

BMJ Paediatrics Open

BMJ Paediatrics Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Paediatrics Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjpaedsopen.bmj.com>).

If you have any questions on BMJ Paediatrics Open's open peer review process please email info.bmjpo@bmj.com

BMJ Paediatrics Open

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

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2024-002887
Article Type:	Original research
Date Submitted by the Author:	08-Jul-2024
Complete List of Authors:	Yoneda, Kota; Tokyo Women's Medical University; Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Health policy and Informatics Shinjo, Daisuke; Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Health policy and informatics Takahashi, Naoto; The University of Tokyo Hospital, Department of Pediatrics Fushimi, Kiyohide; Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Health policy and Informatics
Keywords:	Epidemiology, Child Health, Statistics, COVID-19

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Author Information

Kota Yoneda, MD, PhD, Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School, Tokyo, Japan. Department of Pediatrics, The University of Tokyo Hospital, Tokyo, Japan. ORCID: 0000-0003-1605-5340

Daisuke Shinjo, PhD, Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School, Tokyo, Japan. ORCID: 0000-0002-7495-7409

Naoto Takahashi, MD, PhD, Department of Pediatrics, The University of Tokyo Hospital, Tokyo, Japan. ORCID: 0000-0002-2353-4430

Kiyohide Fushimi, MD, PhD, Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School, Tokyo, Japan. ORCID: 0000-0002-1894-0290

Correspondence to: Daisuke Shinjo, PhD,
Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School, Tokyo, Japan
TEL: +81-3-3813-4028, FAX: +81-3-5803-0357
Email: dshinjo.hci@tmd.ac.jp,

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

22

23 **Abstract**

24 **Background:** Kawasaki disease (KD) is an acute vasculitis primarily affecting children. While

25 some studies suggest a link between KD and PM_{2.5} exposure, findings remain inconsistent.

26

27 **Method:** In this retrospective analysis, we utilised the Japanese administrative claims database

28 to identify the incidence of KD in children under age five in 335 secondary medical care areas

29 across Japan before the COVID-19 pandemic (from July 2014 to December 2019) and after the

30 COVID-19 pandemic (from January 2020 to December 2021). For each of these periods, we

31 developed hierarchical Bayesian models termed conditional autoregressive models that can

32 address the spatiotemporal clustering of KD to investigate the association between the monthly

33 incidence of KD and exposure to PM_{2.5}, NO, NO₂, and SO₂ over 1-month and 12-month

34 durations. The pollution data were collected from publicly available data provided by the

35 National Institute for Environmental Studies.

36

37 **Results:** In pre-pandemic and post-pandemic periods, 55,289 and 14,023 new cases of KD

38 were identified, respectively. The conditional autoregressive models revealed that only 12-

39 month exposure to PM_{2.5} was consistently correlated with KD incidence, and each 1 µg/m³

40 increase in annual PM_{2.5} exposure corresponded to a 3–10% rise in KD incidence. Consistent

41 outcomes were observed in the age-stratified sensitivity analysis.

42

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

46

47

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

48

49 **Key Messages**

50 **What is already known on this topic**

51 ● Previous studies have suggested a potential link between air pollution and Kawasaki

52 Disease (KD), but the evidence has been inconclusive.

53

54 **What this study adds**

55 ● Our spatiotemporal modelling showed that annual exposure to PM_{2.5} was consistently

56 linked with higher KD incidence before and after the COVID-19 pandemic across all age

57 groups of children (0, 1, or 2–4 years).

58 ● A 1 µg/m³ increase in PM_{2.5} concentration corresponded to a 3–10% increase in KD cases.

59

60 **How this study might affect research, practice, or policy**

61 ● This study provides a strong foundation for future research into the underlying

62 mechanisms of KD onset related to air pollution.

63

64

65

66 Introduction

67 Kawasaki disease (KD) is a febrile illness of unknown aetiology that predominantly affects
68 children under five.¹⁻³ Intravenous immunoglobulin (IVIG) therapy has been widely adopted
69 to reduce the risk of fatal coronary artery aneurysms, with approximately 95% of KD cases in
70 Japan receiving IVIG early in the course of the illness.^{2,4-6} Despite treatment advancements,
71 including the combination of corticosteroids with IVIG, as well as the use of cyclosporine A,
72 infliximab, or ulinastatin, coronary artery lesions occur in about 6% of cases,⁷ underscoring the
73 urgent need to uncover clues to understand the disease's pathogenesis.

74

75 The association between KD and PM_{2.5} has been the subject of research. While some studies
76 have indicated no significant effect of short-term exposure to PM_{2.5}, others have shown an
77 impact of annual or intrauterine exposure to PM_{2.5}.⁸⁻¹² These studies may indicate the
78 association between KD and long-term exposure to PM_{2.5}; however, several limitations should
79 be noted. First, most previous studies ignore repeatedly documented spatiotemporal clustering
80 of KD.¹³⁻¹⁷ Spatiotemporal clustering of this disease with unknown aetiology indicates possible
81 autocorrelation in the residuals, comprising the validity of the generalised linear regression and
82 leading to biased estimates. The conditional autoregressive (CAR) models, hierarchical
83 Bayesian models designed for spatial and spatiotemporal analysis, can address residual
84 autocorrelation by incorporating a spatiotemporal term.¹⁸⁻²⁰ Second, studies on KD often focus

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

85 on the exposure defined by a single time length, leaving it uncertain whether observed

86 differences in results are due to the length of time unit or other aspects of the study design.

87 Third, the dramatic reduction in KD after the onset of the COVID-19 pandemic may have

88 disrupted the stationarity assumptions.^{21–23}

89

90 Thus, this paper aims to perform spatiotemporal analysis based on the CAR model to

91 investigate the impact of monthly and annual exposure to PM_{2.5} and other air pollutants on the

92 incidence of KD before and after the advent of the COVID-19 pandemic.

93

94

95 **Methods**

96 **Data source**

97 In this retrospective study, we extracted clinical data from the Japanese administrative claims
98 database named the Diagnosis Procedure Combination (DPC) database, comprising
99 anonymised clinical and administrative claims data featuring baseline information of patients
100 and facilities, diagnostic records, procedural data, device utilisation, and prescription details.
101 As of 2023, over 2,000 hospitals had implemented DPC-based reimbursement systems. This
102 database substantiated its reliability through prior research.²⁴ Data were accessed on August
103 16, 2023. Among hospitalisation data from April 2014 to March 2022, we extracted clinical
104 information on children under five diagnosed with KD, identified by the International
105 Classification of Diseases, Tenth Revision (ICD-10) code of M30.3. To minimise bias
106 associated with misclassification, we focused on hospital admissions where patients received
107 KD-specific medications, namely IVIG, cyclosporine A, infliximab, or ulinastatin.^{3,6,7} We
108 considered the date of first admission with KD treatment as the onset date, excluding cases
109 with unclear onset dates, specifically transfer cases and those not administered IVIG within
110 seven days of the first admission. Cases of KD that occurred in the first and last three months
111 of the observation period were excluded to address uncertainties associated with the
112 identification of initial hospitalisations and to minimise omissions due to delayed reporting.

