardized mortality ratio from both cerebrovascular and cardiovascular diseases. The IPHS cohort members reside in 38 (43%) of all the municipalities in Ibaraki Prefecture.

Follow-Up and Endpoints

The IPHS health check-up data were obtained from the Ibaraki Prefectural Health Plaza, along with information regarding subjects who had died or who had moved out of the municipalities. Data on causes of death are kept by the Ministry of Health, Labour and Welfare, which also codes the underlying causes of death for the National Vital Statistics record according to the International Classification of Diseases, 9th and 10th revisions (ICD-9 [1993–1994] and ICD-10 [1995–2008]). The underlying causes of death in our study cohort were obtained from the Ministry of Health, Labour and Welfare via the normal application procedure. Record matching between the resi-

dence certificates and the underlying causes of death was done by residential area, sex, date of birth, and date of death. We believe we ascertained all deaths that occurred in the cohort, except for subjects who died after they had moved away from their original community, in which case, they were excluded from the study. The proportion of subjects lost to follow-up was 4.61% over the study period. We considered all cardiovascular deaths (codes 401–459 in ICD-9 and codes I00–I99 in ICD-10), deaths from coronary artery disease (410–414 in ICD-9 and I20–I25 in ICD-10), deaths from non-hemorrhagic stroke (433,434,437.7A and B in ICD-9, I63 and I69.3 in ICD-10), and deaths from hemorrhagic stroke (431–432 in ICD-9, I60–I61 and I69.0–I69.1 in ICD-10).

Statistical Analysis

Multivariate adjusted risk ratios (RRs) for cardiovascular mortality were estimated using general mixed Poisson regression models adjusted for age (continuous, treated as a time-dependent covariate), BMI (categorized into 4 groups: <18.5, 18.5–24.9, 25–29.9, 30+), history of diabetes mellitus (defined as the presence of at least one of the following: self-reported history, use of antihyperglycemic drugs, fasting blood glucose of 126 mg/dL or over, and non-fasting blood glucose of 200 mg/dL or over), hypertension (defined as the presence of at least one of the following: use of antihypertensive drugs, systolic diastolic blood pressure of 140 mmHg or over, and diastolic blood pressure of 90 mmHg or over), serum creatinine (continuous), glutamic pyruvic transaminase (<30, 30–49.9, 50+), serum total cholesterol (<160, 160–199, 200–239, 240+), high-density lipoprotein cholesterol (<40/40+), smoking status (never smoked, past smoker, or current smoker), alcohol consumption (never

