Association Between Ground-level Ozone and Kawasaki Disease in Seoul, South Korea

P2-H11

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BACKGROUND

- Kawasaki disease (KD) is a type of acute febrile vasculitis that primarily affects children under 5 years of age and the highest incidence of KD is reported mainly in Northeast Asia, including Japan and Korea.
- Few previous studies have shown the association between the incidence of KD and environmental factors. Factors significantly associated with the occurrence of KD vary by study region.

The aim of the present study was to investigate the short-term effects of environmental factors on Kawasaki disease in Seoul, Korea, and to examine differences in the effect of environmental factors through a stratification analysis by sex.

METHODS

- This study is an ecological study.

Selection of Variables

- **Dependent variable**: KD was defined as patients (< 5 years of age) assigned with the discharge diagnostic code M30.3 in the ICD 10th Revision, by the National Health Insurance Sharing Service. Weekly KD incidence were calculated as total number of KD cases divided by the mid-year population per 100,000 people per year from 2013 to 2017.
- **Independent variables: a. Climate factors:** Weekly average temperature (°C), diurnal temperature range (°C), rainfall (mm), relative humidity (%), wind speed (m/s), atmospheric pressure (hPa), duration of sunshine (h), solar radiation (MJ/m²), and the amount of clouds (×10%) in Seoul between 2013, and 2017 **b. Air pollutants;** Air pollutant measurement data were obtained from 25 observation stations in Seoul between November 11, 2012, and December 31, 2017. Explanatory variables included in the analysis were particulate matter, with a median aerometric diameter of < 10 µm (PM_{10} [µg/m3]), O_3 (in parts per billion [ppb]), SO_2 (ppb), CO (ppb), and NO_2 (ppb), measured at each station.

Statistical Analysis

- **Descriptive analysis**: All variables are expressed as mean ± standard deviation or median (interquartile range). Using Spearman's correlation analysis, the correlation between variables was searched, and the multicollinearity of the regression model was estimated. Highly correlated variables (r > 0.7)
- **Semiparametric general additive model (GAM) analysis:** We performed a time-series analysis to assess the effects of single lag (lag 0–7) and cumulative lag (lag 01–07) weeks for each environmental factor. The Fourier term for seasonality adjustment was applied to the multivariate analysis of the model with the smallest Akaike information criterion (AIC) when placed in the model among sine, cosine, and sine + cosine function. . The model is specified as follow;

$$\log[E(Yt)] = \alpha + s(\text{climate factors}) + s(\text{air pollutants}) + \text{time} + \text{Fourier term}$$

Where t is the week of observation; E(Yt) denotes the estimated number of weekly KD in week t; α is the intercept; s( ) represents the smoothing functions of the environmental variables; time denotes weeks of calendar time in week t.

- For the final model validation, we used residual plots to determine autocorrelation or specific patterns in the model. In addition, a concurvity test was performed to confirm the multicollinearity of the GAM model.
- All statistical analyses were conducted using R software (version 4.2.1) using the mgcv, gamRR, and lubridate packages.

