**Title:**

Maternal smoking as a risk factor for childhood intussusception

**Subtitle title:**

Maternal smoking and intussusception

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## Ethics:

This study was approved by the Institutional Review Board at Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (no.1506-073).

## Conflicts of interests:

The authors have no conflicts of interest to disclose.

**Title:**

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**Abstract:**

Risk factors for intussusception have only rarely been reported. We examined the association between the risk of hospital admission for intussusception and maternal smoking, using nationwide population-based longitudinal survey begun in Japan in 2010. Maternal smoking status was queried at 6 months of age, and responses to questions at 18 months of age about history of hospitalization for intussusception during the previous year were used as an outcome of interest. We conducted logistic regression analyses controlling for potential confounding factors. Maternal smoking increased the risk of hospitalization for intussusception (adjusted OR = 2.75, 95% CI 1.09–6.96) compared with not smoking and a dose-response relationship was observed for the association. Maternal smoking is associated with an increased risk of intussusception development in children between the ages of 6 and 18 months.

**Key Words:**

Children; Epidemiology; Intussusception; Maternal smoking

**Abbreviations:**

CI Confidence interval

MHLW Ministry of Health, Labor, and Welfare

OR Odds ratio

**Contents:**

131 words for abstract,

1988 words for manuscript,

4 tables, and 1 figure

## Introduction

Intussusception is the most common cause of intestinal obstruction among infants and young children. The condition develops when a proximal segment of intestine invaginates into a distal segment of intestine, resulting in intestinal obstruction and constriction of the mesentery. The pathogenesis of idiopathic intussusception is not well established, but it has been hypothesized that altered bowel motility or a mass like enlarged Peyer's patch acting as a lead point induces an imbalance in the longitudinal forces of the intestinal wall and causes intussusception. Reduction is generally accomplished by ultrasonography or fluoroscopically guided enema. If reduction by enema fails, surgical reduction is required. Untreated intussusception eventually leads to bowel necrosis and is potentially fatal. According to one epidemiological study in Japan, annual incidence of intussusception is 170–180 cases per 100,000 children[1].

Despite being a common abdominal emergency disease, risk factors for intussusception have rarely been documented. One well-recognized risk factor is viral and bacterial gastroenteritis[2-4], which may alter bowel motility, causes swelling of the lymphoid tissue of the intestine and lead to an increased risk of intussusception. Considering the possible mechanism of intussusception, identifying other factors that may alter bowel motility is important. Although maternal smoking is reported to increase the risk of gastrointestinal dysregulation in infants (i.e., altering bowel

motility)[5-7], no study to date has evaluated the risk of intussusception in relation to maternal smoking.

We used a nationwide survey to evaluate the effect of maternal smoking on the risk of hospital admission for intussusception between the ages of 6 and 18 months.

## Methods

### Participants

The Japanese Ministry of Health, Labor, and Welfare (MHLW) has conducted an annual survey on newborn infants and their parents since 2010. The purpose of this survey, known as the Longitudinal Survey of Newborns in the 21st Century is to help the MHLW develop strategies in response to the rapidly declining Japanese fertility rate. Questionnaires were sent to all families in Japan with a baby (or babies) born between the 10th and 24th of May 2010, when the newborns were 6 months old. Among the 43,767 questionnaires mailed, 38,554 were completed and returned (a response rate of 88.1%). Follow-up questionnaires have been sent to these participants every year (at age 18, 30, and 42 months, and so on). Data from 2010 to 2012 (i.e., 1st to 3rd survey) are currently available from the MHLW. Birth records from Japanese vital statistics are also linked to each child in this survey. Birth record data include birth length, birth weight, gestational age, singleton or multiple birth, sex, and parental age. Although several reports have suggested the possibility of an increased risk of

intussusception after current rotavirus vaccination (RotaTeq (Merck, Sharp & Dohme, Kenilworth, NJ) and Rotarix (Glaxo SmithKline, Brentford, Middlesex, UK) )[8-10], participants of this survey were born before the introduction of the new rotavirus vaccination program in Japan.

In the present study, we used data from the first (i.e., 6 months) and second surveys (i.e., 18 months), because maternal smoking status was queried only at the first survey and incidence of intussusception is considered to be high during the period (i.e., 6 and 18 months)[11]. Children with missing information on maternal smoking status in the first survey (n = 110) and those with missing information on hospitalization due to intussusception (n = 6,484) were excluded, leaving a total of 31,960 participants for the analysis (Figure 1).

