Early Childhood Exposure to Maternal Smoking and Kawasaki Disease: A Longitudinal Survey in Japan

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Abstract

Kawasaki disease is the leading cause of acquired childhood heart disease in most developed countries, but the etiology of the disease is unknown. An aberrant immune response to some environmental triggers may play a role and involuntary exposure to tobacco smoke can alter immune functions. We thus prospectively examined the association between early childhood exposure to maternal smoking and the incidence of Kawasaki disease. We used a large, nationwide population-based longitudinal survey ongoing since 2010 and restricted participants to a total of 38,444 children for whom information on maternal smoking was available. Maternal smoking status was ascertained at 6 months of age, and responses to questions about hospital admission for Kawasaki disease between the ages of 6 and 30 months were used as outcome. We conducted binomial log-linear regression analyses adjusting for children's, parental, and residential factors with children of non-smoking mothers as our reference group. Maternal smoking increased the risk of admission, in particular for the period between 6 and 18 months of age, in a dose-dependent manner. Compared with children of non-smoking mothers, the children of mothers who smoked had a risk ratio of 1.83 (95% confidence interval: 1.06, 3.35) for hospital admissions between 6 and 30 months of age and a risk ratio of 2.69 (95% confidence interval: 1.56, 4.64) for hospital admissions between 6 and 18 months of age. Early childhood exposure to maternal smoking may increase the risk of Kawasaki disease hospitalizations in childhood.

Keywords

Early childhood exposure; Epidemiology; Mucocutaneous lymph node syndrome; Smoking

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Abbreviations

CI: confidence interval

KD: Kawasaki disease

RR: risk ratio

1. Introduction

Kawasaki disease (KD) is a systemic vasculitis that affects medium-size arteries and is the leading cause of acquired childhood heart disease in most developed countries (Punnoose et al., 2012; Son and Newburger, 2016). Approximately 20–25% of untreated children present with coronary artery abnormalities including aneurysms (Son and Newburger, 2016). KD is seen in children worldwide, but its incidence is highest in Japan (Punnoose et al., 2012) and is increasing (Makino et al., 2015; Uehara and Belay, 2012), posing a growing threat to children's health. The etiology of the disease is, however, unknown; an aberrant immune response to some environmental triggers is considered to play a role among genetically-predisposed children (Dimitriades et al., 2014; Greco et al., 2015; Hayward et al., 2012).

One potential cause of the disease is involuntary exposure to tobacco smoke (secondhand smoke); it has been estimated that 40% of children are exposed to secondhand smoke worldwide (Oberg et al., 2011). A 2006 report by the US Surgeon General listed multiple effects of involuntary exposure to tobacco smoke on child health, including sudden infant death syndrome, acute respiratory infections, ear problems, and asthma (United States. Public Health Service. Office of the Surgeon General., 2006). These conditions are caused by factors such as microbial infections, prenatal alterations in lung structure, inflammation, and allergic responses (United States. Public Health Service. Office of the Surgeon General., 2006). Considering these mechanisms, involuntary exposure to tobacco smoke may also cause KD, but as far as we know, there are no published studies that examine the association between involuntary exposure to tobacco smoke and the incidence of KD.

We therefore examined the association between early childhood exposure to maternal smoking, as an indicator of involuntary exposure to tobacco smoke, and the

incidence of KD using data from a nationwide population-based longitudinal survey in Japan that began in 2010.

2. Methods

2.1. Participants

We included data from the participants of the Longitudinal Survey of Babies in the 21st Century, which is a nationally representative longitudinal survey conducted in Japan by the Ministry of Health, Labour and Welfare (Yorifuji et al., 2016; Yorifuji et al., 2018). When children born between May 10 and May 24, 2010, were 6 months old, baseline questionnaires were sent to all families. Of the 43,767 families queried, 38,554 completed and returned the questionnaires (response rate: 88.1%) (Figure 1). Follow-up questionnaires were sent to participating families each year, when the children were aged 18 months and 30 months. The data for each child were also linked to the child's birth record from the Vital Statistics system of Japan; the record includes birth length; birth weight; gestational age; singleton, twin, or other multiple birth; sex; parity; and parental age at delivery.

