ORIGINAL

Association of short-term ozone exposure with pulmonary function and respiratory symptoms in schoolchildren : A panel study in a western Japanese city

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Abstract : The average annual ozone levels have been increasing in Japan, even though the high ozone levels have decreased in recent years. There is limited information on the relationship between ozone exposure, pulmonary function, and respiratory symptoms in schoolchildren in Japan. The aim of this study was to investigate the effects of short-term ozone exposure on pulmonary function and respiratory symptoms in Japanese schoolchildren. Afternoon peak expiratory flow (PEF) values and respiratory symptom scores were recorded daily in 276 schoolchildren from September to October 2016 and from January to February 2017. The association of daily ozone levels with PEF was assessed using a linear mixed model and that with respiratory symptoms was evaluated by generalized estimating equations logistic regression analysis. There was a significant association of daily ozone levels with PEF values. A 13.6-ppb increment in the interquartile range for ozone exposure was significantly associated with a decrease in PEF of –3.67 L/min (95% confidence interval –4.73, –2.61). However, increased ozone levels were not associated with an increased risk of respiratory symptoms. Our present findings suggest that more attention should be paid to the potential adverse effects of short-term ozone exposure on pulmonary function in schoolchildren. J. Med. Invest. 65 : 236-241, August, 2018

***Keywords* :** *ozone, peak expiratory flow, pulmonary function, respiratory symptoms, schoolchildren*

INTRODUCTION

Mainland East Asia has undergone rapid industrial development in recent decades, which has increased the amount of ozone in the boundary layer and led to this region now being one of the most heavily polluted in the world (1). In recent years, the high levels of photochemical ozone have been decreasing in Japan, but the average annual level remains on an upward trend (1-3). Recent studies suggest that the transboundary transport of ozone from the East Asian continent has contributed to increased ozone levels in Japan, especially in springtime and in the western part of Japan (2, 4-6). Therefore, ozone continues to be a health concern in Japan.

Several studies have investigated the effects of short-term exposure to ozone on respiratory health, particularly in healthy children and children with respiratory diseases such as asthma (7-13). The respiratory system in children is immature and has a surface to volume ratio that is larger than that in adults (14). Children also have higher baseline ventilation rates, are more physically active, and spend more time outside than adults (14-16). Nasal breathing allows inhaled air to reach the lower airway in a state that does not threaten homeostasis, but children are more typically mouth-breathers (14-17). These characteristics may allow air pollutants to penetrate deeper into the lower airways in children than in adults, thereby making clearance slower and more difficult. Thus, children are considered to be more sensitive to ozone than adults.

The toxicological mechanisms underlying the effect of ozone on health have gradually been clarified. There is some evidence demonstrating an association between ozone and intermediary inflammatory outcomes (18-21). According to these in *vitro* and *vivo* analyses, after ozone is engulfed or phagocytosed by cells, various pro-inflammatory mediators, such as interleukin (IL)-6 and IL-8, are secreted by cells. These pro-inflammatory mediators may be generated in response to reactions with the fluid in the epithelial lining of the airway and the cell membranes (22-24).

There have been many studies on the association between exposure to ozone and morbidity in Japan ; however, to the best of our knowledge, there have been no investigations of the effects of short-term exposure to ozone on pulmonary function and respiratory symptoms in Japanese schoolchildren. The aim of this study was to investigate the association of short-term exposure to ozone with pulmonary function and respiratory symptoms in schoolchildren in Japan.

METHODS

Study design

This panel study was approved by the Ethics Committee at the Faculty of Medicine, Tottori University (approval number 1509A 046) and the Matsue City Board of Education. The participating schoolchildren and their parents were informed of the study by their teachers and written consent was obtained.

Two hundred and seventy-six 11–12-year-old schoolchildren from three of the 35 elementary schools in Matsue, the capital city of Shimane Prefecture, southwest Japan, were enrolled in the study in 2016. Matsue has a population of approximately 200,000 and

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covers an area of 530.2 km^2. The three elementary schools are located within 3 km of each other, and all children in the study resided within a 1-km radius of their school. All children walked to school and were potentially exposed to air pollutants.

