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Spatiotemporal Analysis of the Association Between Kawasaki Disease Incidence and $PM_{2.5}$ Exposure: A Nationwide Database Study in Japan

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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.

Method: In this retrospective analysis, we utilised the Japanese administrative claims database to identify the incidence of KD in children under age five in 335 secondary medical care areas across Japan before the COVID-19 pandemic (from July 2014 to December 2019) and after the COVID-19 pandemic (from January 2020 to December 2021). For each of these periods, we developed hierarchical Bayesian models termed conditional autoregressive 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 pre-pandemic and post-pandemic periods, 55,289 and 14,023 new cases of KD were identified, respectively. The conditional autoregressive models revealed that only 12-month exposure to $PM_{2.5}$ was consistently correlated with KD incidence, and each 1 µg/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.

Key Messages

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 after the COVID-19 pandemic across all age groups of children (0, 1, or 2–4 years).
- A 1 μg/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 five.[1–3] Intravenous immunoglobulin (IVIG) therapy has been widely adopted to reduce the risk of fatal coronary artery aneurysms, with approximately 95% of KD cases in Japan receiving IVIG early in the course of the illness.[2,4–6] Despite treatment advancements, including the combination of corticosteroids with IVIG, 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.

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 $PM_{2.5}$.[8–12] These studies may indicate the association between KD and long-term exposure to $PM_{2.5}$; however, several limitations should be noted. First, most previous studies ignore repeatedly documented spatiotemporal clustering of KD.[13–17] Spatiotemporal clustering of this disease with unknown aetiology indicates possible autocorrelation in the residuals, comprising the validity of the generalised linear regression and leading to biased estimates. The conditional autoregressive (CAR) models, hierarchical Bayesian models designed for spatial and spatiotemporal analysis, can address residual autocorrelation by incorporating a spatiotemporal term.[18–20] 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.[21–23]

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 2,000 hospitals had implemented DPC-based reimbursement systems. This database substantiated its reliability through prior research.[24] Data were accessed on August 16, 2023. Among hospitalisation data from April 2014 to March 2022, we extracted clinical information on children under five 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 IVIG, 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 IVIG within seven days of the first admission. Cases of KD that occurred in the first and last three months of the observation period were excluded to address uncertainties associated with the identification of initial hospitalisations and to minimise omissions due to delayed reporting.

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 was defined as the period after the COVID-19 pandemic.

The atmospheric environment database of the National Institute for Environmental Studies publishes pollution data from 2,184 monitoring stations across 319 (95%) of the 335 secondary medical care areas in Japan.[25] Each secondary medical care area, established across 1,718 of the 1,724 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 8,040 spatiotemporal units based on the exposure status in 335 secondary medical 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 were incorporated in the analysis as continuous variables. The logarithm of person-days for each spatiotemporal unit based on the under-five population in the Population Census 2020 was implicitly incorporated in all the statistical models as an offset variable.[26]

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 version 6.1 and CARBayesST library version 5.0 in R version 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.[18,19,27–30] We adopted the model with the lowest widely applicable information criterion (WAIC) among these four Bayesian models.[31] 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 divided into three age groups: 0 years, 1 year, and 2 to 4 years.

Ethics

The Institutional Review Board at Tokyo Medical and Dental University granted ethical approval for this investigation (approval no. M2021-013). Given the anonymised nature of the data, the requirement for informed consent was waived.

Results

We extracted 101,534 admissions of children under five years of age admissions with the ICD-10 code M30.3 from the DPC database (**Figure 1**). In the pre-and post-COVID-19 pandemic periods, 55,289 and 14,023 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. The scatterplot matrix in **Supplementary Figure 1** illustrates significant positive correlations between air pollutants.