1
2
3
4 113 Then, the timeframe from July 2014 to December 2019 was defined as the period before the
5
6
7 114 COVID-19 pandemic, whereas from January 2020 to December 2021 was defined as the period
8
9
10 115 after the COVID-19 pandemic.
11
12
13 116
14
15
16 117 The atmospheric environment database of the National Institute for Environmental Studies
17
18
19 118 publishes pollution data from 2,184 monitoring stations across 319 (95%) of the 335 secondary
20
21
22 119 medical care areas in Japan.²⁵ Each secondary medical care area, established across 1,718 of
23
24
25 120 the 1,724 municipalities and managed by the 47 prefectural governments, ensures general
26
27
28 121 inpatient treatment, including initial treatment of KD. We extracted daily exposure to PM_{2.5},
29
30
31 122 nitric monoxide (NO), nitrogen dioxide (NO₂), and sulphur dioxide (SO₂) for each medical
32
33
34 123 care region, imputed missing values using the prefectural average, and calculated monthly
35
36
37 124 exposure. As a result, we obtained 22,100 and 8,040 spatiotemporal units based on the exposure
38
39
40 125 status in 335 secondary medical areas over 66 months and 24 months before and after the onset
41
42
43 126 of the COVID-19 pandemic, respectively.
44
45
46 127
47
48
49 128 **Outcomes and variables**
50
51
52 129 As an outcome measure, the monthly incidence of KD was counted for each secondary medical
53
54
55 130 care area associated with facilities. The monthly or annual exposure to PM_{2.5}, NO, NO₂, and
56
57
58 131 SO₂ in the corresponding area were incorporated in the analysis as continuous variables. The
59
60

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, NO₂, and SO₂, 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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

184 of KD, whereas NO₂ showed a converse effect.

185

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

190

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/m³ 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 NO₂ mainly comes from sources within 10 kilometres.³² NO has an even shorter dispersal distance compared to NO₂.³³ Their contrasting effects observed in the post-pandemic multivariable CARadaptive model—the optimistic influence of NO and the pessimistic impact of NO₂—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

1
2
3
4 229 were included.²² Although the inclusion criteria were carefully constructed based on the ICD-
5
6
7 230 10 code and KD-specific medications, the level of concordance between the judged and actual
8
9
10 231 onset of KD is yet to be confirmed. The exclusion of untreated cases can be expected to be
11
12
13 232 marginal, considering the ubiquity of early IVIG administration in Japan.² Although the dose-
14
15
16 233 response relationship observed in this study aligns with previous research conducted in
17
18
19 234 geographically close Korea, different results might be obtained in distant countries due to
20
21
22 235 varying sources of PM_{2.5}. Unmeasured substances or microorganisms dispersing similarly to
23
24
25 236 PM_{2.5}, rather than PM_{2.5} itself, might be involved in the onset of KD.^{37,38} Besides, it should be
26
27
28 237 noted that spatiotemporal analysis with different granularities of spatiotemporal units may yield
29
30
31 238 different results.³⁹ Analysis with a finer granularity would pose challenges due to boundary-
32
33
34 239 crossing admissions, while extensive unit aggregation would reduce statistical power. We
35
36
37 240 handled data at the spatiotemporal unit level, thereby not distinguishing between prenatal and
38
39
40 241 postnatal exposures at the individual level. While the impact of annual PM_{2.5} exposure in
41
42
43 242 infants under one year may imply potential influences of prenatal exposure, these effects have
44
45
46 243 not been explicitly examined.
47
48
49 244
50
51
52 245 In conclusion, we utilised the CAR models to address the spatiotemporal aggregation of KD,
53
54
55 246 confirming the robust association between the incidence of KD and annual exposure to PM_{2.5}.
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

247 Further investigation is required to clarify the underlying mechanism of association between
248 the spatiotemporal distribution of KD and PM_{2.5}.

Confidential: For Review Only

249

250 **Acknowledgements**

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

254

255 **Contributors**

256 KY: Conceptualisation, data curation, methodology, formal analysis, and writing of the
257 original draft. DS: Conceptualisation, methodology, review writing, editing, and funding
258 acquisition. NT: Conceptualisation and writing the review. KF: Supervision, resources, review
259 writing, and funding acquisition.

260

261 **Funding**

262 Funding for this research was provided by a Grant-in-Aid for Policy Planning and Evaluation
263 Research from Japan's Ministry of Health, Labour and Welfare (grant identifier 22AA2003
264 [awarded to KF]) and a Grant-in-Aid for Scientific Research (B) through the Japan Society for
265 the Promotion of Science (JSPS KAKENHI, grant identifier 20H03921 [awarded to DS]). The
266 funders did not influence the design or conduct of the study, the gathering or interpretation of
267 data, the decision to submit the results for publication, or the drafting of the research paper.

268

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

Tables

Table 1. Basic Characteristics of Spatiotemporal Units

Characteristic	Before the COVID-19	After the COVID-19	SMD	95% CI
	Pandemic ^a N = 22,110	Pandemic ^a N = 8,040		
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.

290 **Table 2. Non-Bayesian Poisson Regression Models Before and After the COVID-**
291 **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
SO ₂ , 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.

295

296

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 After 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.

References

1. Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. *Arerugi*. 1967;16:178–222.
2. Ae R, Makino N, Kosami K, Kuwabara M, Matsubara Y, Nakamura Y. Epidemiology, Treatments, and Cardiac Complications in Patients with Kawasaki Disease: The Nationwide Survey in Japan, 2017-2018. *J Pediatr*. 2020;225:23-29.e2.
3. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, 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:e927–99.
4. Furusho K, Kamiya T, Nakano H, Kiyosawa N, Shinomiya K, Hayashidera T, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet*. 1984;2:1055–8.
5. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med*. 1991;324:1633–9.
6. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet*. 2012;379:1613–20.
7. Miura M, Ayusawa M, Fukazawa R, Hamada H, Ikeda S, Ito S, et al. Guidelines for Medical Treatment of Acute Kawasaki Disease (2020 Revised Version). *Journal of Pediatric Cardiology and Cardiac Surgery*. 2021;5:41–73.
8. Zeff AS, Burns JC, Yeung RS, McCrindle BW, Newburger JW, Dominguez SR, et al. Kawasaki Disease and Exposure to Fine Particulate Air Pollution. *J Pediatr*. 2016;177:179-183.e1.
9. 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.
10. Yorifuji T, Tsukahara H, Kashima S, Doi H. Intrauterine and Early Postnatal Exposure to Particulate Air Pollution and Kawasaki Disease: A Nationwide Longitudinal Survey in Japan. *J Pediatr*. 2018;193:147-154.e2.

