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ORIGINAL RESEARCH

Ambient Air Pollution and Kawasaki Disease in Korean Children: A Study of the National Health Insurance Claim Data

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BACKGROUND: Kawasaki disease (KD) is a systemic vasculitis of unknown etiology that primarily affects children under 5 years of age. Some researchers suggested a potential triggering effect of air pollution on KD, but the findings are inconsistent and limited by small sample size. We investigated the association between ambient air pollution and KD among the population of South Korea younger than 5 years using the National Health Insurance claim data between 2007 and 2019.

METHODS AND RESULTS: We obtained the data regarding particulate matter ≤10 or 2.5 μm in diameter, nitrogen dioxide, sulfur dioxide, carbon monoxide, and ozone from 235 regulatory monitoring stations. Using a time-stratified case-crossover design, we performed conditional logistic regression to estimate odds ratios (OR) of KD according to interquartile range increases in each air pollutant concentration on the day of fever onset after adjusting for temperature and relative humidity. We identified 51 486 children treated for KD during the study period. An interquartile range increase (14.67 μg/m^3) of particulate matter ≤2.5 μm was positively associated with KD at lag 1 (OR, 1.016; 95% CI, 1.004–1.029). An interquartile range increase (2.79 ppb) of sulfur dioxide concentration was associated with KD at all lag days (OR, 1.018; 95% CI, 1.002–1.034 at lag 0; OR, 1.022; 95% CI, 1.005–1.038 at lag 1; OR, 1.017; 95% CI, 1.001–1.033 at lag 2). Results were qualitatively similar in the second scenario of different fever onset, 2-pollutant model and sensitivity analyses.

CONCLUSIONS: In a KD-focused national cohort of children, exposure to particulate matter ≤2.5 μm and sulfur dioxide was positively associated with the risk of KD. This finding supports the triggering role of ambient air pollution in the development of KD.

Key Words: air pollution ■ Kawasaki disease ■ risk factor

Kawasaki disease (KD) is a systemic vasculitis of unknown etiology that primarily affects children under 5 years of age.[1,2] The common clinical signs are fever, skin rash, red eyes, red lips, enlarged anterior cervical lymph nodes, and joint pain.[3,4] KD can result in coronary artery aneurysms and is the leading cause of acquired heart disease among pediatric patients in high-income countries.[5,6] For children with acute KD, timely initiation of intravenous immunoglobulin (IVIG) treatment reduces the risk of coronary complications.[7,8]

Incidence of KD varies considerably between different racial and ethnic groups, with the highest rates among Asian/Pacific Islander children and the lowest among White children in the United States.[6,9,10] In Asian countries, the incidence of KD is as high as 191 in South Korea,[11] 184.6 in Japan,[2] 68.8 to 107.3 in China,[12] 69 in Taiwan,[13] and 2.1 to 3.4 in Thailand[14] per 100 000 children under 5 years of age. Prior epidemiological studies observed that the development of KD is associated with several respiratory viral infections, early childhood

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CLINICAL PERSPECTIVE

What Is New?

- This study investigated the association between ambient air pollution and development of Kawasaki disease using data from a Kawasaki disease-focused national cohort of children.
- In children aged under 5 years, short-term exposure to particulate matter ≤2.5 μm and sulfur dioxide was positively associated with the risk of Kawasaki disease.

What Are the Clinical Implications?

- Ambient air pollution may have a triggering role in the development of Kawasaki disease among children under 5 years of age.

Nonstandard Abbreviations and Acronyms

CO	carbon monoxide
KD	Kawasaki disease
NO_2	nitrogen dioxide
O_3	ozone
PM_{10} and $PM_{2.5}$	particulate matter ≤10 or 2.5 μm in diameter, respectively
SO_2	sulfur dioxide

environment, and winter season.[15–17] Although the cause of KD remains unknown, clinical findings suggest that a respiratory agent may trigger KD in susceptible children causing inflammation in the upper airway.[18–20] Some research reported a potential triggering effect of wind-borne desert dust and extreme temperature on KD,[21,22] but the findings are inconsistent and limited by small sample size.[23] Therefore, we investigated the association between ambient air pollution and KD using the data of all identified KD cases from the population aged under 5 years in South Korea.

METHODS

Because of the sensitive nature of the data constructed for this study, a subset of the data generated for this study are available from the corresponding author upon reasonable request.

Data Source

The National Health Insurance System is a public, single-payer system covering over 99% of all citizens and residents in South Korea. Following medical services, the provider sends reimbursement claims for medical expenses incurred to the Health Insurance Review & Assessment Service, which reviews the claims, assesses the quality of care provided, and evaluates adequacy for healthcare services.[24] Based on the results of the review by the Health Insurance Review & Assessment Service, the National Health Insurance System reimburses the service providers for the cost of supplying the medical services to patients. Using the Health Insurance Review & Assessment Service data, we constructed a KD-focused national cohort of children aged 0 to 4 years who had the *International Classification of Diseases, Tenth Revision (ICD-10)* code for Kawasaki disease (M30.3) and received IVIG between November 2007 and October 2019. We identified all children with a first episode of KD (n=53 837) and further restricted the population of children to those who lived in the districts with available ambient air pollution monitors (n=51 486). Because the Health Insurance Review & Assessment Service data were anonymized, informed consent was not required. The protocol of this study was approved by the institutional review board (GCI 2020-06-006).

Estimation of Ambient Air Pollution Before the Onset of Disease

We used hourly concentrations of particulate matter ≤10 or 2.5 μm in diameter (PM_{10} and $PM_{2.5}$, respectively), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3) measured at 235 air quality monitoring sites located throughout the country.[25] We obtained the air pollution data between 2007 and 2019 from the National Institute of Environmental Research (https://www.nier.go.kr/). The following daily representative concentrations of the 6 pollutants were determined for each child: 24-hour averages for PM_{10}, $PM_{2.5}$, NO_2, and SO_2 and a maximum of 8-hour moving averages for CO and O_3. The maximum concentrations of CO and O_3 were used because most of their emission is affected by commuter traffic and sunlight, respectively.[26] We used the air pollutant measurements collected from urban background sites to monitor population exposures. When 2 or more urban background sites were present in 1 district, we averaged their daily means. Because the residential addresses were available at the district level, we assigned district averages of air pollution to children living in the same district as individual exposures as applied in previous studies.[27,28] The urban background monitoring sites are mostly located at the community-service centers in largely populated residential areas.[29] Thus, these monitoring sites may well represent air pollution exposure to residents of the district. Majority of the children under 5 years old lived Seoul Metropolitan Area including Seoul and its neighboring metropolitan cities (Incheon and Gyeonggi-do), and there are 66

districts with relatively small sizes (median size=44 km^2 in 2007).[30] In addition, because temporal variability is much larger than spatial variability in daily averages of air pollution exposures,[31] the difference in air pollution concentrations of participants assessed by area averages and concentrations from the nearest monitor would be small and exposure measurement error of spatial misclassification in our health analysis may not be substantial. Given that the diagnosis of KD requires the presence of fever lasting at least 5 days,[7] the onset of fever can be supposed to be almost 1 week before the IVIG administration. According to the American Heart Association, IVIG treatments to prevent a coronary event are recommended by day 7 of KD,[32] and some patients might have received the IVIG treatment at day 5 or earlier, which is suggested to result in a lower risk of cardiac sequelae of KD.[33] Therefore, we presented a second scenario where the alleged onset of KD is 4 days before IVIG administration. We assumed that the children's addresses remained the same within a month of IVIG treatment.

