PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Spatiotemporal Analysis of the Association Between Kawasaki Disease Incidence and PM2.5 Exposure: A Nationwide Database Study in Japan
AUTHORS	Yoneda, Kota; Shinjo, Daisuke; Takahashi, Naoto; Fushimi, Kiyohide

VERSION 1 - REVIEW

REVIEWER NAME	***Arun Kumar Sharma***
REVIEWER AFFILIATION	University College of Medical Sciences, Community Medicine
REVIEWER CONFLICT OF INTEREST	
DATE REVIEW RETURNED	29-Jul-2024

GENERAL COMMENTS	1. The period January 2020 to December 2021 cannot be termed as “after COVID pandemic”, this was the peak period of COVID-19 pandemic, so the preferred terminology should be, “during COVID-19 pandemic” 2. The data on pollution parameters for the period of 66 months and 24 months should be available as supplementary files 3. Are monthly and annual averages, scientifically valid, for finding association with an illness of acute onset. Hypothetically, how can one explain the pollution levels of day 5 of a month affecting an incident illness on say day 21 of the same month. Analysis should be at a more granular level to implicate pollution parameters in causation of Kawasaki Disease by showing a lag period equivalent of the ‘incubation/pathogenesis” period. 4. One of the generic limitations of using single point ambient air quality monitoring data of a specified geographical region for determining association with the occurrence of disease are its inability to determine exposure of individuals, especially in the immediately preceding period of onset of the disease. This has not been mentioned in limitations of the study. 5. Analysis should have adjusted for other known independent variables that influence incidence of Kawasaki Disease. 6. Attributing low incidence to changes in pollution parameters during COVID-19 pandemic has limited academic significance because other factors like use of mask, maintaining physical distances and closure of schools were not accounted for in this study. 7. Lio K et al in their paper on Kawasaki Disease in the Kobe region of Japan have proposed possible viral etiological agents for the disease. This has not been discussed by the authors in their paper. (Ref: 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 Paediatrics Open 2021;5:e001034. doi: 10.1136/bmjpo-2021-001034)

	8. The discussion starts with mention of 55,289 and 14,023 new cases of KD without mentioning that the time periods of cumulative incidences are not identical, thus making an interpretation difficult. 9. The discussion highlights the role of PM2.5, NO2 and NO but fails to mention other independent variables that were not taken into consideration associated with KD incidence, reported in other studies from South Korea and USA. 10. Table 1: The standardized mean difference (SMD) of PM2.5 has an extremely narrow range (0.91, 0.96) to establish any dose response relationship with incidence of KD 11. In Table 1, the observation points are 22,110 and 8,040. It is not explained as to how many missing data points were there. It would affect the model outcome. 12. In table 2, from clinical perspective, in multivariable analysis, IRR for PM2.5 is same in pre and COVID-19 pandemic period. For other variables also, the difference is too small to have any significant public health impact. 13. In table 3, again the IRR 1.00 vs 1.03 (PM2.5), 1.00 vs 0.99 (NO), and similar figures for other variables do not give enough strength to draw such sweeping conclusions about the impact of pollution on incidence of KD. The statistical significance may be due to the large sample size. 14. Overall, the analysis fails to convince that the reduction in incidence of KD during COVID-19 period can be conclusively attributed to pollution levels, specially when confounders have not been accounted for in the analysis.

REVIEWER NAME	***Narendra Bagri***
REVIEWER AFFILIATION	
REVIEWER CONFLICT OF INTEREST	
DATE REVIEW RETURNED	31-Jul-2024

GENERAL COMMENTS	Dear Authors This is an interesting study. However, I have the following comments: 1. Introduction: Please provide a biological basis for correlating air pollution with KD. I understand that this is difficult but give a most plausible explanation. 2. Methods: why the transferred cases have been excluded. Similarly, why patients from 1st and last mon of observation period were excluded.I wonder if this is a retrospective study, and how would this affectit? 3. Results: Could you compare PM2.5 with severity of KD, atypical KD 4 Discussion: The most intriguing observation is a reduction in KD cases of COVID. However, this has to be discussed in light of MISC, which closely resembles KD, and there was a surge of MISC during COVID. Therefore PM2.5 alone may not support the author's hypothesis for its correlation with KD. Infact it is suggested to look at effect of PM2.5 and MISC cases as well

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer 1-1.