Peak expiratory flow (PEF) and respiratory symptoms were monitored daily in the afternoon from September to October 2016 and from January to February 2017. Data on sex, height, weight, asthma, and allergic rhinitis were recorded in September 2016. The subjects were considered to have asthma if they had a diagnosis of asthma made by a pediatrician or had experienced wheezing, used medication for asthma, or visited a hospital because of asthma in the previous 12 months. The subjects were considered to have allergic rhinitis if they had a diagnosis of allergic rhinitis made by a pediatrician, used medication for allergic rhinitis, or visited a hospital because of allergic rhinitis in the previous 12 months.

Recording of daily afternoon PEF and respiratory symptoms

The study participants and their teachers were taught how to measure PEF using a peak flow meter (Mini-Wright, Harlow, UK, American Thoracic Society scale) before the start of the study. On school days from September 1, 2016 to October 31, 2016 and from January 10, 2017 to February 28, 2017, the children recorded their best PEF value of three attempts between 3 pm and 4 pm. The children also recorded their lower respiratory tract symptom scores, including for cough and/or sputum. Symptom scores ranged from 0 (none) to 2 (severe), as in previous studies (25, 26).

Measurement of air pollutant levels

The concentrations of nitrogen dioxide (NO_2), particulate matter less than 2.5 μm in diameter ($PM_{2.5}$), sulfur dioxide (SO_2), and photochemical oxidants recorded in Matsue during the study period were obtained from the Japanese Ministry of the Environment. Photochemical oxidants are comprised mainly of ozone. As in other studies, photochemical oxidant levels were used to indicate the levels of ozone. The daily average NO_2, ozone, SO_2, and $PM_{2.5}$ levels were calculated as the average of the hourly concentrations over 24 hours. Meteorological variables, including daily temperature, humidity, and atmospheric pressure, were obtained from the Japan Meteorological Agency. These data were used to examine the associations of PEF values and respiratory symptom scores with ozone levels.

Statistical analysis

Linear mixed models that take into account the correlations among repeated measurements in the same subject were used to estimate the relationship between daily PEF values and daily mean ozone levels (27). Generalized estimating equation (GEE) logistic regression analyses that also account for correlations between repeated measurements in the same subject were used to estimate the relationship between daily respiratory symptoms and daily average ozone levels (28). A respiratory event was deemed to have occurred when a daily respiratory score ≥ 2 was recorded. The linear mixed and GEE logistic regression models included demographic, anthropometric, and clinical variables (sex, height, weight, asthma, allergic rhinitis, and passive smoking) and meteorological variables (daily temperature, humidity, and atmospheric pressure) as explanatory variables (29-33). The estimates are presented as the absolute difference in PEF values and as the odds ratios (with 95% confidence intervals [CIs]) for respiratory events per interquartile range (IQR) change in ozone levels with 95% CIs. The working correlation matrix was set to exchangeable and robust variance estimators were used to construct the CIs for the odds ratios. Missing covariates data were accounted for by the multiple imputation method to address the uncertainty of imputed values based on multiply generated prediction values for missing data (34). The post-exposure "lagged" effect of ozone on PEF values and respiratory symptom scores from 0 to 3 days (lag 0–3 days) was evaluated. Two-pollutants models were applied to different combinations of air pollutants (NO_2, $PM_{2.5}$, and SO_2) to assess the stability of the effects of ozone on PEF values and respiratory symptom scores after adjustment for individual characteristics (sex, height, weight, asthma, allergic rhinitis, and passive smoking) and meteorological variables (temperature, humidity, and atmospheric pressure). Interaction tests in the regression models were used to assess whether there were significant seasonal differences in the effects of exposure to ozone. The linear mixed models and GEE analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). All quoted P-values are two-sided, with a significance level of 0.05.

RESULTS

Subject characteristics

The characteristics of the 276 children are shown in Table 1. In some cases, data were missing for height (n = 2), body weight (n = 6), and passive smoking (n = 4).