Table 2 presents the non-Bayesian Poisson regression models before and after 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. **Supplementary Table 1** demonstrates that the CARadaptive models achieved the lowest WAIC. **Tables 3 and 4** present the CARadaptive models before and after the COVID-19 pandemic, revealing that 12-month exposure to $PM_{2.5}$ has been the sole consistent contributor to the incidence of KD. Favourable convergence was suggested by the Geweke diagnostics with absolute values less than 2. In univariable analysis before and after the COVID-19 pandemic, monthly exposure to $PM_{2.5}$ was not significantly associated with the onset of KD. In the multivariable CARadaptive model after 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 pre-pandemic and post-pandemic age-stratified multivariable CARadaptive models achieved in the sensitivity analysis. 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 in the post-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 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.[8–12] The 3–10% increase in the incidence of KD for every 1 μg/m^3 increase in $PM_{2.5}$, as demonstrated by the univariable and multivariable CARadaptive models, was congruent with a previous South Korean study.[12]

Previous research has shown that a considerable amount of $PM_{2.5}$ comes from sources over 100 kilometres away, whereas NO_2 mainly comes from sources within 10 kilometres.[32] NO has an even shorter dispersal distance compared to NO_2.[33] Their contrasting effects observed in the post-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 $PM_{2.5}$[34] 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.[13,15] 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.[35,36] 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.[22] 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. The exclusion of untreated cases can be expected to be marginal, considering the ubiquity of early IVIG administration in Japan.[2] 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.[37,38] Besides, it should be noted that spatiotemporal analysis with different granularities of spatiotemporal units may yield different results.[39] 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 one year may imply potential influences of prenatal exposure, these effects have not been explicitly examined.

In conclusion, we utilised the CAR models to address the spatiotemporal aggregation of KD, confirming the robust association between the incidence of KD and annual exposure to $PM_{2.5}$.

247 Further investigation is required to clarify the underlying mechanism of association between

248 the spatiotemporal distribution of KD and $PM_{2.5}$.

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We used open geographic data from the publicly available National Land Numerical Information released by the Japanese Ministry of Land, Infrastructure, Transport and Tourism (https://nlftp.mlit.go.jp/).

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.

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Competing interests

No relevant financial or nonfinancial interest to disclose.

Patient and public involvement

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

Ethics approval

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.

Data availability statement

Due to the confidential nature of the data, it is unavailable for sharing.

Figure legends

Figure 1. Study population and the exclusion criteria.

286 **Tables**

287 Table 1. Basic Characteristics of Spatiotemporal Units

Characteristic	Before the COVID-19 Pandemic [a] N = 22,110	After the COVID-19 Pandemic [a] N = 8,040	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

[a] Median (Interquartile Range); Standardized Mean Difference; CI, Confidence Interval.

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Table 2. Non-Bayesian Poisson Regression Models Before and After the COVID-19 Pandemic

Variable	Univariable			Multivariable			
	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; CI, Confidence Interval; VIF, Variance Inflation Factor.

294 ***Table 3. CARadaptive Models Before the COVID-19 Pandemic***

Variable	Univariable		Multivariable	
	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

IRR, Incidence Rate Ratio; CI, Confidence Interval. *p < 0.05.

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Table 4. CARadaptive Models After the COVID-19 Pandemic

Variable	Univariable		Multivariable	
	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

IRR, Incidence Rate Ratio; CI, Confidence Interval. *p < 0.05.

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300 ***Table 5. Age-Stratified Multivariable CARadaptive Models Before the***
301 ***COVID-19 Pandemic***

Variable	0 Years of Age		1 Year of Age		2–4 Years of Age	
	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

IRR, Incidence Rate Ratio; CI, Confidence Interval. *$p < 0.05$.

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304 ***Table 6. Age-Stratified Multivariable CARadaptive Models After the COVID-19***
305 ***Pandemic***

Variable	0 Years of Age		1 Year of Age		2–4 Years of Age	
	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

IRR, Incidence Rate Ratio; CI, Confidence Interval. *p < 0.05.