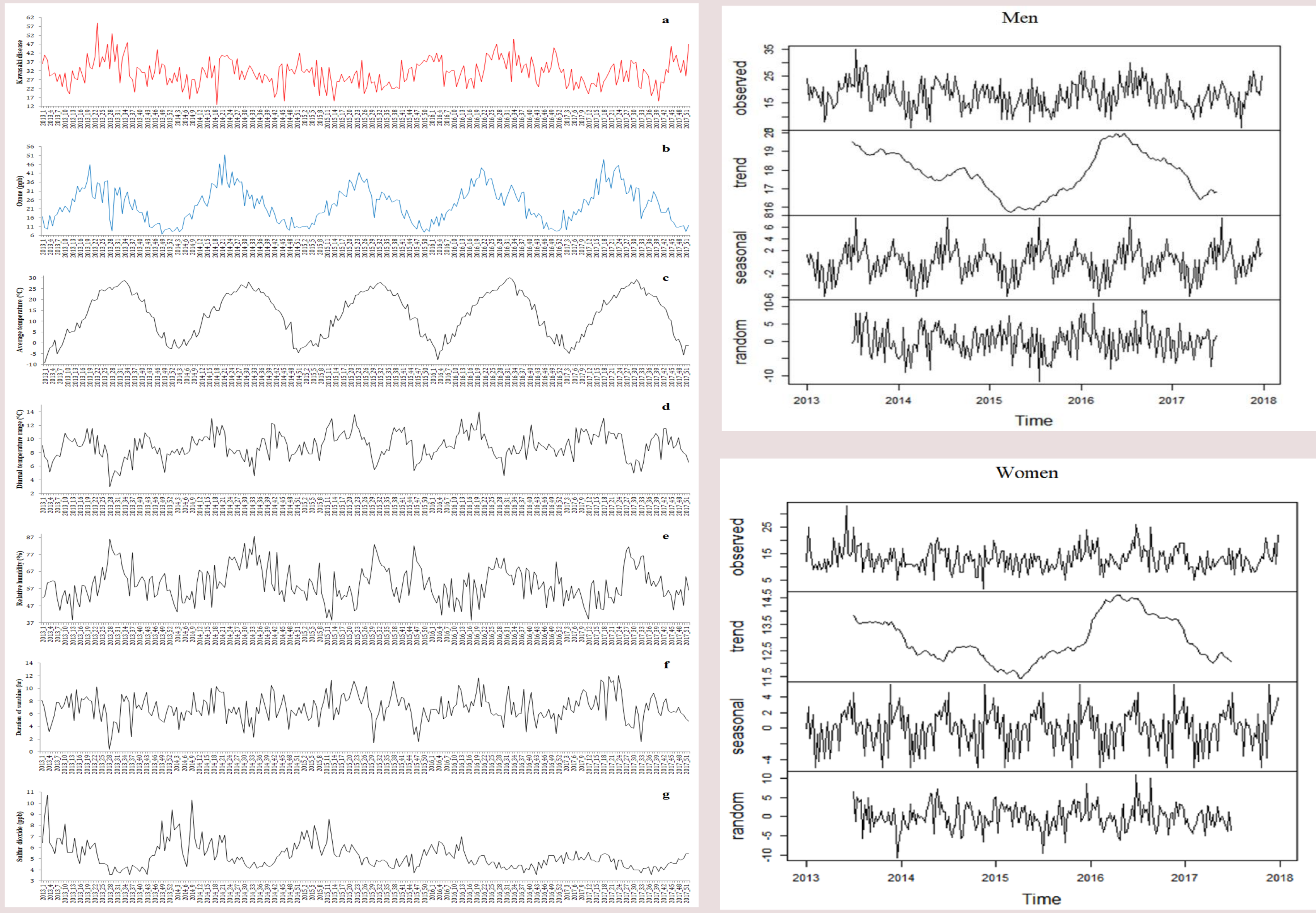
RESULTS

Descriptive Statistics of the Kawasaki disease cases and Environmental Factors, 2012-2017

Weekly data	Mean	SD	Min	P25	P50	P75	Max
Kawasaki disease (N)	30.99	7.459	13	26	31	36	59
Climate factors							
Average temperature (°C)	13.29	10.498	−9.17	2.86	14.66	23	30.13
Diurnal temperature range (°C)	8.97	1.877	3.01	7.73	8.92	10.29	13.96
Relative humidity (%)	59.92	10.073	38.36	52.73	58.82	67.31	87.59
Duration of sunshine (h)	6.89	2.076	0.4	5.7	6.8	8.19	12.01
Air pollutants							
O_3 (parts per billion)	23.31	9.939	6.73	15.14	22.57	30.57	51.43
SO_2 (parts per billion)	5.23	1.159	3.57	4.43	5.0	5.71	10.71

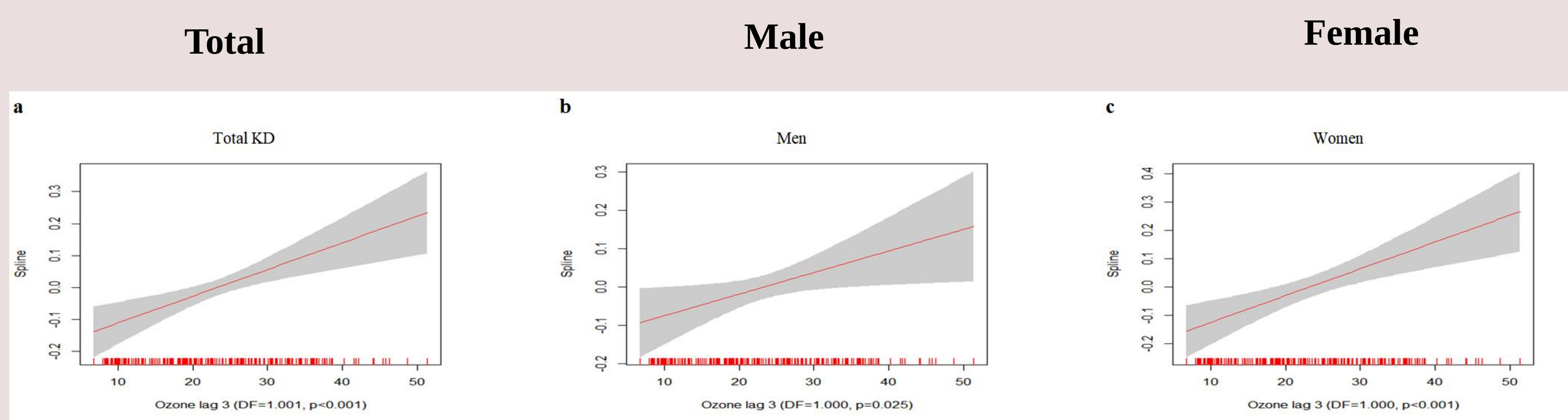
SD, standard deviation; Min, minimum; P, percentile; Max, maximum