Weather conditions were extracted from 510 automatic weather stations across the country (https://data.kma.go.kr/) and used to adjust the association between air pollutants and KD. The average daily values of ambient temperature and relative humidity were assigned to individuals according to their districts. When daily average weather conditions for the monitoring station were not available, we imputed the data using a random forest-based method from the *missForest* function in R package *missForest*.[34,35]

Statistical Analysis

We used a time-stratified case-crossover design to control short-term time-varying confounders and individual baseline risks.[36] In this design, cases serve as their own controls using exposure on the days before or after the case day. Owing to the consistency of the subject across days, this design can control all known and unknown confounding factors that are likely to vary nonrandomly—for example, age, body mass index, socioeconomic factors, health-related behaviors, and genetic predisposition.[37] The time-stratified approach avoids bias from the day of week and seasonality by matching the control days on the same day of the week within the same month and year as the case day. For example, if a KD case was identified on the last Monday of January 2019 (January 28, 2019), all other Mondays within January 2019 were assigned as the control days for that case (January 7, 14, and 21, 2019). This approach resulted in 3 control days for each case.

Six pollutants were introduced into the model one at a time. We estimated the effects of air pollutants on the day of disease onset (lag 0), the day before (lag 1), and the 2 days before (lag 2), assuming the immediate effect of air pollution (lags of 1–5 days for the second scenario, Figure 1).[22,23,38] Within-individual differences in the air pollution level of case days (district-average on lag 0–2 days) and control days were assessed using paired *t* tests. We used Spearman's correlation to examine the pairwise relationships of air pollutants, ambient temperature, and relative humidity. Although $PM_{2.5}$ is the subset of PM_{10} particles and thus both are likely to show a high correlation, we analyzed both separately to compare our findings with those of prior studies. We performed conditional logistic regression to estimate odds ratios (OR) of KD according to interquartile range (IQR) increases in each air pollutant concentration on the day of fever onset. We also explored the lag pattern in the effects using single-day exposure lags of 1 and 2 days to identify the critical exposure period. A spline of daily mean temperature and relative humidity was included in the adjusted models to control potential nonlinear relationships with KD. The most appropriate degrees of freedom of the temperature and relative humidity were determined by minimizing Akaike Information Criterion. Lags for temperature and relative humidity paralleled the modeled air pollution lags. For pollutants that showed significant association with the KD episode, we applied multipollutant models. We conducted sensitivity analyses to explore the robustness of the findings. First, we restricted the data to the Seoul region, where the individual raw data were complete. Second, we changed the degree of freedom for temperature and relative humidity in the adjusted analyses. All statistical analyses were conducted using R version 4.0.3.

RESULTS

Among the total of 51 486 patients with KD, 58.2% were male. 48.7% were <24 months old, and 74.4% lived outside of Seoul. The KD episodes were the highest in winter (Table 1). Annual average PM_{10}, $PM_{2.5}$, NO_2, SO_2, and CO concentrations decreased from 2007 to 2019 for all days included in the study (Table S1 and Figure S1). Annual average O_3 concentration increased. The means of daily PM_{10} and $PM_{2.5}$ concentrations over the case and control days during the study period were 47.99 and 25.04 $\mu g/m^3$, respectively (Table 2). The mean NO_2, SO_2, and O_3 were 26.34, 4.92, and 37.40 ppb, respectively. The mean CO was 0.64 ppm.

In within-individual comparison of 6 air pollutants, case days showed higher daily mean concentration than control days for $PM_{2.5}$ (lag 1 day) and SO_2 (lag 0–2 days, Table S2). In general, the means of 6 air pollutants showed a low-to-moderate pairwise correlation (Table S3). The daily average concentration of CO was highly and positively correlated with NO_2 (r=0.62) and moderately correlated with SO_2 (r=0.47). The

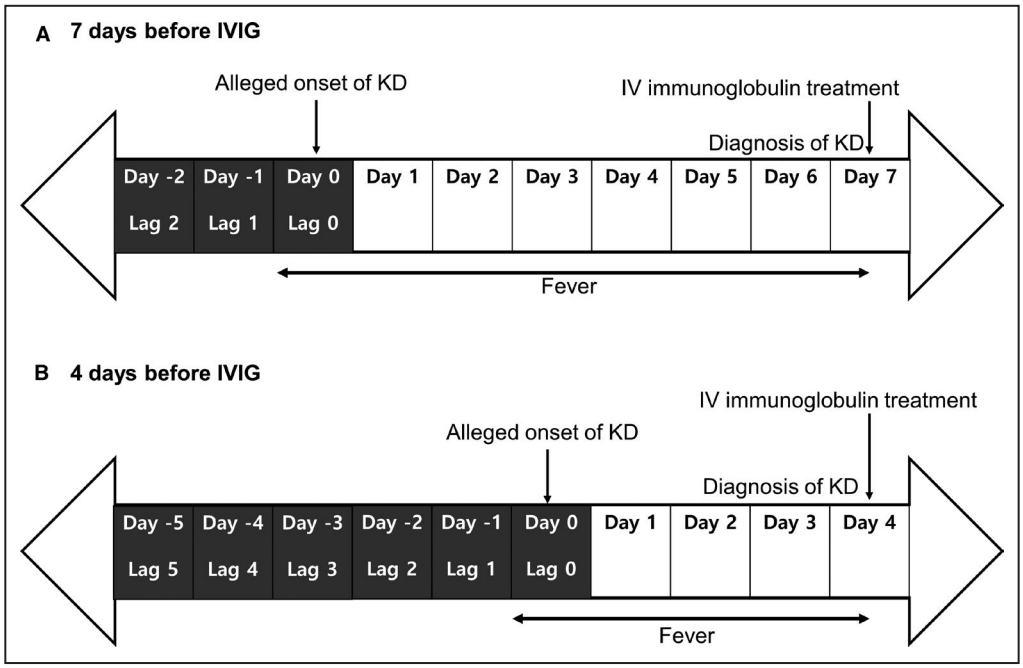

Figure 1. Estimation of the onset of Kawasaki disease (KD) based on the day of intravenous immunoglobulin (IVIG) administration in the National Health Insurance claim data.
Lag 1 and 2 are 1 and 2 days before the alleged onset of KD, respectively. **A**, 7 days before IVIG with lag 0 to 2 days; **B**, 4 days before IVIG with lag 0 to 5 days.

concentration of PM_{10} was moderately and positively correlated with NO_2 (r=0.50) and CO (r=0.54). In general, the daily air pollutant concentrations were negatively correlated with temperature (r ranged from −0.11 to −0.34) and relative humidity (r ranged from −0.02 to −0.09). The mean concentration of air pollution in a given district for a given month or year was relatively stable, for example, in Seoul (Figure S2).

In the single pollutant model adjusting for temperature and relative humidity, the direction of association between air pollutant concentration and KD was positive for PM_{10}, $PM_{2.5}$, SO_2, and CO, specifically at lag 1 (Figure 2A). For example, an IQR increase (per 14.67 μg/m^3 change) of $PM_{2.5}$ concentration was associated with KD at lag 1 (OR, 1.016; 95% CI, 1.004–1.029) (Table S4). An IQR increase (2.79 ppb) in SO_2 concentration was associated with KD at all lag days (lag 0: 1.018; 95% CI, 1.002–1.034; lag 1: 1.022;, 95% CI, 1.005–1.038; lag 2: 1.017; 95% CI, 1.001–1.033). The association between KD and an IQR increase (per 25.38 ppb) in O_3 was negative at lag 2 (0.979; 95% CI, 0.959–0.999). When we assigned the onset of KD as 4 days before IVIG treatment, the associations of SO_2 and O_3 with KD remain the same. An IQR increase in SO_2 concentration was associated with KD at lag 1 to 2 (lag 1: 1.021; 95% CI, 1.004–1.038; lag 2: 1.017; 95% CI, 1.001–1.033 at lag 2) (Figure 2B). The association between KD and an IQR increase in O_3 was also negative at lag 0 to 1 (lag 0: 0.951; 95% CI, 0.953–1.011; lag 1: 0.967; 95% CI, 0.947–0.988).