The period January 2020 to December 2021 cannot be termed as “after COVID pandemic”, this was the peak period of COVID-19 pandemic, so the preferred terminology should be, “during COVID-19 pandemic.”

Author Response

In accordance with your suggestions, we have corrected the terminology. Given the numerous similar modifications (from “after” to “during”), here we have provided a representative example of the changes made.

Line 29:

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.

Line 55:

Our spatiotemporal modelling showed that annual exposure to PM2.5 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).

Line 124:

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.

Reviewer 1-2.

The data on pollution parameters for the period of 66 months and 24 months should be available as supplementary files.

Author Response

In accordance with your suggestions, we have prepared a supplementary file named “supplementary_data.csv”.

Reviewer 1-3.

Are monthly and annual averages, scientifically valid, for finding association with an illness of acute onset. Hypothetically, how can one explain the pollution levels of day 5 of a month affecting an incident illness on say day 21 of the same month. Analysis should be at a more granular level to implicate pollution parameters in causation of Kawasaki Disease by showing a lag period equivalent of the ‘incubation/pathogenesis” period.

Author Response

The association between long-term exposure to PM2.5 and the incidence of Kawasaki disease (KD) observed in our spatiotemporal analysis aligns with previous studies based on simpler models.1–3 Besides KD, long-term exposure to air pollutants has been reported to be associated with various acute diseases such as ischemic heart disease, bronchial asthma, and acute respiratory diseases in children.4–6 These associations may be facilitated through local inflammation. In response to the feedback received, we have added a discussion on the potential mechanisms of the association. The exact mechanism of KD remains unknown, and its “incubation/pathogenesis” period is not well established.

Line 76:

Cytokine-induced oxidative stress has been proposed as a potential mechanism linking chronic exposure to PM2.5 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

Reviewer 1-4.

One of the generic limitations of using single point ambient air quality monitoring data of a specified geographical region for determining association with the occurrence of disease are its inability to determine exposure of individuals, especially in the immediately preceding period of onset of the disease. This has not been mentioned in limitations of the study.

Author Response

The subjects of this study were children under five years old, who typically do not commute, and we considered the impact of exposure outside the region to be limited when evaluating long-term exposure. In response to your comments, we have added the following as a commonly considered limitation:

Line 256:

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.

Reviewer 1-5.

Analysis should have adjusted for other known independent variables that influence incidence of Kawasaki Disease.

Author Response

The aetiology of KD remains unknown, and to the best of our knowledge, there are no spatiotemporal risk factors that have been established as being associated with the incidence of KD independently of long-term PM2.5 exposure.

Reviewer 1-6.

Attributing low incidence to changes in pollution parameters during COVID-19 pandemic has limited academic significance because other factors like use of mask, maintaining physical distances and closure of schools were not accounted for in this study.

Author Response

This study does not attribute the reduction in KD incidence after the onset of the COVID-19 pandemic to the decrease in PM2.5 levels. Rather, we assumed that the relationship between PM2.5 and KD might have changed, considering the significant changes in social factors you pointed out. Given the difficulty of incorporating all such social factors as variables, we created separate predictive models for the periods before and after the onset of the pandemic. We believe that the confirmation of the impact of PM2.5 in both periods demonstrates the robustness of the effects of PM2.5. In response to your comments, we have added the following:

Line 95:

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.

Reviewer 1-7.

Lio K et al in their paper on Kawasaki Disease in the Kobe region of Japan have proposed possible viral etiological agents for the disease. This has not been discussed by the authors in their paper. (Ref: 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 Paediatrics Open 2021;5:e001034. doi: 10.1136/bmjpo-2021-001034)

Author Response

Currently, there is no definitive etiological explanation for KD. The literature you provided reports a decrease in KD incidence after the onset of the COVID-19 pandemic and discusses that this finding is not inconsistent with the viral aetiology. In response to your comments, we have described the proposed aetiological hypothesis as follows:

Line 74:

Some researchers attribute the cause of Kawasaki disease to viral infections, while others point to the association between KD and air pollutants, including PM2.5.8–11 Cytokine-induced oxidative stress has been proposed as a potential mechanism linking chronic exposure to PM2.5 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

Reviewer 1-8.