Plots of weekly Kawasaki disease and environmental factors in Seoul, 2013-2017



(Left) Time series plot of (a) weekly Kawasaki disease, (b) O_3, (c) average temperature, (d) diurnal temperature range, (e) relative humidity, (f) duration of sunshine, and (g) SO_2 in Seoul from 2013 to 2017. (Right) Decomposition plot of additive time series of Kawasaki disease by sex.

Smoothed exposure–response relationship between Kawasaki disease and O_3

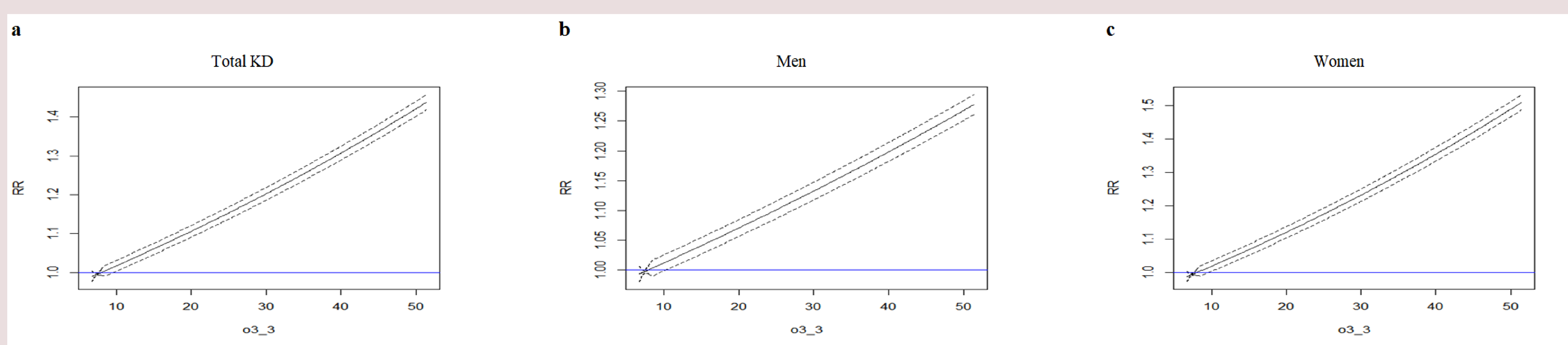


The line shows a spline curve, and the shaded grey area represents the 95% confidence interval. In total KD, which includes both men and women, the incidence of KD increased linearly as the concentration increased at O_3 lag 3.

Effect of a 1-ppb increase in the O_3 concentration on weekly Kawasaki disease

	Lag (week)	Percentage change	95% confidence interval		*p-value*
Total Cases	3	0.84	0.38	1.30	<0.001
Men	3	0.56	0.06	1.07	0.025
Women	3	0.95	0.45	1.45	<0.001

The effect on weekly KD occurrence for each 1-ppb increase in O_3. The incidence of KD positively correlated with O_3 in single-week lag 3 weeks. Models were controlled for average temperature, diurnal temperature range, relative humidity, duration of sunshine, and SO_2, time trend and seasonality.



The relative risk between O_3 (lag 3 weeks) and Kawasaki disease by sex. The line shows central estimates, and the dotted lines represent the 95% upper and lower limits. Models were controlled for average temperature, diurnal temperature range, relative humidity, duration of sunshine, and SO_2, time trend and seasonality

CONCLUSION

- The incidence of KD increased with increasing O_3 concentrations after accounting for potential confounding factors, such as average temperature, diurnal temperature range, relative humidity, duration of sunshine, and SO_2.
- Although the physiological mechanism underlying the effect of O_3 on KD is unclear, O_3 exposure causes intracellular oxidative damage through ozonide and hydroperoxide formation, and in vitro studies have shown that O_3 inhalation causes significant disturbance in coronary vascular function
- These results suggest that sex may affect the incidence of KD depending on the O_3 concentration.

- **All authors have no conflict of interest to declare.**
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