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## Effect modification by temperature on the association between O<sub>3</sub> and emergency ambulance dispatches in Japan: A multi-city study

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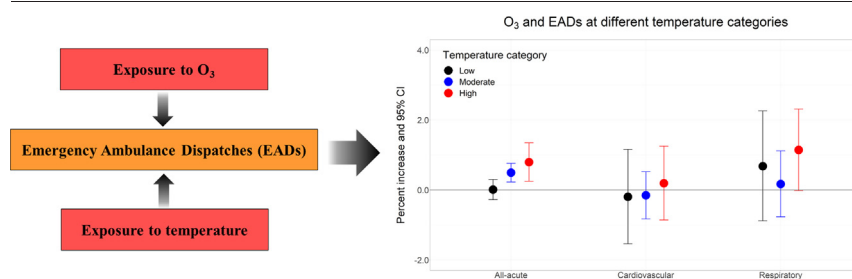
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### HIGHLIGHTS

- Effect modification by temperature on O<sub>3</sub>-EADs association was examined.
- EADs visits for all-cause, cardiovascular, and respiratory illnesses were explored.
- Ambient temperature can modify the association between O<sub>3</sub> and EADs.
- Effect of O<sub>3</sub> on EADs was greater when temperature was higher (>75th percentile).
- Significant effect of O<sub>3</sub> on EADs for all-acute illnesses during hot days was observed.

### GRAPHICAL ABSTRACT



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### ABSTRACT

Numerous epidemiological studies have reported that ozone (O<sub>3</sub>) and temperature are independently associated with health outcomes, but modification of the effects of O<sub>3</sub> on health outcomes by temperature, and vice versa, has not been fully described. This study aimed to investigate effect modification by temperature on the association between O<sub>3</sub> and emergency ambulance dispatches (EADs) in Japan. Data on daily air pollutants, ambient temperature, and EADs were obtained from eight Japanese cities from 2007 to 2015. A distributed lag non-linear model combined with Poisson regression was performed with temperature as a confounding factor and effect modifier to estimate the effects of O<sub>3</sub> on EADs at low (<25th percentile), moderate (25th–75th percentile), and high (>75th percentile) temperature for each city. The estimates obtained from each city were pooled by random-effects meta-analysis. When temperature was entered as a confounder, the estimated effects of O<sub>3</sub> on EADs for all acute, cardiovascular, and respiratory illnesses were largest at lag 0 (current-day lag). Therefore, this lag was used to further estimate the effects of O<sub>3</sub> on EADs in each temperature category. The estimated effects of O<sub>3</sub> on EADs for all acute, cardiovascular, and respiratory illnesses in all eight Japanese cities increased with increasing temperature. Specifically, a 10 ppb increase in O<sub>3</sub> was associated with 0.80% (95% CI: 0.25 to 1.35), 0.19% (95% CI: -0.85 to 1.25), and 1.14% (95% CI: -0.01 to 2.31) increases in the risk of EADs for all acute, cardiovascular, and respiratory illnesses, respectively, when city-specific daily temperature exceeded the 75th percentile. Our findings suggest that the association between O<sub>3</sub> and EADs for all acute, cardiovascular, and respiratory illnesses is the highest during high temperature. Finding of this study can be used to develop potential mitigation measures against O<sub>3</sub> exposure in high temperature environment to reduce its associated adverse health effects.

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## 1. Introduction

Climate change is a significant public health concern that threatens and affects human health with increasingly adverse outcomes (Kjellstrom and McMichael, 2013). According to the Fifth Assessment Report (AR5) of the Intergovernmental Panel on Climate Change (IPCC), the global mean surface temperature is expected to increase by approximately 0.3 °C to 0.7 °C in 2035 (Kirtman et al., 2013). Such an increase in temperature may increase the emission of O<sub>3</sub> and its precursors through changes in chemical reaction rate and mixing height, which influences the vertical mixing of pollutants, as well as changes in biogenic emission from many woody plant species due to land-cover changes (Ebi and McGregor, 2008). A number of previous studies, ranging in scale from local to regional, have shown that tropospheric O<sub>3</sub> concentration and surface temperature is well correlated. With the potential increases of O<sub>3</sub> concentration due to increasing surface temperature under a changing climate (Bell et al., 2007; Chang et al., 2010; Liao et al., 2006; Moghani and Archer, 2020; West et al., 2007), projected O<sub>3</sub> attributable premature mortality is expected to increase in the mid of 21st century (Chang et al., 2010).

O<sub>3</sub> is a photochemical air pollutant formed by chemical reactions under warm and sunny conditions (Pu et al., 2017), with concentrations likely to increase during a high temperature period (Fischer et al., 2004; Kalisa et al., 2018). The interaction between high temperature and high O<sub>3</sub> concentration may enhance the joint effects of temperature and O<sub>3</sub> on human health, relative to those caused by individual factors acting alone (Katsouyanni et al., 1993). Numerous epidemiologic studies have reported that temperature and short-term O<sub>3</sub> exposure are independently associated with morbidity and mortality in many parts of the world (Atkinson et al., 2012; Basu, 2009; Kan et al., 2008; Kotani et al., 2018; Michelozzi et al., 2009; Nuvolone et al., 2013; Phosri et al., 2019; Phung et al., 2016; Samoli et al., 2011). In these studies, temperature is generally treated as a confounder in the association between O<sub>3</sub> and health outcomes, and vice versa. In studies examining association between O<sub>3</sub> and acute morbidity, outpatient department visits and hospital admissions have been commonly utilized. However, daily records of morbidity used for epidemiological studies over multiple spatiotemporal scales have not been fully institutionalized in several countries. In recent years, there has been a growing interest in the use of emergency ambulance dispatches (EADs) as an indicator for human morbidity in examining the health effects of air pollution, including O<sub>3</sub> (Jiang et al., 2021; Michikawa et al., 2022; Sangkharat et al., 2019). Only a few studies have examined the effect modification by ambient temperature on the association between O<sub>3</sub> and health outcomes, such as morbidity (He et al., 2022; Qiu et al., 2018). As temperature is expected to continue to rise under a changing climate, it is important to clarify how the association between O<sub>3</sub> and human health might be modified by increasing temperature, given the potential interaction between O<sub>3</sub> and temperature. To this end, the present study aimed to estimate the effect modification by temperature on association between O<sub>3</sub> and EADs for all acute, cardiovascular, and respiratory illnesses in eight Japanese cities using data from 2007 to 2015.

