Intrauterine and Early Postnatal Exposure to Particulate Air Pollution and Kawasaki Disease: A Nationwide Longitudinal Survey in Japan

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Objectives To examine the effects of prenatal and postnatal exposure to particulate matter on Kawasaki disease (KD) occurrence, using data from a nationwide population-based longitudinal survey in Japan that began in 2010.

Study design Prenatal and postnatal suspended particulate matter concentrations were obtained at municipality level and assigned to participants based on their municipality of birth. We analyzed data from 30 367 participants with data on either exposure period. We used hospital admission for KD from 6 to 30 months of age as the main outcome of interest. We conducted a multilevel logistic regression analysis, adjusting for individual and municipality-level variables.

Results Children who were exposed to higher levels of suspended particulate matter, in particular during pregnancy, were more likely to be hospitalized for KD. The ORs for ≥25 μg/m^3 exposure compared with <20 μg/m^3 exposure were 1.59 (95% CI 1.06, 2.38) for prenatal exposure and 1.41 (0.82, 2.41) for postnatal exposure. Prenatal exposure during mid-to-late gestation seemed to be more relevant for the increased risk.

Conclusions Early life exposure to particulate air pollution, in particular during pregnancy, is associated with an increased risk of KD hospital admission in early childhood in a nationally representative sample in Japan. *(J Pediatr 2017;■■:■■-■■).*

Kawasaki disease (KD) is an acute febrile illness seen in children worldwide,[1] with the highest incidence occurring in Japan, where the rate of KD seems to be increasing in recent years.[2] KD is systemic vasculitis and the leading cause of acquired childhood heart disease in most developed countries.[1,3-6] Approximately 20%-25% of untreated children manifest coronary artery abnormalities such as aneurysms.[1] KD occurs mainly in young children[6]; approximately 88% of cases occurring during the 2-year period from 2011 to 2012 in Japan were in children aged under 5 years.[7,8] Although the etiology of the disease is unknown,[1] KD may occur in genetically susceptible individuals with an aberrant immune response to some environmental triggers.[4,5,9]

Air pollution exposure can induce health effects such as preterm births, infant mortality, asthma, and impaired neurodevelopment among children or fetuses.[10] Two recent epidemiologic studies explored the possible role of ambient air pollution as an environmental trigger for KD.[11,12] These 2 studies examined the effects of short-term exposure (ie, exposure periods of a few days to a week) to air pollution on KD occurrence, but they yielded inconsistent results. One of these studies, in Taiwan, suggested a positive association with ozone exposure,[12] whereas the other study, in the US, showed a null association between particulate matter exposure and KD occurrence.[11] However, these 2 studies focused only on short-term exposure, and further research on the effect of long-term exposure (ie, more than 1 month) on KD occurrence is warranted.[11] Moreover, recent epidemiologic studies have demonstrated that prenatal exposure to air pollution can cause allergic diseases such as asthma in early childhood[13-15]; thus, prenatal exposure to air pollution might also influence KD occurrence.

Therefore, using data from a nationwide population-based longitudinal survey in Japan that began in 2010, we examined the effects of prenatal and postnatal exposure to particulate matter on KD occurrence in early childhood.

Methods

The Japanese Ministry of Health, Labor, and Welfare conducted a nationally representative longitudinal survey (the Longitudinal Survey of Babies in the 21st Century) to follow babies born in Japan from May 10 to May 24, 2010.[16] Roughly 1 of 20 babies born in Japan in 2010 are enrolled in the survey. When the infants in the sample were 6 months old, baseline questionnaires were sent to all of the participating families. Of the 43 767 questionnaires mailed, 38 554 were completed and returned (response rate of 88.1%) (**Figure 1**). Follow-up

KD	Kawasaki disease
SPM	Suspended particulate matter

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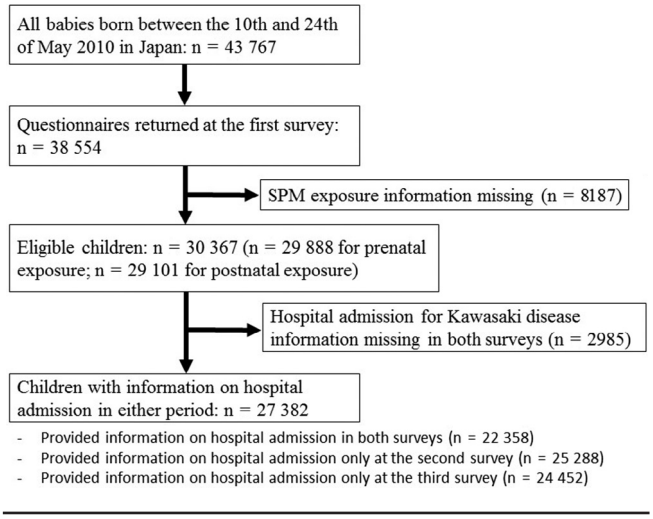