In the present study, we used data from the first, second, and third surveys because of their availability. Respondents were asked about maternal smoking status in the first survey (at 6 months) and about hospital admissions for KD in the second and third surveys (i.e., hospitalizations between 6 and 18 months and between 18 and 30 months). We excluded 110 participants because of missing information on maternal smoking status, for a total of 38,444 participants in the analysis.

2.2. Maternal smoking

We used maternal smoking status, ascertained in the first survey, as an indicator of early

childhood involuntary exposure to tobacco smoke. Respondents were asked about whether mothers smoked and, if they smoked, the number of cigarettes per day. We used two exposure indicators: A dichotomized exposure indicator (non-smoker; smoker) and a categorical exposure indicator for the number of cigarettes smoked daily (non-smoker; light smoker [< 10 cigarettes per day]; and heavy smoker [≥ 10 cigarettes per day]). We could not obtain data on smoking status during pregnancy.

2.3. KD hospital admissions

We used one or more hospital admissions between 6 and 30 months of age as the indicator of incidence of KD because KD cases are usually hospitalized in Japan. Of the 38,444 participants with information on maternal smoking, 3,832 participants lacked information on hospital admissions for KD from both the second and the third surveys. Of the remaining 34,612 participants, 28,224 had information on hospital admissions for KD from both surveys; 31,960 had information on hospital admissions for KD only from the second survey (i.e., hospital admissions between 6 and 18 months of age), and 30,876 had information on hospital admissions for KD only from the third survey (i.e., hospital admissions between 18 and 30 months of age) (Figure 1). Unfortunately, we could not identify the duration or frequency of hospitalization in each period from the survey questionnaires. The diagnostic criteria for KD have not changed in Japan since 2002 (JCS Joint Working Group, 2010; Kawasaki Disease Research Group, 2002).

2.4. Statistical analyses

To evaluate the impact of loss to follow-up (Figure 1), we first compared the baseline characteristics between children with information on maternal smoking (eligible children), children who were included in the analysis, and children who lacked

105 information on hospital admissions for KD between the ages of 6 and 30 months. After excluding the third group, we compared the baseline characteristics between children who were admitted for KD and those who were not.

We then conducted a binomial log-linear regression analysis to evaluate the relationship between a dichotomized exposure indicator (non-smoker and smoker) and
110 KD hospital admissions between the ages of 6 and 30 months. We first estimated a crude risk ratio (RR) and a 95% confidence interval (CI) for the main outcome (crude model), and then adjusted for children's, parental, and residential factors (adjusted model). We also used the categorical exposure indicator (non-smoker, light smoker, and heavy smoker) to assess possible dose-response relationships and also calculated
115 p-values for trend. Children of non-smokers served as the reference group.

Children's factors considered in our analysis included sex (dichotomous), singleton birth status (dichotomous), preterm birth (dichotomous: ≥ 37 vs. < 37 weeks of gestational age), parity (dichotomous: 0 vs. ≥ 1 birth), and daycare attendance (dichotomous). Parental factors included maternal age at delivery (continuous),
120 maternal educational attainment (categorical), paternal smoking status (dichotomous), and paternal educational attainment (categorical). The residential factor considered was the type of municipality in which the children were born (categorical: Ward; city; town or village). Maternal age at delivery and the child's sex, singleton birth status, gestational age, and parity were listed in the birth record. Paternal smoking status was
125 queried in the first survey (at 6 months). In the second survey (at 18 months), parents were asked who usually took care of the child, and we assumed that children reported as being looked after by nursery teachers were attending a daycare center. Maternal and paternal educational attainments, used as an indicator of socioeconomic status, were also obtained from the second survey. We reclassified the original eight education

categories into four: University (four years) or higher; junior college (two years) or vocational school; high school; and junior high school and others. The type of municipality was obtained from the 2010 national census. We selected these potential confounders based on previous studies or prior knowledge of the associations between involuntary exposure to tobacco smoke and certain allergic diseases (den Dekker et al., 2015; Lanari et al., 2015; Thacher et al., 2014).