## 2. Materials and methods

This study was conducted in eight Japanese cities (Fukuoka, Kumamoto, Hiroshima, Nagoya, Osaka, Saitama, Sendai, and Sapporo) across eight prefectures in Japan. Among these cities, Osaka has the largest population number (2.7 million as of 2015), followed by Nagoya, Sapporo, Fukuoka, Saitama, Hiroshima, Sendai, and Kumamoto (Ministry of Internal Affairs and Communications, 2017). The studied areas are spread over northern and southern Japan, as shown in Fig. 1.

### 2.1. Emergency ambulance dispatch (EAD) data

Daily EAD data for each city were obtained from the Japanese Fire and Disaster Management Agency (FDMA) of the Ministry of Internal Affairs and Communications, except for Kumamoto (data were provided by the

local office in the city). In Japan, local fire defense headquarters provide ambulance services free of charge to anyone who makes an emergency call (dial 119) (Tanigawa and Tanaka, 2006). Since people who require emergency ambulance services normally call the local office near their residence, EADs examined in this study were generally considered to have been requested for the residents of the respective cities. Daily EAD counts were extracted for the period between January 1, 2007 and December 31, 2015 for all acute illness and during January 1, 2007 through March 31, 2012 for cardiovascular and respiratory illnesses due to unavailable data after 2012. Each anonymized EAD record included information on age, sex, reason for EAD, date of event, and primary diagnosis as determined by the emergency physician upon arrival at the nearest emergency center. Among 14 categories of reasons for EAD, only the “acute illnesses” category was considered to this study in order to avoid the inclusion of health outcomes that are not related to the main exposure (i.e., O<sub>3</sub> and temperature). Specifically, EADs for all acute illnesses (excluding traumatic and accidental illnesses) as well as cardiovascular and respiratory illnesses, were included in the analysis. The cause of dispatch was coded according to the International Classification of Disease, 10th revision (ICD-10), in which I00-I99 has been coded for cardiovascular disease and J00-J99 for respiratory disease. This study was approved by the Ethics Review Committee of Kyoto University Graduate School of Engineering.

### 2.2. Air pollution and meteorological data

Hourly air pollutant data, including concentrations of PM<sub>2.5</sub> (µg/m<sup>3</sup>), suspended particulate matter (SPM; µg/m<sup>3</sup>), photochemical oxidant (O<sub>x</sub>; ppb), nitrogen dioxide (NO<sub>2</sub>; ppb), and sulfur dioxide (SO<sub>2</sub>; ppb), were obtained from the National Institute for Environmental Studies (NIES) database. PM<sub>2.5</sub> data for Saitama city during the study period were provided by the Center for Environmental Science in Saitama, as these data were not available from the database. Importantly, this study used O<sub>x</sub>, which is a mixture of ozone (O<sub>3</sub>) and other secondary oxidants generated by photochemical reactions, as a proxy for O<sub>3</sub>. A photochemical reaction is initiated when ultraviolet (UV) light from the sun reacts with nitrogen oxides (NO<sub>x</sub>) in the atmosphere through a complex reaction with hydrocarbon to form photochemical oxidants (O<sub>x</sub>), which contain many secondary pollutants, such as O<sub>3</sub>, peroxyacetylnitrate (PAN), and aldehydes (World Health Organization, 2000). The major component of O<sub>x</sub> is O<sub>3</sub> formed by the photochemical reaction. Specifically, oxygen molecule is broken by UV light from the sun into two oxygen atoms and each atom of oxygen then quickly reacts with oxygen molecule in the air to form O<sub>3</sub>. The concentration of O<sub>x</sub> in this study was measured by the photometric method with UV light (Acid Deposition and Oxidant Research Center, 2006). Hourly data for these air pollutants were collected from one background monitoring station located in each city. Daily 24-hour average concentrations of PM<sub>2.5</sub>, SPM, NO<sub>2</sub>, and SO<sub>2</sub>, and daily 8-hour maximum concentration of O<sub>3</sub> were calculated. We assumed that days with >25 % missing hourly observations, or simply more than or equal to 6 h missing measurements, were encoded with an “NA” (Vichit-Vadakan et al., 2008). Daily average temperature (°C) and relative humidity (%) data were obtained from the Japan Meteorological Agency (JMA).

### 2.3. Statistical analysis

The association between O<sub>3</sub> and EADs for all acute illness was examined using the data from 2007 to 2015 in eight Japanese cities included in this study, excepting for Saitama, Sendai, and Sapporo. In particular, we preliminarily observed high number of EADs in those three cities during 2011 due to the consequence of the Great East Japan Earthquake. Therefore, we excluded such period in the analyses for such cities. We also examined the association of O<sub>3</sub> with EADs for cardiovascular and respiratory illnesses using the data spanning from 2007 to 2012 because cause-specific acute illnesses were not available after 2012. The analyses for Saitama city was performed using the data from April 2009 to March 2011, and those for Sendai and