Meteorological data and air pollutant levels

Table 2 presents the average and IQR values for daily average temperature, humidity, and barometric pressure and the average NO_2, ozone, $PM_{2.5}$, and SO_2 levels from September 1, 2016 to October 31, 2016 and from January 1, 2017 to February 28, 2017. There were significant differences in the daily average temperature, humidity, and barometric pressure recordings and in the average concentrations of NO_2, ozone, $PM_{2.5}$, and SO_2 between September to October 2016 and January to February 2017. Figure 1 shows the hourly levels of ozone for each day in September 2016, October 2016, January 2017, and February 2017.

PEF and respiratory symptom scores

Changes in PEF values in relation to IQR changes in the ozone level are presented in Table 3. A 13.6-ppb increase in ozone concentration was significantly associated with a −3.67 L/min decrease in PEF. The significant relationship between PEF and ozone level persisted until the next day (lag 1). However, there was no significant association between respiratory symptom scores and ozone levels (Table 4). In the two-pollutants models adjusted for NO_2, $PM_{2.5}$, and SO_2, ozone levels were significantly associated with PEF values but not with respiratory symptom scores (Tables 5 and 6). Table 7 shows the differences in changes in PEF values and the odds ratios for respiratory symptom scores with IQR increases in ozone levels between September to October 2016 and January to February 2017. The change in PEF values for September to October 2016 was significantly associated with the ozone level. However, there was no significant association between the change in PEF values for January to February 2017 and ozone levels. The change in PEF values for September to October 2016 was significantly smaller than that for January to February 2017 ($P < 0.001$). There was no relationship between the odds ratios for respiratory symptom scores and ozone levels in either September to October 2016 or January to February 2017. The odds ratios for respiratory symptom scores for September to October 2016 was significantly larger than those for January to February 2017 ($P = 0.023$). Table 8 shows the differences in changes in PEF values and odds ratios for respiratory symptom scores with IQR increases in ozone levels between children with and without asthma. There was a significant relationship between PEF and the ozone level in children without asthma but not in those with asthma. There was no significant association of respiratory symptom scores with ozone levels whether asthma was present or not.

Table 1. Characteristics of the 276 children included in this study

Boys/Girls	133/143
Height (cm)	147.5 ± 7.4
Boys	146.9 ± 7.3
Girls	147.8 ± 7.5
Weight (kg)	38.5 ± 7.4
Boys	38.6 ± 7.4
Girls	39.1 ± 6.7
Asthma	28 (10.1%)
Allergic rhinitis	68 (24.6%)
Best PEF (L/min)	428.3 ± 63.0

The data are shown as the mean ± standard deviation or n (%). In some cases, data were missing for height (n = 2), body weight (n = 6), and passive smoking (n = 4). PEF, peak expiratory flow.

DISCUSSION

The ozone level has increased over a wide area of Japan during recent years because of increased emission of precursors of ozone, such as volatile organic compounds and nitrogen oxides, in East Asia (33, 34). The present study was conducted to determine the association of short-term exposure to current ozone levels with pulmonary function and respiratory symptoms in schoolchildren in Japan. We found that ozone levels were significantly associated with pulmonary function but not with respiratory symptoms. These results suggest that more attention should be paid to the potential adverse respiratory effects of short-term exposure to ozone in children.

Although the daily average ozone level for January to February 2017 was larger than that for September to October 2016, there was a significant association between the ozone level and pulmonary function for September to October 2016 but not for January to

Table 2. Average daily weather conditions and air pollutant concentrations

	Sep-Oct, 2016 and Jan-Feb, 2017		Sep-Oct 2016		Jan-Feb 2017	
Variable	Average	IQR	Average	IQR	Average	IQR
Temperature (°C)	13.5 ± 8.6	16.7	20.8 ± 3.7	5.8	4.4 ± 2.2	2.9
Humidity (%)	81.4 ± 9.6	12.5	85.0 ± 8.3	11.0	77.0 ± 9.4	12.0
Atmospheric pressure (hPa)	1014.9 ± 6.0	8.6	1013.0 ± 4.9	6.5	1017.4 ± 6.3	8.6
NO_2 (ppb)	2.7 ± 1.4	1.2	2.2 ± 0.9	1.1	3.3 ± 1.8	2.9
Ozone (ppb)	33.8 ± 9.0	13.6	30.1 ± 8.6	9.2	38.5 ± 7.2	8.0
$PM_{2.5}$ (μg/m³)	9.2 ± 4.9	5.3	8.7 ± 5.0	4.7	9.7 ± 4.7	6.4
SO_2 (ppb)	1.2 ± 1.3	0.9	0.5 ± 0.5	0.6	2.0 ± 1.5	2.2