1
2
3
4 340 11. Buteau S, Belkaibech S, Bilodeau-Bertrand M, Hatzopoulou M, Smargiassi A, Auger N.
5 341 Association between Kawasaki Disease and Prenatal Exposure to Ambient and Industrial Air
6 342 Pollution: A Population-Based Cohort Study. *Environ Health Perspect.* 2020;128:107006.
7
8
9 343 12. Kim H, Jang H, Lee W, Oh J, Lee J-Y, Kim M-H, et al. Association between long-term
10 344 PM2.5 exposure and risk of Kawasaki disease in children: A nationwide longitudinal cohort
11
12 345 study. *Environ Res.* 2023;244:117823.
13
14 346 13. Yashiro M, Nakamura Y, Ojima T, Tanihara S, Oki I, Yanagawa H. [Ten Year Observation
15 347 of Time-space Relationship on Incidences of Kawasaki Disease in Japan, Analyses in
16 348 Hokkaido and Shikoku]. *The journal of the Japan Pediatric Society.* 1999;103:832–7.
17
18
19
20 349 14. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Monthly
21 350 observation of the number of patients with Kawasaki disease and its incidence rates in Japan:
22 351 chronological and geographical observation from nationwide surveys. *J Epidemiol.*
23 352 2008;18:273–9.
24
25
26
27 353 15. Sano T, Makino N, Aoyama Y, Ae R, Kojo T, Kotani K, et al. Temporal and geographical
28 354 clustering of Kawasaki disease in Japan: 2007-2012. *Pediatr Int.* 2016;58:1140–5.
29
30
31 355 16. Burney JA, DeHaan LL, Shimizu C, Bainto EV, Newburger JW, DeBiasi RL, et al.
32 356 Temporal clustering of Kawasaki disease cases around the world. *Sci Rep.* 2021;11:22584.
33
34
35 357 17. Kim J, Hong K, Yoo D, Chun BC. Spatiotemporal clusters of Kawasaki disease in South
36 358 Korea from 2008 to 2017: A municipal-level ecological study. *Front Pediatr.* 2022;10:1054985.
37
38
39 359 18. Lee D. CARBayes: An R Package for Bayesian Spatial Modeling with Conditional
40 360 Autoregressive Priors. *J Stat Softw.* 2013;55:1–24.
41
42
43 361 19. Lee D, Rushworth A, Napier G. Spatio-Temporal Areal Unit Modeling in R with
44 362 Conditional Autoregressive Priors Using the CARBayesST Package. *Journal of Statistical*
45 363 *Software.* 2018;84:1–39.
46
47
48 364 20. Robert P. Haining GL. *Modelling Spatial and Spatial-Temporal Data: A Bayesian*
49 365 *Approach.* Chapman and Hall/CRC; 2020.
50
51
52 366 21. Iio K, Matsubara K, Miyakoshi C, Ota K, Yamaoka R, Eguchi J, et al. Incidence of
53 367 Kawasaki disease before and during the COVID-19 pandemic: a retrospective cohort study in
54 368 Japan. *BMJ Paediatr Open.* 2021;5:e001034.
55
56
57
58 369 22. Ae R, Makino N, Kuwabara M, Matsubara Y, Kosami K, Sasahara T, et al. Incidence of
59 370 Kawasaki Disease Before and After the COVID-19 Pandemic in Japan: Results of the 26th

- 371 Nationwide Survey, 2019 to 2020. *JAMA Pediatr.* 2022;176:1217–24.
- 372 23. Burney JA, Roberts SC, DeHaan LL, Shimizu C, Bainto EV, Newburger JW, et al.
 373 Epidemiological and Clinical Features of Kawasaki Disease During the COVID-19 Pandemic
 374 in the United States. *JAMA Netw Open.* 2022;5:e2217436.
- 375 24. Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of
 376 diagnoses, procedures, and laboratory data in Japanese administrative data. *J Epidemiol.*
 377 2017;27:476–82.
- 378 25. Air Pollution Continuous Monitoring Data. National Institute for Environmental Studies.
 379 <https://tenbou.nies.go.jp/>. Accessed 20 Feb 2024.
- 380 26. 2020 Population Census. Portal Site of Official Statistics of Japan. 2021. [https://www.e-](https://www.e-stat.go.jp/en/stat-search/files?page=1&toukei=00200521&tstat=000001136464)
 381 [stat.go.jp/en/stat-search/files?page=1&toukei=00200521&tstat=000001136464](https://www.e-stat.go.jp/en/stat-search/files?page=1&toukei=00200521&tstat=000001136464). Accessed 20
 382 Feb 2024.
- 383 27. Leroux BG, Lei X, Breslow N. Estimation of Disease Rates in Small Areas: A new Mixed
 384 Model for Spatial Dependence. In: *Statistical Models in Epidemiology, the Environment, and*
 385 *Clinical Trials*. Springer New York; 2000. p. 179–91.
- 386 28. R Core Team. *R: A Language and Environment for Statistical Computing*. 2023.
- 387 29. Rushworth A, Lee D, Mitchell R. A spatio-temporal model for estimating the long-term
 388 effects of air pollution on respiratory hospital admissions in Greater London. *Spat*
 389 *Spatiotemporal Epidemiol.* 2014;10:29–38.
- 390 30. Rushworth A, Lee D, Sarra C. An Adaptive Spatiotemporal Smoothing Model for
 391 Estimating Trends and Step Changes in Disease Risk. *J R Stat Soc Ser C Appl Stat.*
 392 2017;66:141–57.
- 393 31. Watanabe S. Asymptotic Equivalence of Bayes Cross Validation and Widely Applicable
 394 Information Criterion in Singular Learning Theory. *J Mach Learn Res.* 2010;11:3571–94.
- 395 32. Wang Y, Bechle MJ, Kim S-Y, Adams PJ, Pandis SN, Pope CA, et al. Spatial
 396 decomposition analysis of NO₂ and PM_{2.5} air pollution in the United States. *Atmos Environ.*
 397 2020;241:117470.
- 398 33. Fraigneau Y, Gonzalez M, Coppalle A. Turbulence effects upon the NO₂NO conversion in
 399 the vicinity of an urban area. *Sci Total Environ.* 1996;189–190:293–300.
- 400 34. Zhang Y, Wu W, Li Y, Li Y. An investigation of PM_{2.5} concentration changes in Mid-

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

401 Eastern China before and after COVID-19 outbreak. *Environ Int.* 2023;175:107941.

402 35. Lehmann EL, Casella G. Normal Linear Models. In: *Theory of Point Estimation*. 2nd ed.
403 Springer New York; 1998. p. 176–87.