In the 2-pollutant model that simultaneously included terms for SO_2 or O_3, which showed significant association with KD, the point estimates did not change compared with the single pollutant model for all lag periods (Figure S3), indicating the independent effects of both pollutants. In the subgroup analysis using only data from Seoul to address exposure misclassification due to imputation, effect estimates were not meaningfully altered, and CIs widened with losses of subjects (Table S5). The change in the degree of freedom for temperature and relative humidity did not substantially affect the estimated effects of all air pollutants within the range of 2 to 10 degrees of freedom. Different smoothing approaches do not change the ORs in the magnitude and direction (result not shown).

DISCUSSION

Using national data of all KD events from the population under age 5 years in South Korea, we observed a positive association between daily variations in ambient air pollution and KD. More specifically, an IQR increase in SO_2 and $PM_{2.5}$ concentrations before the onset of KD were associated with higher odds of KD. Although the effect estimates were generally positive, the association was not statistically significant for PM_{10}, NO_2, and CO. The association between KD and O_3 was in

Table 1. Demographic Data of Kawasaki Disease Cases (n=51 486) From November 2007 to October 2019

Variable	Frequency (%)
Sex	
Male	29 982 (58.2)
Female	21 504 (41.8)
Age group	
Less than 12 mo	12 925 (25.1)
12–23 mo	12 166 (23.6)
24–35 mo	11 062 (21.5)
36–47 mo	8999 (17.5)
48–59 mo	6334 (12.3)
Region	
Seoul	13 170 (25.6)
Outside of Seoul	38 316 (74.4)
Year of KD onset	
2007–2011	15 616 (30.3)
2012–2015	19 009 (36.9)
2016–2019	16 143 (31.4)
Month of Kawasaki disease onset	
March–May	12 821 (24.9)
June–August	13 024 (25.3)
September–November	12 026 (23.4)
December–February	13 615 (26.4)

a negative direction at lag 1 to 2. This association did not change in the 2-pollutant model for lag 0 to 2 days where SO_2 and O_3 were concurrently incorporated.

Previous studies showed that air pollution might be positively associated with the risk of KD but did not always reach statistical significance. Similar to our findings, a study of 224 cases in Japan reported that SO_2 was significantly associated with an increased KD incidence.[39] A study of 2344 KD cases in Shanghai, China, found a positive but statistically insignificant association between KD incidence and PM_{10}, NO_2, and SO_2.[22] Another study of 3009 KD cases in 7 metropolitan regions of North America observed some positive effect estimates of $PM_{2.5}$ exposure on KD, which were statistically insignificant at lagged periods varying from 2 to 14 days.[23] Similarly, a recent single-center cohort study of 711 KD cases in South Korea showed the null association between KD and ambient $PM_{2.5}$ without adjusting for weather conditions.[40] Inconsistencies between the previous studies and our current findings could result from a difference in sample size, variation in the concentration of air pollutants, and adjustment of confounders. For example, the study in North America had the mean concentration of $PM_{2.5}$ ranged from 7.0 to 17.2 μg/m^3, which is much lower than those of our study population.

The underlying pathogenesis behind the association between KD and short-term exposure to air pollutants is not yet fully elucidated. Acute exposure to a high concentration of SO_2 is known to cause airway irritation and inflammation, aggravating bronchoconstriction in patients with asthma.[41] When exposed to a high level of $PM_{2.5}$ and SO_2, proinflammatory cytokines and enzymes from injured bronchoepithelial cells may induce a rapid systematic inflammatory reaction, damaging the arterial wall and possibly leading to KD symptoms.[42–44] The other air pollutants are also respiratory irritants causing inflammatory responses. The close-to-null association of KD with the other air pollutants may reflect some specific role of SO_2 in the pathogenesis of KD, and further investigation is needed to evaluate this potential biological mechanism.

Notably, the inverse association of KD with O_3 exposure in the 2 days before the onset of KD (lag 2) of our study was also observed in a study of 695 KD cases in Taiwan, whereas the ambient O_3 level decreased during the research period of their study.[38] This finding may be explained by the ozone alert, which is adopted in many countries.[45,46] Starting from 2005, this ozone

Table 2. Daily Concentration of Air Pollutants, Temperature, and Relative Humidity Measures on Case and Control Days Among 51 486 Patients With Kawasaki Disease Aged Under 5 Years of South Korea, 2007 to 2019

Daily environmental variable	Mean (SD)	Min	Quartile 1	Quartile 2	Quartile 3	Max	Interquartile range
Air pollutants							
PM_{10}, μg/m^3	47.99 (27.92)	1.33	30.24	42.72	58.92	708.75	28.68
$PM_{2.5}$, μg/m^3	25.04 (12.84)	0.04	16.37	22.86	31.04	161.53	14.67
Nitrogen dioxide, ppb	26.34 (13.21)	0.12	16.42	23.88	33.83	136.00	17.42
Sulfur dioxide, ppb	4.92 (2.52)	0.08	3.21	4.46	6.00	81.83	2.79
Carbon monoxide, ppm	0.64 (0.31)	0.07	0.44	0.57	0.76	5.47	0.32
Ozone, ppb	37.40 (18.94)	0.25	23.62	34.75	49.00	163.79	25.38
Weather conditions							
Temperature, °C	12.69 (6.62)	–19.70	10.13	12.90	15.60	34.30	5.47
Relative humidity (%)	64.03 (12.88)	0.10	57.63	65.51	72.28	99.90	14.66

PM_{10} and $PM_{2.5}$ indicates particulate matter ≤10 and 2.5 μm in diameter.