Maternal smoking

Maternal smoking status data were collected at the first survey. Based on responses to whether a mother smoked, maternal smoking status was used to divide participants into non-smokers and smokers. Smoker status was further categorized into two levels based on responses about the number of cigarettes smoked per day: light smokers (≤ 10 cigarettes/d) and heavy smokers (> 10 cigarettes/d).

Hospital admission for intussusception

Hospital admission for intussusception was queried at the second survey. Responses to a question about history of hospitalization owing to intussusception during the past year (i.e., between the ages of 6 and 18 months) were used as outcomes of interest.

## Statistical Analysis

To evaluate the impact of excluded children, we first compared baseline characteristics between eligible children, children who were included in the analysis, and those who were excluded from the study. We then carried out a univariate analysis to investigate associations between children who had been hospitalized owing to intussusception (intussusception cases) and baseline characteristics of children and parents.

To evaluate the relationship between maternal smoking (non-smoker vs. smoker) and hospital admission for intussusception, we conducted logistic regression analysis. We first estimated crude ORs with CIs for the hospital admission, using non-smokers as a reference. We then adjusted for sex and maternal age at delivery. Finally, we adjusted for child and parental factors. Child factors included sex (dichotomous), singleton birth or not (dichotomous), term or preterm birth (< 37 weeks of gestation age) (dichotomous), infant feeding status (exclusively formula fed, partially breast fed, and exclusively breast fed; categorical) and parity (0 and > 1 birth; dichotomous). Family factors included maternal age at delivery (< 25, 25–29, 30–34, ≥ 35 years old; categorical), and paternal smoking status (dichotomous).

Sex of the child, singleton birth or not, term or preterm birth, parity, and maternal age at delivery were listed in the birth record. Infant feeding practice and paternal smoking status were ascertained at the first survey (i.e., 6 months of age).

The same analysis was repeated to determine dose–response relationships between maternal smoking and the risk of intussusception by further categorizing the smoker status into three levels. We used the following categories for maternal smoking status: non-smoker, light smoker, and heavy smoker. Again, we used the category of non-smoker as a reference.

All CIs were calculated at 95% and P values < 0.05 were considered statistically significant. STATA statistical software (STATA SE version 13, STATA Corp., College Station, TX) was used for all the analyses.

This study was approved by the Institutional Review Board at Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (no.1506-073).

**Results**

Characteristics of the Study Population

Table 1 shows the baseline characteristics of eligible children, those who were included in the analyses, and those who were excluded. Compared with the included children, those who were excluded from the study were more likely to be preterm births,

formula fed, and to have young mothers and parents who smoked.

Univariate Analysis of Factors Associated with Hospitalization

The risks of hospitalization for intussusception according to the demographic characteristics of children and parents are shown in Table 2. A total of 50 intussusception cases were reported with an incidence of 166 cases/100,000 children/y. Despite a slight predominance among boys, and in the categories of term birth, parity > 1, partially or exclusively breast fed, and maternal age at delivery of 30–34 year, none of the characteristics increased the risk statistically significantly.

Multivariate Analysis of Factors Associated with Intussusception

Table 3 shows crude and adjusted ORs with 95% CIs for the risk of intussusception in relation to maternal smoking. Maternal smoking was associated with increased risk of hospitalization owing to intussusception in the fully adjusted model (adjusted OR = 2.75, 95% CI 1.09–6.96).

When we further categorized the smoker status into three levels, we observed a dose–response relationship between maternal smoking status and the risk of intussusception (Table 4). The risk became strongest when mothers smoked heavily (i.e., more than 10 cigarettes/d) and the adjusted ORs were 1.76 (95% CI 0.52–5.98) for light smokers and 6.82 (95% CI 1.98–23.52) for heavy smokers compared with

non-smokers.

**Discussion**

We examined the association between maternal smoking and the risk of hospital admission for intussusception among young children in a nationally representative sample in Japan. We found that maternal smoking increased the risk of hospital admission for intussusception between the ages of 6 and 18 months. We also observed a dose–response relationship between maternal smoking status and the risk of intussusception. To the best of our knowledge, this is the first population-based study to examine the association between maternal smoking and the development of intussusception.

Several risk factors for intussusception have previously been examined. Both viral and bacterial gastroenteritis were reported as important risk factors for the development of intussusception [2-4]. Current rotavirus vaccines were also identified as a possible risk factor for intussusception, but the magnitude of the association varied between countries[8-10]. Although potential confounding-by-indication could not be ruled out, antibiotic use in childhood was shown to increase the risk of intussusception[12]. Exclusive breast-feeding, which stimulates bowel peristalsis to a greater extent than formula feeding, was reported to be a risk factor for intussusception in a case-control study[13]. All of these risk factors have an effect on bowel motility, supporting the

hypothesis that altered bowel motility may be part of a possible mechanism, explaining the associations between these risk factors and the development of intussusception.

