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RESEARCH ARTICLE

Short-term associations of ambient air pollution with hospital admissions for ischemic stroke in 97 Japanese cities

Kohei Hasegawa[1] · **Teruomi Tsukahara**[1,2] · **Tetsuo Nomiyama**[1,2]

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Abstract

The short-term association between ambient air pollution and hospital admissions for ischemic stroke is not fully understood. We examined the association between four regularly measured major ambient air pollutants, i.e., sulfur dioxide (SO_2), nitrogen dioxide (NO_2), photochemical oxidants (O_x), and particulate matter with aerodynamic diameters ≤ 2.5 μm ($PM_{2.5}$), and hospital admissions for ischemic stroke by analyzing 3 years of nationwide claims data from 97 cities in Japan. We first estimated city-specific results by using generalized additive models with a quasi-Poisson regression, and we obtained the national average by combining city-specific results with the use of random-effect models. We identified a total of 335,248 hospital admissions for ischemic stroke during the 3-year period. Our analysis results demonstrated that interquartile range increases in the following four ambient air pollutants were significantly associated with hospital admissions for ischemic stroke on the same day: SO_2 (1.05 ppb), 1.05% (95% CI: 0.59–1.50%); NO_2 (6.40 ppb), 1.10% (95% CI: 0.61–1.59%); O_x (18.32 ppb), 1.43% (95% CI: 0.81–2.06%); and $PM_{2.5}$ (7.86 μg/m^3), 0.90% (95% CI: 0.35–1.45%). When the data were stratified by the hospital admittees' medication use, we observed stronger associations with SO_2, NO_2, and $PM_{2.5}$ among the patients who were taking antihypertensive drugs and weaker associations with SO_2, NO_2, and O_x among those taking antiplatelet drugs. Short-term exposure to ambient air pollution was associated with increased hospital admissions for ischemic stroke, and medication use and season may modify the association.

Keywords Ambient air pollution · Short-term association · Ischemic stroke · Hospital admission · Morbidity

Introduction

Stroke is a global public health concern, accounting for 5.5 million deaths in 2016 (Naghavi et al. 2017). In Japan, the age-adjusted mortality rate for stroke has decreased rapidly over the past decades but is still one of the leading causes of death (Ueshima 2007; WHO Global Health Observatory 2020). Epidemiological studies have suggested that ambient air pollution is associated with ischemic stroke (Verhoeven et al. 2021), which is the predominant stroke subtype. Several mechanisms are suspected to underlie this association, including inflammation, oxidative stress, lipid modification, and autonomic dysfunction (Lee et al. 2018). However, the existing epidemiological studies often used mortality as an outcome (Hong et al. 2002; Zanobetti and Schwartz 2009; Chen et al. 2017; Yorifuji et al. 2011; Michikawa et al. 2019; Shah et al. 2015; Niu et al. 2021). Hospital admission data are expected to be more sensitive and to capture the broader burden of air pollution, but most of the studies that used hospital admission data were based on a single city or region (Chan et al. 2006; Villeneuve et al. 2012; Collart et al. 2018; Montresor-López et al. 2016; Matsuo et al. 2016; Huang et al. 2017; Chen et al. 2019; Qi et al. 2020), which are susceptible to publication bias (Anderson et al. 2005). Several multi-city studies have been conducted, but most of these included a small number of cities (~ 10 cities) (Le Tertre 2002; Wellenius et al. 2005; Barnett et al. 2006; Larrieu et al. 2007; O'Donnell et al. 2011). The number of multi-city studies with large sample sizes is increasing

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✉ Kohei Hasegawa
koheih@shinshu-u.ac.jp

[1] Department of Preventive Medicine and Public Health, School of Medicine, Shinshu University, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan

[2] Department of Occupational Medicine, School of Medicine, Shinshu University, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan

(Tian et al. 2018; Gu et al. 2020; Stafoggia et al. 2020) but remains limited.

Moreover, the identification of subgroups that are especially susceptible to environmental pollutants is crucial for revealing underlying mechanisms and subgroups that should avoid exposure. Several studies suggested that patient characteristics may modify the association between ambient air pollution and ischemic stroke (O'Donnell et al. 2011; Villeneuve et al. 2012; Ho et al. 2018; Qi et al. 2020), but their results are unclear and based on small sample sizes. Large-scale studies with high statistical power are needed to clarify the association between air pollution and ischemic stroke.

We thus conducted the present study to examine the association between short-term exposure to ambient air pollutants and daily hospital admissions for ischemic stroke on a national scale in Japan. We used data from a nationwide claims database, which allowed us to include 97 cities across Japan. By using a large sample size, we examined modifications by patient characteristics that often require high statistical power.

Materials and methods

Study area and period

This study included 97 largest cities in Japan (Suppl. Fig. S1). All of the cities had a total population ≥ 200,000, and the cities included 50.4% of the national population as of the 2015 national census (Statistics Bureau, Ministry of Internal Affairs and Communications 2021). The study period was from 1 April 2016 to 31 March 2019 in all of the included cities.

