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# Spatiotemporal analysis of the association between Kawasaki disease incidence and $PM_{2.5}$ exposure: a nationwide database study in Japan

Kota Yoneda ,[1,2] Daisuke Shinjo ,[1] Naoto Takahashi,[2] Kiyohide Fushimi[1]

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[1]Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Bunkyo-ku, Japan
[2]Department of Pediatrics, The University of Tokyo Hospital, Bunkyo-ku, Japan

**Correspondence to**
Dr Daisuke Shinjo; dshinjo.hci@tmd.ac.jp

## ABSTRACT

**Background** Kawasaki disease (KD) is an acute vasculitis primarily affecting children. While some studies suggest a link between KD and $PM_{2.5}$ exposure, findings remain inconsistent. This study aimed to perform spatiotemporal analysis to investigate the impact of monthly and annual exposure to $PM_{2.5}$ and other air pollutants on the incidence of KD before and after the advent of the COVID-19 pandemic.

**Methods** In this retrospective analysis, we used the Japanese administrative claims database to identify the incidence of KD in children under age 5 in 335 secondary medical care areas across Japan before (from July 2014 to December 2019) and during (from January 2020 to December 2021) the COVID-19 pandemic. For each of these periods, we developed hierarchical Bayesian models termed conditional autoregressive (CAR) models that can address the spatiotemporal clustering of KD to investigate the association between the monthly incidence of KD and exposure to $PM_{2.5}$, NO, $NO_2$ and $SO_2$ over 1-month and 12-month durations. The pollution data were collected from publicly available data provided by the National Institute for Environmental Studies.

**Results** In the before-pandemic and during-pandemic periods, 55 289 and 14 023 new cases of KD were identified, respectively. The CAR models revealed that only 12-month exposure to $PM_{2.5}$ was consistently correlated with KD incidence, and each 1 $\mu g/m^3$ increase in annual $PM_{2.5}$ exposure corresponded to a 3%–10% rise in KD incidence. Consistent outcomes were observed in the age-stratified sensitivity analysis.

**Conclusions** Annual exposure to $PM_{2.5}$ was robustly linked with the onset of KD. Further research is needed to elucidate the underlying mechanism by which the spatiotemporal distribution of $PM_{2.5}$ is associated with KD.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have suggested a potential link between air pollution and Kawasaki disease (KD), but the evidence has been inconclusive.

### WHAT THIS STUDY ADDS

⇒ Our spatiotemporal modelling showed that annual exposure to $PM_{2.5}$ was consistently linked with higher KD incidence before and during the COVID-19 pandemic across all age groups of children (0, 1 or 2–4 years).

⇒ Each 1 $\mu g/m^3$ increase in $PM_{2.5}$ concentration corresponded to a 3%–10% increase in KD cases.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a strong foundation for future research into the underlying mechanisms of KD onset related to air pollution.

## INTRODUCTION

Kawasaki disease (KD) is a febrile illness of unknown aetiology that predominantly affects children under 5.[1–3] Intravenous immunoglobulin (IG) therapy has been widely adopted to reduce the risk of fatal coronary artery aneurysms, with approximately 95% of KD cases in Japan receiving intravenous IG early in the course of the illness.[2 4–6] Despite treatment advancements, including the combination of corticosteroids with intravenous IG, as well as the use of cyclosporine A, infliximab or ulinastatin, coronary artery lesions occur in about 6% of cases,[7] underscoring the urgent need to uncover clues to understand the disease's pathogenesis. Some researchers attribute the cause of KD to viral infections, while others point to the association between KD and air pollutants, including $PM_{2.5}$.[8–11] Cytokine-induced oxidative stress has been proposed as a potential mechanism linking chronic exposure to $PM_{2.5}$ with the onset of KD.[11] Association between Candida influx and the onset of KD has also been reported, which may imply that certain substances within air pollutants could trigger the disease.[8 12]

The association between KD and $PM_{2.5}$ has been the subject of research. While some studies have indicated no significant effect of short-term exposure to $PM_{2.5}$, others have shown an impact of annual or intrauterine exposure to $PM_{2.5}$.[9–11 13 14] These studies may indicate the association between KD and