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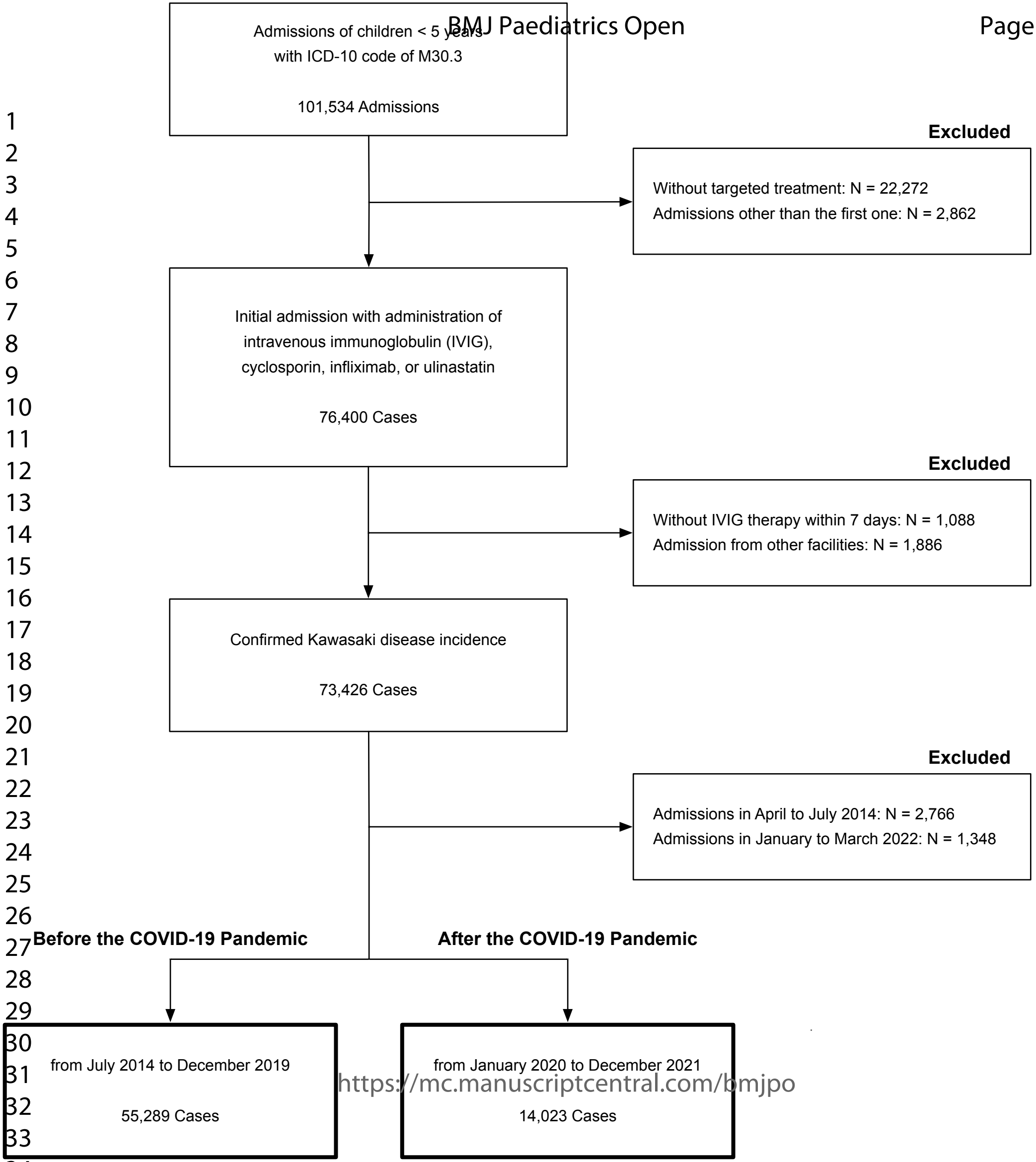
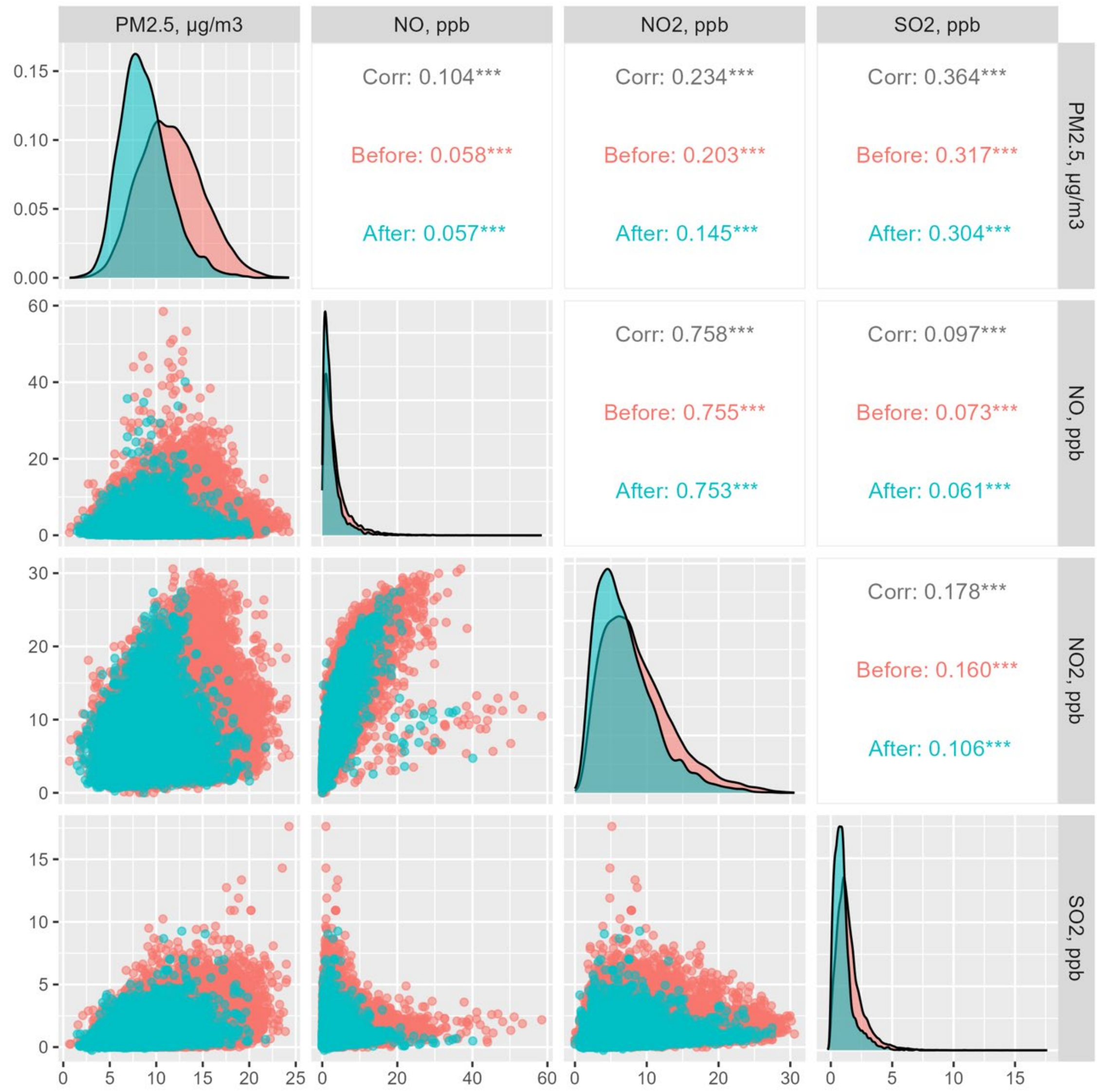