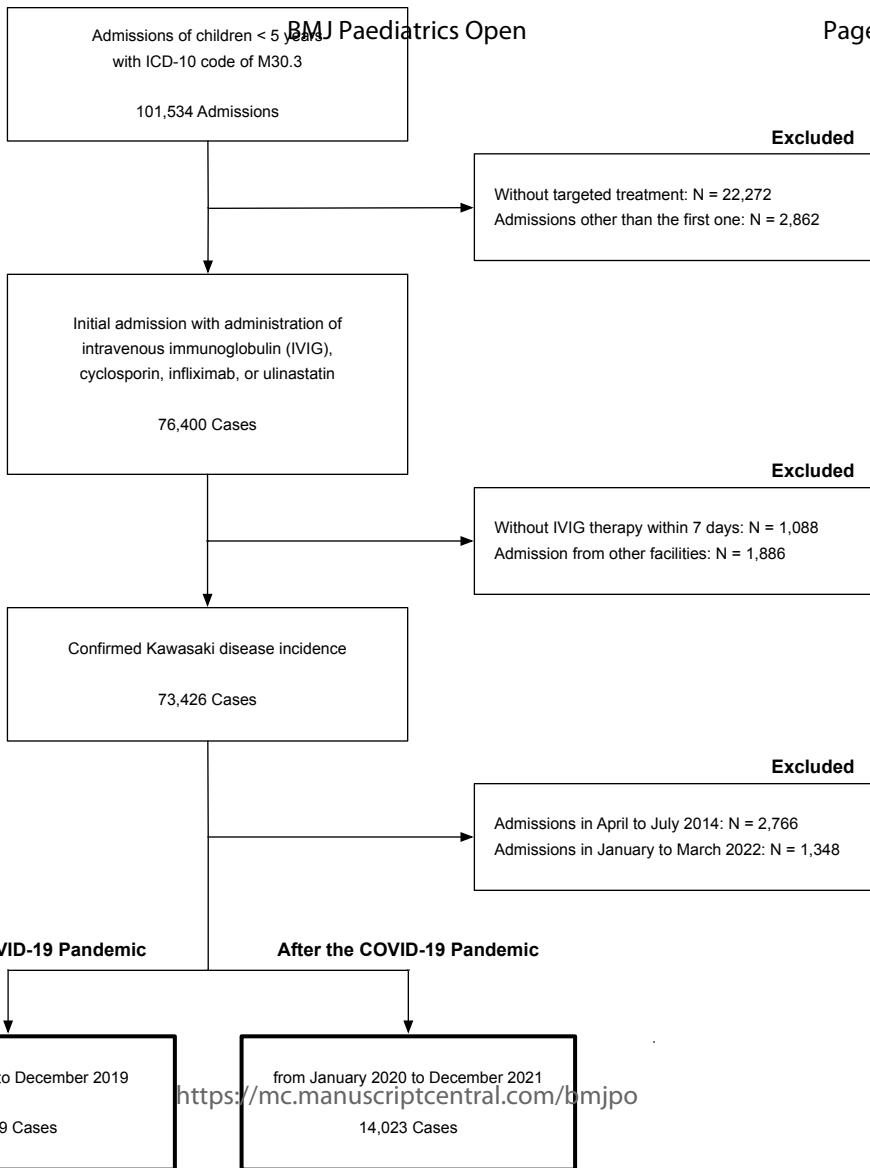
404 36. Majumdar S, Flynn C, Mitra R. Detecting Bias in the Presence of Spatial Autocorrelation.
405 2022;171:6–18.

406 37. Rodó X, Curcoll R, Robinson M, Ballester J, Burns JC, Cayan DR, et al. Tropospheric
407 winds from northeastern China carry the etiologic agent of Kawasaki disease from its source
408 to Japan. *Proc Natl Acad Sci U S A.* 2014;111:7952–7.

409 38. El-Askary H, LaHaye N, Linstead E, Sprigg WA, Yacoub M. Remote sensing observation
410 of annual dust cycles and possible causality of Kawasaki disease outbreaks in Japan. *Glob
411 Cardiol Sci Pract.* 2017;2017:e201722.

412 39. Wang Y, Di Q. Modifiable areal unit problem and environmental factors of COVID-19
413 outbreak. *Sci Total Environ.* 2020;740:139984.

414

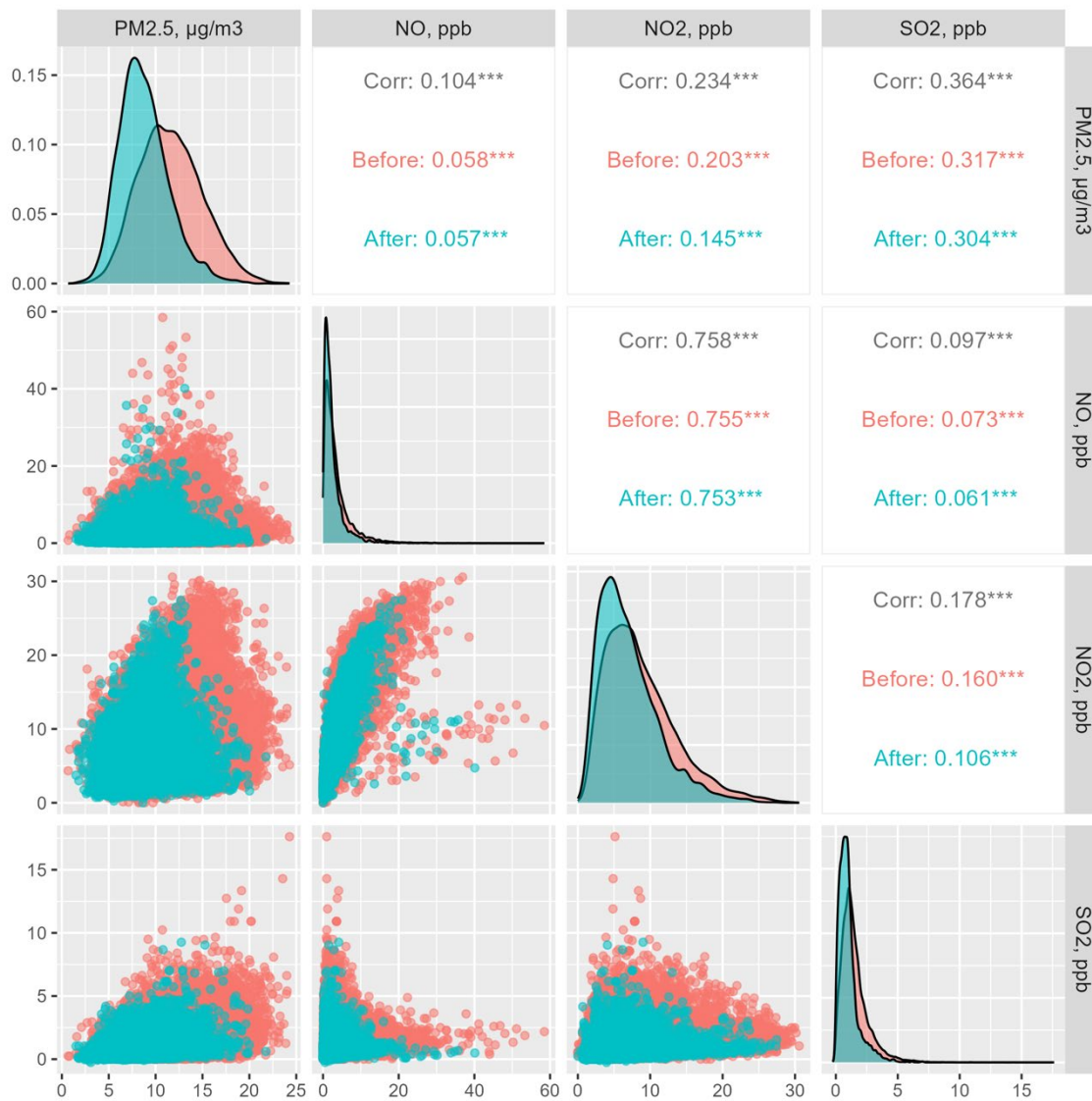


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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. * $p < 0.001$**

BMJ Paediatrics Open

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

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2024-002887.R1
Article Type:	Original research
Date Submitted by the Author:	05-Sep-2024
Complete List of Authors:	Yoneda, Kota; Tokyo Women's Medical University; Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Health policy and Informatics Shinjo, Daisuke; Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Health policy and informatics Takahashi, Naoto; The University of Tokyo Hospital, Department of Pediatrics Fushimi, Kiyohide; Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Health policy and Informatics
Keywords:	Epidemiology, Child Health, Statistics, COVID-19

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Author Information

Kota Yoneda, MD, PhD, Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School, Tokyo, Japan. Department of Pediatrics, The University of Tokyo Hospital, Tokyo, Japan. ORCID: 0000-0003-1605-5340

Daisuke Shinjo, PhD, Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School, Tokyo, Japan. ORCID: 0000-0002-7495-7409

Naoto Takahashi, MD, PhD, Department of Pediatrics, The University of Tokyo Hospital, Tokyo, Japan. ORCID: 0000-0002-2353-4430

Kiyohide Fushimi, MD, PhD, Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School, Tokyo, Japan. ORCID: 0000-0002-1894-0290

Correspondence to: Daisuke Shinjo, PhD,
Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School, Tokyo, Japan
TEL: +81-3-3813-4028, FAX: +81-3-5803-0357
Email: dshinjo.hci@tmd.ac.jp,

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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, NO₂, and SO₂ 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/m³ increase in annual PM_{2.5} exposure corresponded to a 3–10% rise in KD incidence. Consistent

42 outcomes were observed in the age-stratified sensitivity analysis.