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long-term exposure to $PM_{2.5}$; however, several limitations should be noted. First, most previous studies ignore repeatedly documented spatiotemporal clustering of KD.[15–19] Spatiotemporal clustering of this disease with unknown aetiology indicates possible autocorrelation in the residuals, comprising the validity of the generalised linear regression and leads to biased estimates. The conditional autoregressive (CAR) models, which are hierarchical Bayesian models designed for spatial and spatiotemporal analysis, can address residual autocorrelation by incorporating a spatiotemporal term.[20–22] Second, studies on KD often focus on the exposure defined by a single time length, leaving it uncertain whether observed differences in results are due to the length of time unit or other aspects of the study design. Third, the dramatic reduction in KD after the onset of the COVID-19 pandemic may have disrupted the stationarity assumptions.[8 23 24] Changes in social factors, such as mask-wearing and physical distancing, may also have modified the impact of air pollutants on the incidence of KD.

Thus, this paper aims to perform spatiotemporal analysis based on the CAR model to investigate the impact of monthly and annual exposure to $PM_{2.5}$ and other air pollutants on the incidence of KD before and after the advent of the COVID-19 pandemic.

## METHODS

### Data source

In this retrospective study, we extracted clinical data from the Japanese administrative claims database named the Diagnosis Procedure Combination (DPC) database, comprising anonymised clinical and administrative claims data featuring baseline information of patients and facilities, diagnostic records, procedural data, device utilisation and prescription details. As of 2023, over 2000 hospitals had implemented DPC-based