The data are shown as the mean ± standard deviation. IQR, interquartile range ; NO_2, nitrogen dioxide ; $PM_{2.5}$, particulate matter smaller than 2.5 μm ; SO_2, sulfur dioxide.

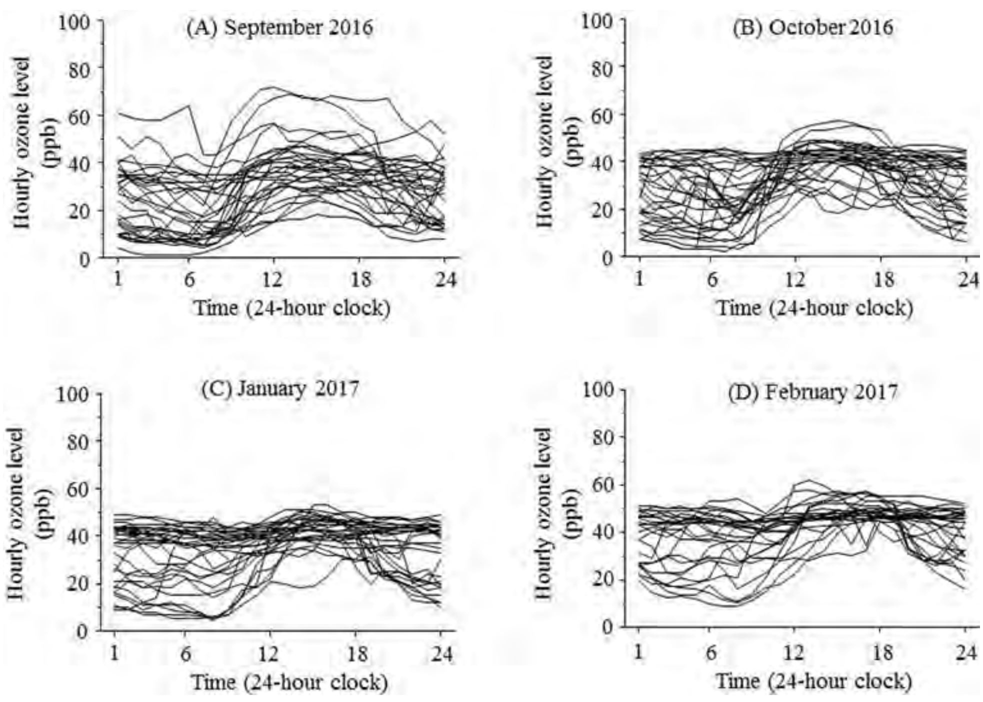

Figure 1. The transition of hourly levels of ozone on each day in (A) September, 2016, (B) October, 2016, (C) January, 2017, and (D) February, 2017.

Table 3. Estimated changes in daily PEF values with IQR increases in ozone levels according to multivariate analysis using linear mixed models

Days	Change in PEF (L/min)	95% CI	*P*–value
Lag 0	−3.67	−4.73, −2.61	< 0.01
Lag 1	−1.29	−2.24, −0.33	< 0.01
Lag 2	1.47	0.52, 2.41	< 0.01
Lag 3	0.59	−0.33, 1.50	NS

CI, confidence interval ; IQR, interquartile range ; NS, not statistically significant ; PEF, peak expiratory flow.