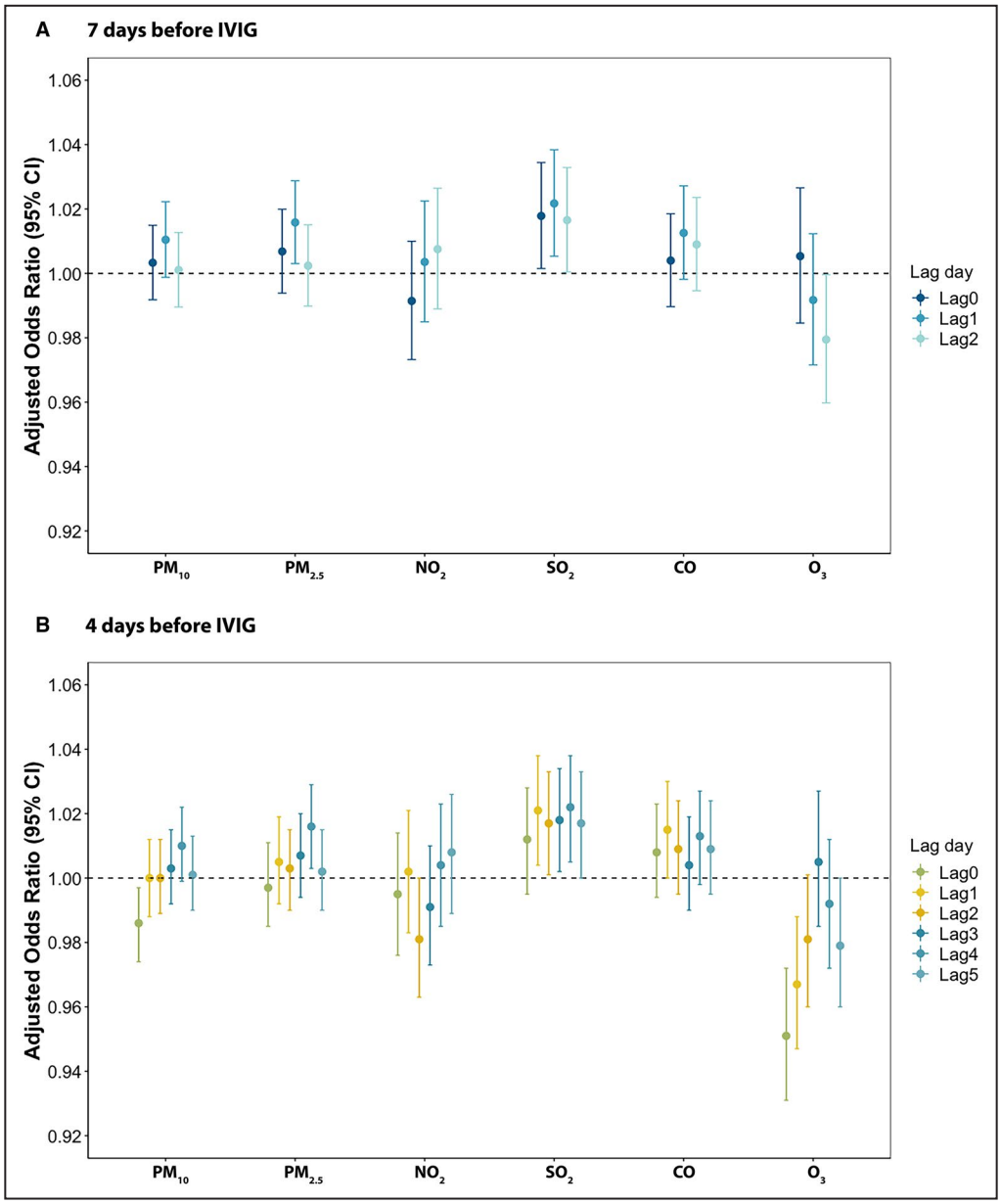

Figure 2. Associations between Kawasaki disease (KD) and air pollution at different lag days among 51 486 patients in South Korea aged under 5 years with KD, 2007 to 2019.
The associations are shown as odds ratio (OR) with 95% CI for interquartile range (IQR) increases in exposure. All models were adjusted for ambient temperature and relative humidity. **A**, 7 days before IVIG; **B**, 4 days before IVIG. CO indicates carbon monoxide; IVIG, intravenous immunoglobulin; NO_2, nitrogen dioxide; O_3, ozone; PM_{10} and $PM_{2.5}$, particulate matter ≤10 and 2.5 μm in diameter; and SO_2, sulfur dioxide.

warning system advises children, senior citizens, and patients with respiratory diseases to limit their outdoor activities when the ozone level is considered high (Annual O_3 Alert Trend, www.airkorea.or.kr).[47] Except ozone, the studied air pollutants are largely produced from fossil fuel combustion. Imprecise risk estimates for NO_2 and CO in our study may be because of different pattern of spatial variation of these pollutants.

Our study had some potential limitations. First, air pollutant data were accessed from ambient air pollution monitoring stations rather than measured at personal exposure levels and could not represent the indoor concentration of air pollutants. Second, data on the potential confounders, including genetic, infectious, and socioeconomic factors, were not available in this study. However, we attempted to account for personal invariant factors such as genetic susceptibilities by applying the case-crossover design. Third, the date of IVIG treatment was the only available information on the timing of the KD event in our data source. The definition of KD onset based on the day of IVIG administration may lead to potential misclassification of exposure because the

date does not necessarily represent the actual timing of the disease. Given that the mean duration of fever before IVIG administration was 6 to 7 days among children under-5 years diagnosed with KD,[48,49] we believe that the possibility of misclassification would be minimal. In addition, laboratory findings were not included in our analysis because they are not available in the National Health Insurance System claim database, which is constructed for administrative purpose. To confirm our findings, future studies may benefit from using clinical inflammatory indicators such as white blood cell count or C-reactive protein, as intermediate markers for KD.

CONCLUSIONS

This study adds to the growing body of evidence implicating the positive association between short-term variations in air pollution and the development of KD, supporting the hypothesis that the short-term elevations in $PM_{2.5}$ and SO_2 may trigger the onset of KD among children under 5 years of age. This finding needs to be confirmed in future studies with different study designs and among different populations.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S5
Figures S1–S3

REFERENCES

1. Burns JC, Kushner HI, Bastian JF, Shike H, Shimizu C, Matsubara T, Turner CL. Kawasaki disease: a brief history. *Pediatrics*. 2000;106:E27. doi: 10.1542/peds.106.2.e27
2. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005–2006. *J Epidemiol*. 2008;18:167–172. doi: 10.2188/jea.JE2008001
3. Chang FY, Hwang B, Chen SJ, Lee PC, Meng CCL, Lu JH. Characteristics of Kawasaki disease in infants younger than six months of age. *Pediatr Infect Dis J*. 2006;25:241–244. doi: 10.1097/01.inf.0000202067.50975.90
4. Kim SH, Kim KH, Kim DS. Clinical characteristics of Kawasaki disease according to age at diagnosis. *Indian Pediatr*. 2009;46:585–590.
5. Noval Rivas M, Arditi M. Kawasaki disease: pathophysiology and insights from mouse models. *Nat Rev Rheumatol*. 2020;16:391–405. doi: 10.1038/s41584-020-0426-0
6. Rife E, Gedalia A. Kawasaki disease: an update. *Curr Rheumatol Rep*. 2020;22:75. doi: 10.1007/s11926-020-00941-4
7. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135:e927–e999. doi: 10.1161/CIR.0000000000000484
8. Mori M, Miyamae T, Imagawa T, Katakura S, Kimura K, Yokota S. Meta-analysis of the results of intravenous gamma globulin treatment of coronary artery lesions in Kawasaki disease. *Mod Rheumatol*. 2004;14:361–366. doi: 10.3109/s10165-004-0324-3
9. Holman RC, Christensen KY, Belay ED, Steiner CA, Effler PV, Miyamura J, Forbes S, Schonberger LB, Melish M. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. *Hawaii Med J*. 2010;69:194–197.
10. Maddox RA, Person MK, Joseph LJ, Haberling DL, Steiner CA, Schonberger LB, Belay ED. Monitoring the occurrence of Kawasaki syndrome in the United States. In: *Oral presentation at: 11th International Kawasaki Disease Symposium*, Honolulu, Hawaii, February, 2015.
11. Kim GB, Eun LY, Han JW, Kim SH, Yoon KL, Han MY, Yu JJ, Choi JW, Rhim JW. Epidemiology of Kawasaki disease in South Korea: a nationwide survey 2015–2017. *Pediatr Infect Dis J*. 2020;39:1012–1016. doi: 10.1097/INF.0000000000002793
12. Xie LP, Yan WL, Huang M, Huang MR, Chen S, Huang GY, Liu F; Grp SKDR. Epidemiologic features of Kawasaki disease in Shanghai from 2013 through 2017. *J Epidemiol*. 2020;30:429–435. doi: 10.2188/jea.JE20190065
13. Huang WC, Huang LM, Chang IS, Chang LY, Chiang BL, Chen PJ, Wu MH, Lue HC, Lee CY; Grp KDR. Epidemiologic features of Kawasaki disease in Taiwan, 2003–2006. *Pediatrics*. 2009;123:e401–e405. doi: 10.1542/peds.2008-2187
14. Durongpisitkul K, Sangtawesin C, Khongphatthanayopthin A, Panamonta M, Sopontammarak S, Sittiwangkul R, Pongpanich B. Epidemiologic study of Kawasaki disease and cases resistant to IVIG therapy in Thailand. *Asian Pac J Allergy Immunol*. 2006;24:27–32.
15. Fujiwara T, Shobugawa Y, Matsumoto K, Kawachi I. Association of early social environment with the onset of pediatric Kawasaki disease. *Ann Epidemiol*. 2019;29:74–80. doi: 10.1016/j.annepidem.2018.10.010
16. Nagao Y, Urabe C, Nakamura H, Hatano N. Predicting the characteristics of the aetiological agent for Kawasaki disease from other paediatric infectious diseases in Japan. *Epidemiol Infect*. 2016;144:478–492. doi: 10.1017/S0950268815001223
17. Burns JC, Herzog L, Fabri O, Tremoulet AH, Rodó X, Uehara R, Burgner D, Bainto E, Pierce D, Tyree M, et al. Seasonality of Kawasaki disease: a global perspective. *PLoS One*. 2013;8:e74529. doi: 10.1371/journal.pone.0074529
18. Kanegaye JT, Van Cott E, Tremoulet AH, Salgado A, Shimizu C, Kruk P, Hauschildt J, Sun XY, Jain S, Burns JC. Lymph-node-first presentation of Kawasaki disease compared with bacterial cervical adenitis and typical Kawasaki disease. *J Pediatr*. 2013;162:1259–1263.e2. doi: 10.1016/j.jpeds.2012.11.064
19. Rypdal M, Rypdal V, Burney JA, Cayan D, Bainto E, Skochko S, Tremoulet AH, Creamean J, Shimizu C, Kim J, et al. Clustering and climate associations of Kawasaki disease in San Diego County suggest environmental triggers. *Sci Rep*. 2018;8:16140. doi: 10.1038/s41598-018-33124-4
20. Leuin SC, Shanbhag S, Lago D, Sato Y, Sun XY, Jain S, Burns JC, Tremoulet AH. Hoarseness as a presenting sign in children with Kawasaki disease. *Pediatr Infect Dis J*. 2013;32:1392–1394. doi: 10.1097/INF.0b013e3182a0960b
21. Jorquera H, Borzutzky A, Hoyos-Bachiloglu R, Garcia A. Association of Kawasaki disease with tropospheric winds in Central Chile: is wind-borne desert dust a risk factor? *Environ Int*. 2015;78:32–38. doi: 10.1016/j.envint.2015.02.007