Hospital admission data

Japan achieved universal health insurance coverage in 1961, and most people now receive medical treatments under the system. Almost all of the health insurance claims issued under the system are collected and stored in a national claims database called the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), which the Ministry of Health, Labour and Welfare of Japan (MHLW) manages. The MHLW provides researchers anonymized data from the database on request, and several studies have been conducted using the data from the database (Ishimaru et al. 2018; Izumi et al. 2018; Okumura et al. 2019).

We applied to the MHLW and obtained anonymized data from the NDB. The provided data consists of clinical information including anonymized personal identifiers, age groups, sex, date of admission, diagnosis codes linked with the 10th edition of the International Classification of Disease (ICD-10), codes for procedures and prescriptions, and the city of the hospital that issued the claim. To prevent the identification of individual patients, the MHLW provided only the city of the hospital and did not provide the names of the hospitals. The MHLW also provided only anonymized personal identifiers, called identifier (ID)1 (generated from the date of birth, sex, and the ID number of an insurer) and ID2 (generated from the date of birth, sex, and name) instead of individual numbers. We used the two anonymized IDs; if one or both IDs matched, we regarded the data as belonging to the same patient.

From the provided data, we identified individuals who were hospitalized with a primary diagnosis of ischemic stroke using ICD-10 code I63. We used the MHLW's algorithm to decide the primary diagnoses (Ministry of Health, Labour and Welfare 2015; Okumura et al. 2019). As rehospitalization within a few days was regarded as a single episode of hospitalization and only the date for the first admission was available (Hayashida et al. 2021), we included only the first admission for such rehospitalization admissions. To further exclude recurrent or re-hospitalizations for ischemic stroke, we excluded the patients with outpatient or inpatient claims with an ischemic stroke disease code within 36 months before their current admission. We also excluded both patients without records of procedure codes for brain computed tomography (CT) or magnetic resonance imaging (MRI) after their hospital admission (in order to reduce diagnostic error) and the patients aged < 20 old because the number of these patients was too few.

Supplementary Figure S2 is the patient selection flow chart. For each patient, we examined the medication use of antihypertensive drugs, oral hypoglycemic drugs or insulin, lipid-modifying drugs, antiplatelet drugs, and anticoagulant drugs by using their pharmacy claims data in the 3 months prior to their admittance to the hospital (Fukai et al. 2020). Supplementary Table S1 shows the list of Anatomical Therapeutic Chemical codes for each medication.

We used the alternate definition of hospital admission for ischemic stroke as a sensitivity analysis. We limited the analyses to patients who were emergently hospitalized to a diagnosis procedure combination (DPC) hospital, which are top-ranked in Japan's medical system, with DPC claims (Ando et al. 2018). We used the diagnosis codes recorded in the greatest-resource condition, trigger-for-hospitalization condition, or main condition, and we included patients with ischemic stroke (ICD-10 codes: I63) in any of the three conditions (Ando et al. 2018). As in the main analysis, we further excluded patients with outpatient or inpatient claims with an ischemic stroke disease code within 36 months before their admission, patients without records of brain CT or MRI after their hospital admission, and patients aged < 20 years.

Ambient air pollution and meteorological data

We obtained the hourly ambient air measurements of sulfur dioxide (SO_2), nitrogen dioxide (NO_2), photochemical oxidants (O_x), and particulate matter with an aerodynamic diameter of ≤ 2.5 μm ($PM_{2.5}$) for each of the 97 cities from Japan's National Institute for Environmental Studies. As there are no routine measurements for ozone (O_3) in Japan, we used O_x as a proxy for O_3 as in earlier studies (Bae et al. 2015; Vicedo-Cabrera et al. 2020; Ito et al. 2021). All of the included cities had more than one monitoring station for each included ambient air pollutant. These monitoring stations were located at sites that reflect the ambient exposure of the residents (Ministry of the Environment 2010). We calculated the daily mean concentrations for SO_2, NO_2, and $PM_{2.5}$ and the daily maximum 8-h mean concentrations for O_x from the hourly measurements. We conducted the calculations only if > 18 hourly measurements were available; otherwise, the data were considered missing. We averaged across monitors for the cities with two or more monitoring stations. Data on ambient SO_2, NO_2, O_x, and $PM_{2.5}$ were missing on 0.35%, 0.49%, 0.20%, and 0.84% of the days. We excluded these days from the analysis.

We also obtained daily mean ambient temperature and relative humidity data from the Japan Meteorological Agency (JMA). For cities without measurements for temperature ($n = 25$) or relative humidity ($n = 46$), we used the data measured at the nearest monitor in the same prefecture. Data on ambient temperature and relative humidity were missing on 0.02% and 0.12% of the days. We also excluded these days from the analyses.

Statistical analyses

We used a two-stage approach to examine the associations between ambient air pollution and hospital admissions for ischemic stroke. In the first stage, we built city-specific models using generalized additive models with quasi-Poisson regression for the hospital admissions. In the second stage, we used a random-effects meta-analysis with the restricted maximum likelihood estimation method to obtain the national average estimates from the first stage. We used the I^2 statistics to examine heterogeneity between cities.