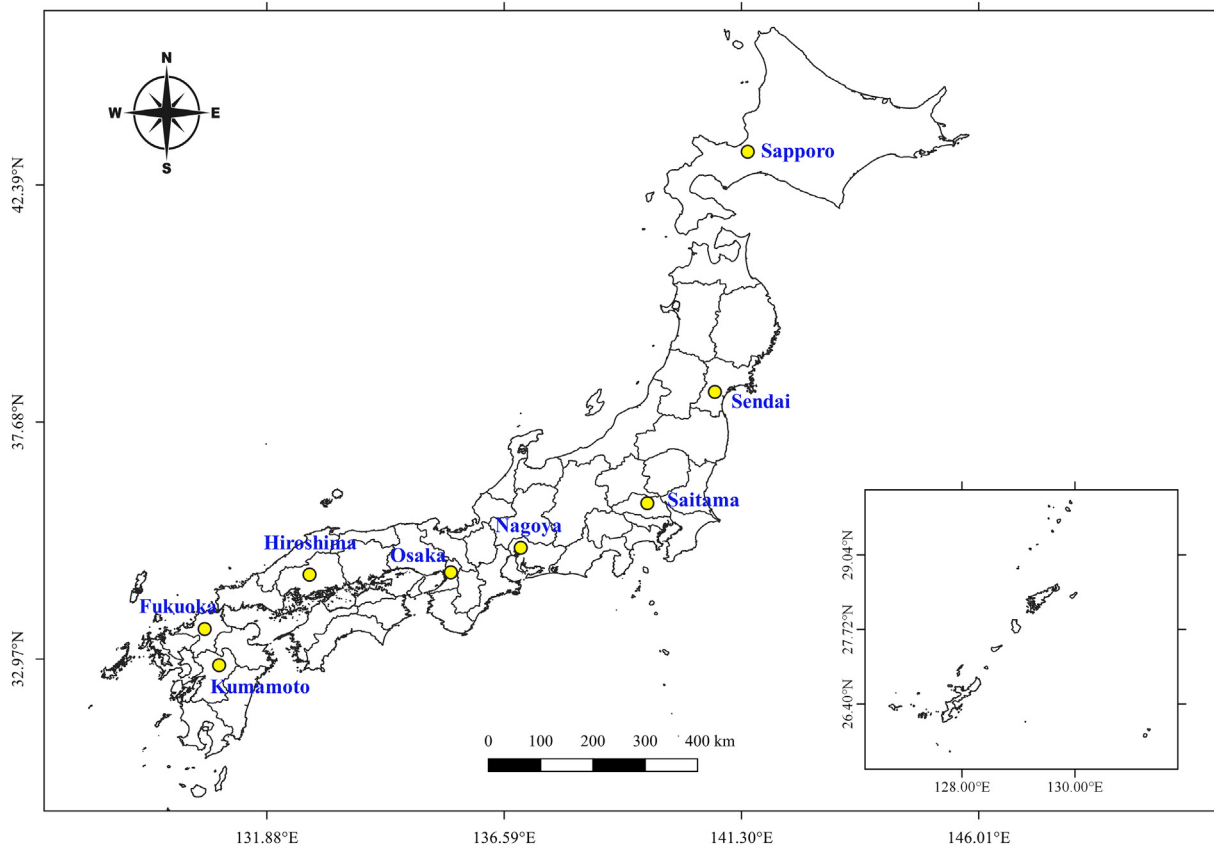


Fig. 1. Locations of study areas across eight prefectures in Japan.

Sapporo was conducted using the data spanning from January 2007 to March 2010 to avoid the influence of the Great East Japan Earthquake.

We used a two-stage approach to examine the association between  $O_3$  and EADs. First, city-specific associations were evaluated using a distributed lag non-linear model (DLNM) with Poisson regression analysis, controlling for secular trends and a number of potential confounders. Specifically, the cross-basis matrix of  $O_3$  and lag was generated using a linear function for  $O_3$  and a natural cubic spline function with 3 degrees of freedom ( $df$ ) on a logarithmic scale of lags up to 7 days since preliminary analysis revealed that the estimate was stable after 7-day lag (Fig. 2). A natural cubic spline function with 7  $df$  per year for calendar time was used to adjust for long-term trend and seasonality (Phung et al., 2018). In addition, the cross-basis matrix of temperature/relative humidity and lag was used to adjust for confounding by weather variables, in which a natural cubic spline function with 4  $df$  for temperature/relative humidity was applied by

placing knots at an equal interval (Chen et al., 2010). A 7-day maximum lag was utilized for both temperature and relative humidity, parameterized with a natural cubic spline function with 4  $df$  on a logarithmic scale with equally spaced knots (Kotani et al., 2018). Indicator variables for day of the week and public holidays were also included into the model. The main model used to examine the city-specific associations between  $O_3$  and EADs is as follows:

$$\log(E(Y_t)) = \alpha + \beta Z_{t,l} + \gamma \text{Temp}_{t,l} + \lambda \text{RH}_{t,l} + \text{ns}(\text{time}_t, 7 \text{ dfs per year}) + \text{dow}_t + \text{holiday}_t \quad (1)$$

where  $E(Y_t)$  is the expected number of EADs at time  $t$ ;  $\alpha$  is the model intercept;  $\beta$  is the vector of coefficients of the cross-basis matrix of  $O_3$  and lag on EADs;  $Z_{t,l}$  is the concentration of  $O_3$  on day  $t$  and lag  $l$ ;  $\gamma$  is the vector of coefficients of the cross-basis matrix of temperature and lag;  $\lambda$  is the vector of