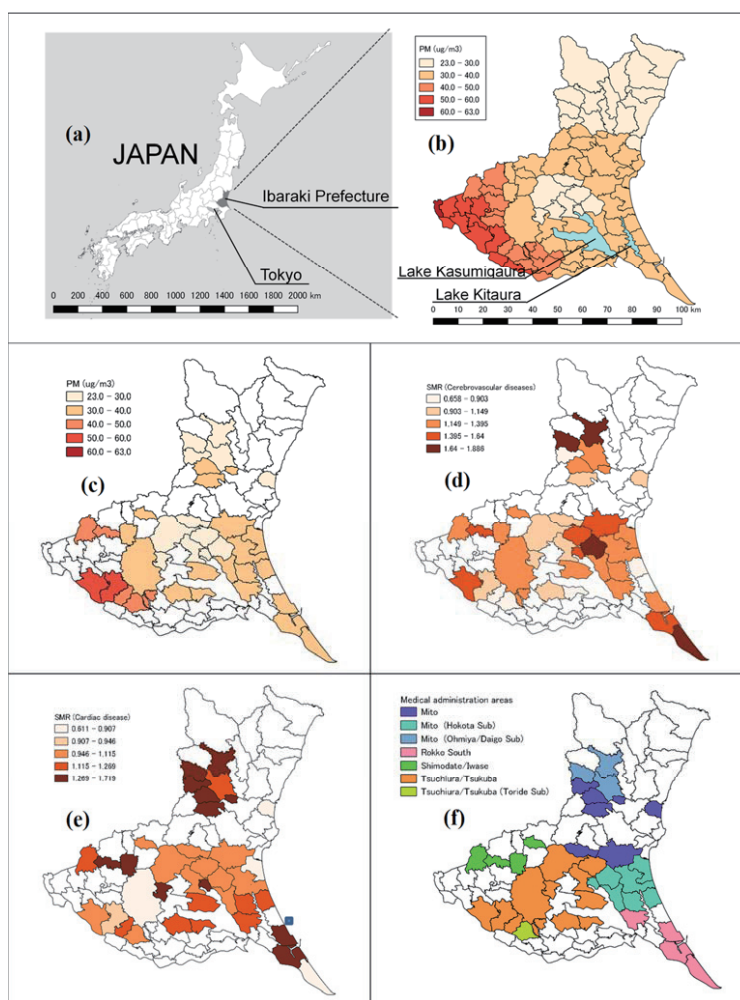


Fig. 2. Map of Japan (a), SPM concentrations in the various municipalities of Ibaraki Prefecture in 1990 (b), SPM concentrations in 38 municipalities where the participants resided at the time of baseline survey (c), Standardized Mortality Ratio from cerebrovascular diseases for women in 2003 (d), Standardized Mortality Ratio from cardiovascular diseases for women in 2003 (e) and medical administration areas (f)

The map (a, f) is based on GSI Tiles published by the Geospatial Information Authority of Japan. The map (b, c) is based on National Land Numerical Information published by the Ministry of Land, Infrastructure, Transport and Tourism of Japan. Standardized Mortality Ratio (d, e) is based on the Ibaraki prefecture health index 2003 (Ibaraki prefecture health science center), and only the map for women was shown.

drank, past drinker, or current drinker), annual mean temperature, and standard deviation for each municipality at baseline (1993). To adjust for differences in local medical facilities and socioeconomic status, we used a medical administration area (seven areas within the IPHS) as a random effect. Men and women were analyzed separately because there is a big difference by sex in cardiovascular mortality in Japan.

For the main analysis, the SPM concentration at baseline was used as the exposure index, and adjusted RRs and 95% confidence intervals (CIs) were estimated for each $10 \mu\text{g}/\text{m}^3$ increase in SPM concentration. In addition to RRs for all cardiovascular mortality, a sub-group of cardiovascular disease RRs was also

estimated: coronary artery disease, non-hemorrhagic stroke, and hemorrhagic stroke. Because SPM concentrations declined over the course of the study period while the death rate of the subjects increased, we carried out a sensitivity analysis by dividing the total cohort into the first (1993–2004) and the second halves (2005–2010) so that half of the total death events occurred in the first half, and the other half in the second half; each cohort was analyzed separately. For these analyses, the average annual SPM levels between 1990 and 1995 and between 2005 and 2009 were used as the exposure index for the first and the second half of the study period, respectively. In the second half cohort, only those subjects who had sur-

Table 1. Characteristics of the study population

	Total Mean (SD) or Number	Men Mean (SD) or Number	Women Mean (SD) or Number
Number	91808	31011	60797
Person-years of follow-up	1435304.80	466708.04	968596.76
Age	58.82 (10.40)	60.5 (10.19)	57.93 (10.40)
BMI	23.48 (3.14)	23.30 (2.97)	23.57 (3.22)
BMI category (%)			
< 18.5	4.20	4.42	4.08
18.5–25	66.40	68.13	65.51
25–30	26.68	25.77	27.15
30+	2.72	1.67	3.26
Smoking Status (%)			
Never smoked	69.96	22.16	94.34
Past smoker	9.40	26.37	0.74
Current smoker	20.64	51.47	4.92
Drinking habit (%)			
Never drank	69.35	28.74	90.07
Past drinker	1.94	5.39	0.18
Current drinker	28.71	65.87	9.75
Systolic blood pressure (mmHg)	133.21 (17.93)	136.29 (17.46)	131.63 (17.96)
Total cholesterol (mg/dL)	202.5 (35.22)	192.96 (33.92)	207.37 (34.87)
Serum creatinine (mg/dL)	0.87 (0.20)	1.00 (0.21)	0.80 (0.15)
Glutamic pyruvic transaminase (IU/L)	20.46 (15.70)	24.78 (19.26)	18.25 (12.99)
Diabetes mellitus (%)	6.02	8.74	4.63
Hypertension (%)	47.85	54.75	44.33
Per 100,000 person-years			
All cardiovascular mortality	345.43	494.74	273.49
Coronary artery mortality	86.95	136.49	63.08
Non-hemorrhagic stroke mortality	92.25	149.77	64.53
Hemorrhagic stroke mortality	61.45	72.21	56.27