We included the following covariates based on previous studies: (1) a natural cubic smooth function of calendar time with seven degrees of freedom (*df*) per year for long-term trends (Dominici et al. 2006; Tian et al. 2018); (2) indicator variables for the days of the week and public holidays (Tian et al. 2018; Gu et al. 2020), and (3) a natural spline function of the 3-day moving average temperature (six *df*) and relative humidity (three *df*) to adjust for weather conditions (Dominici et al. 2006; Chen et al. 2017).

The final model is below:

$$\ln\left[E\left(\mathrm{HA}_t\right)\right] = \alpha + f(X_t) + ns(\text{calendar time}, df = 7 \text{ per year} \times 3 \text{ years}) + ns\left(\text{temperature}_t, df = 6\right) + ns\left(\text{relative humidity}_t, df = 3\right) + \mathrm{DOW}_t + \text{holiday}_t$$

where $E(HA_t)$ is the expected number of hospital admissions for ischemic stroke on day t; α is the intercept; X_t is the air pollutant concentrations on day t; f is a function defining the exposure–response relationship; $ns(.)$ is the natural cubic spline function; time is the calendar time; DOW_t is a categorical variable for the day of the week on day t; holiday_t is an indicator variable of public holidays on day t; temperature_t is the 3-day moving average temperature on day t; relative humidity_t is the 3-day moving average relative humidity on day t.

We used single-pollutant models that contained one air pollutant at a time as the main models. We examined the association with the air pollutant concentrations of the same day (lag 0) throughout this study based on earlier studies (Shah et al. 2015; Tian et al. 2018). We also examined the air pollutant concentrations of the prior day (lag 1) and 2 days ago (lag 2) to explore temporal associations. The function f for the main models was defined in the following equation:

$$f\left(X_t\right) = \beta_p x_{p,t-l}$$

where $x_{p,t-l}$ is a concentration of an air pollutant, $p = SO_2$, NO_2, O_x, or $PM_{2.5}$, on day t, with lagged day $l = 0, 1, 2$; and β_p is the parameter to estimate.

We further performed multi-pollutant model analyses to examine the stability of the estimated associations and to differentiate the role of each air pollutant by including air pollutants that were significant in the single-pollutant model. The function f for multi-pollutant models was defined in the following equation:

$$f\left(X_t\right) = \beta_p x_{p,t} + \beta_q x_{q,t} + \ldots$$

We additionally estimated the exposure–response curve to get the overall shape of the associations for each pollutant (Samoli et al. 2005; Chen et al. 2012). From an explanatory graphical analysis, we used cubic spline functions with knots at 0.6 and 1.5 ppb for SO_2, 7.0 and 14.0 ppb for NO_2, 30.0 and 50.0 ppb for O_x, and 7.5 and 15.0 μg/m^3 for $PM_{2.5}$. These values are almost the 25th and 75th percent quantiles of the distributions for many of the included cities. We estimated five regression coefficients of the cubic spline functions and the corresponding variance–covariance matrix in each city and obtained the national average by random-effect models. We restricted this analysis to days with concentrations above the 0.5th and below the 99.5th quantile because extreme values could overly impact the whole exposure–response

curves. The function *f* for the exposure–response curve was defined in the following equation (Samoli et al. 2005):

$$f(X_t) = \sum_{j=0}^{3} \beta_{0j} \, (x_{p,t})^j + \sum_{i=1}^{2} \beta_{i3} \, (x_{p,t} - x_{p,i})_+^3$$

where $x_{p,i}$ is the place of the *i*th knot for the air pollutant, *p*; and $()_+$ is a notation representing a constant function of 0 for negative inputs and an identity function for non-negative inputs.

We performed stratification analyses by age group (20–64, 65–74, and ≥ 75 years), sex, medication use (i.e., antihypertensive drugs, oral hypoglycemic drugs or insulin, lipid-modifying drugs, antiplatelet drugs, and anticoagulant drugs), region (East and West Japan), and season (warm and cool season). We divided the cities into those in East Japan and West Japan based on the definition by the JMA (The Japan Meteorological Agency 2021) with the modification of incorporating North Japan into East Japan. We excluded the city of Naha from the stratification analysis by region, as it is located on a remote island (Suppl. Fig. S1). We defined the warm season as April–September and the cold season as October–March. The statistical significance of the differences in the estimates between groups was tested by calculating the 95% confidence interval (CI) as follows:

$$\left(\widehat{Q}_1 - \widehat{Q}_2\right) \pm 1.96\sqrt{\widehat{SE}_1 + \widehat{SE}_2}$$

where $\widehat{Q}_1$ and $\widehat{Q}_2$ are effect estimates for each group, and $\widehat{SE}_1$ and $\widehat{SE}_2$ are their respective standard errors (Zeka et al. 2006). We performed the following sensitivity analyses: (1) using alternative *df* values for calendar time (5–9 per year), temperature (3–7), and relative humidity (2–6), and (2) using the alternate definition for hospital admissions for ischemic stroke.