Table 4. Estimated odds ratios and 95% confidence intervals for daily respiratory symptom scores with interquartile range increases in ozone levels according to generalized estimating equation logistic regression analyses

Days	OR	95% CI	*P*–value
Lag 0	1.01	0.98, 1.04	NS
Lag 1	1.01	0.94, 1.03	NS
Lag 2	1.00	0.97, 1.02	NS
Lag 3	1.01	0.99, 1.03	NS

CI, confidence interval ; NS, not statistically significant ; OR, odds ratio

Table 5. Estimated changes in daily PEF values with interquartile range increases in ozone levels according to two-pollutant models after adjustment for NO_2, $PM_{2.5}$, and SO_2

Adjustment	Change in PEF value (L/min)	95% CI	*P*–value
For NO_2	−5.26	−6.43, −4.09	< 0.01
For $PM_{2.5}$	−3.45	−4.64, −2.52	< 0.01
For SO_2	−3.58	−4.54, −2.37	< 0.01

CI, confidence interval ; NO_2, nitrogen dioxide ; PEF, peak expiratory flow ; $PM_{2.5}$, particulate matter smaller than 2.5 μm ; SO_2, sulfur dioxide.

Table 6. Estimated odds ratios and 95% confidence intervals for daily respiratory symptom scores with interquartile range increases in ozone levels according to two-pollutants models after adjustment for NO_2, $PM_{2.5}$, and SO_2

Adjustment	OR	95% CI	*P*–value
For NO_2	1.01	0.93, 1.09	NS
For $PM_{2.5}$	1.03	0.96, 1.10	NS
For SO_2	1.01	0.95, 1.10	NS

CI, confidence interval ; NO_2, nitrogen dioxide ; NS, not significant ; OR, odds ratio ; $PM_{2.5}$, particulate matter smaller than 2.5 μm ; SO_2, sulfur dioxide.

February 2017. Furthermore, there was a significant difference in the changes in PEF values between September to October 2016 and January to February 2017. There were more days with high ozone levels during the daytime (10 am to 6 pm) in September to October 2016 than in January to February 2017. During the study period, there were two days (both in September 2016) on which the hourly ozone level was higher than the Japanese environmental standard of 0.06 ppm. The difference in the association of ozone levels with pulmonary function between September to October 2016 and January to February 2017 may reflect the daytime ozone levels. This relationship may also explain why the respiratory symptom scores for September to October 2016 were significantly higher than those for January to February 2017. Furthermore, although there was no significant association between respiratory symptom scores and ozone levels, the odds ratio for the 95% CI in September to October 2016 ranged from 1.00 to 1.18 and almost reached significant difference. Another reason may be the difference in time spent outdoors. In Japan, schoolchildren spend more time outdoors on school days in the warmer months of September and October than in the colder months of January and February.

The transport of ozone from mainland East Asia to Japan is more noticeable on the western side of the main island of Japan because of location and climatic factors. This study was conducted in a representative sample of the general population of schoolchildren in the city of Matsue, Shimane Prefecture, Japan. Matsue provides a unique opportunity to study the relationship between ozone levels and respiratory health because it is located on the western side of Japan, is a small city, and does not have any large air pollution source, such as an industrial plant. Therefore, it can be argued that the increased ozone levels in Matsue are associated with the heavy air pollution in mainland East Asia and that the air pollutants emanating from this region are having an effect on lung function in

Table 7. Differences in changes in PEF values and odds ratios for respiratory symptom scores with interquartile range increases in ozone levels between September to October 2016 and January to February 2017

Study period	Change in PEF values (L/min)	95% CI	*P*–value
September to October 2016	−4.76	−6.03, −3.50	< 0.01
January to February 2017	−0.42	−1.99, 1.14	NS
	OR for respiratory symptom scores	95% CI	*P*–value
September to October 2016	1.09	1.00, 1.18	NS
January to February 2017	0.92	0.83, 1.04	NS

CI, confidence interval ; NS, not significant ; OR, odds ratios ; PEF, peak expiratory flow

Table 8. Differences in changes in PEF values and odds ratios for respiratory symptom scores with interquartile range increases in ozone levels between children with and without asthma

Subjects	Change in PEF values (L/min)	95% CI	*P*–value
Children with asthma (n = 28)	−1.20	−4.37, 1.96	NS
Children without asthma (n = 248)	−3.84	−4.98, −2.71	< 0.01
	OR for respiratory symptom scores	95% CI	*P*–value
Children with asthma (n = 28)	1.16	0.92, 1.46	NS
Children without asthma (n = 248)	1.95	0.93, 1.09	NS

CI, confidence interval ; NS, not significant ; OR, odds ratio ; PEF, peak expiratory flow.

schoolchildren in Japan.