22. Lin Z, Meng X, Chen R, Huang G, Ma X, Chen J, Huang M, Huang M, Gui Y, Chu C, et al. Ambient air pollution, temperature and Kawasaki disease in Shanghai, China. *Chemosphere*. 2017;186:817–822. doi: 10.1016/j.chemosphere.2017.08.054
23. Zeft AS, Burns JC, Yeung RS, McCrindle BW, Newburger JW, Dominguez SR, Anderson MS, Arrington C, Shulman ST, Yoon J, et al. Kawasaki disease and exposure to fine particulate air pollution. *J Pediatr*. 2016;177:179–183.e1. doi: 10.1016/j.jpeds.2016.06.061
24. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *J Korean Med Sci*. 2017;32:718–728. doi: 10.3346/jkms.2017.32.5.718
25. Song I, Kim OJ, Choe SA, Kim SY. Spatial heterogeneity in the association between particulate matter air pollution and low birth weight in South Korea. *Environ Res*. 2020;191:110096. doi: 10.1016/j.envres.2020.110096
26. Kim SY, O'Neill MS, Lee JT, Cho Y, Kim J, Kim H. Air pollution, socioeconomic position, and emergency hospital visits for asthma in Seoul, Korea. *Int Arch Occup Environ Health*. 2007;80:701–710. doi: 10.1007/s00420-007-0182-3
27. Choe SA, Jun YB, Lee WS, Yoon TK, Kim SY. Association between ambient air pollution and pregnancy rate in women who underwent IVF. *Hum Reprod*. 2018;33:1071–1078. doi: 10.1093/humrep/dey076
28. Choe SA, Jang J, Kim MJ, Jun YB, Kim SY. Association between ambient particulate matter concentration and fetal growth restriction stratified by maternal employment. *BMC Pregnancy Childbirth*. 2019;19:246. doi: 10.1186/s12884-019-2401-9
29. Min KD, Kwon HJ, Kim K, Kim SY. Air pollution monitoring design for epidemiological application in a densely populated city. *Int J Environ Res Public Health*. 2017;14:686. doi: 10.3390/ijerph14070686
30. Kim OJ, Lee SH, Kang SH, Kim SY. Incident cardiovascular disease and particulate matter air pollution in South Korea using a population-based and nationwide cohort of 0.2 million adults. *Environ Health*. 2020;19:113. doi: 10.1186/s12940-020-00671-1
31. Yi SJ, Kim H, Kim SY. Exploration and application of regulatory PM10 measurement data for developing long-term prediction models in South Korea. *J Korean Soc Atmos Environ*. 2016;32:114–126.
32. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2004;110:2747–2771. doi: 10.1161/01.CIR.0000145143.19711.78
33. Tse SM, Silverman ED, McCrindle BW, Yeung RS. Early treatment with intravenous immunoglobulin in patients with Kawasaki disease. *J Pediatr*. 2002;140:450–455. doi: 10.1067/mpd.2002.122469
34. Alsaber AR, Pan JZ, Al-Hurban A. Handling complex missing data using random forest approach for an air quality monitoring dataset: a case study of Kuwait environmental data (2012 to 2018). *Int J Environ Res Public Health*. 2021;18:1333. doi: 10.3390/ijerph18031333
35. Stekhoven DJ, Buhlmann P. MissForest–non-parametric missing value imputation for mixed-type data. *Bioinformatics*. 2012;28:112–118. doi: 10.1093/bioinformatics/btr597
36. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology*. 2005;16:717–726. doi: 10.1097/01.ede.0000181315.18836.9d
37. Karr C, Lumley T, Shepherd K, Davis R, Larson T, Ritz B, Kaufman J. A case-crossover study of wintertime ambient air pollution and infant bronchiolitis. *Environ Health Perspect*. 2006;114:277–281. doi: 10.1289/ehp.8313
38. Jung CR, Chen WT, Lin YT, Hwang BF. Ambient air pollutant exposures and hospitalization for Kawasaki disease in Taiwan: a case-crossover study (2000–2010). *Environ Health Perspect*. 2017;125:670–676. doi: 10.1289/EHP137
39. Fujii F, Egami N, Inoue M, Koga H. Weather condition, air pollutants, and epidemics as factors that potentially influence the development of Kawasaki disease. *Sci Total Environ*. 2020;741:140469. doi: 10.1016/j.scitotenv.2020.140469
40. Oh J, Lee JH, Kim E, Kim S, Kim HS, Ha E. Is short-term exposure to $PM_{2.5}$ relevant to childhood Kawasaki disease? *Int J Environ Res Public Health*. 2021;18:924. doi: 10.3390/ijerph18030924
41. Reno AL, Brooks EG, Ameredes BT. Mechanisms of heightened airway sensitivity and responses to inhaled SO_2 in asthmatics. *Environ Health Insights*. 2015;9:13–25.
42. Yasukawa K, Terai M, Shulman ST, Toyozaki T, Yajima S, Kohno Y, Rowley AH. Systemic production of vascular endothelial growth factor and fms-like tyrosine kinase-1 receptor in acute Kawasaki disease. *Circulation*. 2002;105:766–769.
43. Gavin PJ, Crawford SE, Shulman ST, Garcia FL, Rowley AH. Systemic arterial expression of matrix metalloproteinases 2 and 9 in acute Kawasaki disease. *Arterioscler Thromb Vasc Biol*. 2003;23:576–581. doi: 10.1161/01.ATV.0000065385.47152.FD
44. Rowley AH, Shulman ST. Pathogenesis and management of Kawasaki disease. *Expert Rev Anti Infect Ther*. 2010;8:197–203. doi: 10.1586/eri.09.109
45. Kelly FJ, Fuller GW, Walton HA, Fussell JC. Monitoring air pollution: use of early warning systems for public health. *Respirology*. 2012;17:7–19. doi: 10.1111/j.1440-1843.2011.02065.x
46. Lyons RA, Rodgers SE, Thomas S, Bailey R, Brunt H, Thayer D, Bidmead J, Evans BA, Harold P, Hooper M, et al. Effects of an air pollution personal alert system on health service usage in a high-risk general population: a quasi-experimental study using linked data. *J Epidemiol Community Health*. 2016;70:1184–1190. doi: 10.1136/jech-2016-207222
47. Annual O3 alert trend. 2021. Available at: https://www.airkorea.or.kr/eng/O3Alert?pMENU_NO=162. Accessed May 31, 2021.
48. Do YS, Kim KW, Chun JK, Cha BH, Namgoong MK, Lee HY. Predicting factors for refractory Kawasaki disease. *Korean Circ J*. 2010;40:239–242. doi: 10.4070/kcj.2010.40.5.239
49. Lee KY, Han JW, Hong JH, Lee HS, Lee JS, Whang K-T. Inflammatory processes in Kawasaki disease reach their peak at the sixth day of fever onset: laboratory profiles according to duration of fever. *J Korean Med Sci*. 2004;19:501–504. doi: 10.3346/jkms.2004.19.4.501

SUPPLEMENTAL MATERIAL

Table S1. Summary statistics of annual average values for daily mean concentrations of air pollution from monitoring stations during 2007-2019.