We performed cross-sectional dependency tests to examine the cross-sectional interdependence between included cities. We used Pesaran's *CD* test (Pesaran 2021) defined by the following equation:

$$CD = \sqrt{\frac{2T}{N(N-1)}}\left(\sum_{i=1}^{N-1}\sum_{j=i+1}^{N} \widehat{\rho}_{ij}\right)$$

where *N* is the number of cities; *T* is the number of days during the study period; and $\widehat{\rho}_{ij}$ is the correlation among response residuals between city *i* and city *j*. We present the estimated effects and their 95% CIs as the percent change (PC) per one interquartile range (IQR) range increase in air pollutants. We used the mean of the IQRs of the 97 cities: 1.05 ppb for SO_2, 6.40 ppb for NO_2, 18.32 ppb for O_x, and 7.86 μg/m^3 for $PM_{2.5}$. Probability (*p*)-values < 0.05 were considered significant. We used R (ver. 4.1.1) for the statistical analyses and used the "metafor" package to conduct the meta-analysis (Viechtbauer 2010). We also used the "mixmeta" package to estimate the exposure–response curves (Sera et al. 2019).

Results

Descriptive analysis

A total of 335,248 hospital admissions in the 97 Japanese cities during the period from 1 April 2016 to 31 March 2019 were analyzed. Table 1 summarizes the demographic characteristics of the included patients, and Table 2 provides the summary statistics of ambient air pollutants and meteorological conditions in the 97 Japanese cities during the study period. The mean of the annual means of ambient air pollutants in each city was 1.6 ppb for SO_2, 10.25 ppb for NO_2, 41.98 ppb for O_x, and 11.65 μg/m^3 for $PM_{2.5}$. Supplementary Table S2 lists Pearson's correlation coefficients between ambient air pollutants and meteorological conditions. The concentrations of ambient air pollutants were positively correlated, except for the correlation between NO_2 and O_x.

Regression analysis

The national average estimates of the associations between ambient air pollutant levels and hospital admissions for ischemic stroke are given in Table 3. We observed small between-city heterogeneity for all four of the ambient air pollutants and lag structure combinations, where the I^2 statistic ranged from 0.0 to 18.55%. The analysis results demonstrated that IQR increases in the concentrations of SO_2, NO_2, O_x, and $PM_{2.5}$ on the same day were associated with

Table 1 Demographic characteristics of hospital admissions for ischemic stroke in 97 cities in Japan, April 2016–March 2019

Variable	*n*	%
Overall	335,248	100.00
Age, years:		
20–64	57,130	17.04
65–74	81,744	24.38
≥ 75	196,374	58.58
Male	188,792	56.31
Female	146,456	43.69
Medication use:		
Antihypertensive drugs	157,884	47.09
Oral hypoglycemic drugs or insulin	48,803	14.56
Lipid-modifying drugs	74,366	22.18
Antiplatelet drugs	84,498	25.20
Anticoagulant drugs	29,336	8.75

Table 2 Summary statistics for annual mean air pollutant concentration and meteorological conditions in 97 cities in Japan, April 2016–March 2019

Variable	Mean	SD	Min	Percentile			Max
				25th	50th	75th	
Air pollutant:							
SO_2, ppb	1.60	1.07	0.20	0.82	1.30	1.95	4.88
NO_2, ppb	10.25	3.46	2.43	7.26	10.15	13.08	18.53
O_x, ppb	41.98	2.70	33.94	40.81	42.46	43.79	47.87
$PM_{2.5}$, μg/m^3	11.65	1.92	7.32	10.30	11.78	12.93	15.45
Meteorological conditions:							
Temperature, C°	15.44	2.45	6.53	14.92	15.98	16.75	23.90
Relative humidity, %	68.97	4.41	62.23	65.63	67.87	72.72	78.05

Table 3 Percent changes for ischemic stroke admissions associated with interquartile range increase of SO_2, NO_2, O_x, and $PM_{2.5}$ concentration at different lag days

Air pollutant	Lag	PC[a]	95% CI	I^2	p
SO_2	Lag 0	1.05	0.59, 1.50	4.52	< 0.001
	Lag 1	−0.22	−0.65, 0.20	0.96	0.306
	Lag 2	−0.78	−1.19, −0.37	0.48	< 0.001
NO_2	Lag 0	1.10	0.61, 1.59	1.28	< 0.001
	Lag 1	0.35	−0.28, 0.99	18.55	0.274
	Lag 2	−1.16	−1.71, −0.60	3.98	< 0.001
O_x	Lag 0	1.43	0.81, 2.06	0.00	< 0.001
	Lag 1	−0.65	−1.28, −0.01	0.00	0.048
	Lag 2	−0.22	−0.85, 0.40	0.89	0.484
$PM_{2.5}$	Lag 0	0.90	0.35, 1.45	10.99	0.001
	Lag 1	0.23	−0.32, 0.77	5.69	0.414
	Lag 2	−0.89	−1.38, −0.38	0.00	< 0.001

[a]Adjusted for calendar time, temperature, relative humidity, public holidays, and the day of the week. *PC* percent change

Table 4 Percent changes for ischemic stroke admissions associated with interquartile range increase in same days (lag 0) of SO_2, NO_2, O_x, and $PM_{2.5}$ concentration in a multi-pollutant model

Air pollutant	PC[a]	95% CI	p
SO_2	0.40	−0.08, 0.88	0.106
NO_2	1.23	0.48, 1.97	0.001
O_x	1.65	0.91, 2.40	< 0.001
$PM_{2.5}$	−0.47	−1.25, 0.30	0.232

[a]Adjusted for calendar time, temperature, relative humidity, public holidays, and the day of the week. *PC* percent change

1.05% (95% CI: 0.59–1.50%), 1.10% (95% CI: 0.61–1.59%), 1.43% (95% CI: 0.81–2.06%), and 0.90% (95% CI: 0.35–1.45%) increases in hospital admissions for ischemic stroke, respectively.