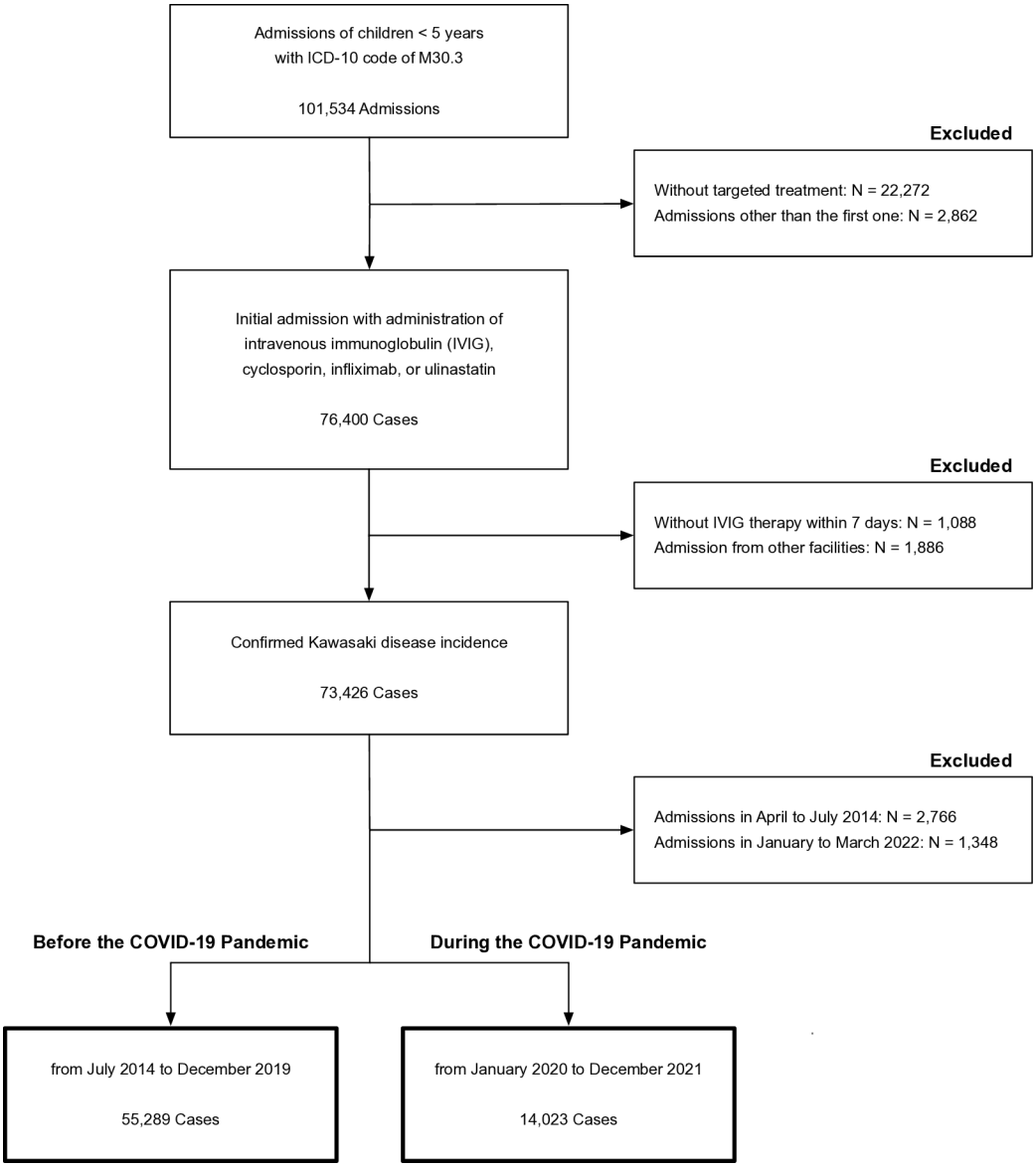


**Figure 1** Study population and the exclusion criteria. ICD-10, International Classification of Diseases, Tenth Revision.



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reimbursement systems. This database substantiated its reliability through prior research.[25] Data were accessed on 16 August 2023. Among hospitalisation data from April 2014 to March 2022, we extracted clinical information on children under 5 diagnosed with KD, identified by the International Classification of Diseases, Tenth Revision (ICD-10) code of M30.3. To minimise bias associated with misclassification, we focused on hospital admissions where patients received KD-specific medications, namely intravenous IG, cyclosporine A, infliximab or ulinastatin.[3 6 7] We considered the date of first admission with KD treatment as the onset date, excluding cases with unclear onset dates, specifically transfer cases and those not administered intravenous IG within 7 days of the first admission. To address uncertainties associated with identifying of initial hospitalisations, cases of KD that occurred in the first 3 months of the observation period were excluded, given the risk of misinterpreting the middle of a series of hospitalisations that began before the observation period as the onset. Cases from the last 3 months of the period were also excluded, as the number of onsets during this period may be underestimated due to administrative delays in medical claims processing. Then, the timeframe from July 2014 to December 2019 was defined as the period before the COVID-19 pandemic, whereas from January 2020 to December 2021, it was defined as the period during the COVID-19 pandemic.

The atmospheric environment database of the National Institute for Environmental Studies publishes pollution data from 2184 monitoring stations across 319 (95%) of the 335 secondary medical care areas in Japan.[26] Each secondary medical care area, established across 1718 of the 1724 municipalities and managed by the 47 prefectural governments, ensures general inpatient treatment, including initial treatment of KD. We extracted daily exposure to $PM_{2.5}$, nitric monoxide (NO), nitrogen dioxide ($NO_2$) and sulphur dioxide ($SO_2$) for each medical care region, imputed missing values using the prefectural average and calculated monthly exposure. As a result, we obtained 22 100 and 8040 spatiotemporal units based on the exposure status in 335 secondary medical care areas over 66 months and 24 months before and after the onset of the COVID-19 pandemic, respectively.

## Outcomes and variables

As an outcome measure, the monthly incidence of KD was counted for each secondary medical care area associated with facilities. The monthly or annual exposure to $PM_{2.5}$, NO, $NO_2$ and $SO_2$ in the corresponding area was incorporated in the analysis as continuous variables. The logarithm of person-days for each spatiotemporal unit based on the under 5 population in the Population Census 2020 was implicitly incorporated in all the statistical models as an offset variable.[27]