Air pollutants	Year	Mean (SD)	Min	Q1	Q2	Q3	Max
PM_{10} ($\mu g/m^3$)	2007	61.84 (31.59)	12.54	41.34	53.71	73.19	369.42
	2008	55.12 (32.08)	4.17	34.90	49.17	66.92	620.71
	2010	50.61 (30.56)	1.33	30.46	44.67	62.54	658.08
	2009	53.30 (31.38)	4.75	33.54	46.75	64.33	353.92
	2011	48.49 (32.56)	1.33	28.85	42.93	59.06	516.79
	2012	43.33 (21.27)	2.12	28.00	39.77	54.29	182.38
	2013	48.16 (25.09)	5.38	30.58	42.96	59.50	258.33
	2014	48.43 (26.86)	2.04	30.08	42.38	60.38	237.71
	2015	48.56 (33.43)	2.67	31.54	42.99	58.17	708.75
	2016	47.52 (22.92)	2.83	32.38	43.19	58.17	243.15
	2017	45.94 (23.36)	1.52	30.32	42.18	56.19	299.21
	2018	41.76 (22.96)	3.18	25.62	37.65	52.79	200.77
	2019	42.76 (25.08)	1.58	26.58	37.69	52.62	228.57
$PM_{2.5}$ ($\mu g/m^3$)	2007	29.94 (13.72)	6.97	20.67	26.76	35.67	114.43
	2008	25.83 (12.12)	2.62	17.62	23.88	31.62	117.29
	2010	24.86 (12.12)	2.91	16.81	22.83	30.39	140.71
	2009	25.49 (12.11)	2.25	17.32	23.26	30.88	112.83
	2011	24.37 (11.27)	1.47	16.52	22.87	30.31	117.99
	2012	23.70 (10.51)	2.00	16.28	22.08	29.17	96.32
	2013	25.94 (12.07)	3.55	17.51	23.71	32.04	108.58
	2014	25.07 (11.79)	3.17	16.84	22.90	31.09	104.33
	2015	25.63 (13.20)	0.25	16.46	23.30	31.88	144.46
	2016	26.22 (12.49)	1.58	17.62	24.08	32.58	103.75
	2017	25.28 (13.83)	0.04	15.41	22.92	31.98	126.06
	2018	23.15 (14.61)	0.88	12.45	20.13	30.17	135.46
	2019	23.64 (17.39)	0.25	13.42	20.14	28.44	161.53
NO_2 (ppb)	2007	33.67 (15.87)	1.25	22.42	31.54	42.04	136.00

Air pollutants	Year	Mean (SD)	Min	Q1	Q2	Q3	Max
	2008	28.35 (14.12)	0.12	17.77	26.04	36.58	98.42
	2010	27.63 (13.81)	1.00	17.00	25.37	36.06	124.38
	2009	27.96 (13.81)	1.62	17.58	25.54	36.00	129.81
	2011	27.37 (13.96)	1.00	16.94	24.71	35.55	96.83
	2012	26.12 (12.83)	1.21	16.50	23.88	33.50	91.29
	2013	27.61 (13.82)	1.29	17.12	24.89	35.58	99.29
	2014	27.64 (13.69)	1.25	17.21	25.29	35.54	104.46
	2015	26.42 (12.98)	0.67	16.71	24.02	33.75	99.64
	2016	24.96 (11.40)	1.12	16.38	23.08	31.58	103.25
	2017	24.22 (11.47)	1.23	15.63	22.19	30.83	83.20
	2018	23.75 (12.13)	1.00	14.58	21.31	30.79	84.88
	2019	21.45 (10.89)	1.50	13.52	19.60	26.75	77.62
SO_2 (ppb)	2007	7.41 (3.84)	0.21	4.65	6.60	9.36	30.17
	2008	5.56 (3.33)	0.42	3.30	4.81	6.90	81.83
	2010	4.88 (2.55)	0.12	3.08	4.41	6.08	36.97
	2009	5.14 (2.76)	0.58	3.22	4.54	6.38	33.19
	2011	4.96 (2.55)	0.12	3.17	4.48	6.12	31.22
	2012	5.26 (2.68)	1.00	3.50	4.78	6.42	34.04
	2013	5.47 (2.81)	1.00	3.65	4.96	6.68	32.50
	2014	5.31 (2.51)	0.88	3.54	4.92	6.50	26.27
	2015	5.02 (2.25)	0.17	3.52	4.76	6.17	32.33
	2016	4.48 (1.84)	0.26	3.25	4.25	5.46	27.84
	2017	4.30 (1.80)	0.08	3.08	4.10	5.21	27.22
	2018	4.00 (1.72)	1.00	2.81	3.71	4.88	22.08
	2019	3.83 (1.57)	1.00	2.75	3.60	4.58	22.62
CO (ppm)	2007	0.97 (0.48)	0.07	0.62	0.89	1.24	4.09
	2008	0.72 (0.36)	0.09	0.48	0.63	0.86	3.53
	2010	0.66 (0.35)	0.10	0.44	0.58	0.78	4.68
	2009	0.68 (0.36)	0.10	0.42	0.58	0.81	3.20
	2011	0.65 (0.32)	0.07	0.44	0.59	0.76	4.99

Air pollutants	Year	Mean (SD)	Min	Q1	Q2	Q3	Max
	2012	0.64 (0.30)	0.10	0.44	0.58	0.75	5.47
	2013	0.65 (0.34)	0.07	0.43	0.57	0.76	4.01
	2014	0.65 (0.31)	0.10	0.44	0.58	0.78	3.62
	2015	0.64 (0.29)	0.10	0.44	0.57	0.78	3.00
	2016	0.60 (0.25)	0.10	0.44	0.56	0.72	3.19
	2017	0.59 (0.24)	0.10	0.43	0.54	0.70	2.58
	2018	0.58 (0.25)	0.07	0.41	0.54	0.71	2.92
	2019	0.56 (0.23)	0.10	0.41	0.52	0.65	2.54
O_3 (ppb)	2007	21.28 (9.93)	1.00	13.88	21.25	27.67	73.62
	2008	34.12 (17.04)	0.50	21.25	32.17	44.88	126.62
	2010	33.77 (17.67)	0.25	21.62	31.00	43.50	147.62
	2009	35.78 (18.38)	0.38	22.22	33.38	47.62	119.50
	2011	34.48 (17.24)	0.75	22.00	32.21	44.50	115.06
	2012	36.13 (18.02)	1.00	23.25	33.38	46.88	116.78
	2013	37.90 (19.51)	1.00	23.21	34.75	50.12	140.43
	2014	38.41 (19.44)	1.00	24.12	35.50	50.62	125.06
	2015	38.01 (18.94)	0.88	24.12	35.94	50.50	123.88
	2016	39.39 (19.95)	1.00	25.00	36.27	52.44	129.62
	2017	40.55 (19.44)	2.00	26.38	38.00	53.12	132.38
	2018	38.84 (18.99)	1.62	25.31	36.25	49.30	137.88
	2019	45.75 (19.18)	2.67	32.06	43.75	57.19	163.79
Temperature (°C)	2007	8.54 (5.14)	-8.30	5.20	9.40	12.40	22.90
	2008	12.98 (7.20)	-11.40	9.80	13.11	16.80	32.10
	2010	12.75 (7.42)	-17.10	9.53	12.89	15.80	30.80
	2009	12.93 (7.25)	-13.90	9.77	13.37	16.90	30.70
	2011	12.84 (6.44)	-18.20	10.82	13.13	15.44	30.25
	2012	12.54 (6.67)	-17.43	10.35	12.97	15.40	32.60
	2013	12.72 (6.55)	-17.70	10.30	12.77	15.30	32.60
	2014	12.61 (6.15)	-13.15	10.50	12.92	15.13	32.00
	2015	12.41 (6.06)	-12.10	9.90	12.77	15.10	32.10