Table 4 shows the estimates from the multi-pollutant model, which included SO_2, NO_2, O_x, and $PM_{2.5}$. We observed that the associations of NO_2 and O_x remained significant. Figure 1 depicts the exposure–response curves between air pollutant concentrations and hospital admissions for ischemic stroke, indicating generally positive concentration–response curves. We observed an apparent elevation in relative risks even at relatively low air pollutant concentrations in the exposure–response curves of SO_2, NO_2, and $PM_{2.5}$.

Stratification and sensitivity analysis

Figure 2 illustrates the estimated effects modified by age group, sex, medication use, region, and season. We observed significantly stronger associations with SO_2, NO_2, and $PM_{2.5}$ among the patients taking antihypertensive drugs but significantly weaker associations with SO_2, NO_2, and O_x among the patients taking antiplatelet drugs. We observed stronger associations with O_x during the warm season. The estimates for alternative *df* values are provided in Supplementary Table S3, and the demographic characteristics of the patients by the alternate definition of hospital admissions for ischemic stroke are summarized in Supplementary Table S4. Supplementary Table S5 shows the estimates for the alternate definition. We obtained similar estimates as in the main analysis after changing the *df* values and when using the alternate definition for hospital admissions for ischemic stroke. Supplementary Table S6 provides the results of the cross-sectional dependency tests. We observed significant cross-sectional dependences in all of the tested models.

Discussion

In this time-series study, we examined the associations between the concentrations of four ambient air pollutants and the hospital admissions for ischemic stroke in 97 cities in Japan. We observed that increases in the same-day concentrations of ambient SO_2, NO_2, and $PM_{2.5}$ were positively associated with hospital admissions for ischemic stroke, and the data for NO_2 and O_x remained significant in the multi-pollutant model. The stratification analysis revealed that the associations with SO_2, NO_2, and $PM_{2.5}$ were stronger among