## Statistical analysis

To capture the fundamental relationship between KD incidence and exposure to $PM_{2.5}$, NO, $NO_2$ and $SO_2$, we developed non-Bayesian Poisson regression models, both univariable and multivariable, using overall exposure levels during the two distinct periods before and after the onset of the COVID-19 pandemic. Subsequently, we performed Markov chain Monte Carlo (MCMC) simulations with the CARBayes library V.6.1 and CARBayesST library V.5.0 in R V.4.3.2 to create four types of multivariable Bayesian Poisson regression models predicting the monthly incidence of KD based on 1-month and 12-month exposure to these air pollutants: 'GLM model' is a Bayesian implementation of a generalised linear model that ignores spatiotemporal autocorrelations; 'CARar(1) model' is a first-order CAR model, where 'first-order' indicates that the model accounts for dependencies on the immediately previous time step; 'CARar(2) model' is an extension of the CARar(1) model, incorporating dependencies on the past two time steps; and 'CARadaptive model' is another first-order CAR model, which includes an adapted spatial weight matrix to handle spatial heterogeneity.[20 21 28–31] We adopted the model with the lowest widely applicable information criterion (WAIC) among these four Bayesian models.[32] Univariable models were also developed to assess the impact of individual air pollutants. The parameters were estimated from distributions derived from 40 000 MCMC samples, equating to 400 000 iterations with a thinning factor of 10 to reduce autocorrelation. This estimation followed an initial burn-in period of 100 000 iterations to stabilise the sampling process. In the sensitivity analysis, we developed comparative Bayesian models with subjects

**Table 1** Basic characteristics of spatiotemporal units

| Characteristic | Before the COVID-19 pandemic,* n=22 110 | During the COVID-19 pandemic,* n=8040 | SMD | 95% CI |
|---|---|---|---|---|
| Incidence | 1.0 (0.0, 3.0) | 0.0 (0.0, 2.0) | 0.21 | 0.18, 0.23 |
| $PM_{2.5}$, μg/m$^3$ | 11.4 (9.2, 13.9) | 8.5 (6.9, 10.3) | 0.94 | 0.91, 0.96 |
| NO, ppb | 2.47 (1.22, 4.52) | 1.72 (0.88, 3.07) | 0.34 | 0.31, 0.36 |
| $NO_2$, ppb | 7.8 (5.0, 11.4) | 6.2 (4.0, 9.2) | 0.38 | 0.35, 0.40 |
| $SO_2$, ppb | 1.27 (0.79, 1.94) | 0.83 (0.47, 1.24) | 0.52 | 0.50, 0.55 |

*Median (IQR).
ppb, parts per billion; SMD, standardised mean difference.



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Table 2 Non-Bayesian Poisson regression models before and during the COVID-19 pandemic

| | Univariable | | | Multivariable | | | |
|---|---|---|---|---|---|---|---|
| Variable | IRR | 95% CI | P value | IRR | 95% CI | P value | VIF |
| Before the COVID-19 pandemic | | | | | | | |
| $PM_{2.5}$, μg/m$^3$ | 1.02 | 1.02, 1.03 | <0.001 | 1.03 | 1.02, 1.03 | <0.001 | 1.40 |
| NO, ppb | 0.99 | 0.99, 1.00 | <0.001 | 1.00 | 1.00, 1.01 | 0.13 | 4.02 |
| $NO_2$, ppb | 1.00 | 0.99, 1.00 | <0.001 | 0.99 | 0.99, 0.99 | <0.001 | 4.45 |
| SO2, ppb | 1.02 | 1.02, 1.03 | <0.001 | 1.01 | 1.00, 1.02 | 0.011 | 1.24 |
| After the COVID-19 pandemic | | | | | | | |
| $PM_{2.5}$, μg/m$^3$ | 1.04 | 1.03, 1.05 | <0.001 | 1.03 | 1.02, 1.05 | <0.001 | 1.33 |
| NO, ppb | 0.98 | 0.97, 0.98 | <0.001 | 0.97 | 0.96, 0.99 | <0.001 | 3.80 |
| $NO_2$, ppb | 0.99 | 0.99, 1.00 | <0.001 | 1.00 | 0.99, 1.01 | 0.6 | 3.99 |
| $SO_2$, ppb | 1.08 | 1.06, 1.11 | <0.001 | 1.06 | 1.04, 1.09 | <0.001 | 1.23 |

IRR, incidence rate ratio; ppb, parts per billion; VIF, variance inflation factor.

divided into three age groups: 0 years, 1 year and 2–4 years.

## Patient and public involvement

Patients and/or the public were not involved in this study's design, conduct or dissemination.

## RESULTS

We extracted 101 534 admissions of children under 5 years of age admissions with the ICD-10 code M30.3 from the DPC database (figure 1). In the before-COVID-19 and during-COVID-19 pandemic periods, 55 289 (837.7 per month) and 14 023 (584.3 per month) onsets of KD were identified, respectively. The basic characteristics in table 1 indicate the significant reduction in KD incidence and exposure to air pollutants following the COVID-19 pandemic. Intergroup differences with standardised mean differences greater than 0.1 were observed. The scatterplot matrix in online supplemental figure 1 illustrates significant positive correlations between air pollutants. As shown in online supplemental table 1, the missing rates of daily air pollutant data at the secondary medical care area level were within a few per cent.