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

46

47

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

48

49

50

51

52

53

54

55

56

57

58

59

60

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/m³ 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.

66

67 Introduction

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

81

82 The association between KD and PM_{2.5} has been the subject of research. While some studies
83 have indicated no significant effect of short-term exposure to PM_{2.5}, others have shown an
84 impact of annual or intrauterine exposure to PM_{2.5}.^{9-11,13,14} These studies may indicate the
85 association between KD and long-term exposure to PM_{2.5}; however, several limitations should

1
2
3
4 86 be noted. First, most previous studies ignore repeatedly documented spatiotemporal clustering
5
6
7 87 of KD.^{15–19} Spatiotemporal clustering of this disease with unknown etiology indicates possible
8
9
10 88 autocorrelation in the residuals, comprising the validity of the generalized linear regression and
11
12
13 89 leads to biased estimates. The conditional autoregressive (CAR) models, which are hierarchical
14
15
16 90 Bayesian models designed for spatial and spatiotemporal analysis, can address residual
17
18
19 91 autocorrelation by incorporating a spatiotemporal term.^{20–22} Second, studies on KD often focus
20
21
22 92 on the exposure defined by a single time length, leaving it uncertain whether observed
23
24
25 93 differences in results are due to the length of time unit or other aspects of the study design.
26
27
28 94 Third, the dramatic reduction in KD after the onset of the COVID-19 pandemic may have
29
30
31 95 disrupted the stationarity assumptions.^{8,23,24} Changes in social factors, such as mask-wearing
32
33
34 96 and physical distancing, may also have modified the impact of air pollutants on the incidence
35
36
37 97 of Kawasaki disease.
38
39
40 98
41
42
43 99 Thus, this paper aims to perform spatiotemporal analysis based on the CAR model to
44
45
46 100 investigate the impact of monthly and annual exposure to PM_{2.5} and other air pollutants on the
47
48
49 101 incidence of KD before and after the advent of the COVID-19 pandemic.
50
51
52 102

103

104 **Methods**

105 **Data source**

106 In this retrospective study, we extracted clinical data from the Japanese administrative claims
107 database named the Diagnosis Procedure Combination (DPC) database, comprising
108 anonymized clinical and administrative claims data featuring baseline information of patients
109 and facilities, diagnostic records, procedural data, device utilization, and prescription details.
110 As of 2023, over 2,000 hospitals had implemented DPC-based reimbursement systems. This
111 database substantiated its reliability through prior research.²⁵ Data were accessed on August
112 16, 2023. Among hospitalization data from April 2014 to March 2022, we extracted clinical
113 information on children under five diagnosed with KD, identified by the International
114 Classification of Diseases, Tenth Revision (ICD-10) code of M30.3. To minimize bias
115 associated with misclassification, we focused on hospital admissions where patients received
116 KD-specific medications, namely IVIG, cyclosporine A, infliximab, or ulinastatin.^{3,6,7} We
117 considered the date of first admission with KD treatment as the onset date, excluding cases
118 with unclear onset dates, specifically transfer cases and those not administered IVIG within 7
119 days of the first admission. To address uncertainties associated with identifying of initial
120 hospitalizations, cases of KD that occurred in the first three months of the observation period
121 were excluded, given the risk of misinterpreting the middle of a series of hospitalizations that

1
2
3
4 122 began before the observation period as the onset. Cases from the last 3 months of the period
5
6
7 123 were also excluded, as the number of onsets during this period may be underestimated due to
8
9
10 124 administrative delays in medical claims processing. Then, the timeframe from July 2014 to
11
12
13 125 December 2019 was defined as the period before the COVID-19 pandemic, whereas from
14
15
16 126 January 2020 to December 2021 was defined as the period during the COVID-19 pandemic.
17
18
19 127
20
21
22 128 The atmospheric environment database of the National Institute for Environmental Studies
23
24
25 129 publishes pollution data from 2,184 monitoring stations across 319 (95%) of the 335 secondary
26
27
28 130 medical care areas in Japan.²⁶ Each secondary medical care area, established across 1,718 of
29
30
31 131 the 1,724 municipalities and managed by the 47 prefectural governments, ensures general
32
33
34 132 inpatient treatment, including initial treatment of KD. We extracted daily exposure to PM_{2.5},
35
36
37 133 nitric monoxide (NO), nitrogen dioxide (NO₂), and sulphur dioxide (SO₂) for each medical
38
39
40 134 care region, imputed missing values using the prefectural average, and calculated monthly
41
42
43 135 exposure. As a result, we obtained 22,100 and 8,040 spatiotemporal units based on the exposure
44
45
46 136 status in 335 secondary medical care areas over 66 months and 24 months before and after the
47
48
49 137 onset of the COVID-19 pandemic, respectively.
50
51

52 138
53
54
55 139 **Outcomes and variables**
56

57
58 140 As an outcome measure, the monthly incidence of KD was counted for each secondary medical
59
60

care area associated with facilities. The monthly or annual exposure to PM_{2.5}, NO, NO₂, and SO₂ 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, NO₂, and SO₂, 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

177

178 **Results**

179 We extracted 101,534 admissions of children under 5 years of age admissions with the ICD-
 180 10 code M30.3 from the DPC database (**Figure 1**). In the before-and during-COVID-19
 181 pandemic periods, 55,289 (837.7 per month) and 14,023 (584.3 per month) onsets of KD were
 182 identified, respectively. The basic characteristics in **Table 1** indicate the significant reduction
 183 in KD incidence and exposure to air pollutants following the COVID-19 pandemic. Intergroup
 184 differences with standardized mean differences greater than 0.1 were observed. The scatterplot
 185 matrix in **Supplementary Figure 1** illustrates significant positive correlations between air
 186 pollutants. As shown in **Supplementary Table 1**, the missing rates of daily air pollutant data
 187 at the secondary medical care area level were within a few percent.

188

189 **Table 2** presents the non-Bayesian Poisson regression models before and during the COVID-
 190 19 pandemic, indicating that overall exposure to $PM_{2.5}$ has been the only consistent contributor
 191 to the incidence of KD. Multicollinearity was within acceptable limits, with no variance
 192 inflation factors above 5. **Supplementary Table 2** demonstrates that the CARadaptive models
 193 achieved the lowest WAIC. **Tables 3 and 4** present the CARadaptive models before and during
 194 the COVID-19 pandemic, revealing that 12-month exposure to $PM_{2.5}$ has been the sole
 195 consistent contributor to the incidence of KD. Favorable convergence was suggested by the
 196 Geweke diagnostics with absolute values less than 2. In univariable analysis before and during

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 NO₂ 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}.