The discussion starts with mention of 55,289 and 14,023 new cases of KD without mentioning that the time periods of cumulative incidences are not identical, thus making an interpretation difficult.

Author Response

Since comparing the periods before and after the onset of the COVID-19 pandemic is not the primary aim of this study, we initially omitted this information. However, in response to your comments, we have included the monthly average of the case numbers.

Line 178:

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.

Reviewer 1-9.

The discussion highlights the role of PM2.5, NO2 and NO but fails to mention other independent variables that were not taken into consideration associated with KD incidence, reported in other studies from South Korea and USA.

Author Response

We were unable to determine which studies were mentioned and which "other independent variables" were referred to. The possible correlation between PM2.5 and other air pollutants can lead to the association between other air pollutants with the incidence of KD. Additionally, multiple comparisons might reveal spurious associations. To the best of our knowledge, there are no other air pollutants widely accepted as being associated with the incidence of KD independently of PM2.5.2,3,7 While some studies suggest a relationship with meteorological data,8 adjusting for meteorological conditions could complicate the interpretation of results, as these conditions may influence KD onset through PM2.5 as an intermediary factor. Moreover, there is no consensus on how to incorporate meteorological data into the analysis. We stated below that it is fundamentally challenging to determine whether the causative agent is PM2.5 itself or other air pollutants associated with PM2.5.

Line 254:

Unmeasured substances or microorganisms dispersing similarly to PM2.5, rather than PM2.5 itself, might be involved in the onset of KD.

Reviewer 1-10.

Table 1: The standardized mean difference (SMD) of PM2.5 has an extremely narrow range (0.91, 0.96) to establish any dose response relationship with incidence of KD

Author Response

As previously mentioned, we are not asserting the impact of PM2.5 based on differences between groups; rather, we are examining the impact of PM2.5 using data within each group. Standardized Mean Difference (SMD) is frequently used for balance diagnosis after propensity score matching and SMDs greater than 0.1 are considered indicative of an imbalance between treated and control groups. We believe that the narrow 95% confidence intervals for the SMD are not problematic in our within-group analysis. We added as follows:

Line 181.

Intergroup differences with standardised mean differences greater than 0.1 were observed.

Reviewer 1-11.

In Table 1, the observation points are 22,110 and 8,040. It is not explained as to how many missing data points were there. It would affect the model outcome.

Author Response

Missing data, if not imputed, hinders the application of Markov chain Monte Carlo methods in hierarchical Bayesian modelling. Therefore, as stated in the Methods section, we imputed the missing

daily averages for each air pollutant in each secondary medical area with the corresponding values at the prefectural level before calculating the monthly and annual averages. In response to your comments, we detailed the missing rates for the daily averages of each air pollutant in each secondary medical area in Supplementary Table 1. We also mentioned that imputing missing values with averages could bias the impact of these air pollutants towards the null.

Line 184:

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.

Line 249:

Imputation of exposure at the prefectural level for the small amount of missing data may have biased the analyses toward the null.

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

PM2.5, % 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)

NO2, % 0.0 (0.0, 1.1) 0.0 (0.0, 0.8)

SO2, % 0.1 (0.0, 3.6) 0.1 (0.0, 1.9)

Median (Interquartile Range)

Reviewer 1-12.

In table 2, from clinical perspective, in multivariable analysis, IRR for PM2.5 is same in pre and COVID-19 pandemic period. For other variables also, the difference is too small to have any significant public health impact.

Author Response

In this study, we considered the differences in various social factors before and after the onset of the COVID-19 pandemic and conducted separate analyses for each period, recognizing that the impact of

PM2.5 may not be equivalent across these periods. The finding that the impact of PM2.5 was consistent across both periods demonstrates the robustness of the effects of PM2.5.

Reviewer 1-13.

In table 3, again the IRR 1.00 vs 1.03 (PM2.5), 1.00 vs 0.99 (NO), and similar figures for other variables do not give enough strength to draw such sweeping conclusions about the impact of pollution on incidence of KD. The statistical significance may be due to the large sample size.