Admissions of children < 5 years
with ICD-10 code of M30.3
101,534 Admissions
Excluded
Without targeted treatment: N = 22,272
Admissions other than the first one: N = 2,862
Initial admission with administration of
intravenous immunoglobulin (IVIG),
cyclosporin, infliximab, or ulinastatin
76,400 Cases
Excluded
Without IVIG therapy within 7 days: N = 1,088
Admission from other facilities: N = 1,886
Confirmed Kawasaki disease incidence
73,426 Cases
Excluded
Admissions in April to July 2014: N = 2,766
Admissions in January to March 2022: N = 1,348
Before the COVID-19 Pandemic
After the COVID-19 Pandemic
from July 2014 to December 2019
55,289 Cases
from January 2020 to December 2021
14,023 Cases

Supplementary Table 1. Widely Applicable Information Criteria of the Bayesian Models

Model	Before the COVID-19 Pandemic	After the COVID-19 Pandemic
GLM model	76,061	23,873
CARar(1) model	56,931	18,350
CARar(2) model	57,038	18,485
CARadaptive model	**56,140**	**18,313**

GLM, Generalized Linear Regression; CARar(1), Conditional Autoregression with order 1; CARar(2), Conditional Autoregression with order 2; CARadaptive, Conditional Autoregression with an Adaptive Spatial Autocorrelation Structure



Supplementary Figure 1. Scatter plot matrix of air pollutants stratified before and after the COVID-19 pandemic groups. ***p < 0.001

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Spatiotemporal Analysis of the Association Between Kawasaki Disease Incidence and PM2.5 Exposure: A Nationwide Database Study in Japan

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Spatiotemporal Analysis of the Association Between Kawasaki Disease Incidence and $PM_{2.5}$ Exposure: A Nationwide Database Study in Japan

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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 utilized the Japanese administrative claims database to identify the incidence of KD in children under age five 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 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 conditional autoregressive models revealed that only 12-month exposure to $PM_{2.5}$ was consistently correlated with KD incidence, and each 1 μg/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.

Key Messages

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 μg/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 five.[1–3] Intravenous immunoglobulin (IVIG) therapy has been widely adopted to reduce the risk of fatal coronary artery aneurysms, with approximately 95% of KD cases in Japan receiving IVIG early in the course of the illness.[2,4–6] Despite treatment advancements, including the combination of corticosteroids with IVIG, 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 Kawasaki disease 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 Kawasaki disease.[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 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 etiology indicates possible autocorrelation in the residuals, comprising the validity of the generalized 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 Kawasaki disease.

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 anonymized clinical and administrative claims data featuring baseline information of patients and facilities, diagnostic records, procedural data, device utilization, and prescription details. As of 2023, over 2,000 hospitals had implemented DPC-based reimbursement systems. This database substantiated its reliability through prior research.[25] Data were accessed on August 16, 2023. Among hospitalization data from April 2014 to March 2022, we extracted clinical information on children under five diagnosed with KD, identified by the International Classification of Diseases, Tenth Revision (ICD-10) code of M30.3. To minimize bias associated with misclassification, we focused on hospital admissions where patients received KD-specific medications, namely IVIG, 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 IVIG within 7 days of the first admission. To address uncertainties associated with identifying of initial hospitalizations, cases of KD that occurred in the first three months of the observation period were excluded, given the risk of misinterpreting the middle of a series of hospitalizations 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 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 2,184 monitoring stations across 319 (95%) of the 335 secondary medical care areas in Japan.[26] Each secondary medical care area, established across 1,718 of the 1,724 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 8,040 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 were incorporated in the analysis as continuous variables. The logarithm of person-days for each spatiotemporal unit based on the under-five 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 version 6.1 and CARBayesST library version 5.0 in R version 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 generalized 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 stabilize the sampling process. In the sensitivity analysis, we developed comparative Bayesian models with subjects divided into three age groups: 0 years, 1 year, and 2 to 4 years.

Ethics

The Institutional Review Board at Tokyo Medical and Dental University granted ethical approval for this investigation (approval no. M2021-013). Given the anonymized nature of the data, the requirement for informed consent was waived.

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-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 standardized mean differences greater than 0.1 were observed. The scatterplot matrix in **Supplementary Figure 1** illustrates significant positive correlations between air pollutants. As shown in **Supplementary Table 1**, the missing rates of daily air pollutant data at the secondary medical care area level were within a few percent.

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. **Supplementary 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 of KD. Favorable 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 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 kilometers away, whereas NO_2 mainly comes from sources within 10 kilometres.[33] NO has an even shorter dispersal distance compared to 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] The exclusion of untreated cases can be expected to be marginal, considering the ubiquity of early IVIG 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 utilized 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 $PM_{2.5}$.

Acknowledgements

We used open geographic data from the publicly available National Land Numerical Information released by the Japanese Ministry of Land, Infrastructure, Transport and Tourism (https://nlftp.mlit.go.jp/).