In subsequent analyses, to assess a possible mechanism between maternal smoking and KD incidence, we examined the association of maternal smoking and several outcomes during the same period, such as hospitalization for any infection (such as respiratory disease, gastroenteritis disease, otitis media, and viral exanthems), hospitalization for respiratory disease, hospitalization for bronchial asthma, and hospital visits for bronchial asthma, as respiratory disease and bronchial asthma are considered to be associated with involuntary exposure to tobacco smoke (United States. Public Health Service. Office of the Surgeon General., 2006). A hospital visit was defined as an occasion when the child was seen by a doctor at least once between the ages of 6 and 30 months.

In the sensitivity analysis, because we could not obtain information on smoking during pregnancy, we restricted the cohort to children born as term birth (≥ 37 weeks of gestational age) and term non-low birthweight (birthweight ≥ 2,500 g); this was done to remove prenatal exposure to tobacco smoke as a confounder. We further adjusted for paternal income in 2010 as an indicator of socioeconomic status (categorical: tertile), region in which the children were born (categorical: eight regional divisions in Japan), breastfeeding status at 6 months (categorical: formula feeding; partial breastfeeding; exclusive breastfeeding), or prenatal particulate matter exposure (categorical: <20; 20-25; ≥25 $\mu g/m^3$). The latter two variables were entered because they were associated

with the risk of KD in our previous studies (Yorifuji et al., 2016; Yorifuji et al., 2018).

All CIs were calculated at the 95% level. Stata SE version 15 (StataCorp, College Station, TX, USA) was used for all analyses. This study was approved by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences Institutional Review Board (No. 1506-073).

3. Results

Children with missing information on hospital admissions for KD in the second and third surveys were more likely to be multiple births, preterm births, and in daycare, to have mothers who were young, parents who smoked, and parents with a relatively low-level education, and to be born in rural areas compared with the children included in the analyses (Online Table 1 in the Supplemental material).

Table 1 shows the baseline characteristics of children by KD hospital admission status. For the 28,228 children included in the analysis, there were 229 admissions for KD in total (an incidence of 0.81%) during the two years of study. 11 cases were admitted in both periods (i.e., between 6 and 18 months of age and between 18 and 30 months of age). Children with hospital admissions for KD tended to have more siblings, older mothers, and smoking mothers, and be born in urban areas, compared with children without admissions.

When we conducted a binomial log-linear regression analysis, maternal smoking increased the risk of admission, in particular for younger children (Table 2). Even after adjusting for all covariates, compared with children of non-smoking mothers, RRs were 1.83 (95% CI: 1.06, 3.15) for hospital admission between 6 and 30 months of age and 2.69 (95% CI: 1.56, 4.64) for hospital admission between 6 and 18 months of age.

When we used categorical exposure, children of mothers who were heavy smokers were more likely to be hospitalized for KD (Table 3). Compared with children of non-smokers, the adjusted RRs for hospitalization between 6 and 30 months of age were 1.20 (95% CI: 0.44, 3.29) for children of light smokers and 2.26 (95% CI: 1.22, 4.18) for children of heavy smokers.

Although effect estimates were imprecise, maternal smoking tended to increase the risk of hospital admission for any infection, respiratory disease, and bronchial asthma, as well as the risk of hospital visit for bronchial asthma, in particular during the period between 6 and 18 months of age (Table 4).

In sensitivity analyses, even after restricting the cohort to term and term non-low birthweight children, although some effect estimates were attenuated and became unstable, the overall findings did not change notably (Online Table 2 in the Supplemental material). Moreover, even after adjusting for paternal income, region, breastfeeding status, or prenatal particulate matter exposure, the findings did not change substantially.

4. Discussion

In the present study, we examined the association between early childhood exposure to maternal smoking, as an indicator of involuntary exposure to tobacco smoke, and the development of KD between the ages of 6 and 30 months, using data from a nationwide, population-based, longitudinal survey in Japan. We found that maternal smoking increased the risk of admission, in particular for the period between 6 and 18 months of age, in a dose-dependent manner.

Although no published studies are available on the association between involuntary exposure to tobacco smoke and the incidence of KD, our findings are to

some extent in line with those of previous studies that demonstrated the adverse effects of involuntary exposure to tobacco smoke on asthma (Burke et al., 2012; Silvestri et al., 2015), other allergic diseases (Thacher et al., 2014), and allergic sensitization (Thacher et al., 2016).