Table 2 presents the non-Bayesian Poisson regression models before and during the COVID-19 pandemic, indicating that overall exposure to $PM_{2.5}$ has been the only consistent contributor to the incidence of KD. Multicollinearity was within acceptable limits, with no variance inflation factors above 5. Online supplemental table 2 demonstrates that the CARadaptive models achieved the lowest WAIC. Tables 3 and 4 present the CARadaptive models before and during the COVID-19 pandemic, revealing that 12-month exposure to $PM_{2.5}$ has been the sole consistent contributor to the incidence

Table 3 CARadaptive models before the COVID-19 pandemic

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| Variable | IRR | 95% CI | IRR | 95% CI |
| 1-month exposure to air pollutants | | | | |
| $PM_{2.5}$, μg/m$^3$ | 1.00 | 1.00, 1.01 | 1.00 | 0.99, 1.01 |
| NO, ppb | 1.00 | 1.00, 1.01 | 1.00 | 0.99, 1.01 |
| $NO_2$, ppb | 1.00 | 1.00, 1.01 | 1.00 | 0.99, 1.01 |
| $SO_2$, ppb | 1.02 | 1.00, 1.04 | 1.01 | 0.99, 1.04 |
| 12-month exposure to air pollutants | | | | |
| $PM_{2.5}$, μg/m$^3$ | 1.03* | 1.01, 1.05 | 1.03* | 1.01, 1.06 |
| NO, ppb | 1.00 | 0.99, 1.01 | 0.99 | 0.97, 1.01 |
| $NO_2$, ppb | 1.01 | 1.00, 1.02 | 1.01 | 0.99, 1.03 |
| $SO_2$, ppb | 1.02 | 0.99, 1.06 | 1.00 | 0.96, 1.04 |

*P<0.05.
IRR, incidence rate ratio; ppb, parts per billion.

Table 4 CARadaptive models during the COVID-19 pandemic

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| Variable | IRR | 95% CI | IRR | 95% CI |
| 1-month exposure to air pollutants | | | | |
| $PM_{2.5}$, μg/m$^3$ | 1.00 | 0.98, 1.02 | 0.98* | 0.97, 1.00 |
| NO, ppb | 1.01 | 0.99, 1.03 | 1.02 | 0.99, 1.05 |
| $NO_2$, ppb | 1.02* | 1.01, 1.03 | 1.01 | 0.98, 1.03 |
| $SO_2$, ppb | 1.01 | 0.96, 1.06 | 1.02 | 0.96, 1.09 |
| 12-month exposure to air pollutants | | | | |
| $PM_{2.5}$, μg/m$^3$ | 1.09* | 1.04, 1.15 | 1.10* | 1.04, 1.17 |
| NO, ppb | 0.99 | 0.95, 1.02 | 0.90* | 0.84, 0.95 |
| $NO_2$, ppb | 1.02 | 1.00, 1.05 | 1.07* | 1.02, 1.12 |
| $SO_2$, ppb | 1.02 | 0.94, 1.10 | 0.94 | 0.85, 1.04 |

*P<0.05.
IRR, incidence rate ratio; ppb, parts per billion.

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Table 5 Age-stratified multivariable CARadaptive models before the COVID-19 pandemic