207

208 Discussion

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

216

217 The remarkable reduction in WAIC associated with the CARadaptive models substantiated
218 their efficiency and adequacy in the analysis. The convergence of these models and the
219 consistency of the results bolster the validity and robustness of our research. The comparative
220 analysis of 1-month and 12-month exposure underscored the criticality of the exposure duration.
221 The climb in KD incidence with annual rather than monthly exposure to PM_{2.5} aligns with
222 previous research.^{9–11,13,14} The univariable and multivariable CARadaptive models
223 demonstrated a 3–10% increase in the incidence of KD for every 1 µg/m³ increase in PM_{2.5}.
224 This increase corresponds to a 16–61% rise with a 5 µg/m³ increase and is consistent with
225 findings from a previous South Korean study.¹¹

1
2
3
4 226 Previous research has shown that a considerable amount of PM_{2.5} comes from sources over 100
5
6
7 227 kilometers away, whereas NO₂ mainly comes from sources within 10 kilometres.³³ NO has an
8
9
10 228 even shorter dispersal distance compared to NO₂.³⁴ Their contrasting effects observed in the
11
12
13 229 during-pandemic multivariable CARadaptive model—the optimistic influence of NO and the
14
15
16 230 pessimistic impact of NO₂—can jointly modify predictions towards less incidence of KD in
17
18
19 231 areas experiencing nearby air pollution. It may be that the remarkable reduction in distantly
20
21
22 232 originated PM_{2.5}³⁵ necessitated adjustments for the less harmful PM_{2.5} derived from proximate
23
24
25 233 pollution sources.
26
27
28 234
29
30
31 235 The strength of this study lies in the adept use of CAR models that address the well-documented
32
33
34 236 spatiotemporal aggregation of KD.^{15,17} Spatiotemporal autocorrelation of the error term caused
35
36
37 237 by this aggregation violates the Gauss–Markov theorem’s assumptions, enhancing the
38
39
40 238 prevalence of type I and type II errors.^{36,37} Given the unknown pathogenesis of KD, measuring
41
42
43 239 all the confounders with spatial effects to eradicate autocorrelation of the error term is not
44
45
46 240 feasible, thus necessitating the adoption of clustering-aware models.
47
48
49 241

51
52 242 **Limitations**
53
54

55 243 Selection bias is a concern in observational studies. In light of the incidence rates of KD
56
57
58 244 reported in previous studies, it can be estimated that approximately 70% of the domestic cases
59
60

1
2
3
4 245 were included.²³ Although the inclusion criteria were carefully constructed based on the ICD-
5
6
7 246 10 code and KD-specific medications, the level of concordance between the judged and actual
8
9
10 247 onset of KD is yet to be confirmed. In this real-world data study, information on symptoms and
11
12
13 248 clinical findings was not available. We considered the risk of misclassification with
14
15
16 249 Multisystem Inflammatory Syndrome in Children (MIS-C) to be negligible based on the rarity
17
18
19 250 of MIS-C cases in Japan.⁸ The exclusion of untreated cases can be expected to be marginal,
20
21
22 251 considering the ubiquity of early IVIG administration in Japan.² Imputation of exposure at the
23
24
25 252 prefectural level for the small amount of missing data may have biased the analyses toward the
26
27
28 253 null. Although the dose-response relationship observed in this study aligns with previous
29
30
31 254 research conducted in geographically close Korea, different results might be obtained in distant
32
33
34 255 countries due to varying sources of PM_{2.5}. Unmeasured substances or microorganisms
35
36
37 256 dispersing similarly to PM_{2.5}, rather than PM_{2.5} itself, might be involved in the onset of KD.^{39,40}
38
39
40 257 Besides, it should be noted that spatiotemporal analysis with different granularities of
41
42
43 258 spatiotemporal units may yield different results.⁴¹ Given the limited geographic activity range
44
45
46 259 of children under the age of five, the impact of exposure outside their secondary medical care
47
48
49 260 area would be minimal. Analysis with a finer granularity would pose challenges due to
50
51
52 261 boundary-crossing admissions, while extensive unit aggregation would reduce statistical power.
53
54
55 262 We handled data at the spatiotemporal unit level, thereby not distinguishing between prenatal
56
57
58 263 and postnatal exposures at the individual level. While the impact of annual PM_{2.5} exposure in
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

264 infants under 1 year may imply potential influences of prenatal exposure, these effects have
265 not been explicitly examined.
266
267 In conclusion, we utilized the CAR models to address the spatiotemporal aggregation of KD,
268 confirming the robust association between the incidence of KD and annual exposure to PM_{2.5}.
269 Further investigation is required to clarify the underlying mechanism of association between
270 the spatiotemporal distribution of KD and PM_{2.5}.

271

272 Acknowledgements

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

276

277 Contributors

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

285

286 Funding

287 Funding for this research was provided by a Grant-in-Aid for Policy Planning and Evaluation
288 Research from Japan's Ministry of Health, Labour and Welfare (grant identifier 22AA2003
289 [awarded to KF]) and a Grant-in-Aid for Scientific Research (B) through the Japan Society for
290 the Promotion of Science (JSPS KAKENHI, grant identifier 20H03921 [awarded to DS]). The

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

291 funders did not influence the design or conduct of the study, the gathering or interpretation of
292 data, the decision to submit the results for publication, or the drafting of the research paper.

293
294 **Competing interests**

295 No relevant financial or nonfinancial interest to disclose.

296
297 **Ethics approval**

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

301
302 **Data availability statement**

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

304
305 **Figure legends**

306 **Figure 1. Study population and the exclusion criteria.**

308 **Tables**309 ***Table 1. Basic Characteristics of Spatiotemporal Units***

Characteristic	Before the COVID-19	During the COVID-19	SMD	95% CI
	Pandemic ^a	Pandemic ^a		
	N = 22,110	N = 8,040		
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.

310

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

311 **Table 2. Non-Bayesian Poisson Regression Models Before and During the**
312 **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
SO ₂ , 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.

Review Only

314

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.

315

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

316

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.

317

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.

References

1. Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. *Arerugi*. 1967;16:178–222.
2. Ae R, Makino N, Kosami K, et al. Epidemiology, Treatments, and Cardiac Complications in Patients with Kawasaki Disease: The Nationwide Survey in Japan, 2017-2018. *J Pediatr*. 2020;225:23-29.e2.
3. McCrindle BW, Rowley AH, Newburger JW, 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:e927–99.
4. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet*. 1984;2:1055–8.
5. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med*. 1991;324:1633–9.
6. Kobayashi T, Saji T, Otani T, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet*. 2012;379:1613–20.
7. Miura M, Ayusawa M, Fukazawa R, et al. Guidelines for Medical Treatment of Acute Kawasaki Disease (2020 Revised Version). *Journal of Pediatric Cardiology and Cardiac Surgery*. 2021;5:41–73.
8. Iio K, Matsubara K, Miyakoshi C, et al. Incidence of Kawasaki disease before and during the COVID-19 pandemic: a retrospective cohort study in Japan. *BMJ Paediatr Open*. 2021;5:e001034.
9. Yorifuji T, Tsukahara H, Kashima S, et al. Intrauterine and Early Postnatal Exposure to Particulate Air Pollution and Kawasaki Disease: A Nationwide Longitudinal Survey in Japan. *J Pediatr*. 2018;193:147-154.e2.
10. Buteau S, Belkaibech S, Bilodeau-Bertrand M, et al. Association between Kawasaki Disease and Prenatal Exposure to Ambient and Industrial Air Pollution: A Population-Based Cohort Study. *Environ Health Perspect*. 2020;128:107006.
11. Kim H, Jang H, Lee W, et al. Association between long-term PM2.5 exposure and risk of Kawasaki disease in children: A nationwide longitudinal cohort study. *Environ Res*. 2023;244:117823.