Abbreviations: SD, standard deviation. BMI, body mass index.

vived to the end of 2004 were included in the analysis. We applied further adjustment by other air pollutants (SO₂, NO₂, and O_x in the baseline) one by one in addition to SPM. $P < 0.05$ was considered statistically significant.

Results

During the total 1,435,304.80 person-years (466,708.04 for men, and 968,596.76 for women) of follow-up (median follow-up period: 17 years), we documented 4,958 deaths from all cardiovascular diseases, 1,248 from coronary artery disease, 1,324 from non-hemorrhagic stroke, and 882 from hemorrhagic stroke. The mortality for each endpoint per 100,000 person-years is shown in [Table 1](#), along with baseline characteristics. The prevalence of current smoking was high among men (51%), and 48% of men and women had hypertension. As expected, mortality from stroke

(particularly non-hemorrhagic stroke) was higher than that from coronary artery disease.

The median SPM concentrations in the municipalities at baseline and in the first and the second halves of the study period were 32.7 $\mu\text{g}/\text{m}^3$ (range: 24.0–54.3), 31.7 (24.7–52.9), and 22.0 (16.9–31.0), respectively. [Fig. 3](#) shows the changes in SPM concentrations during this study period. The SPM concentrations in each municipality, particularly the highest concentrations, consistently decreased throughout the period.

As shown in [Table 2](#), long-term exposure to SPM in 1990 was associated with an increased risk of mortality from all cardiovascular diseases, coronary artery disease, and stroke. The multivariate-adjusted RRs (95% CI) per 10 $\mu\text{g}/\text{m}^3$ increase in SPM concentration were 1.147 (1.014–1.300) for men, and 1.097 (0.985–1.222) for women. The point estimate of the RR was highest for non-hemorrhagic stroke in men

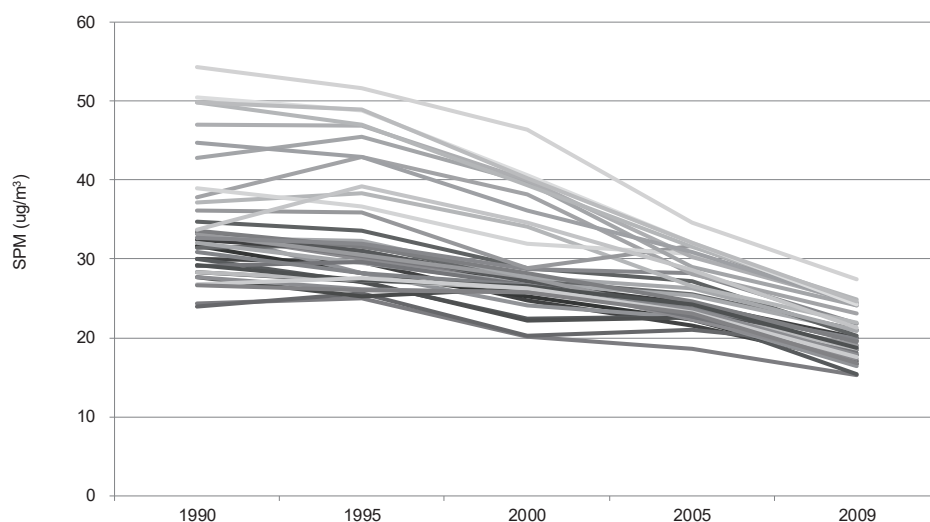


Fig. 3. Changes in SPM concentrations between 1990 and 2009 in 38 municipalities of Ibaraki Prefecture (The darker the color, the more northerly located in Ibaraki Prefecture the municipality is)