Contributors

KY: Conceptualization, data curation, methodology, formal analysis, and writing of the original draft. DS: Conceptualization, methodology, review writing, editing, and funding acquisition. NT: Conceptualization 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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funders did not influence the design or conduct of the study, the gathering or interpretation of data, the decision to submit the results for publication, or the drafting of the research paper.

Competing interests

No relevant financial or nonfinancial interest to disclose.

Ethics approval

This study was approved by the institution review board at the Tokyo Medical and Dental University (Registration no. M2021-013). Given the anonymized nature of the data, the requirement for informed consent was waived.

Data availability statement

Due to the confidential nature of the data, it is unavailable for sharing.

Figure legends

Figure 1. Study population and the exclusion criteria.

Tables

Table 1. Basic Characteristics of Spatiotemporal Units

Characteristic	Before the COVID-19 Pandemic [a] N = 22,110	During the COVID-19 Pandemic [a] N = 8,040	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

[a] Median (Interquartile Range); SMD, Standardized Mean Difference; CI, Confidence Interval.

Table 2. Non-Bayesian Poisson Regression Models Before and During the COVID-19 Pandemic

Variable	Univariable			Multivariable			
	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; CI, Confidence Interval; VIF, Variance Inflation Factor.

Table 3. CARadaptive Models Before the COVID-19 Pandemic

Variable	Univariable		Multivariable	
	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

IRR, Incidence Rate Ratio; CI, Confidence Interval. *$p < 0.05$.

Table 4. CARadaptive Models During the COVID-19 Pandemic

Variable	Univariable		Multivariable	
	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

IRR, Incidence Rate Ratio; CI, Confidence Interval. *$p < 0.05$.

Table 5. Age-Stratified Multivariable CARadaptive Models Before the COVID-19 Pandemic

Variable	0 Years of Age		1 Year of Age		2–4 Years of Age	
	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

IRR, Incidence Rate Ratio; CI, Confidence Interval. *p < 0.05.

Table 6. Age-Stratified Multivariable CARadaptive Models During the COVID-19 Pandemic

Variable	0 Years of Age		1 Year of Age		2–4 Years of Age	
	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

IRR, Incidence Rate Ratio; CI, Confidence Interval. *p < 0.05.