1
2
3
4 356 12. Rodó X, Ballester J, Cayan D, et al. Association of Kawasaki disease with tropospheric
5 357 wind patterns. *Sci Rep*. 2011;1:152.
6
7 358 13. Zeft AS, Burns JC, Yeung RS, et al. Kawasaki Disease and Exposure to Fine Particulate
8 359 Air Pollution. *J Pediatr*. 2016;177:179-183.e1.
9
10
11 360 14. Oh J, Lee JH, Kim E, et al. Is Short-Term Exposure to PM2.5 Relevant to Childhood
12 361 Kawasaki Disease? *Int J Environ Res Public Health*. 2021;18.
13
14
15 362 15. Yashiro M, Nakamura Y, Ojima T, et al. [Ten Year Observation of Time-space
16 363 Relationship on Incidences of Kawasaki Disease in Japan, Analyses in Hokkaido and Shikoku].
17 364 *The journal of the Japan Pediatric Society*. 1999;103:832–7.
18
19
20
21 365 16. Nakamura Y, Yashiro M, Uehara R, et al. Monthly observation of the number of patients
22 366 with Kawasaki disease and its incidence rates in Japan: chronological and geographical
23 367 observation from nationwide surveys. *J Epidemiol*. 2008;18:273–9.
24
25
26 368 17. Sano T, Makino N, Aoyama Y, et al. Temporal and geographical clustering of Kawasaki
27 369 disease in Japan: 2007-2012. *Pediatr Int*. 2016;58:1140–5.
28
29
30 370 18. Burney JA, DeHaan LL, Shimizu C, et al. Temporal clustering of Kawasaki disease cases
31 371 around the world. *Sci Rep*. 2021;11:22584.
32
33
34 372 19. Kim J, Hong K, Yoo D, et al. Spatiotemporal clusters of Kawasaki disease in South Korea
35 373 from 2008 to 2017: A municipal-level ecological study. *Front Pediatr*. 2022;10:1054985.
36
37
38 374 20. Lee D. CARBayes: An R Package for Bayesian Spatial Modeling with Conditional
39 375 Autoregressive Priors. *J Stat Softw*. 2013;55:1–24.
40
41
42 376 21. Lee D, Rushworth A, Napier G. Spatio-Temporal Areal Unit Modeling in R with
43 377 Conditional Autoregressive Priors Using the CARBayesST Package. *Journal of Statistical*
44 378 *Software*. 2018;84:1–39.
45
46
47
48 379 22. Robert P. Haining GL. *Modelling Spatial and Spatial-Temporal Data: A Bayesian*
49 380 *Approach*. Chapman and Hall/CRC; 2020.
50
51
52 381 23. Ae R, Makino N, Kuwabara M, et al. Incidence of Kawasaki Disease Before and After the
53 382 COVID-19 Pandemic in Japan: Results of the 26th Nationwide Survey, 2019 to 2020. *JAMA*
54 383 *Pediatr*. 2022;176:1217–24.
55
56
57 384 24. Burney JA, Roberts SC, DeHaan LL, et al. Epidemiological and Clinical Features of
58 385 Kawasaki Disease During the COVID-19 Pandemic in the United States. *JAMA Netw Open*.
59
60

386 2022;5:e2217436.

387 25. Yamana H, Moriwaki M, Horiguchi H, et al. Validity of diagnoses, procedures, and
388 laboratory data in Japanese administrative data. *J Epidemiol.* 2017;27:476–82.

389 26. Air Pollution Continuous Monitoring Data. National Institute for Environmental Studies.
390 <https://tenbou.nies.go.jp/>. Accessed 20 Feb 2024.

391 27. 2020 Population Census. Portal Site of Official Statistics of Japan. 2021. [https://www.e-](https://www.e-stat.go.jp/en/stat-search/files?page=1&toukei=00200521&tstat=000001136464)
392 [stat.go.jp/en/stat-search/files?page=1&toukei=00200521&tstat=000001136464](https://www.e-stat.go.jp/en/stat-search/files?page=1&toukei=00200521&tstat=000001136464). Accessed 20
393 Feb 2024.

394 28. Leroux BG, Lei X, Breslow N. Estimation of Disease Rates in Small Areas: A new Mixed
395 Model for Spatial Dependence. In: *Statistical Models in Epidemiology, the Environment, and*
396 *Clinical Trials*. Springer New York; 2000. p. 179–91.

397 29. R Core Team. *R: A Language and Environment for Statistical Computing*. 2023.

398 30. Rushworth A, Lee D, Mitchell R. A spatio-temporal model for estimating the long-term
399 effects of air pollution on respiratory hospital admissions in Greater London. *Spat*
400 *Spatiotemporal Epidemiol.* 2014;10:29–38.

401 31. Rushworth A, Lee D, Sarra C. An Adaptive Spatiotemporal Smoothing Model for
402 Estimating Trends and Step Changes in Disease Risk. *J R Stat Soc Ser C Appl Stat.*
403 2017;66:141–57.

404 32. Watanabe S. Asymptotic Equivalence of Bayes Cross Validation and Widely Applicable
405 Information Criterion in Singular Learning Theory. *J Mach Learn Res.* 2010;11:3571–94.

406 33. Wang Y, Bechle MJ, Kim S-Y, et al. Spatial decomposition analysis of NO₂ and PM_{2.5}
407 air pollution in the United States. *Atmos Environ.* 2020;241:117470.

408 34. Fraigneau Y, Gonzalez M, Coppalle A. Turbulence effects upon the NO₂NO conversion in
409 the vicinity of an urban area. *Sci Total Environ.* 1996;189–190:293–300.

410 35. Zhang Y, Wu W, Li Y, Li Y. An investigation of PM_{2.5} concentration changes in Mid-
411 Eastern China before and after COVID-19 outbreak. *Environ Int.* 2023;175:107941.

412 36. Lehmann EL, Casella G. Normal Linear Models. In: *Theory of Point Estimation*. 2nd ed.
413 Springer New York; 1998. p. 176–87.

414 37. Majumdar S, Flynn C, Mitra R. Detecting Bias in the Presence of Spatial Autocorrelation.
415 2022;171:6–18.