Air pollutants	Year	Mean (SD)	Min	Q1	Q2	Q3	Max
	2016	12.69 (6.54)	-18.30	10.03	12.89	15.42	32.50
	2017	12.45 (6.33)	-12.73	10.10	12.80	15.27	31.70
	2018	12.53 (6.57)	-19.70	10.13	12.60	15.15	34.30
	2019	14.21 (6.25)	-8.73	11.20	13.93	17.87	32.10
Relative Humidity (%)	2007	56.86 (14.97)	0.10	48.29	59.79	67.38	88.84
	2008	51.48 (19.33)	0.10	40.04	55.85	65.92	97.33
	2010	64.18 (11.90)	0.10	57.71	65.47	72.11	99.90
	2009	59.62 (13.71)	0.10	51.80	61.47	69.25	98.24
	2011	66.28 (12.03)	0.18	59.28	66.79	73.78	99.90
	2012	66.04 (11.47)	9.12	59.61	66.80	73.30	99.90
	2013	66.65 (11.96)	1.00	59.97	67.04	73.75	99.90
	2014	65.49 (10.18)	12.80	59.67	66.26	72.37	98.14
	2015	65.66 (10.02)	8.60	59.99	66.34	72.40	96.83
	2016	66.14 (9.92)	8.60	60.30	66.75	72.85	96.33
	2017	64.95 (12.86)	0.20	57.36	65.90	73.30	99.90
	2018	64.57 (11.61)	0.20	57.89	65.78	72.54	97.71
	2019	65.02 (11.40)	4.40	58.62	66.17	72.92	97.42

PM_{10} and $PM_{2.5}$, particulate matter less than or equal to 10 and 2.5 micrometers in diameter; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide; O_3, ozone; SD, standard deviation; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; IQR, interquartile range.

Table S2. Within-individual difference in the air pollution level of case and control days in case-crossover study of ambient air pollutants and KD, 2007-2019.

Air pollutants	Mean difference (95% CI)		
	Lag 0	Lag 1	Lag 2
PM_{10} ($\mu g/m^3$)	0.045 (-0.134, 0.225)	0.146 (-0.030, 0.322)	-0.024 (-0.201, 0.154)
$PM_{2.5}$ ($\mu g/m^3$)	0.053 (-0.029, 0.136)	**0.111 (0.028, 0.195)**	0.003 (-0.081, 0.087)
NO_2 (ppb)	-0.061 (-0.130, 0.007)	-0.027 (-0.095, 0.040)	-0.002 (-0.070, 0.066)
SO_2 (ppb)	**0.018 (0.006, 0.031)**	**0.019 (0.007, 0.032)**	**0.016 (0.004, 0.028)**
CO (ppm)	0.000 (-0.001, 0.002)	0.001 (-0.001, 0.003)	0.001 (-0.001, 0.002)
O_3 (ppb)	0.027 (-0.064, 0.118)	-0.064 (-0.155, 0.027)	-0.116 (-0.208, -0.025)

PM_{10} and $PM_{2.5}$, particulate matter less than or equal to 10 and 2.5 micrometers in diameter; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide; and O_3, ozone.

Table S3. Pairwise correlation between daily average air pollutants, temperature, and relative humidity from November 2007 to October 2019. P values for all correlations are < 0.01.

Exposures	PM_{10}	$PM_{2.5}$	NO_2	SO_2	CO	O_3	Temperature	Humidity
PM_{10}	1							
$PM_{2.5}$	0.87	1						
NO_2	0.50	0.49	1					
SO_2	0.49	0.46	0.50	1				
CO	0.54	0.56	0.62	0.47	1			
O_3	0.07	0.08	-0.29	-0.15	-0.29	1		
Temperature	-0.16	-0.11	-0.24	-0.23	-0.34	0.42	1	
Humidity	-0.02	0.03	-0.09	-0.07	-0.04	-0.03	0.14	1

PM_{10} and $PM_{2.5}$, particulate matter less than or equal to 10 and 2.5 micrometers in diameter; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide; and O_3, ozone.

Table S4. Odds ratios (95% confidence intervals) of the association between Kawasaki disease (KD) and air pollution from single pollutant models among 51,486 KD patients aged under five of South Korea, 2007–2019.

	Lag 0		Lag 1		Lag 2	
Air pollutants per IQR change	OR (95% CI)	Adjusted OR for weather conditions (95% CI)[a]	OR (95% CI)	Adjusted OR for weather conditions (95% CI)[a]	OR (95% CI)	Adjusted OR for weather conditions (95% CI)[a]
PM_{10}	1.002 (0.991, 1.013)	1.003 (0.992, 1.015)	1.007 (0.995, 1.018)	1.010 (0.999, 1.022)	0.999 (0.988, 1.010)	1.001 (0.990, 1.013)
$PM_{2.5}$	1.006 (0.993, 1.018)	1.007 (0.994, 1.020)	1.012 (0.999, 1.024)	1.016 (1.003, 1.029)	1.0003 (0.988, 1.013)	1.002 (0.990, 1.015)
NO_2	0.989 (0.971, 1.007)	0.991 (0.973, 1.010)	0.995 (0.977, 1.013)	1.004 (0.985, 1.023)	0.999 (0.982, 1.018)	1.008 (0.989, 1.026)
SO_2	1.017 (1.001, 1.034)	1.018 (1.002, 1.034)	1.018 (1.002, 1.035)	1.022 (1.005, 1.038)	1.015 (0.999, 1.031)	1.017 (1.001, 1.033)
CO	1.002 (0.988, 1.016)	1.004 (0.990, 1.019)	1.006 (0.992, 1.020)	1.013 (0.998, 1.027)	1.004 (0.990, 1.018)	1.009 (0.995, 1.024)
O_3	1.004 (0.985, 1.024)	1.005 (0.985, 1.027)	0.990 (0.970, 1.010)	0.992 (0.972, 1.012)	0.982 (0.963, 1.002)	0.979 (0. 959, 0.999)

OR, odds ratio; IQR, interquartile range; PM_{10} and $PM_{2.5}$, particulate matter less than or equal to 10 and 2.5 micrometers in diameter; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; CO, carbon monoxide; and O_3, ozone. [a]adjusted for daily mean temperature and relative humidity.

Table S5. Odds ratio (95% confidence interval) for Kawasaki disease from single pollutant models in Seoul (n = 13,170) from November 2007 to October 2019.