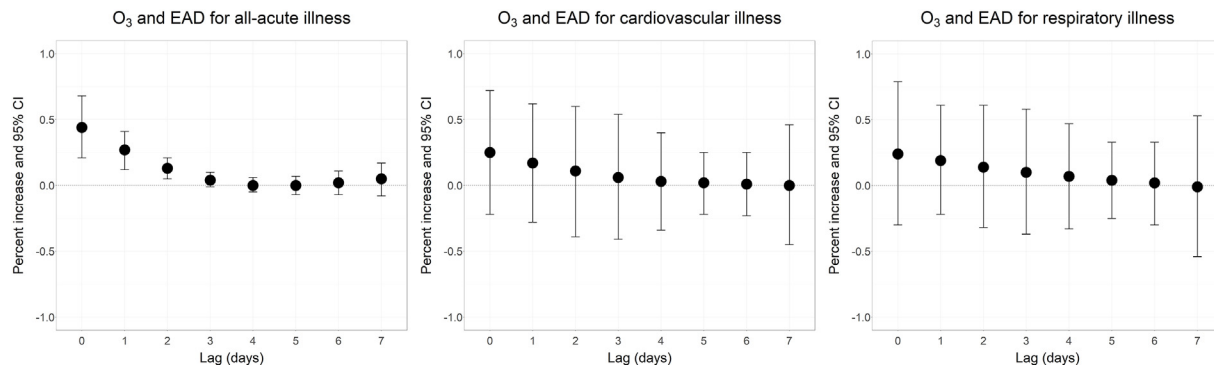


Fig. 2. Percent increase in the risk of EADs for all acute, cardiovascular, and respiratory illnesses associated with a 10 ppb increase in  $O_3$  concentration in eight Japanese cities with different lag structures.

coefficients of the cross-basis matrix of relative humidity and lag;  $Temp_{t,l}$  and  $RH_{t,l}$  are temperature and relative humidity on day  $t$  and lag  $l$ , respectively;  $ns()$  is the natural spline function with 7 *dfs* per year; and  $dow_t$  and  $holiday_t$  are indicator variables for day of the week and public holidays on day  $t$ , respectively. To examine the robustness of the effect estimate, a two-pollutant model was also examined by adding other air pollutants one at a time using the same lag.

In examining the effect modification by temperature on the association between  $O_3$  and EADs, daily temperature was stratified into three categories ( $k$ ) using 25th and 75th percentile cut-offs according to previous studies (Kotani et al., 2018; Zhan et al., 2018): low (<25th percentile), moderate (25th–75th percentile), and high (>75th percentile). The association of  $O_3$  on EADs were then examined for each temperature category  $k$ . Zhan et al. (2018) and Kotani et al. (2018) reported a U-shaped risk function of temperature with EAD, whereby the 27th and 37th percentile of ambient temperature corresponded to the optimum temperature for EAD (the lowest risk of EAD associated with temperature), respectively, suggesting that any temperature below and above the 27th or 37th percentile is likely to be associated with an increased risk of EADs for acute illnesses. As the cut-off temperatures used in the present study were arbitrary selected, sensitivity analyses were also performed using different temperature percentile cut-offs (i.e., 20th, 80th percentile; 15th, 85th percentile; 10th, 90th percentile; and 5th, 95th percentile). The model accounting for effect modification is represented by the following equation:

$$\log(E(Y_t)) = \alpha + \delta temp_{tk} + \eta[Z_{t,0} : temp_{tk}] + \gamma Temp_{t,l} + \lambda RH_{t,l} + ns(time_t, 7\ dfsperyear) + dow_t + holiday_t \quad (2)$$

where  $Z_{t,0}$  is the concentration of  $O_3$  at time  $t$  and current-day lag (based on the main results, we found an immediate effect of  $O_3$  on EADs at lag 0, and thus have decided to further examine whether this acute effect is modified by temperature in the subsequent analysis);  $temp_{tk}$  is an indicator variable of temperature category  $k$  on day  $t$ ;  $\delta$  is the vector of coefficients of temperature category  $k$  on EADs; and  $\eta$  is the vector of coefficients of  $O_3$  on EADs at temperature category  $k$  (Kim et al., 2015).  $\gamma$  and  $\lambda$  are the vector of coefficients of the cross-basis matrix of temperature and relative humidity on day  $t$  and lag  $l$ , respectively. The significant changes of the estimated effects in different temperature categories were also examined using linear interaction terms between  $O_3$  and temperature categories at  $p$ -value <0.05.

In the second stage analysis, the meta-analysis was performed by pooling city-specific estimates of the effects of  $O_3$  on EADs not classified by temperature category, as well as those of each temperature category obtained from the first stage. A random-effects meta-analysis with restricted maximum likelihood estimation (REML) was applied to pool the city-specific results (Berkey et al., 1998). The effect estimate was then expressed as percent increase in the risk of EADs per 10 ppb increase in  $O_3$  concentration for each temperature category. A  $p$ -value <0.05 is statistically significant. All analyses were performed using R software environment (version 3.2.3) using the “*dlnm*” package in examining the  $O_3$ -EAD association and the “*mvmeta*” package for the meta-analysis.

### 3. Results

Summary statistics for daily number of EADs, daily concentration of air pollutants, and meteorological variables by city are shown in Table 1. Daily mean numbers of EADs for all acute, cardiovascular, and respiratory illnesses (mean ± standard deviation) in eight Japanese cities during the study period are 132 ± 87, 28 ± 17, and 15 ± 10 cases, respectively. Daily average  $O_3$  concentration is 35.37 ± 15.78 ppb, ranged from 31.63 ± 11.43 (Sapporo) to 39.43 ± 16.96 (Fukuoka) ppb (Table S1). The concentration of  $O_3$  was higher in summer (46.83 ± 14.55 ppb) and lower in winter (26.64 ± 10.51 ppb) (Table S2). Daily average temperature during the study period over eight Japanese cities is 15.38 ± 8.92 °C, ranged from 9.52 ± 9.52 °C in Sapporo to 17.41 ± 8.25 °C in Kumamoto (Table S1), and that of relative humidity is 66.81 ± 10.82 %, ranged from 63.23 ± 9.57 % in Osaka to 71.09 ± 11.65 % in Sendai (Table S1). The city-specific

**Table 1**

Summary statistic for daily number of EADs, daily air pollutant concentrations, and weather variables across eight cities during the study periods (2007–2015).