| | 0 years of age | | 1 year of age | | 2–4 years of age | |
|---|---|---|---|---|---|---|
| Variable | IRR | 95% CI | IRR | 95% CI | IRR | 95% CI |
| 1-month exposure to air pollutants | | | | | | |
| $PM_{2.5}$, µg/m$^3$ | 1.00 | 0.99, 1.01 | 1.00 | 0.99, 1.01 | 1.00 | 0.99, 1.01 |
| NO, ppb | 1.00 | 0.99, 1.01 | 1.00 | 0.99, 1.01 | 1.00 | 0.99, 1.01 |
| $NO_2$, ppb | 1.00 | 0.99, 1.01 | 1.00 | 0.99, 1.01 | 1.00 | 0.99, 1.01 |
| $SO_2$, ppb | 1.01 | 0.99, 1.04 | 1.01 | 0.99, 1.04 | 1.01 | 0.99, 1.04 |
| 12-month exposure to air pollutants | | | | | | |
| $PM_{2.5}$, µg/m$^3$ | 1.03* | 1.00, 1.06 | 1.03* | 1.00, 1.06 | 1.03* | 1.00, 1.06 |
| NO, ppb | 0.99 | 0.97, 1.01 | 0.99 | 0.97, 1.01 | 0.99 | 0.97, 1.01 |
| $NO_2$, ppb | 1.01 | 0.99, 1.03 | 1.01 | 0.99, 1.04 | 1.01 | 1.00, 1.03 |
| $SO_2$, ppb | 0.99 | 0.95, 1.03 | 0.99 | 0.96, 1.03 | 1.00 | 0.96, 1.04 |

*P<0.05.
IRR, incidence rate ratio; ppb, parts per billion.

of KD. Favourable convergence was suggested by the Geweke diagnostics with absolute values less than 2. In univariable analysis before and during the COVID-19 pandemic, monthly exposure to $PM_{2.5}$ was not significantly associated with the onset of KD. CARadaptive model during the COVID-19 pandemic, 1-month exposure to $PM_{2.5}$ and 12-month exposure to NO were associated with a decreased incidence of KD, whereas $NO_2$ showed a converse effect.

Tables 5 and 6 display the age-stratified multivariable CARadaptive models achieved in the sensitivity analysis for the before pandemic and during pandemic. The reactivity to each air pollutant was aligned with the primary analysis, which revealed sustained significant associations between the onset of KD and 12-month exposure to $PM_{2.5}$.

## DISCUSSION

Before the COVID-19 pandemic, 55 289 new cases of KD were identified, and 14 023 cases were detected during the pandemic period. The classical method of non-Bayesian Poisson regression suggested a fundamental correlation between KD incidence in the secondary medical care area and the regional level of $PM_{2.5}$. A detailed analysis through the CAR models revealed that 12-month exposure to $PM_{2.5}$ was the exclusive variable consistently associated with KD incidence (tables 3 and 4). Parallel outcomes were observed in the sensitivity analysis stratified by age (tables 5 and 6).

The remarkable reduction in WAIC associated with the CARadaptive models substantiated their efficiency and adequacy in the analysis. The convergence of these models and the consistency of the results bolster the

Table 6 Age-stratified multivariable CARadaptive models during the COVID-19 pandemic

| | 0 years of age | | 1 year of age | | 2–4 years of age | |
|---|---|---|---|---|---|---|
| Variable | IRR | 95% CI | IRR | 95% CI | IRR | 95% CI |
| 1-month exposure to air pollutants | | | | | | |
| $PM_{2.5}$, µg/m$^3$ | 0.98* | 0.97, 1.00 | 0.98* | 0.97, 1.00 | 0.98* | 0.97, 1.00 |
| NO, ppb | 1.02 | 0.99, 1.04 | 1.02 | 0.99, 1.04 | 1.02 | 0.99, 1.05 |
| $NO_2$, ppb | 1.01 | 0.98, 1.03 | 1.01 | 0.98, 1.03 | 1.01 | 0.98, 1.03 |
| $SO_2$, ppb | 1.02 | 0.96, 1.09 | 1.02 | 0.96, 1.09 | 1.02 | 0.96, 1.09 |
| 12-month exposure to air pollutants | | | | | | |
| $PM_{2.5}$, µg/m$^3$ | 1.10* | 1.04, 1.16 | 1.10* | 1.04, 1.17 | 1.11* | 1.04, 1.17 |
| NO, ppb | 0.90* | 0.85, 0.95 | 0.90* | 0.85, 0.96 | 0.89* | 0.84, 0.95 |
| $NO_2$, ppb | 1.05* | 1.01, 1.10 | 1.06* | 1.01, 1.11 | 1.07* | 1.02, 1.12 |
| $SO_2$, ppb | 0.94 | 0.84, 1.04 | 0.94 | 0.85, 1.04 | 0.93 | 0.84, 1.03 |

*P<0.05.
IRR, incidence rate ratio; ppb, parts per billion.