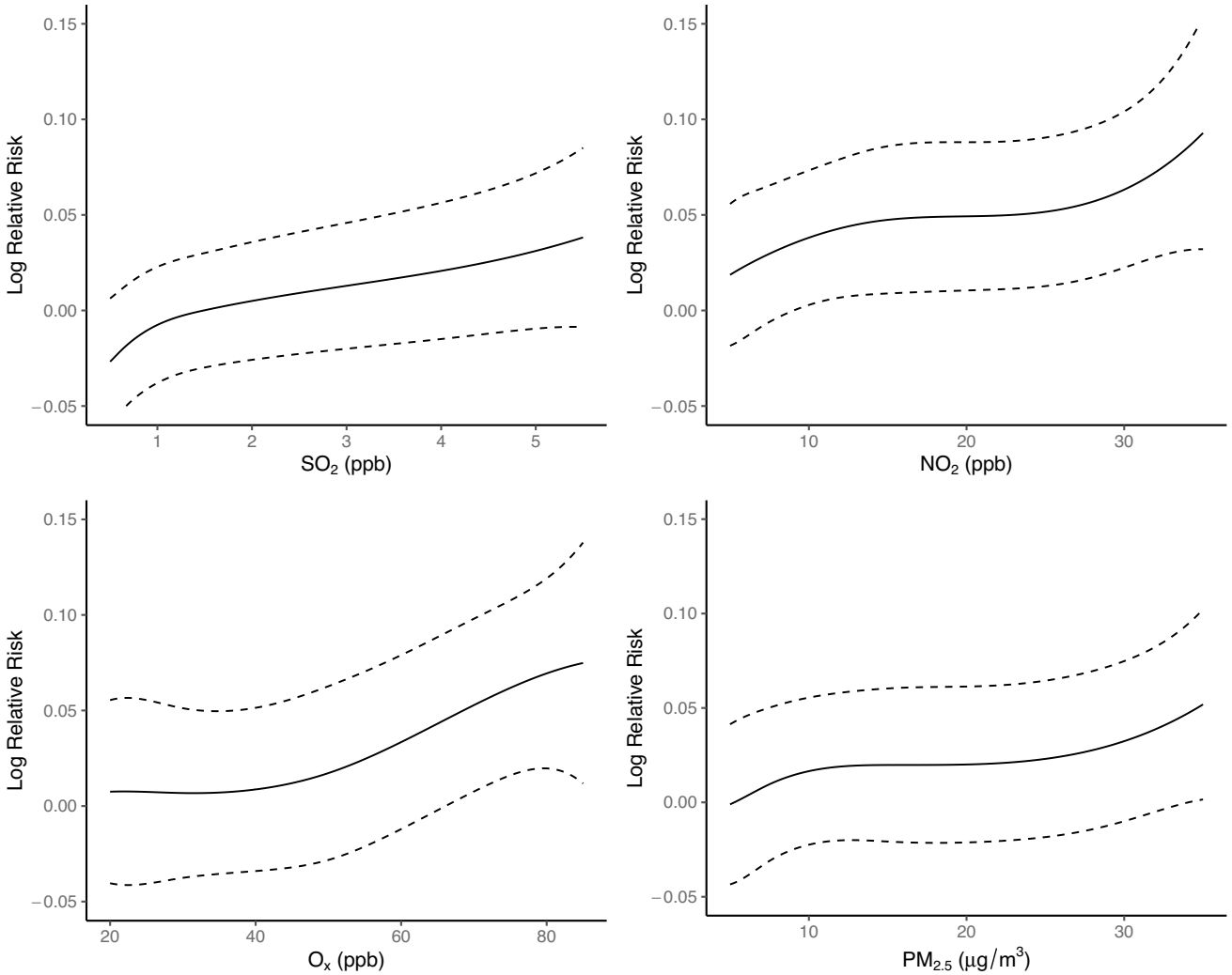

Fig. 1 The exposure–response curve for concentrations of sulfur dioxide, nitrogen dioxide, photochemical oxidants, and particulate matter with an aerodynamic diameter of ≤ 2.5 μm associated with hospital admissions for ischemic stroke in 97 cities in Japan, April 2016–March 2019. The *x*-axis is the concentrations of air pollutants on the same day of admissions for ischemic stroke. The *y*-axis is the log relative risk. The solid line represents the mean estimates, and the dotted line shows their 95% confidence intervals

the patients taking antihypertensive drugs, and weaker associations with SO_2, NO_2, and O_x were present among the patients taking antiplatelet drugs. The association between the hospital admissions and O_x was stronger in the warm season.

Although several large-scale studies have examined the association between exposure to ambient air pollutants and hospital admissions for ischemic stroke, their results have been inconsistent. A study of Medicare beneficiaries aged ≥ 65 years in nine US cities indicated that an IQR increase in the ambient particulate matter with aerodynamic diameter ≤ 10 μm (PM_{10}) (22.96 μg/m^3), CO (0.71 ppm), NO_2 (11.93 ppb), and SO_2 (6.96 ppb) concentrations on the same day were associated with 1.03% (95% CI: 0.04–2.04%), 2.83% (95% CI: 1.23–4.46%), 2.94% (95% CI: 1.78–4.12%), and 1.35% (95% CI: 0.43–2.29%) increases in hospital admissions for ischemic stroke, respectively (Wellenius et al. 2005). A study of 172 Chinese cities revealed that a 10-μg/m^3 increase in ambient $PM_{2.5}$, SO_2, NO_2, and O_3, and a 1-mg/m^3 increase in ambient CO in the same day were associated with 0.39% (95% CI: 0.20–0.48%), 1.37% (95% CI: 1.05–1.70%), 1.82% (95% CI: 1.455–2.19%), 0.01% (95% CI: − 0.14–0.16%), and 3.24% (95% CI: 2.055–4.43%) increases in hospital admissions for ischemic stroke, respectively (Tian et al. 2018). A nationwide study from Taiwan reported that an IQR increase in $PM_{2.5}$ (22.26 μg/m^3) concentrations in the 2 days prior to admission was associated with an adjusted odds ratio of 1.055 (95% CI: 1.014–1.097) in hospital admissions for ischemic stroke (Yang et al. 2021).

On the other hand, several studies did not observe significant positive associations between ambient air pollutants and hospital admissions for ischemic stroke. A study