Variables	Mean	SD	Min	P25	P50	P75	Max
Emergency ambulance dispatches							
All-cause (cases)	132	87	23	71	101	160	514
Cardiovascular (cases) <sup>a</sup>	28	17	0	11	26	37	82
Respiratory (cases) <sup>a</sup>	15	10	1	6	12	20	62
Environmental data							
$O_3$ (ppb)	35.37	15.78	0.00	24.30	33.88	45.00	114.25
$PM_{2.5}$ ( $\mu\text{g}/\text{m}^3$ )	15.96	9.60	0.00	9.13	13.88	20.64	94.75
SPM ( $\mu\text{g}/\text{m}^3$ ) <sup>a</sup>	22.41	13.82	1.65	12.59	19.75	29.04	209.71
$NO_2$ (ppb)	14.50	8.28	0.54	8.33	12.79	18.92	61.92
$SO_2$ (ppb)	10.95	18.05	0.00	1.04	2.92	13.75	170.42
Temperature (°C)	15.38	8.92	-9.20	7.80	16.00	22.60	33.40
Humidity (%)	66.81	10.82	24.00	58.00	67.00	74.00	98.00

<sup>a</sup> Data are available from 2007 to 2012. SD, Standard Deviation; Min, Minimum; P25, 25th percentile; P50, 50th percentile; P75, 75th percentile; Max, Maximum.

summary statistics for EADs and all related environmental data, city-specific  $O_3$  concentration in different seasons, and city-specific temperature percentiles during 2007 to 2012 and from 2007 to 2015 are shown in Tables S1, S2, S3 and S4, respectively.

When temperature was adjusted as a confounder (Eq. (1)), the effect estimates of  $O_3$ -EAD associations for all acute, cardiovascular, and respiratory illnesses were largest at lag 0. In particular, with every 10 ppb increase in  $O_3$ , the EAD risk for all acute, cardiovascular, and respiratory illnesses increases by 0.44 % (95 % CI: 0.21 to 0.68), 0.25 % (95 % CI: -0.22 to 0.72), and 0.24 % (95 % CI: -0.30 to 0.79), respectively; only all acute illness exhibiting statistically significant association with  $O_3$  exposure at  $p$ -value <0.05 and the effect estimates of  $O_3$ -EAD associations were attenuated over longer lagged day (Fig. 2). In the cumulative lagged effects of  $O_3$  on EADs, the estimates were stronger than single lag day but their confidence interval (CI) became wider, indicating that the effect estimates are relatively variable (Table 2). In the subsequent analysis, we examined the effect modification by temperature on the association between  $O_3$  and EADs at lag 0 (i.e., current-day lag) because the estimates of  $O_3$ -EAD associations at lag 0 were greater than those at other single-lag days and those enabled more precise compared to cumulative effects. City-specific and pooled estimates of the effects of  $O_3$  on EADs for all acute, cardiovascular, and respiratory illnesses at different lags are shown in Table S5. Moreover, the results of the two-pollutant model as sensitivity analysis indicated that, for all acute illnesses, the estimates were slightly attenuated after adjusting

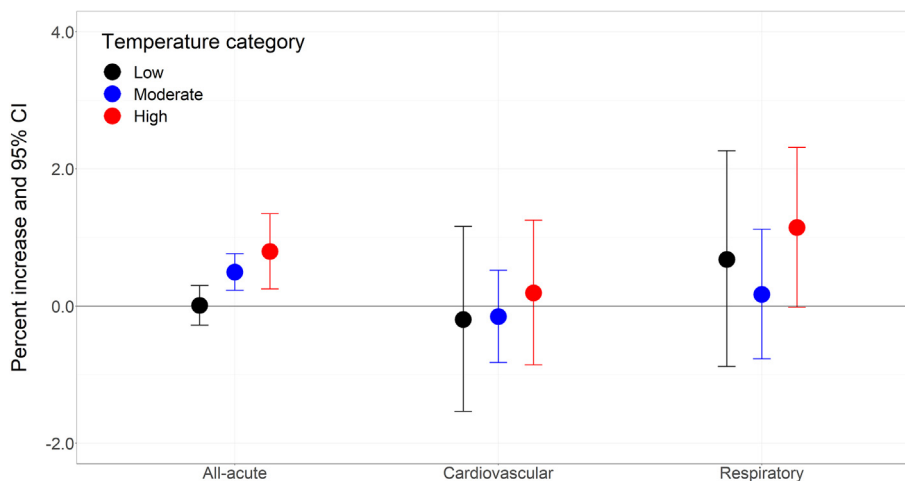
**Table 2**

Percent increase and its 95 % confidence interval (CI) of EADs for all-acute, cardiovascular, and respiratory illnesses associated with 10 ppb increase in  $O_3$  at different lag structures.

Lag (days)	All-acute illness			Cardiovascular illness			Respiratory illness		
	Percent	Lower CI	Upper CI	Percent	Lower CI	Upper CI	Percent	Lower CI	Upper CI
0	0.44*	0.21	0.68	0.25	-0.22	0.72	0.24	-0.30	0.79
1	0.27*	0.12	0.41	0.17	-0.28	0.62	0.19	-0.22	0.61
2	0.13*	0.05	0.21	0.11	-0.39	0.60	0.14	-0.32	0.61
3	0.04	-0.01	0.10	0.06	-0.41	0.54	0.10	-0.37	0.58
4	0.00	-0.05	0.06	0.03	-0.34	0.40	0.07	-0.33	0.47
5	0.00	-0.07	0.07	0.02	-0.22	0.25	0.04	-0.25	0.33
6	0.02	-0.07	0.11	0.01	-0.23	0.25	0.02	-0.30	0.33
7	0.05	-0.08	0.17	0.00	-0.45	0.46	-0.01	-0.54	0.53
0-1	0.71*	0.33	1.09	0.42	-0.46	1.30	0.44	-0.46	1.34
0-2	0.84*	0.40	1.29	0.53	-0.78	1.85	0.58	-0.64	1.81
0-3	0.88*	0.42	1.35	0.59	-1.13	2.33	0.68	-0.87	2.27
0-4	0.89*	0.43	1.35	0.62	-1.41	2.69	0.75	-1.10	2.64
0-5	0.89*	0.45	1.33	0.64	-1.56	2.88	0.80	-1.24	2.87
0-6	0.91*	0.48	1.33	0.64	-1.52	2.86	0.81	-1.26	2.93
0-7	0.95*	0.52	1.39	0.65	-1.34	2.67	0.80	-1.23	2.88

\* Statistical significance at  $p$ -value <0.05.