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validity and robustness of our research. The comparative analysis of 1-month and 12-month exposure underscored the criticality of the exposure duration. The climb in KD incidence with annual rather than monthly exposure to $PM_{2.5}$ aligns with previous research.[9–11 13 14] The univariable and multivariable CARadaptive models demonstrated a 3%–10% increase in the incidence of KD for every 1 µg/m³ increase in $PM_{2.5}$. This increase corresponds to a 16%–61% rise with a 5 µg/m³ increase and is consistent with findings from a previous South Korean study.[11]

Previous research has shown that a considerable amount of $PM_{2.5}$ comes from sources over 100 km away, whereas $NO_2$ mainly comes from sources within 10 km.[33] NO has an even shorter dispersal distance compared with $NO_2$.[34] Their contrasting effects observed in the during-pandemic multivariable CARadaptive model—the optimistic influence of NO and the pessimistic impact of $NO_2$—can jointly modify predictions towards less incidence of KD in areas experiencing nearby air pollution. It may be that the remarkable reduction in distantly originated $PM_{2.5}$[35] necessitated adjustments for the less harmful $PM_{2.5}$ derived from proximate pollution sources.

The strength of this study lies in the adept use of CAR models that address the well-documented spatiotemporal aggregation of KD.[15 17] Spatiotemporal autocorrelation of the error term caused by this aggregation violates the Gauss-Markov theorem's assumptions, enhancing the prevalence of type I and type II errors.[36 37] Given the unknown pathogenesis of KD, measuring all the confounders with spatial effects to eradicate autocorrelation of the error term is not feasible, thus necessitating the adoption of clustering-aware models.

## Limitations

Selection bias is a concern in observational studies. In light of the incidence rates of KD reported in previous studies, it can be estimated that approximately 70% of the domestic cases were included.[23] Although the inclusion criteria were carefully constructed based on the ICD-10 code and KD-specific medications, the level of concordance between the judged and actual onset of KD is yet to be confirmed. In this real-world data study, information on symptoms and clinical findings was not available. We considered the risk of misclassification with multisystem inflammatory syndrome in children (MIS-C) to be negligible based on the rarity of MIS-C cases in Japan.[8 38] The exclusion of untreated cases can be expected to be marginal, considering the ubiquity of early intravenous IG administration in Japan.[2] Imputation of exposure at the prefectural level for the small amount of missing data may have biased the analyses toward the null. Although the dose–response relationship observed in this study aligns with previous research conducted in geographically close Korea, different results might be obtained in distant countries due to varying sources of $PM_{2.5}$. Unmeasured substances or microorganisms dispersing similarly to $PM_{2.5}$, rather than $PM_{2.5}$ itself, might be involved in the onset of KD.[39 40] Besides, it should be noted that spatiotemporal analysis with different granularities of spatiotemporal units may yield different results.[41] Given the limited geographic activity range of children under the age of five, the impact of exposure outside their secondary medical care area would be minimal. Analysis with a finer granularity would pose challenges due to boundary-crossing admissions, while extensive unit aggregation would reduce statistical power. We handled data at the spatiotemporal unit level, thereby not distinguishing between prenatal and postnatal exposures at the individual level. While the impact of annual $PM_{2.5}$ exposure in infants under 1 year may imply potential influences of prenatal exposure, these effects have not been explicitly examined.

In conclusion, we used the CAR models to address the spatiotemporal aggregation of KD, confirming the robust association between the incidence of KD and annual exposure to $PM_{2.5}$. Further investigation is required to clarify the underlying mechanism of association between the spatiotemporal distribution of KD and $PM_{2.5}$.

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**Contributors** KY: Conceptualisation, data curation, methodology, formal analysis and writing of the original draft. DS: Conceptualisation, methodology, review writing, editing and funding acquisition. NT: Conceptualisation and writing the review. KF: Supervision, resources, review writing and funding acquisition. All authors have accepted responsibility for the entire content of this manuscript and approved its submission. The guarantor (DS) accepts full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants. This study was approved by the institution review board at the Tokyo Medical and Dental University (registration no. M2021-013). Given the anonymised nature of the data, the requirement for informed consent was waived.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available. Due to the confidential nature of the data, it is unavailable for sharing.

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**ORCID iDs**
Kota Yoneda http://orcid.org/0000-0003-1605-5340
Daisuke Shinjo http://orcid.org/0000-0002-7495-7409

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