Table 2. Adjusted risk ratios of mortality per 10 $\mu\text{g}/\text{m}^3$ increase in SPM

		Age-adjusted Risk Ratio	95% CI	Multivariate-adjusted Risk Ratio [§]	95% CI
Men	All cardiovascular mortality	1.051	(0.961–1.149)	1.147	(1.014–1.300)
	Coronary artery mortality	1.115	(0.938–1.326)	1.213	(0.954–1.543)
	Non-hemorrhagic stroke mortality	1.094	(0.958–1.249)	1.248	(0.991–1.571)
	Hemorrhagic stroke mortality	1.091	(0.870–1.368)	1.14	(0.831–1.565)
Women	All cardiovascular mortality	1.074	(0.995–1.160)	1.097	(0.984–1.221)
	Coronary artery mortality	1.076	(0.915–1.266)	1.169	(0.933–1.466)
	Non-hemorrhagic stroke mortality	1.049	(0.933–1.180)	1.069	(0.852–1.342)
	Hemorrhagic stroke mortality	1.030	(0.865–1.227)	1.025	(0.799–1.316)

Abbreviations: CI, confidence interval

[§]The multivariate adjusted risk ratios for mortality per 10 $\mu\text{g}/\text{m}^3$ increase in SPM in 1990 were calculated using general mixed Poisson regression models. The adjusted variables were age, BMI, history of diabetes mellitus, hypertension, serum creatinine, GPT, serum total cholesterol, high density lipoprotein cholesterol, smoking status, alcohol consumption, and annual mean temperature and standard deviation for each city at baseline. We used a medical administration area (seven areas within the IPHS) as a random effect.

(1.248 [0.991–1.571]), but CI overlaps the unity (no effect). The RRs for the first and the second halves of the IPHS are shown in Fig. 4. The RRs were slightly lower in the second half than in the first half for four outcomes, though the CIs widened in the second half. Among the men, the adjusted RRs (95% CIs) per 10 $\mu\text{g}/\text{m}^3$ increase in SPM concentration for all cardiovascular mortality were 1.162 (1.004–1.346) in the first half, falling slightly to 1.082 (0.706–1.658) in the second half, which is not statistically significant. Among the women, the corresponding figures were 1.106 (0.974–1.256) and 1.056 (0.741–1.505) for the first and second halves, respectively. Further adjustment for SO_2 , NO_2 , and Ox did not change the

results substantially for either men or women (Supplementary Fig. 1 and 2).

Discussion

This is the first study to demonstrate an association between long-term exposure to SPM and increased risk of cardiovascular mortality in Japan, specifically for men, after adjusting for major individual cardiovascular risk factors. The study also suggests a possible association between SPM exposure and stroke, particularly non-hemorrhagic stroke, although it did not reach statistical significance.