### O<sub>3</sub> and EADs at different temperature categories



**Fig. 3.** Percent increase in the risk of EADs per 10 ppb increase in O<sub>3</sub> concentration in the low (<25th percentile), moderate (25th–75th percentile), and high (>75th percentile) temperature categories.

for PM<sub>2.5</sub> and SO<sub>2</sub> in the model, but were slightly elevated after NO<sub>2</sub> adjustment. For cardiovascular and respiratory illnesses, the estimates were slightly attenuated after adjusting for PM<sub>2.5</sub>, SO<sub>2</sub>, and NO<sub>2</sub>. However, these estimates were not significantly different from those of single-pollutant model, suggesting that the model used in this study is robust to the adjustment of other pollutants (Fig. S1 and Table S6).

When temperature was stratified into three categories using city-specific 25th and 75th percentile cut-offs, the largest pooled effects of O<sub>3</sub> on EADs for all acute, cardiovascular, and respiratory illnesses were observed in the high temperature category (>75th percentile), although the effect of O<sub>3</sub> on EADs for cardiovascular and respiratory illnesses was not statistically significant. In particular, for all acute illnesses, a 10 ppb increase in O<sub>3</sub> concentration was associated with 0.01 % (95 % CI: -0.28 to 0.30), 0.50 % (95 % CI: 0.23 to 0.76), and 0.80 % (95 % CI: 0.25 to 1.35) change in the risk of EADs for all acute illnesses in the low, moderate, and high temperature categories, respectively. For cardiovascular illnesses, a 10 ppb increase in O<sub>3</sub> concentration was associated with -0.20 % (95 % CI: -1.53 to 1.16), -0.15 (95 % CI: -0.82 to 0.52), and 0.19 % (95 % CI: -0.85 to 1.25) change in the risk of EADs for cardiovascular illnesses in the low, moderate, and high temperature categories, respectively. For respiratory illnesses, a 10 ppb increase in O<sub>3</sub> concentration was associated with 0.68 % (95 % CI: -0.88 to 2.26), 0.17 % (95 % CI: -0.77 to 1.12), and 1.14 % (95 % CI: -0.01 to 2.31) increment in the risk of EADs for respiratory illnesses in the low, moderate, and high temperature categories, respectively (Fig. 3 and Table 3). City-specific and pooled estimates of the effects of O<sub>3</sub> on EADs for all acute, cardiovascular, and respiratory illnesses by temperature category are presented in Fig. S2 and Table S7.

To examine whether effect modification by temperature varies by threshold used to define temperature categories, sensitivity analyses were performed using alternative temperature percentile cut-offs (i.e., 20th and 80th percentile; 15th and 85th percentile; 10th and 90th percentile; and 5th and 95th percentile). The effects of O<sub>3</sub> on EADs for all acute illnesses

and respiratory illnesses were estimated to be higher in the high temperature category than in the moderate and low categories, regardless of the threshold used. Moreover, the effects of O<sub>3</sub> on EADs for all acute and respiratory illnesses in high temperature category trend to linearly increase when higher temperature percentiles were applied. Specifically, a 10 ppb increase in O<sub>3</sub> concentration was associated with 0.80 % (95 % CI: 0.25 to 1.35), 0.92 % (95 % CI: 0.38 to 1.46), 1.05 % (95 % CI: 0.51 to 1.60), 1.14 % (95 % CI: 0.69 to 1.59), and 1.15 % (95 % CI: 0.60 to 1.71) increment in the risk of EADs for all acute illnesses in the high temperature category as defined using 75th, 80th, 85th, 90th, and 95th percentile temperatures, respectively (Table S8) and the risk of EADs for all acute illnesses associated with O<sub>3</sub> exposure in low temperature category trend to linearly decrease when lower temperature percentiles were applied (Fig. 4). Similarly, a 10 ppb increase in O<sub>3</sub> concentration was associated with 1.14 % (95 % CI: -0.01 to 2.31), 1.69 % (95 % CI: -0.36 to 3.77), 2.25 % (95 % CI: 0.85 to 3.68), 2.08 % (95 % CI: 0.39 to 3.79), and 2.95 % (95 % CI: 0.52 to 5.44) increment in the risk of EADs for respiratory illnesses in the high temperature category as defined using 75th, 80th, 85th, 90th, and 95th percentile temperatures, respectively (Table S8). However, the effect of O<sub>3</sub> on EADs for cardiovascular illnesses was estimated to be similar for the low, moderate, and high temperature categories and the risk of EADs for cardiovascular illnesses in high temperature category defined by different temperature percentile cut-offs was similar with no statistical significance. In particular, a 10 ppb increase in O<sub>3</sub> concentration was associated with 0.19 % (95 % CI: -0.85 to 1.25), 0.30 % (95 % CI: -0.62 to 1.22), -0.14 % (95 % CI: -1.21 to 0.94), 0.17 % (95 % CI: -1.12 to 1.48), and 0.89 % (95 % CI: -0.94 to 2.76) increment in the risk of EADs for cardiovascular illnesses in the high temperature category as defined using 75th, 80th, 85th, 90th, and 95th percentile temperatures, respectively (Fig. 4). These findings show that the association between O<sub>3</sub> and EADs for all acute illnesses and cardiovascular illnesses at high temperature category is insensitive, in terms of statistically significant association,

**Table 3**

Percent increase and its 95 % confidence interval (CI) of EADs for all-acute, cardiovascular, and respiratory illnesses per 10 ppb increase of O<sub>3</sub> at different temperature categories, defined by 25th and 75th percentiles.