Air pollutants	OR (95% CI)	Adjusted OR (95% CI)
PM_{10}		
per IQR change	0.994 (0.972, 1.015)	0.994 (0.973, 1.016)
$PM_{2.5}$		
per IQR change	1.001 (0.979, 1.025)	1.001 (0.978, 1.025)
NO_2		
per IQR change	0.993 (0.962, 1.024)	0.995 (0.962, 1.028)
SO_2		
per IQR change	1.002 (0.972, 1.033)	1.003 (0.972, 1.035)
CO		
per IQR change	1.008 (0.980, 1.036)	1.010 (0.981, 1.040)
O_3		
per IQR change	0.998 (0.960, 1.037)	1.001 (0.960, 1.043)

PM_{10} and $PM_{2.5}$, particulate matter less than or equal to 10 and 2.5 micrometers in diameter; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide; and O_3, ozone; IQR, interquartile range; CI, confidence interval.

Figure S1. The distribution of daily average concentration of air pollutants and weather conditions from monitoring stations during 2007 to 2019. PM_{10}, $\mu g/m^3$; $PM_{2.5}$, $\mu g/m^3$; NO_2, ppb; SO_2, ppb; CO, ppm; O_3, ppb.

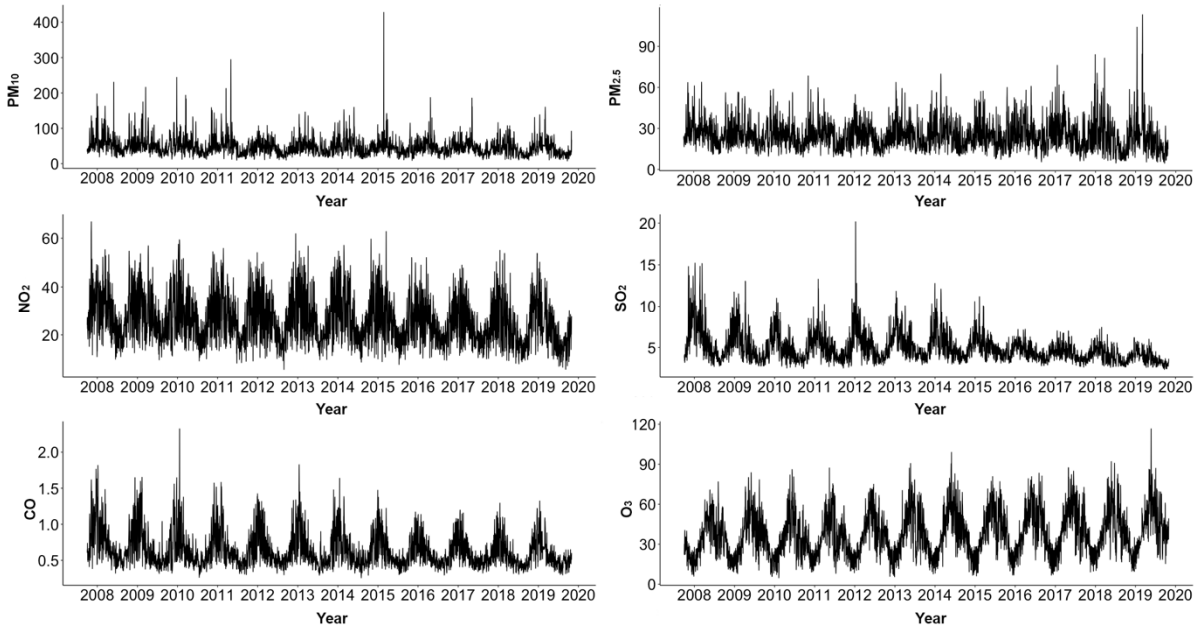

Figure S2. The concentration of air pollutant between case days and average of the district. A) The concentration of air pollution between case days on lag 1 and monthly average of Seoul; B) The concentration of air pollution between case days on lag 0-2 days and annual average of Seoul

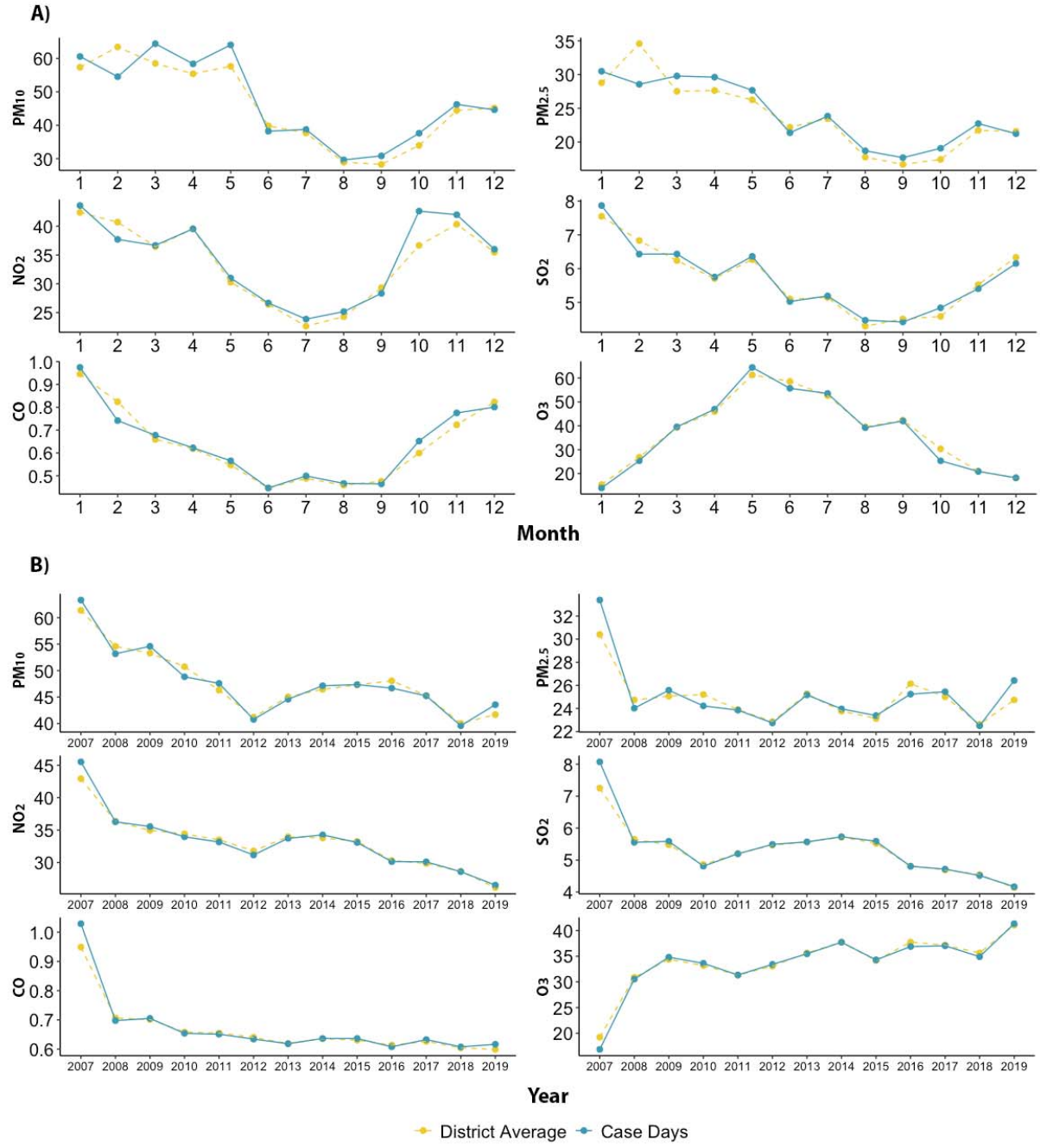

Figure S3. Associations between Kawasaki disease and air pollution from two-pollutant models, 2007–2019. The associations are shown as odds ratio (OR) with 95% confidence interval (CI) for interquartile range (IQR) increases in exposure. All models were adjusted for ambient temperature and relative humidity. A) 7 days before IVIG; B) 4 days before IVIG. SO_2, sulfur dioxide; and O_3, ozone.