We consider there to be at least two reasons for the putative effects of early childhood exposure to maternal smoking on the development of KD. First, involuntary exposure to maternal smoking increases the risk of infections, including respiratory infections (DiFranza et al., 2012; Jones et al., 2011), which may trigger KD. Although not precise, the effect estimates for the associations of maternal smoking with the risk of hospital admissions for any infection and for respiratory disease were slightly elevated during the period between 6 and 18 months of age (Table 4). Second, tobacco smoke alters immune functions, resulting in the development of KD. The gas and particulate phases of tobacco smoke contain more than 7,000 compounds and some constituents of tobacco smoke are known to activate or suppress certain facets of the innate and adaptive immune system (United States. Public Health Service. Office of the Surgeon General., 2014). We actually observed maternal smoking tended to increase the risk of hospital admission and visit for bronchial asthma (Table 4).

Another potential explanation is the effect of prenatal exposure to tobacco smoke (den Dekker et al., 2015). Because mothers who smoke during pregnancy tend to keep smoking after birth, the effects of pre- and postnatal exposure to tobacco smoke is difficult to parse. Although we attempted to reduce the effect of prenatal exposure to tobacco smoke by restricting the cohort to term and term non-low birthweight children, we cannot totally exclude the potential adverse role of prenatal exposure on the development of KD. Prenatal exposure to tobacco smoke can induce KD through mechanisms such as impaired lung development (Gibbs et al., 2016), altered immune

function (Mercelina-Roumans et al., 1996; Pachlopnik Schmid et al., 2007), and epigenetic changes (Gibbs et al., 2016; Renauer et al., 2016). Even if prenatal smoking plays a major role in inducing KD, the harmful effects of secondhand smoke during the early childhood period cannot be ruled out.

The reason for the increased risk observed during the earlier period (6 to 18 months of age) is unclear. But children older than 18 months spend more time with other caregivers (daycare), away from the smoking parent. The younger the child, the more hours per day he/she spends with the mother. The smaller number of KD cases treated in the period between 18 and 30 months may render the effect estimates unstable.

The present study has several strengths. First, it included a large, nationally representative sample, of roughly 1/20 of the children born in Japan in 2010. Second, the baseline high response rate (88.1%) strengthens the validity of the findings. Third, we conducted the study in the country with the highest KD incidence in the world (Punnoose et al., 2012).

We must also note several limitations. First, information on maternal smoking was self-reported by parents when the children were 6 months of age. Thus, misclassification is possible. However, the information on maternal smoking was queried before the health outcomes were obtained; thus, the misclassification was not affected by disease status and would be non-differential, which could move the effect estimates toward the null (Rothman, 2012).

Second, information on hospital admissions for KD was also queried by survey questions; therefore, we cannot exclude the possibility of disease misclassification. However, the diagnostic method should be similar throughout the country during the study period, because the diagnostic criteria for KD in Japan have not changed since

2002 (JCS Joint Working Group, 2010; Kawasaki Disease Research Group, 2002). Moreover, Japanese citizens have good access to healthcare because of a universal health insurance system that covers all citizens; thus, most patients with KD see their physicians and are then hospitalized. The incidence rates of KD hospitalization from 6 to 18 months (0.50%) and from 18 to 30 months (0.36%) (calculated from Table 2) are similar to the age-specific incidence rates for KD in Japan reported by the Nationwide Survey: 0.33–0.41% for children aged 6–17 months and 0.24–0.30% for children aged 18–29 months (Japan Kawasaki Disease Research Center, 2013; Makino et al., 2015). Even if some misclassification occurred, owing to incomplete cases or limited reports by parents, it would be non-differential, moving the effect estimates toward the null (Rothman, 2012).

Third, loss to follow-up may be a concern. Because loss to follow-up was more common among children with smoking mothers (Table S1 in the Supplemental information), we might be underestimating the effects of maternal smoking on the development of KD.

Fourth, residual confounding is possible. However, because we adjusted extensively for potential confounders in the main and sensitivity analyses, it is unlikely that residual confounding can fully explain our findings.