Category	EADs for all acute illness	EADs for cardiovascular illness	EADs for respiratory illness
Low	0.01 (95 % CI: -0.28, 0.30)	-0.20 (95 % CI: -1.53, 1.16)	0.68 (95 % CI: -0.88, 2.26)
Moderate	0.50 (95 % CI: 0.23, 0.76)	-0.15 (95 % CI: -0.82, 0.52)	0.17 (95 % CI: -0.77, 1.12)
High	0.80 (95 % CI: 0.25, 1.35)	0.19 (95 % CI: -0.85, 1.25)	1.14 (95 % CI: -0.01, 2.31)

Note: Pooled results at lag 0 are reported, where temperature categories are divided into low (<25th city-specific temperature percentile), moderate (25th – 75th city-specific temperature percentile), and high (>75th city-specific temperature percentile).

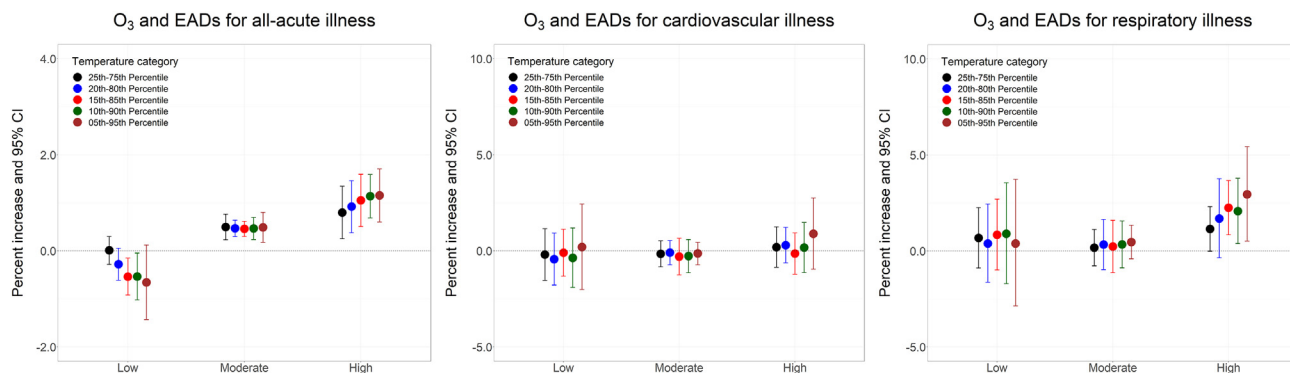


Fig. 4. Percent increase in the risk of EADs per 10 ppb increase in O<sub>3</sub> concentration by temperature category, as defined according to different percentile cut-offs.

to the threshold used, whereas that for respiratory illnesses at high temperature category is sensitive to the threshold used as defined by different temperature percentile cut-offs because the statistically significant association was not robust throughout the defined percentile cut-offs. Moreover, the association between O<sub>3</sub> and EADs for cardiovascular and respiratory illnesses at low temperature category is insensitive to the threshold used, whereas that for all acute illnesses is sensitive to the threshold used, where the statistically significant association was not robust throughout the temperature percentile cut-offs. City-specific and pooled estimates of the effects of O<sub>3</sub> on EADs for all acute, cardiovascular, and respiratory illnesses by temperature category, according to different percentile cut-offs, are shown in Table S8.

#### 4. Discussion

We examined effect modification of the association between short-term O<sub>3</sub> exposure and EADs by temperature in eight Japanese cities, and found that the estimated effects of O<sub>3</sub> on EADs for all acute, cardiovascular and respiratory illnesses increased with increasing temperature, although those of O<sub>3</sub> on EADs for cardiovascular illnesses and respiratory illnesses were not statistically significant. This result has important public health implications in the context of increasing temperature under a changing climate, and likewise provides useful insights for investigating the health effects of O<sub>3</sub> under different climate change scenarios in the future.

A number of previous studies have examined whether ambient temperature modifies the association between air pollution and health outcomes, with inconsistent results. In particular, a previous study conducted in nine European cities, revealed that there was the interaction effects between O<sub>3</sub> and high temperature on all natural causes of deaths, where the risk of mortality for all natural causes associated with exposure to apparent temperature was greater during high O<sub>3</sub> days (Analitis et al., 2018). Similar finding was also observed in a nationwide multicounty study in China, suggesting that high temperature escalate the effects of O<sub>3</sub> on non-accidental, cardiovascular, and respiratory mortality (Shi et al., 2020), which is in agreement with the association pattern observed in the current study. However, a study in 97 US cities found no significant effect modification by temperature on the association between O<sub>3</sub> and mortality (Jhun et al., 2014), while another study reported significant effect modification on the O<sub>3</sub>-mortality association in the 60 large eastern US communities, indicating that simultaneous exposure to high temperature and high O<sub>3</sub> levels is associated with an increased risk of non-accidental mortality in the northeast region, but such association was not observed in the southeast region (Ren et al., 2008). The reason for this inconsistency may be explained by the differences in temperature, and population and geographical characteristics (Ren and Tong, 2008).

In the present study, the association between O<sub>3</sub> and EADs for all acute, cardiovascular, and respiratory illnesses was higher in the high temperature category compared to the moderate and low temperature categories, although the associations between O<sub>3</sub> and EADs for cardiovascular and respiratory illnesses were not statistically significant. This finding is

consistent with the previous studies, reporting that O<sub>3</sub> is highly correlated with temperature (Camalier et al., 2007; Lacour et al., 2006), where the effects of O<sub>3</sub> on respiratory mortality were modified by high temperature and those on respiratory admission were increased during warm season (Areal et al., 2022). An increase in temperature is substantially associated with an increase in O<sub>3</sub> concentration, as the rate of chemical reactions changes with temperature (Bloomer et al., 2009; Camalier et al., 2007; Jacob and Winner, 2009). Consequently, health effects of O<sub>3</sub> are more pronounced during high temperature periods (Bell et al., 2005; Ito et al., 2005). Previous studies have also reported that O<sub>3</sub> is an important contributor that aggravates heat-related mortality during heat-wave days in Europe, including in the Netherlands (Fischer et al., 2004), Belgium (Sartor et al., 1995), and France (Dear et al., 2005).