Figure 1. Flowchart of participants.

questionnaires were sent to participating families each year, with the next 2 waves being at the ages of 18 months and 30 months. In the present study, we used data from the first, second, and third survey waves because of the availability of data. Respondents were asked about hospital admission for KD during the previous year in the second and third survey waves (ie, hospitalizations from 6 to 18 months and from 18 to 30 months of age). Birth records from the Japanese vital statistics system are also linked to each child surveyed. Birth record data include birth length; birth weight; gestational age; singleton, twin, or other multiple birth; sex; parity; and parental age at delivery.

Particulate Matter Exposure

In the present study, we focused on municipality-level prenatal and postnatal outdoor suspended particulate matter (SPM) exposure as the main exposure variable. In Japan, particulate matter is measured as SPM, and it accounts for particulate matter with an aerodynamic diameter less than 7 μm. We used SPM exposure during the 9 months before birth (August 2009-April 2010) as prenatal exposure and SPM exposure from 6 to 30 months of age (January 2011-December 2012) as postnatal exposure.

First, we obtained monthly concentrations of SPM measured at all general monitoring stations throughout Japan during the above-mentioned study periods from the environmental database managed by the National Institute for Environmental Studies in Japan. We then calculated municipality-representative monthly average concentrations of SPM using monthly concentrations measured at the monitoring stations in each municipality. Subsequently, we calculated the average concentrations of SPM during the prenatal and postnatal periods in each municipality. We used only those sampling stations at which SPM was measured throughout the entire 9 months for the prenatal period and the entire 24 months for the postnatal period. There were 1901 municipalities in Japan according to the 2010 national census, and we were able to obtain air pollution information from more than 1100 municipalities for both periods. Most municipalities from which we were unable to obtain air pollution information were towns or villages. The median size of municipalities with available data was 97.9 km^2 and 94.7 km^2 for the prenatal and postnatal periods, respectively.

Finally, we assigned the prenatal and postnatal SPM exposures in each municipality to the participants who were born in the corresponding municipality. The municipality at birth for each participant was obtained from the birth record. Among the 38 554 eligible infants, we were able to assign prenatal SPM exposure to 29 888 and postnatal SPM exposure to 29 101. A total of 30 367 participants had data on either exposure (**Figure 1**). We also assigned trimester-specific SPM exposure (ie, August-October 2009: first trimester; November 2009-January 2010: second trimester; and February-April 2010: third trimester) to the participants.

We used 1 or more hospital admissions from 6 to 30 months of age as the main outcome of interest. Of the 30 367 participants with SPM data for either period, 2985 were missing information on hospital admission for KD from both the second and the third survey waves. Of the remaining 27 382 participants, 22 358 had information on hospital admission for KD from both survey waves; 25 288 had these data only from the second wave; and 24 452 had these data only from the third wave (**Figure 1**).

The diagnostic criteria for KD have not changed in Japan since 2002.[17,18] The KD incidence for the studied age groups (aged 6-30 months) is high, with about 50% of KD cases in Japan occurring in this age group during the 2-year period from 2011 to 2012.[7,8]

Statistical Analyses

To evaluate the impact of loss to follow-up (**Figure 1**), we first compared baseline characteristics between children with information on SPM at either period (eligible children), children who were included in the analysis, and children who lacked information on hospital admission for KD at both survey waves. After excluding those who lacked information on KD hospital admission from both surveys, we conducted a descriptive analysis on the exposure data. We also compared baseline characteristics between the participants who were admitted for KD and those who were not.

We then conducted a multilevel logistic regression analysis to evaluate the relationships between prenatal and postnatal SPM exposure and hospital admission from 6 to 30 months of age, considering that participants were nested in each municipality. We entered both SPM exposures into the model in 2 ways: as linear terms and as categorized variables (<20 μg/m^3, 20-25 μg/m^3, and ≥ 25 μg/m^3). The reason for this categorization was to allow the results of the prenatal and postnatal SPM exposures to be comparable. The concentrations of 20 μg/m^3 and 25 μg/m^3 almost correspond to the median and the top decile of prenatal and postnatal SPM exposures, respectively. We examined the effect of prenatal and postnatal SPM exposure independently (ie, in a single-pollutant model). We first estimated a crude OR and a 95% CI for the main outcome

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