The American Heart Association (AHA) con-

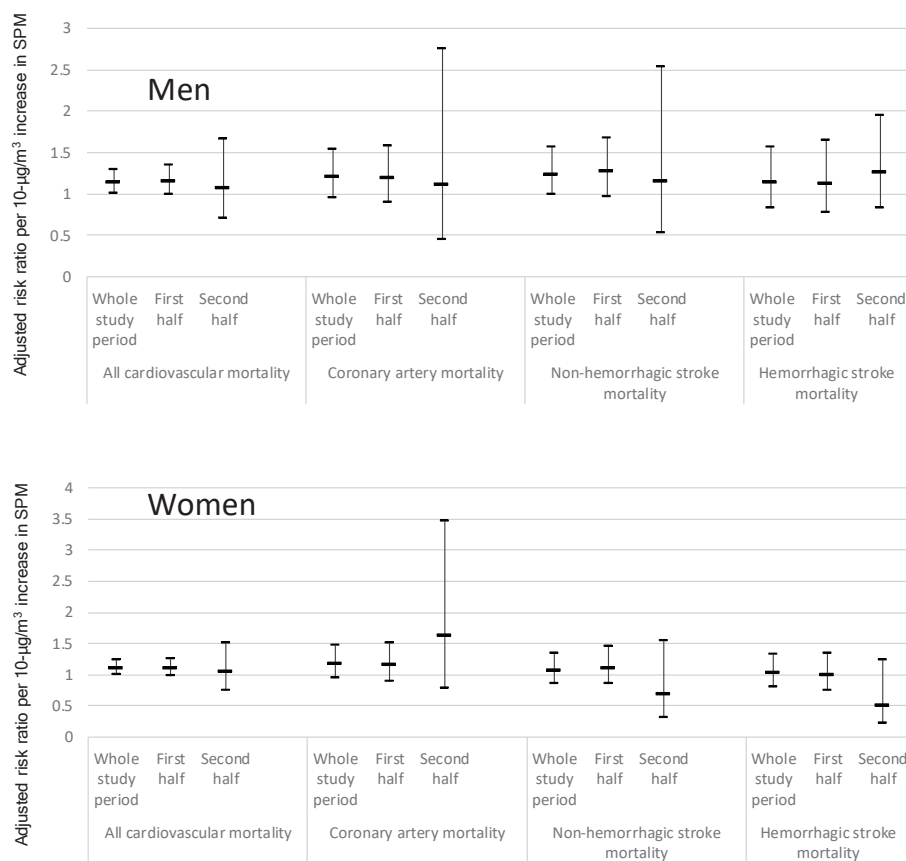


Fig. 4. Adjusted risk ratios per 10 µg/m³ increase in SPM for the whole study period and for the first and second halves by sex

cluded in its Scientific Statement of 2010 that long-term exposure to PM air pollution contributes to cardiovascular mortality^{6, 23}, and a number of epidemiological studies have shown that PM is associated with cardiovascular mortality in North America and Europe. However, evidence from Asia was inconsistent⁸⁻¹⁰. Su *et al.* pointed out that reports from Asia accounted for less than 10% of the 426 references in the AHA Scientific Statement of 2010²⁴, even though south and east Asia contributed 59% of the 4.2 million global deaths attributable to PM_{2.5} in 2015²⁵. The Asian region has the largest population in the world, and it also has the largest number of patients with cardiovascular disease. This number is increasing^{26, 27}; therefore, more evidence from Asian populations is clearly required.

Three precedent studies examined the association between long-term exposure to PM and cardiovascular mortality in Japan. The first, a 3-prefecture study, found higher cardiovascular mortality in less polluted areas than in more heavily polluted areas, but the study provided no information on such important covariates as blood pressure and cholesterol²⁸. The

second, the JPHC study, showed that cases of myocardial infarction increased in proportion to PM concentrations, but it also found an inverse association between PM exposure and stroke mortality¹⁴. In the third study, the NIPPON DATA80 Study, a tendency for all cardiovascular mortality and stroke mortality to decrease as PM concentrations increased was found¹³. The discrepancies between these results and those of the United States and European studies can at least partially be explained by the higher mortality from stroke in the northern part of Japan and by the low PM levels in this area as compared with other areas²⁹.

In the current study, by contrast, we used data from a population-based cohort study carried out in a single prefecture (namely, Ibaraki), and we obtained results that were, for the first time, consistent with those of studies from Western countries. Ibaraki Prefecture provided an adequate range of PM levels, and the residents' dietary habits, including salt intake, were deemed relatively uniform.

The adjusted RRs in our study for cardiovascular mortality per 10 µg/m³ increase in SPM concentration were 1.147 for men and 1.094 for women. This

was in line with the 10.6% increase in mortality per $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ levels cited in a review by Hoak *et al.*, though the direct comparison is difficult because SPM was used as the exposure index in our study. The same review also reported that the summary estimate for PM_{10} was smaller than that for $\text{PM}_{2.5}$, but that there was significant heterogeneity for the estimate for PM_{10} ³⁰). The consistency of our results from Asia, where the profiles of cardiovascular risk factors differ from those in Western countries, with those of the United States and European studies strengthens the case for a causal relationship between PM exposure and cardiovascular death.