Finally, we were only able to include KD admissions between the ages of 6 to 30 months because of data availability; thus we could not examine the effect of maternal smoking on admissions after that period. However, approximately 50% of KD cases in Japan occur in this age group (Japan Kawasaki Disease Research Center, 2013; Makino et al., 2015), and the adverse effect of maternal smoking may be more pronounced at a younger age (Tables 2 and 3). Thus, the lack of data would not cause a serious problem.

5. Conclusions

The present study shows that early childhood exposure to maternal smoking can increase the risk of KD hospital admissions. Based on the present finding as well as the accumulated evidence on adverse effects of secondhand smoke, involuntary exposure to tobacco smoke should be avoided for children.

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Conflict of interest statement

The authors have no financial relationships relevant to this article to disclose.

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Figure Legend

Figure 1. Flow chart of participants

Figure 1

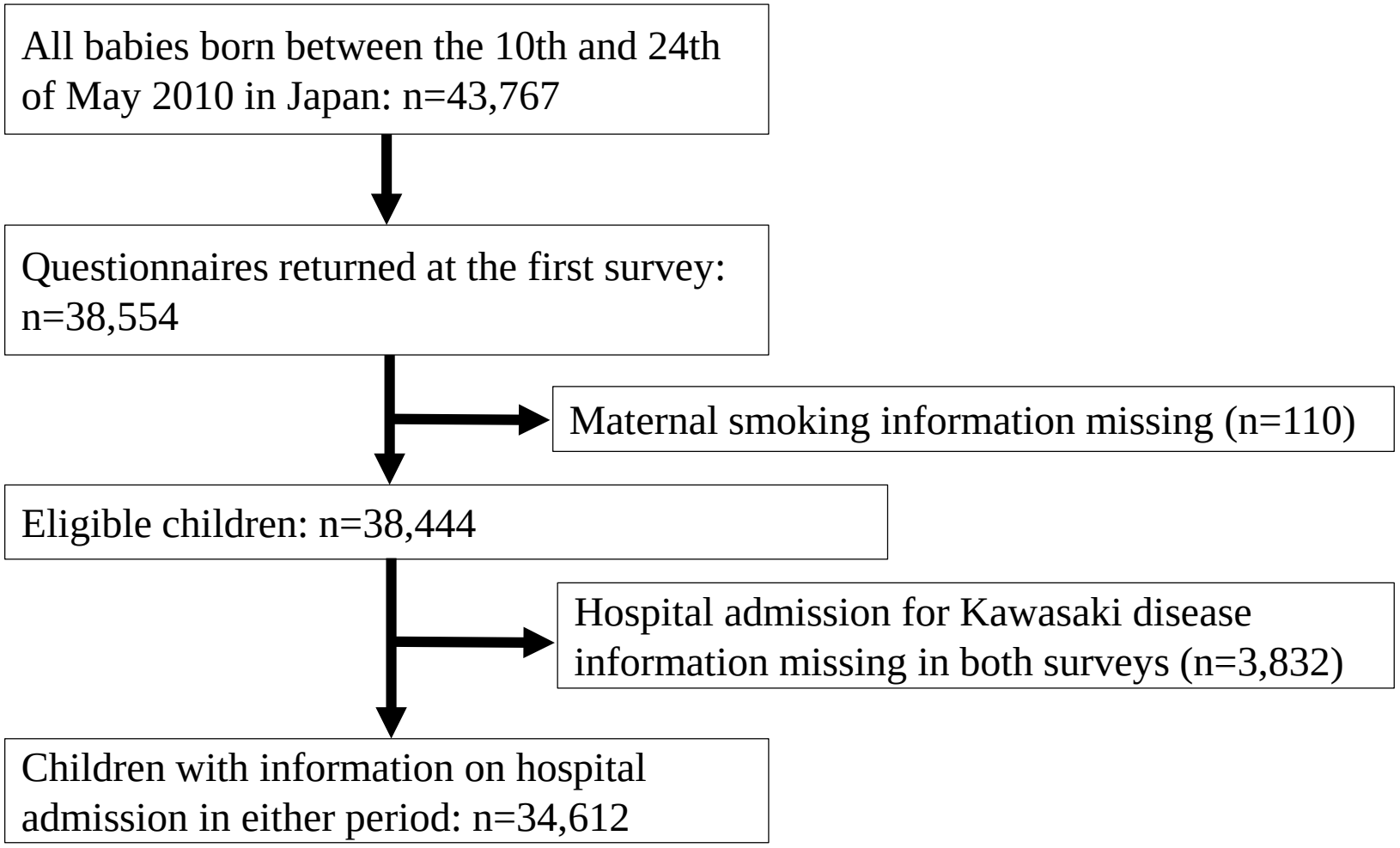
All babies born between the 10th and 24th of May 2010 in Japan: n=43,767
Questionnaires returned at the first survey: n=38,554
Maternal smoking information missing (n=110)
Eligible children: n=38,444
Hospital admission for Kawasaki disease information missing in both surveys (n=3,832)
Children with information on hospital admission in either period: n=34,612
- Provided information on hospital admission in both surveys (n=28,224)
- Provided information on hospital admission only at the second survey (n=31,960)
- Provided information on hospital admission only at the third survey (n=30,876)