Author Response

We felt that there might have been an impression that the impact of PM2.5 is minimal. What the IRR of 1.03–1.10 indicates is that "an increase of just 1 ppm in PM2.5, which is usually around 10 ppm, results in a 3%–10% increase in KD incidence." If PM2.5 levels rise from 10 ppm to 15 ppm, the risk of KD increases by a factor of 1.035–1.105, which means a 16–61% increase. This non-negligible increase is consistent with previous studies. Following these studies, we have also included the risk increase for a 5 ppm rise in PM2.5 levels.

Line 220:

The univariable and multivariable CARadaptive models demonstrated a 3–10% increase in the incidence of KD for every 1 μg/m³ increase in PM2.5. 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.

Reviewer 1-14.

Overall, the analysis fails to convince that the reduction in incidence of KD during COVID-19 period can be conclusively attributed to pollution levels, specially when confounders have not been accounted for in the analysis.

Author Response

As we have noted repeatedly, we do not intend to assert that the reduction in KD incidence during the COVID-19 period is attributable to pollution levels. Rather, we examined the impact of PM2.5 on the incidence of KD separately before and after the onset of the COVID-19 pandemic and confirmed its consistent effect.

Reviewer: 2

Reviewer 2-1.

Introduction: Please provide a biological basis for correlating air pollution with KD. I understand that this is difficult but give a most plausible explanation.

Author Response

We discussed the potential mechanisms.

Line 74.

Some researchers attribute the cause of Kawasaki disease to viral infections, while others point to the association between KD and air pollutants, including PM2.5. Cytokine-induced oxidative stress has been proposed as a potential mechanism linking chronic exposure to PM2.5 with the onset of Kawasaki disease. 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.

Reviewer 2-2.

Methods: why the transferred cases have been excluded. Similarly, why patients from 1st and last month of observation period were excluded. I wonder if this is a retrospective study, and how would this affect it?

Author Response

The DPC database used in this study is not a case registry but rather a collection of general patient information and data related to hospital medical claims. Therefore, detailed medical histories before administration to each hospital are not available. We excluded cases transferred from other hospitals from the analysis, as these cases likely include those with inadequate responses to treatments, making it difficult to determine the onset.

We considered the first hospitalization diagnosed with KD during the observation period as the onset of the disease. Therefore, for cases with the first hospitalization in the first three months of the observation period, there is a risk of misinterpreting the middle of a series of hospitalizations that began before the observation period as the "onset." Additionally, for cases in the last three months of the observation period, there is a risk of missing the "onset" due to administrative delays in medical claims processing. To reduce "false positives" and "false negatives" of the onset, we excluded the first and last three months of the observation period from the analysis. We have added the following statement to explain our intention:

Line 119:

To address uncertainties associated with the identification of initial hospitalisations, 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 hospitalisations that began before the observation period as

the onset. Cases from the last three 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.

Reviewer 2-3.

Results: Could you compare PM2.5 with severity of KD, atypical KD

Author Response

This analysis is based on information obtained from a medical claims database, and information on symptoms and test findings is unavailable. We have added the following:

Line 245:

In this real-world data study, information on symptoms and clinical findings was not available.

Reviewer 2-4

Discussion: The most intriguing observation is a reduction in KD cases of COVID. However, this has to be discussed in light of MISC, which closely resembles KD, and there was a surge of MISC during COVID. Therefore PM2.5 alone may not support the author's hypothesis for its correlation with KD. In fact, it is suggested to look at effect of PM2.5 and MISC cases as well.

Author Response

The aim of this study is not to investigate the causes of the previously reported decrease in KD incidence after the onset of the COVID-19 pandemic. Rather, it aims to demonstrate the association between PM2.5 and the incidence of KD. In Japan, where KD cases are common, it has been reported that cases of Multisystem Inflammatory Syndrome in Children (MIS-C) among children under five were very rare 9. Therefore, we considered the impact of MIS-C to be limited when examining the incidence of KD. In response to your comments, we have addressed MIS-C as follows:

Line 246:

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.

VERSION 2 – REVIEW

REVIEWER NAME	***Arun Kumar Sharma***
REVIEWER AFFILIATION	University College of Medical Sciences, Community Medicine
REVIEWER CONFLICT OF INTEREST	
DATE REVIEW RETURNED	09-Sep-2024

GENERAL COMMENTS	The revisions are satisfactory and answered all my queries. Thank you.