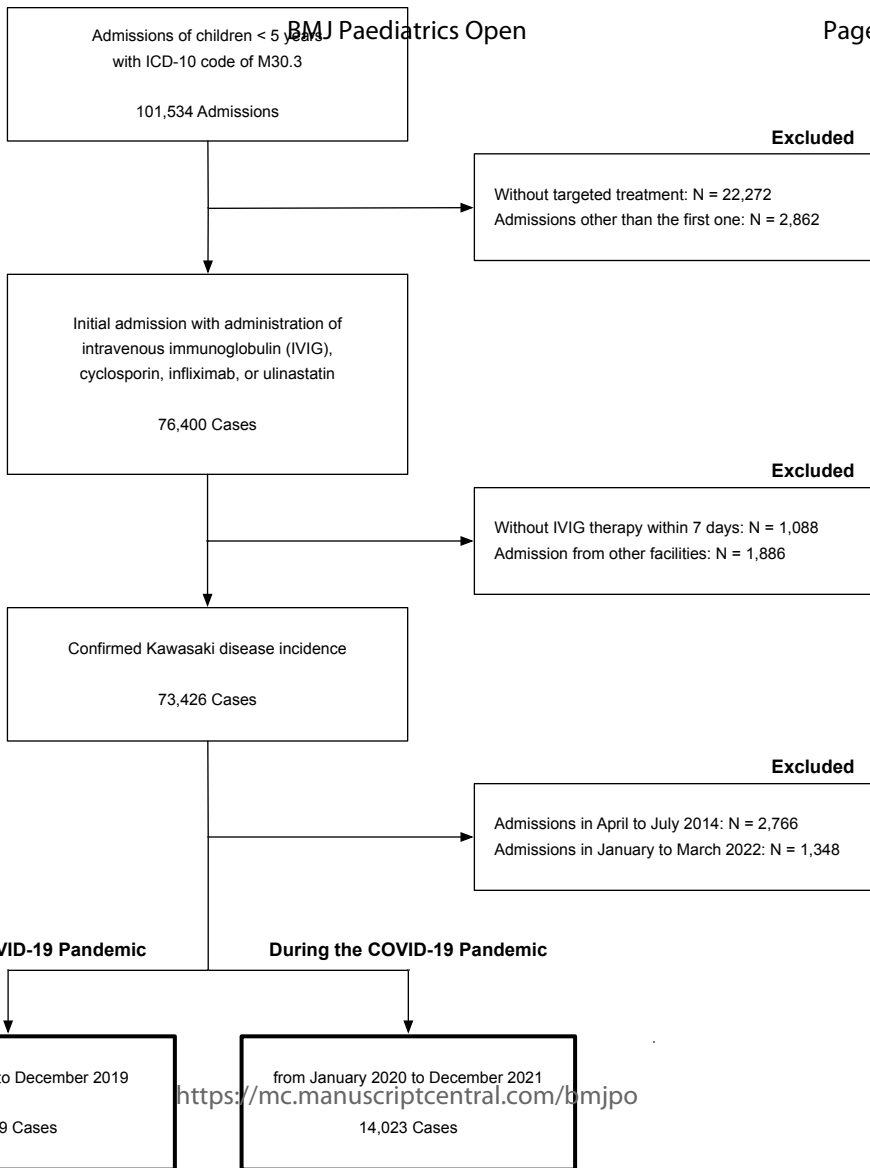
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

38. Matasubara D, Matsubara Y, Ayusawa M, et al. Nationwide survey of multisystem inflammatory syndrome in children associated with Coronavirus disease 2019 in japan. Social Science Research Network. 2024.

39. Rodó X, Curcoll R, Robinson M, et al. Tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan. Proc Natl Acad Sci U S A. 2014;111:7952–7.

40. El-Askary H, LaHaye N, Linstead E, et al. Remote sensing observation of annual dust cycles and possible causality of Kawasaki disease outbreaks in Japan. Glob Cardiol Sci Pract. 2017;2017:e201722.

41. Wang Y, Di Q. Modifiable areal unit problem and environmental factors of COVID-19 outbreak. Sci Total Environ. 2020;740:139984



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

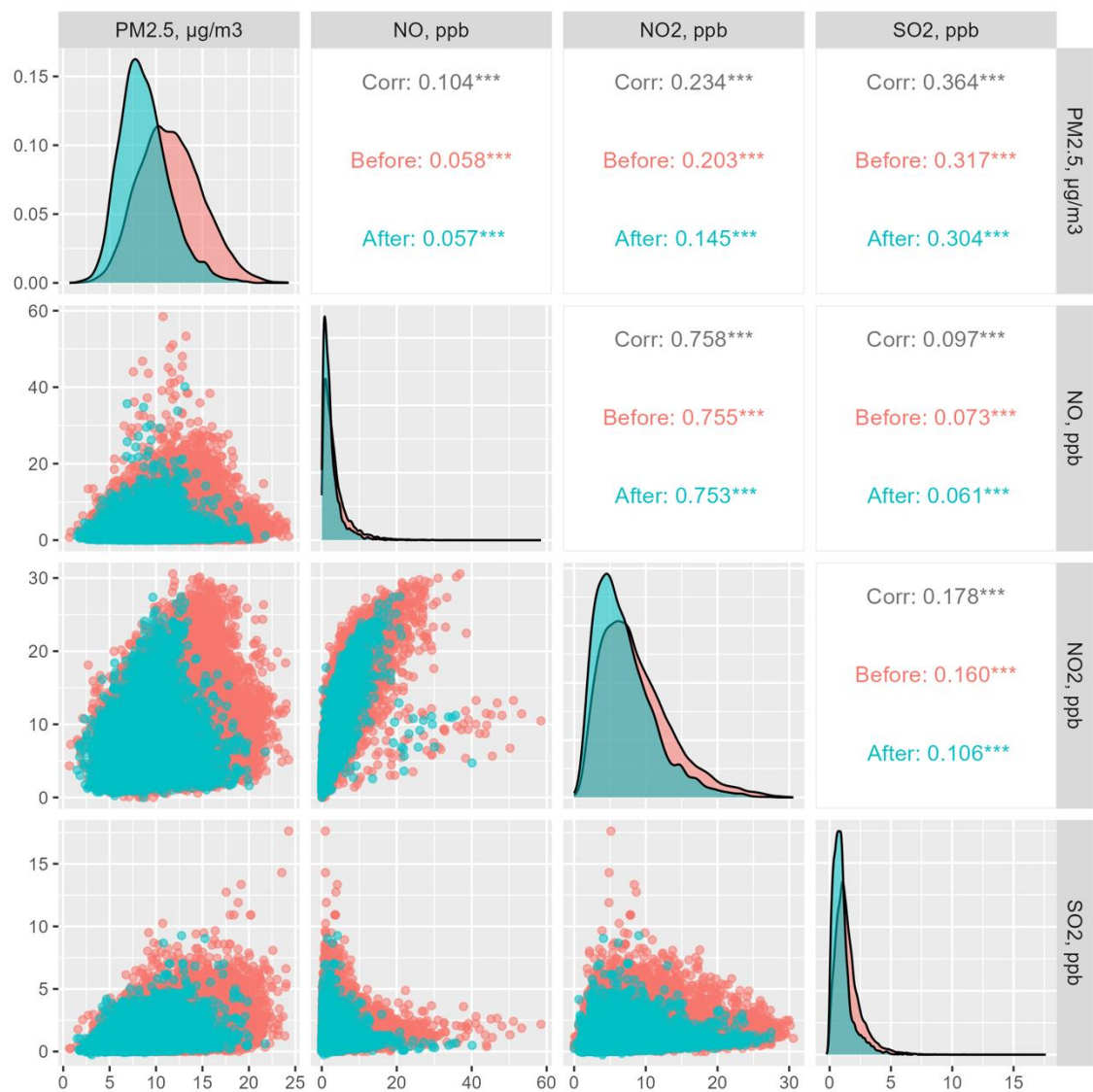
Supplementary Table 1. Missing Rates of Daily Air Pollutant Data at the Secondary Medical Care Area Level

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**