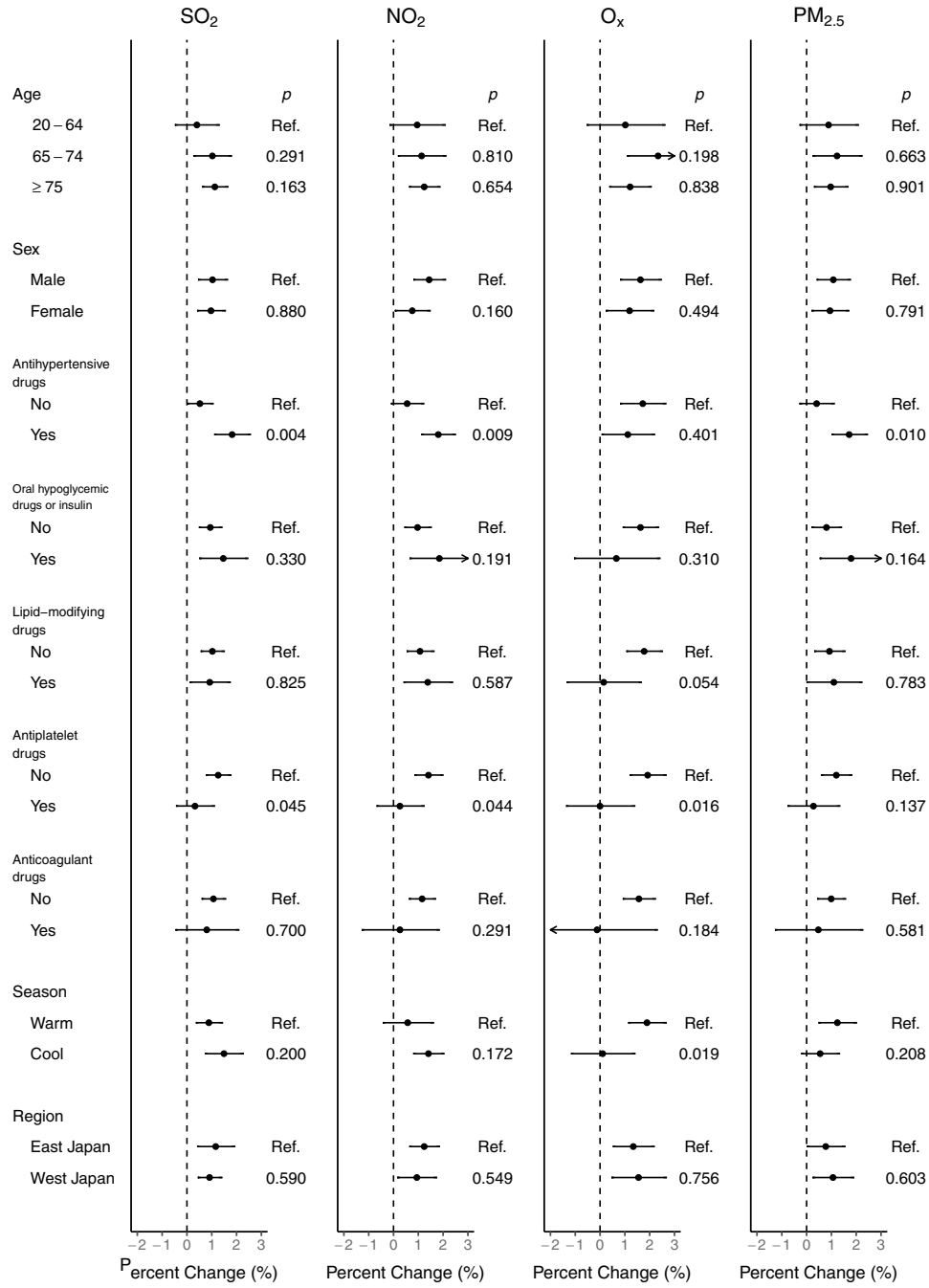

Fig. 2 Percent changes and 95% confidence intervals for ischemic stroke admissions associated with interquartile range increase in same days (lag 0) of SO_2, NO_2, O_x, and $PM_{2.5}$ concentration stratified by age, sex, medication use, season, and city of residence

of eight urban cities in France reported that an increase of 10 μg/m^3 in ambient PM_{10}, NO_2, and O_3 concentrations was associated with 0.2% (95% CI: − 1.6–1.9%), − 0.2% (95% CI: − 1.1–0.7%), and − 0.4% (95% CI: − 1.2–0.3%) changes in hospital admissions for stroke, respectively (Larrieu et al. 2007). An investigation of eight cities in Canada reported that an increase of 10 μg/m^3 in ambient $PM_{2.5}$ was associated with a − 0.7% (95% CI: − 6.3–5.1%) change in hospital admissions for stroke (O'Donnell et al. 2011). Another examination of eight cities across Europe reported that PM_{10} and black smoke concentrations were not associated with hospital admission for smoke (Le Tertre 2002). A study of seven cities in New Zealand and Australia reported that ambient NO_2, CO, $PM_{2.5}$, PM_{10}, and O_3 concentrations were not associated with hospital admission for stroke (Barnett et al. 2006). The inconsistency of the results of the above-cited studies may be partly explained by differences such as ambient air pollutants levels, meteorological conditions, population characteristics, sample sizes, and study designs (Verhoeven et al. 2021).

Our present findings regarding the exposure–response curve for SO_2, NO_2, and $PM_{2.5}$ showed seeming elevations

in the relative risks even at relatively low concentrations of these pollutants. Similar to these findings, earlier studies described exposure–response curves with elevations in the relative risks even at low concentrations of pollutants (Huang et al. 2017; Gu et al. 2020; Stafoggia et al. 2020). These results suggested that reducing these ambient air pollutants below these concentrations may still benefit public health.

Although several studies have examined whether patient characteristics may modify the association between ambient air pollution and ischemic stroke, the results have been unclear. For example, a study from Canada examined possible modifications of the association between $PM_{2.5}$ and ischemic stroke by a history of diabetes, atrial fibrillation, hypertension, stroke or transient ischemic attack, smoking, and sex (O'Donnell et al. 2011). They reported that the association was significantly stronger among patients with a history of diabetes, whereas no significant differences in other characteristics were identified. Another study from Canada examined effect modification by a history of heart disease, stroke, hypertensive medication, diabetes medication, antiplatelet medication, and anticoagulant medication on the association between NO_2 and ischemic stroke in the warm season; none of these factors exerted a significant effect (Villeneuve et al. 2012). A study from China reported that patients with hyperlipidemia showed stronger associations between PM_{10} and O_3 and ischemic stroke in the warm season, but the heterogeneity test did not show significant differences between patients with and without hyperlipidemia (Qi et al. 2020).