Generally, point estimates of RR in the second half of our study seemed slightly lower than those in the first half. Although SPM levels declined throughout the study period, the relative SPM levels in each study area did not change substantially during the study period (Fig. 3). If the largest improvements in cardiovascular health due to advances in medical care and prevention programs for cardiovascular diseases were in the municipalities with higher SPM levels, this phenomenon could be explained. In Ibaraki Prefecture, the municipalities with higher SPM levels were more southerly located, more urban, and closer to Tokyo. It is unlikely that differences in medical resources between the north and the south of the prefecture could account for differences in the association between SPM levels and cardiovascular death because the public health insurance system and health check-up system makes healthcare fairly uniform across the whole of Japan. We propose, rather, that because the subjects in the second half were more resilient (having survived the first half), they were perhaps less susceptible to the effects of SPM. In the extended follow-up of the Harvard Six Cities Study, the proportional hazards rate ratio for a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ was comparable in both the first and the second periods. However, we should note that the CIs for RR estimates widened in the second half. A careful interpretation of these results is necessary.

The main strength of the present study was that individual cardiovascular risk factors, including smoking, blood pressure, and lipid profiles, were directly controlled: in Japan, annual medical examinations are carried out and regulated by law, which enables us to obtain precise data collected and quantified by uniform techniques. Another strength was the high overall follow-up rate (loss to follow-up was only 4.61%), with little difference between the northern part of the prefecture (4.54%), the central part (4.67%), and the southern part (5.03%). Moreover, it may be an advantage of this study that we were able to examine hemorrhagic and non-hemorrhagic stroke separately. Such

investigations are few³¹).

However, there were also several limitations. First, because we relied on interpolation data, we used the mean SPM concentration in each municipality as the exposure level of all subjects in that municipality rather than measuring individual exposure levels. Although many previous studies have used similar methods, this might have led to a bias towards the null. Second, determining appropriate exposure time windows was difficult, as in previous studies. Although some researchers have suggested that exposure over a few years is a long enough window lead to observable cardiovascular effects³²), no definite time frame has been established. In this study, we used two different exposure indexes: the 1990 baseline concentration and average concentration for the first half of the study period (1990–1995), and the average concentration for the second half (2005–2009). If an updated SPM is better than the baseline or average SPM as the exposure index, we should apply a model that includes SPM concentration as a time-dependent variable. However, we had similar point estimates of RR by this model (data not shown). The issue of the appropriate time window needs further discussion. Third, the only information we had on covariates, such as smoking status, BMI, and blood pressure, were those collected at baseline. Fourth, as we focused on the homogeneous nutrition intake within the cohort, our cohort is from a single prefecture; thus, external validity is low. Last, we did not have information on the individual-level socioeconomic status in this cohort.

Conclusion

After adjusting for individual risk factors, we showed that long-term exposure to SPM is associated with an increased risk of all cardiovascular mortality for men in the Ibaraki prefecture of Japan.

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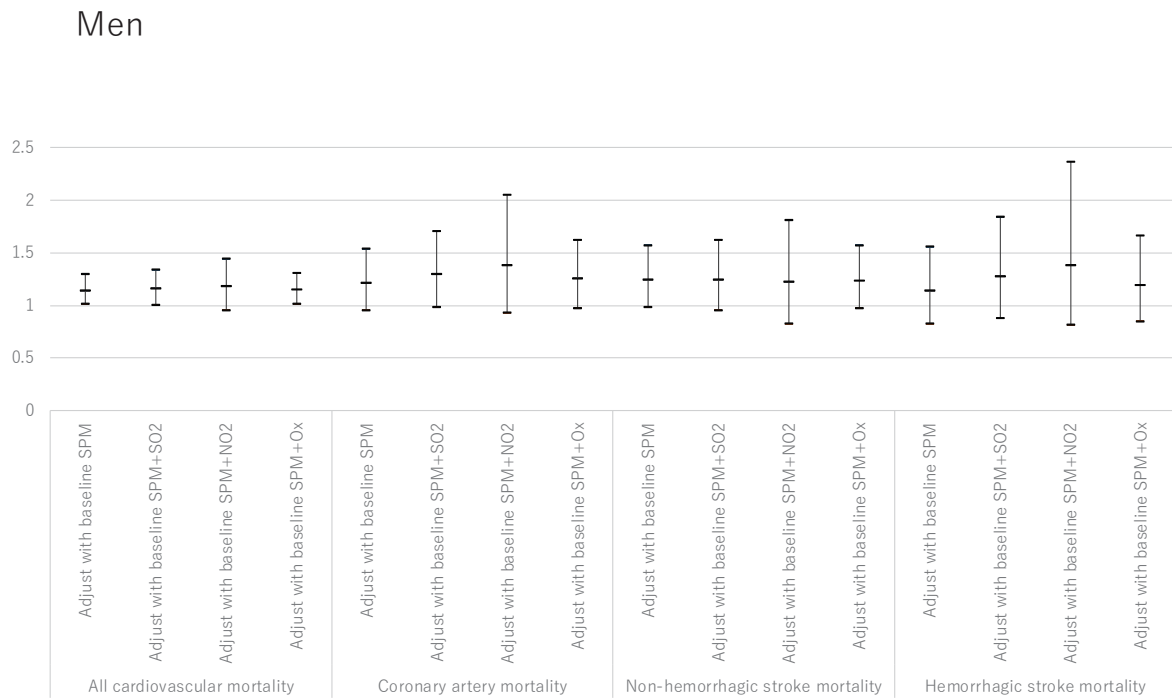
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All authors declare that there is no conflict of interest.