The average PEF value decreased from −4.73 L/min to −2.61 L/min with an IQR increase in the ozone level of 13.6 ppb. The decrease may be small for the best PEF value. Therefore, although there was a significant association between pulmonary function and the ozone level, the decrease in PEF might be attributable to an error in the statistical analysis arising from relative variations during PEF examinations and the interactive effects of the combinations. Karakatsani *et al*. found a significant association of short–term exposure to ozone and pulmonary function in children (35). In that study, the extent of the decrease in pulmonary function depended on forced vital capacity and forced expiratory volume in 1 second with an increase of 10 $\mu g/m^3$ in weekly ozone concentration were about 1% for basic values. Therefore, the decrease in pulmonary function arising from short–term exposure to ozone was small, as in the present study. However, there may be a susceptibility factor for ozone exposure. Previous studies have suggested a strong trend of decreasing pulmonary function in response to increasing ozone exposure in children with respiratory diseases such as asthma when compared with children without such diseases (7-13). Only 10.1% of children in the present study had asthma, so the number of children who experienced a decrease in PEF in response to ozone exposure may have been small and could have accounted for the small reduction in PEF values.

Although airway hyperresponsiveness is the characteristic functional abnormality of asthma that results in narrowing of the airways in response to a known or unknown stimulus, in this study there was a significant association between the ozone level and pulmonary function in children without asthma but not in those with asthma. Similarly, we did not find an association of respiratory symptom scores with ozone in children with asthma. These results may be attributable to the small number of children with asthma in our study.

This study has several limitations. First, we were unable to measure the ozone exposure levels in individual subjects. However, PEF values and respiratory symptom scores were recorded on school days. The difference in the amount of ozone exposure would be smaller during school time than in non-school time. Second, we did not determine if there was a difference in the amount of time spent outdoors between September to October 2016 and January to February 2017. Third, respiratory symptom scores were not able to be confirmed because validated respiratory symptom scoring instruments for children with and without respiratory disease are not available in Japan. Therefore, as in previous investigations of the association of $PM_{2.5}$ with respiratory symptoms, we used a respiratory symptom scoring system based on cough and/or sputum that ranges from 0 (no symptoms) to 2 (severe symptoms) (25, 26). Fourth, arrival of ozone from the East Asian continent increases ozone levels in Japan, especially in spring (2, 4-6). Therefore, PEF and respiratory symptoms should also be monitored during spring. However, because of the changes in grades and classes in April, it was difficult to secure the cooperation of teachers with the survey in spring, so we were unable to assess the association of ozone with pulmonary function and respiratory symptoms. Finally, it was not possible to confirm that asthma and allergic rhinitis were diagnosed by a physician. The percentages of children with asthma and allergic rhinitis in this study were 10.1% and 24.6%, respectively. According to a survey by the Japanese Ministry of Health, Labor and Welfare in 2003 (36), the prevalence rate was 11%–14% for asthma and 20%–25% for allergic rhinitis in Japan. Our percentages for children with asthma and those with allergic rhinitis seem reasonable in view of the previously reported prevalence rates in Japan.

The present study found a significant association of exposure to ozone with decreased pulmonary function but not with respiratory symptoms in schoolchildren in Japan. The adverse effect of ozone on pulmonary function was more marked in September and October than in January and February. The ozone concentration has increased across a wide area of Japan in recent years because of the increasing problem of air pollution emanating from East Asia (1-6). Our present findings suggest that more attention should be paid to the potential adverse effects of short-term exposure to ozone on respiratory health in schoolchildren.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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