Our stratification analyses showed that the associations between hospital admissions for stroke and the values of SO_2, NO_2, and $PM_{2.5}$ were about ≥ 3 times greater among the patients taking antihypertensive drugs. In line with this finding, several research groups have reported a modification effect of hypertension on the association with heart rate variability, suggesting that hypertension may modify the association between ambient air pollution and cardiovascular diseases through cardiac autonomic dysfunction (Holguín et al. 2003; Liao 2004; Park et al. 2005, 2010). This hypothesis may explain the observed modification effect among patients taking antihypertensive drugs in the present study. In addition, as hypertension and air pollution cause similar physiological changes associated with cardiovascular diseases, e.g., systemic inflammation and oxidative stress (Briones and Touyz 2010; Lee et al. 2018), this similarity may explain our present results.

The stratification analysis also showed that the associations with SO_2, NO_2, and O_x were almost null among the patients taking antiplatelet drugs, in contrast to the patients not taking these medications. Exposure to air pollutants was reported to lead to platelet activation (Lucking et al. 2008; Jacobs et al. 2010), which is the central mechanism in ischemic stroke pathophysiology (Fisher et al. 1982; Joseph et al. 1989). One explanation for the present study's results may be that antiplatelet drugs may have reduced these patients' platelet activation by exposure to ambient air pollution and prevented ischemic stroke. However, as the patients taking antiplatelet drugs were likely to have more comorbidities and spend less time outdoors, the results may be attributable in part to the differences in exposure to ambient air pollution rather than physiological mechanisms. Further studies with more detailed individual-level data are needed to clarify.

There are several study limitations to address. First, as we used data from a claims database, misclassifications of the outcomes could have occurred due to diagnostic or coding errors. These errors are likely to be independent of air pollution concentrations and may have biased our estimates toward the null. However, we obtained similar estimates using the alternate definition for hospital admissions for ischemic stroke, suggesting the robustness of our estimates. Second, we used the average of all monitoring stations in each city instead of personal exposure to ambient air pollutants. This exposure assessment may have caused an exposure measurement error, which may have biased our estimates toward the null (Zeger et al. 2000).

Third, as we included only the four ambient air pollutants, unmeasured air pollutants may mediate the actual associations from the same source. For example, NO_2 serves as a proxy for other unmeasured traffic-related pollutants, including noise, road dust, and ultrafine particles (Seaton 2003; Ito et al. 2007). Alternatively, combined effects of air pollutants such as the oxidant capacity rather than individual pollutants may be responsible for the observed association (Williams et al. 2014). We also did not consider the components of the $PM_{2.5}$, due to a lack of data. Fourth, as we used the medication status to characterize patient characteristics, we could not discriminate whether the observed effect modification was from the treated disease, the medication itself, and/or the characteristics of the patients taking medications. Fifth, we observed significant cross-sectional dependency implying spillover effects of air pollution and/or unmeasured factors, such as infectious disease outbreaks or other hazardous air pollutants. Future studies should consider these factors. Lastly, this study included only relatively populated cities in order to minimize model convergence issues, and thus the generalizability of the results is limited.

Conclusion and policy recommendation

We observed significant associations between exposure to ambient air pollutants and hospital admissions for ischemic stroke in 97 cities in Japan. Our results also indicate that medication use and the season might modify these

associations. However, as there are several study limitations due to our secondary use of claims data, our findings should be confirmed by studies with more detailed and precise data, such as registry-based data.

Our results suggest the following policy recommendation: the air quality standards in Japan should be reconsidered. In 2018, the ratios of monitoring stations that complied with the air quality standards were almost 100% for SO_2 and NO_2, 93.5% for $PM_{2.5}$, and almost 0% for O_x (Ito et al. 2021). These results implied that most of the areas were considered at the "safe levels" for SO_2, NO_2, and $PM_{2.5}$. However, we observed significant positive associations between these air pollutants and hospital admissions for ischemic stroke, suggesting that the current air quality standards might not be adequate from a public health perspective. Moreover, the exposure–response curve for SO_2, NO_2, and $PM_{2.5}$ showed seeming elevations in the relative risks even at relatively low concentrations of these pollutants, implying that further reductions in the levels of these air pollutants might still be beneficial.

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Author contribution K. Hasegawa: conceptualization, methodology, software, formal analysis, investigation, resources, data curation, writing (original draft), visualization. T. Tsukahara: conceptualization, methodology, validation, writing (review and editing). T. Nomiyama: conceptualization, methodology, writing (review and editing), supervision, project administration.

Data Availability The dataset analyzed in this study is not publicly available due to data protection requirements from Japan's MHLW.

Declarations

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Committee for Medical Ethics of Shinshu University School of Medicine (protocol code: 4550; date of approval: 13 November 2019).

Consent to participate Not applicable.

Consent to publish Not applicable.

Conflict of interest The authors declare no competing interests.

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