High temperature and O<sub>3</sub> have been associated with various adverse health effects (i.e., mortality and morbidity). For example, exposure to high temperature has been linked to dehydration, increased blood viscosity, and arterial thrombosis (Gostimirovic et al., 2020), all of which can lead to coronary thrombosis and many other cardiovascular diseases (Lubczyńska et al., 2015; Michelozzi et al., 2009). Exposure to high levels of O<sub>3</sub> is also likely to be associated with injuries to the nasal cavity, trachea, and central acinar region by altering the metabolic and physiologic activities in the respiratory system (Thurston and Ito, 1999), increase vascular markers of inflammation, and cause changes in fibrinolytic markers and autonomic control of heart rate, with possible damage to the circulatory system (Devlin et al., 2012). However, the biological pathway underlying the interaction effect of O<sub>3</sub> and high temperature has rarely been reported. A previous study showed that simultaneous exposure to O<sub>3</sub> (0.5 ppm) and high temperature (33 °C) decreases the Forced Vital Capacity (FVC) and the Forced Expiratory Volume in one second (FEV<sub>1</sub>). A recent study has also reported that estimated effect of O<sub>3</sub> on respiratory diseases significantly varied by seasons (Bergmann et al., 2020), and the effects of O<sub>3</sub> on hospital admissions due to pneumonia and chronic obstructive pulmonary disease was pronounced during warm season (Medina-Ramón et al., 2006), suggesting an interaction effect of high O<sub>3</sub> level and high temperature on the respiratory system (Grigorieva and Lukyanets, 2021). Moreover, exposure to O<sub>3</sub> at high temperature induces an increase in Plasminogen Activator Inhibitor-1 (PAI-1), a parallel increase in plasminogen and a decrease in D-dimer (i.e., fibrin degradation product), thereby reducing the efficiency of preventing blood clots (Kahle et al., 2015). These reports suggest that exposure to O<sub>3</sub> on high temperature days might increase the risk of cardiovascular illnesses (e.g., thrombosis), especially in susceptible individuals. In other words, exposure to both O<sub>3</sub> and high temperature simultaneously may multiply their individual effects on human health outcomes. As for a possible explanation for the enhanced effects of O<sub>3</sub> on high temperature days, spending more time outdoors or keeping windows open for natural cross-ventilation may increase the amount of O<sub>3</sub> exposure (Iwashita and Akasaka, 1997; Salonen et al., 2018).

This study is the first to report on the interactive effect of O<sub>3</sub> and temperature on the risk of EADs in Japan. Our findings provide evidence for

the enhanced short-term effect of O<sub>3</sub> due to high temperature. However, the present study has some limitations worth noting. First, we used data from only eight cities in Japan. Thus, our results may not be generalizable to the whole country. Second, similar to previous studies, we extracted air pollution data from only one fixed-site monitoring station in each city, which might not accurately reflect personal exposure levels, thereby introducing a possibility of misclassification error and biasing the estimates toward the null hypothesis. Nevertheless, previous studies revealed that O<sub>3</sub> concentration measured at fixed-site monitoring stations is well correlated with that measured by personal exposure (Haga et al., 2021), and outdoor O<sub>3</sub> concentration is contributed significantly to personal exposure (Tang et al., 2012). Therefore, stationary measurement is valid to apply as proxy for personal exposure in environmental health risk assessment studies, to some extent. Third, we did not handle missing exposure value prior to analysis in this study, in which 1.2 % of daily O<sub>3</sub> concentration over eight cities during the study period was missing. Although keeping incomplete data is a simple strategy, bias may be introduced (Bhaskaran et al., 2013). Therefore, imputation of missing data in time-series analysis should be considered in the future studies (Junger and Ponce de Leon, 2015). Fourth, we analyzed the association between O<sub>3</sub> and EADs for all acute illness utilizing the data from 2007 to 2015 in eight Japanese cities, but that for cardiovascular and respiratory illnesses was performed using the data between 2007 and 2012, which is a little old as of 2022, due to unavailable data for cause-specific acute illnesses after 2012. However, the association patterns observed from this study can contribute to the implications of mitigating O<sub>3</sub> exposure under ongoing climate change to further reduce public health burden, to some extent. Finally, explanatory variables (i.e., air conditioner use, activity patterns) that could modify the effects of O<sub>3</sub> on EADs in different temperature categories were not addressed in the present study due to limited available data, where future studies should clarify the possible role of those explanatory variables on the effect of O<sub>3</sub> on EADs in different temperature categories.

## 5. Conclusions

The estimated effects of O<sub>3</sub> on EADs for all acute, cardiovascular, and respiratory illnesses increased as temperature becomes higher, although those of O<sub>3</sub> on EADs for cardiovascular and respiratory illnesses were not statistically significant. Our results provide valuable insights for investigating the health effects of simultaneous exposure to O<sub>3</sub> and high temperature, with important implications for public health interventions in Japan. As temperature is expected to rise in the future, our findings underpin the need to enhance the mitigation measures against O<sub>3</sub> pollution to prevent the interactive health impacts by simultaneous exposure to O<sub>3</sub> and high temperature.

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## Ethics approval

This study was approved by the Ethics Review Committee of Kyoto University Graduate School of Engineering. Written informed consent was not required because aggregated secondary data were used in this study.

## CRedit authorship contribution statement

**Arthit Phosri:** Conceptualization, Method, Formal analysis, Data curation, Writing – original draft, Visualization. **Kayo Ueda:** Supervision, Writing – review & editing, Funding acquisition. **Xerxes Seposo:** Methodology, Writing – review & editing. **Akiko Honda:** Supervision. **Hirohisa Takano:** Supervision.

## Data availability

The data are available in supplementary file and from the corresponding author on reasonable request.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2022.160725>.

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