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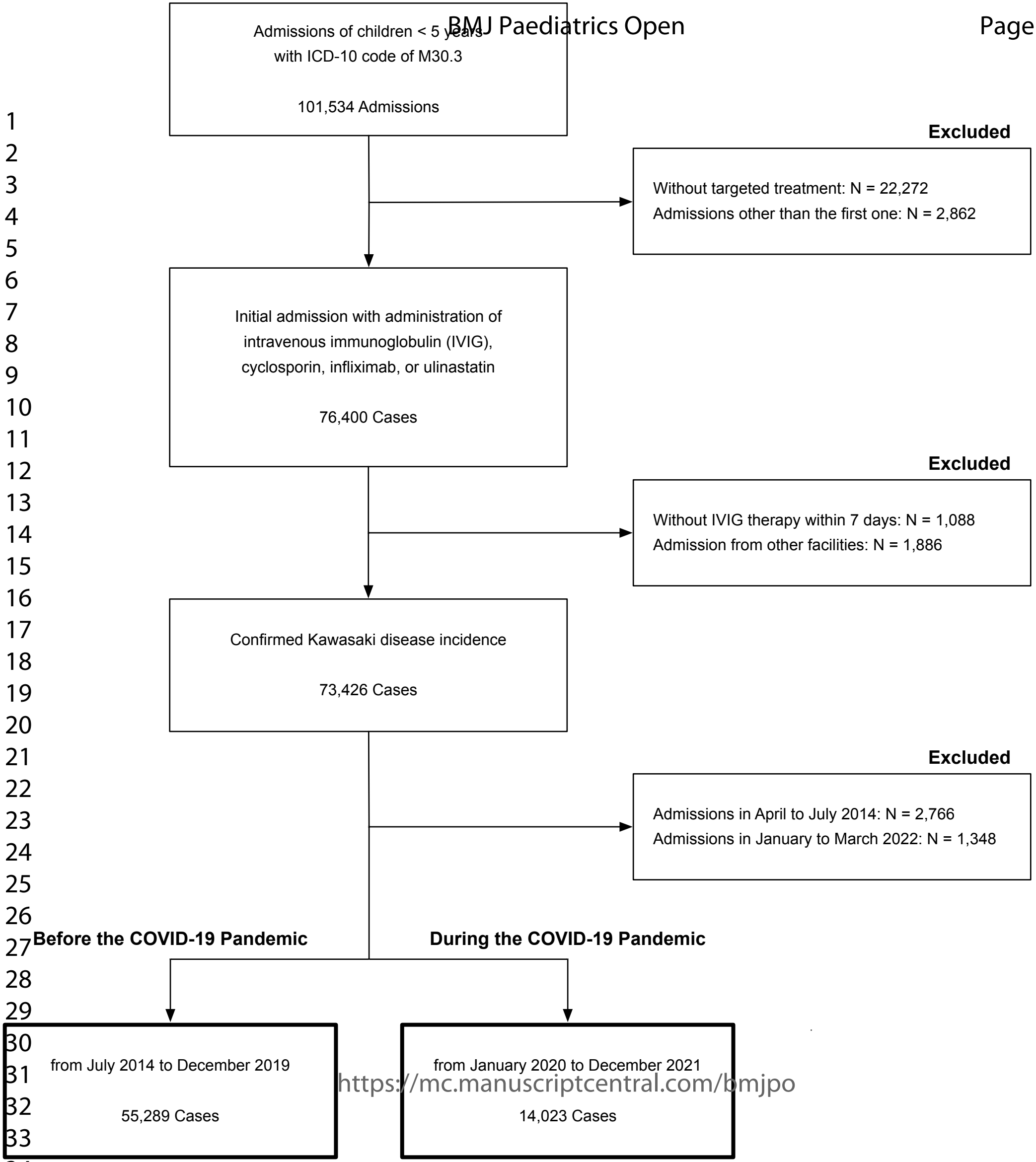

Admissions of children < 5 years
with ICD-10 code of M30.3
101,534 Admissions
Excluded
Without targeted treatment: N = 22,272
Admissions other than the first one: N = 2,862
Initial admission with administration of
intravenous immunoglobulin (IVIG),
cyclosporin, infliximab, or ulinastatin
76,400 Cases
Excluded
Without IVIG therapy within 7 days: N = 1,088
Admission from other facilities: N = 1,886
Confirmed Kawasaki disease incidence
73,426 Cases
Excluded
Admissions in April to July 2014: N = 2,766
Admissions in January to March 2022: N = 1,348
Before the COVID-19 Pandemic
During the COVID-19 Pandemic
from July 2014 to December 2019
55,289 Cases
from January 2020 to December 2021
14,023 Cases

Supplementary Table 1. Missing Rates of Daily Air Pollutant Data at the Secondary Medical Care Area Level