Table 1. Characteristics of eligible children and Kawasaki disease hospital admissions between 6 and 30 months of age (n = 28,224).

	Total (n=28,224)	No admission (N=27,995)	Admission (N=229)
Characteristics of children			
Sex, n (%)[a]			
Boys	14600 (51.7)	14472 (51.7)	128 (55.9)
Girls	13624 (48.3)	13523 (48.3)	101 (44.1)
Singleton birth or not, n (%)[a]			
Singleton birth	27720 (98.2)	27498 (98.2)	222 (96.9)
Multiple birth	504 (1.8)	497 (1.8)	7 (3.1)
Preterm birth, n (%)[a]			
Term birth	26766 (94.8)	26551 (94.8)	215 (93.9)
Preterm birth	1458 (5.2)	1444 (5.2)	14 (6.1)
Parity, n (%)[a]			
0	13200 (46.8)	13110 (46.8)	90 (39.3)
>= 1	15024 (53.2)	14885 (53.2)	139 (60.7)
Daycare attendance, n (%)[b]			
Not attend	27261 (96.6)	27041 (96.6)	220 (96.1)
Attend	962 (3.4)	953 (3.4)	9 (3.9)
Parental characteristics			
Maternal age at delivery (years), mean (SD)[a]	31.9 (4.7)	31.9 (4.7)	32.8 (4.5)
Maternal smoking status, n (%)[b]			
Non-smoker	26815 (95)	26603 (95)	212 (92.6)
Smoker	1409 (5)	1392 (5)	17 (7.4)
Paternal smoking status, n (%)[b]			
Non-smoker	17074 (61.5)	16932 (61.5)	142 (63.1)
Smoker	10692 (38.5)	10609 (38.5)	83 (36.9)
Maternal educational attainment, n (%)[c]			
University or higher	7850 (27.9)	7777 (27.8)	73 (31.9)
Junior college or vocational school	11802 (41.9)	11713 (41.9)	89 (38.9)
High school	7346 (26.1)	7288 (26.1)	58 (25.3)
Junior high school and others	1175 (4.2)	1166 (4.2)	9 (3.9)
Paternal educational attainment, n (%)[c]			
University or higher	12661 (45.6)	12544 (45.6)	117 (52.2)
Junior college or vocational school	5131 (18.5)	5091 (18.5)	40 (17.9)
High school	8255 (29.7)	8200 (29.8)	55 (24.6)
Junior high school and others	1714 (6.2)	1702 (6.2)	12 (5.4)
Residential area, n (%)			
Wards	8120 (28.8)	8042 (28.7)	78 (34.1)
Cities	17862 (63.3)	17723 (63.3)	139 (60.7)
Towns or villages	2242 (7.9)	2230 (8)	12 (5.2)

SD, standard deviation. [a]Obtained from birth records. [b]Obtained from the first survey (at 6 months of age). [c]Obtained from the second survey (at 18 months of age).

Table 2. Maternal smoking and children's Kawasaki disease hospital admissions between 6 and 30 months of age.