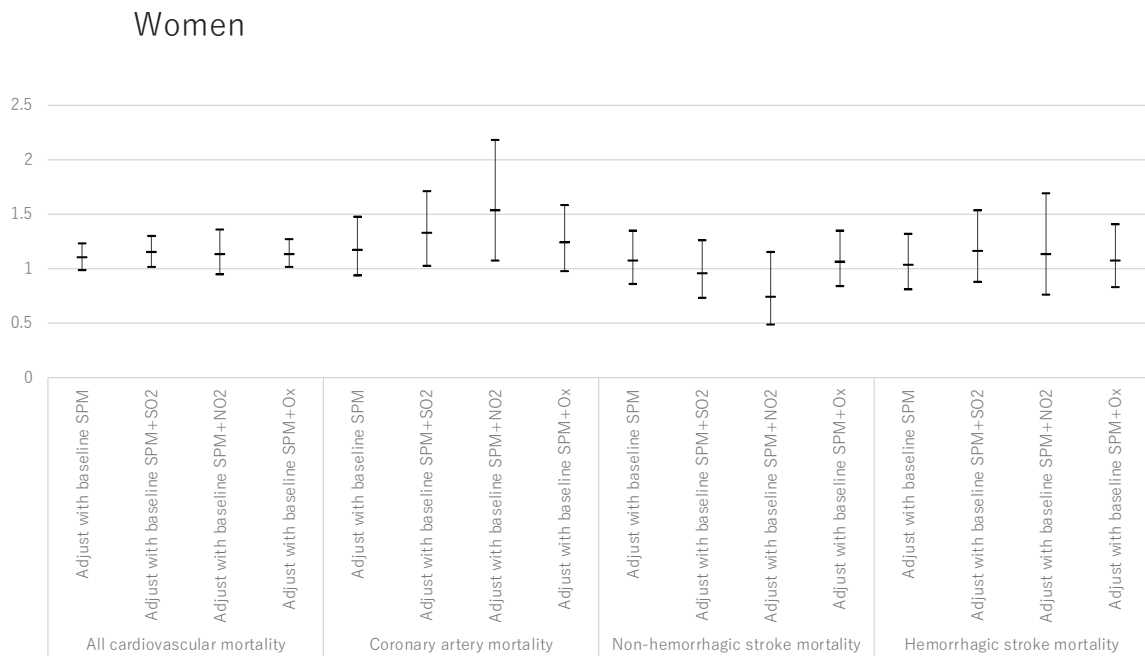
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Supplementary Fig. 1. Risk ratios per 10 $\mu\text{g}/\text{m}^3$ increase in SPM further adjusted for SO_2 , NO_2 , and Ox (men)



Supplementary Fig. 2. Risk ratios per 10 $\mu\text{g}/\text{m}^3$ increase in SPM further adjusted for SO_2 , NO_2 , and Ox (women)