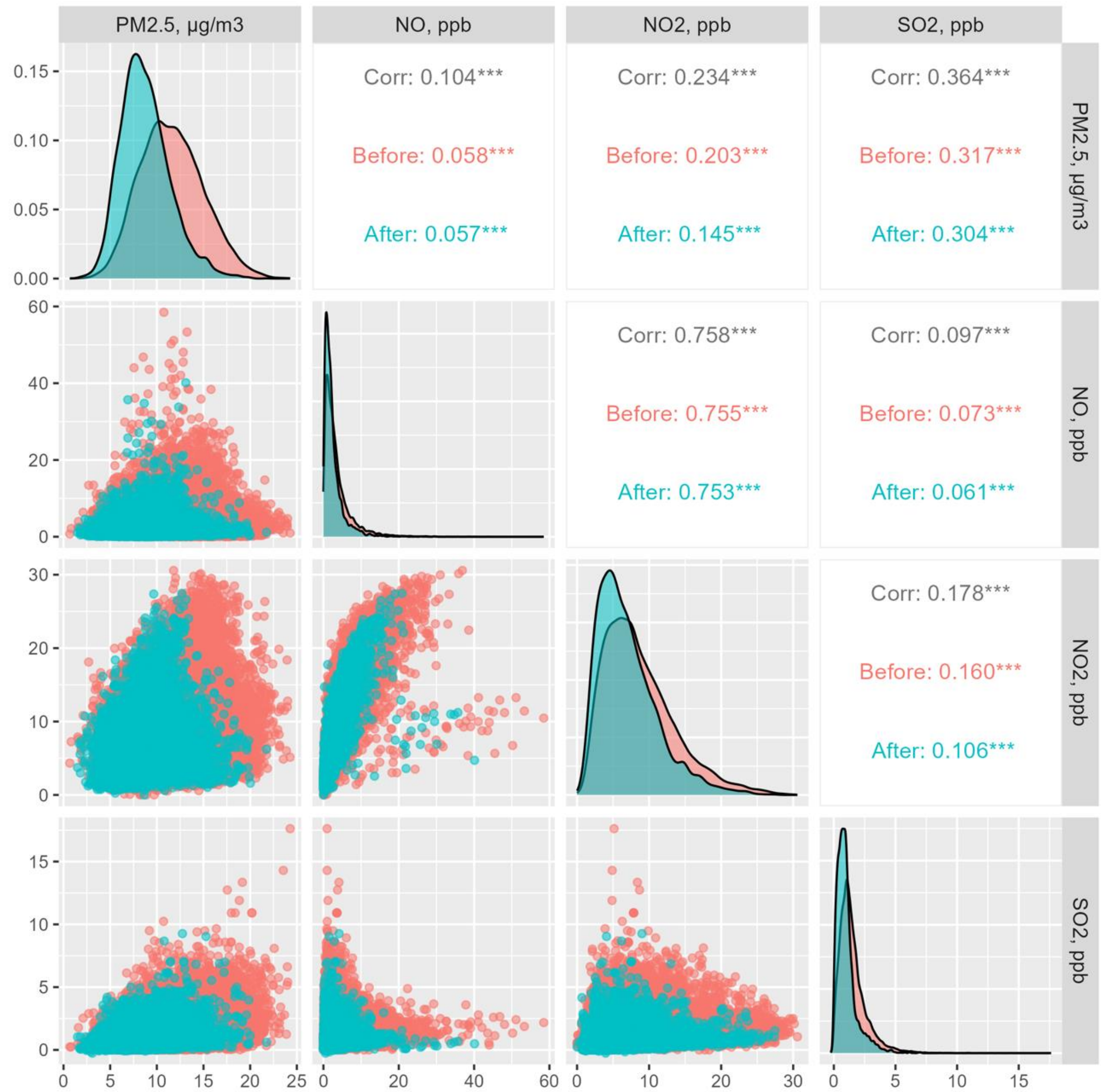
Characteristic	**Before the COVID-19 Pandemic** N = 335	**During the COVID-19 Pandemic** N = 335
$PM_{2.5}$, %	0.2 (0.0, 2.4)	0.3 (0.0, 1.4)
NO, %	0.0 (0.0, 1.1)	0.0 (0.0, 0.8)
NO_2, %	0.0 (0.0, 1.1)	0.0 (0.0, 0.8)
SO_2, %	0.1 (0.0, 3.6)	0.1 (0.0, 1.9)

Median (Interquartile Range)

Supplementary Table 2. Widely Applicable Information Criteria of the Bayesian Models

Model	Before the COVID-19 Pandemic	During the COVID-19 Pandemic
GLM model	76,061	23,873
CARar(1) model	56,931	18,350
CARar(2) model	57,038	18,485
CARadaptive model	**56,140**	**18,313**

GLM, Generalized Linear Regression; CARar(1), Conditional Autoregression with order 1; CARar(2), Conditional Autoregression with order 2; CARadaptive, Conditional Autoregression with an Adaptive Spatial Autocorrelation Structure



Supplementary Figure 1. Scatter plot matrix of air pollutants stratified before and after the COVID-19 pandemic groups. ***p < 0.001