	Kawasaki disease hospital admission / Total number	% of hospital admission	Risk ratios (95% confidence interval)	
			Crude model	Adjusted model[a]
Hospital admission from 6 to 30 months of age				
With non-smoking mothers	212 / 26815	0.79	1 (reference)	1 (reference)
With smoking mothers	17 / 1409	1.21	1.53 (0.93, 2.49)	1.83 (1.06, 3.15)
Hospital admission from 6 to 18 months of age				
With non-smoking mothers	141 / 30170	0.47	1 (reference)	1 (reference)
With smoking mothers	19 / 1790	1.06	2.27 (1.41, 3.66)	2.69 (1.56, 4.64)
Hospital admission from 18 to 30 months of age				
With non-smoking mothers	106 / 29172	0.36	1 (reference)	1 (reference)
With smoking mothers	4 / 1704	0.23	0.65 (0.24, 1.75)	0.91 (0.32, 2.58)

[a]Adjusted for children's characteristics (sex, singleton birth, preterm birth, parity, and daycare attendance), parental characteristics (maternal age, maternal education, paternal smoking, and paternal education), and residential area.

Table 3. Maternal smoking status and children's Kawasaki disease hospital admissions between 6 and 30 months of age.

	Kawasaki disease hospital admission / Total number	% of hospital admission	Risk ratios (95% confidence interval)		
			Crude model	Adjusted model[a]	P-value for trend
Hospital admission from 6 to 30 months of age					
With non-smoking mothers	212 / 26815	0.79	1 (reference)	1 (reference)	0.01
With light smoking mothers (<10 cigarettes per day)	4 / 530	0.75	0.95 (0.36, 2.56)	1.21 (0.44, 3.29)	
With heavy smoking mothers (>=10 cigarettes per day)	13 / 864	1.5	1.9 (1.09, 3.32)	2.26 (1.22, 4.18)	
Hospital admission from 6 to 18 months of age					
With non-smoking mothers	141 / 30170	0.47	1 (reference)	1 (reference)	<0.001
With light smoking mothers (<10 cigarettes per day)	5 / 680	0.74	1.57 (0.65, 3.83)	2.01 (0.80, 5.02)	
With heavy smoking mothers (>=10 cigarettes per day)	14 / 1089	1.29	2.75 (1.59, 4.75)	3.18 (1.71, 5.92)	
Hospital admission from 18 to 30 months of age					
With non-smoking mothers	106 / 29172	0.36	1 (reference)	1 (reference)	0.99
With light smoking mothers (<10 cigarettes per day)	1 / 629	0.16	0.44 (0.06, 3.13)	0.60 (0.08, 4.34)	
With heavy smoking mothers (>=10 cigarettes per day)	3 / 1058	0.28	0.78 (0.25, 2.45)	1.12 (0.34, 3.70)	

[a]Adjusted for children's characteristics (sex, singleton birth, preterm birth, parity, and daycare attendance), parental characteristics (maternal age, maternal education, paternal smoking, and paternal education), and residential area.

Table 4. Maternal smoking and children's hospital admissions for any cause or for bronchial asthma.

	Adjusted risk ratios (95% confidence interval)[a]		
	6 to 30 months	6 to 18 months	18 to 30 months
Hospital admission for any infection			
With non-smoking mothers	1 (reference)	1 (reference)	1 (reference)
With smoking mothers	1.01 (0.85, 1.18)	1.07 (0.90, 1.28)	0.96 (0.75, 1.24)
Hospital admission for respiratory disease			
With non-smoking mothers	1 (reference)	1 (reference)	1 (reference)
With smoking mothers	1.00 (0.82, 1.21)	1.08 (0.89, 1.32)	0.84 (0.61, 1.15)
Hospital admission for bronchial asthma			
With non-smoking mothers	1 (reference)	1 (reference)	1 (reference)
With smoking mothers	1.32 (0.85, 2.03)	1.28 (0.77, 2.13)	1.03 (0.56, 1.91)
Hospital visit for bronchial asthma			
With non-smoking mothers	1 (reference)	1 (reference)	1 (reference)
With smoking mothers	1.06 (0.88, 1.29)	1.18 (0.94, 1.49)	0.99 (0.79, 1.24)

[a]Adjusted for children's characteristics (sex, singleton birth, preterm birth, parity, and daycare attendance), parental characteristics (maternal age, maternal education, paternal smoking, and paternal education), and residential area.