The observed association between maternal smoking and intussusception would be biologically plausible because smoking affects bowel motility. Shenassa et al. reported that maternal smoking could be linked to infantile colic through gastrointestinal dysregulation (i.e., altered bowel motility)[5]. The physiological explanation of this association is that smoking increases plasma and intestinal motilin levels[14], and high levels of motilin cause gastrointestinal dysregulation. Motilin is a gut hormone that is produced in the duodenal and jejunal mucosa and is associated with gastrointestinal peristalsis[15]. Other studies also showed that infants with colic had higher serum motilin levels than those without colic independent of feeding type[16].

Another possible explanation is that maternal smoking increases the risk of gastroenteritis, which leads to the development of intussusception. Indeed, Newman et al. demonstrated that maternal smoking was associated with gastroenteritis hospitalization (OR1.2, 95% CI 1.1–1.4)[17]. Other studies have also noted that environmental tobacco smoke exposure could lead to acute gastroenteritis, especially in young children [18,19].

The strength of our study is its large nationally representative sample and prospective cohort design, which supports the generalizability of our findings. Approximately 5% of all infants born within a 1-year period in Japan were included in

this survey. The large sample size allowed us to examine the effect of maternal smoking on a disease with a rare incidence (i.e., intussusception), even in the analysis that aimed to elucidate the dose–response relationship between maternal smoking and the hospitalization for intussusception.

There are some limitations to this study. First, the information for maternal smoking status and hospitalization for intussusception were based on self-reporting by family members, which has the potential for misclassification. However, the misclassification would be non-differential, moving the effect estimates toward the null[20]. Second, a lack of an objective tool to determine maternal tobacco smoking status, such as cotinine measurement, or a lack of information on change in maternal smoking behavior during the study period would cause another potential misclassification bias, which may also move the effect estimates toward the null. Third, loss to follow-up may be a concern. Because a loss was more common among the group with possible high-risk factors for intussusception, such as children with smoking mothers, we may have underestimated the positive association between maternal smoking and the development of intussusception. Fourth, we only included the hospitalization for intussusception between 6 and 18 months of age, which may limit generalizability of the finding. However, approximately 58.0% of the intussusception cases in Japan were reported to occur under the age of 1 y [11] and the incidence of 166 cases/100,000 children per year in this study was very close to the

annual incidence of intussusception in Japan reported previously (170–180 cases per 100,000 children)[1]. Thus, most of the hospitalizations for intussusception were considered to occur during the period we examined in our study.

In conclusion, this is the first population-based study to show an association between maternal smoking and the development of intussusception. Although further studies are warranted to confirm this finding, maternal smoking cessation may reduce incidence of intussusception. The result has a significant implication for the importance of smoking cessation, especially among childbearing women.

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Table 1. Demographic characteristics of eligible children (n=38444)

| | Total (eligible) (N=38444) | Included (N=31960) | Excluded (N=6484) | p-values[c] |
|---|---|---|---|---|
| Characteristics of children | | | | |
| Sex, n (%)[a] | | | | |
| Boys | 19796 (51.5) | 16504 (51.6) | 3292 (50.8) | 0.20 |
| Girls | 18648 (48.5) | 15456 (48.4) | 3192 (49.2) | |
| Singleton or Multiple[a] | | | | |
| Singleton birth, n (%) | 37721 (98.1) | 31378 (98.2) | 6343 (97.8) | 0.06 |
| Multiple birth, n (%) | 723 (1.9) | 582 (1.8) | 141 (2.2) | |
| Maturity at birth[a] | | | | |
| Term birth, n (%) | 36353 (94.6) | 30276 (94.7) | 6077 (93.7) | <0.01 |
| Preterm birth, n (%) | 2091 (5.4) | 1684 (5.3) | 407 (6.3) | |
| Parity, n (%)[a] | | | | |
| 0 | 18030 (46.9) | 14965 (46.8) | 3065 (47.3) | 0.51 |
| ≥ 1 | 20414 (53.1) | 16995 (53.2) | 3419 (52.7) | |
| Breast Feeding Status,n (%)[b] | | | | |
| Exclusively formula fed | 1337 (3.5) | 1007 (3.2) | 330 (5.1) | <0.01 |
| Partially breast fed | 23928 (62.2) | 19786 (61.9) | 4142 (63.9) | |
| Exclusively breast fed | 12853 (33.4) | 10937 (34.2) | 1916 (29.6) | |
| Unknown | 326 (0.9) | 230 (0.7) | 96 (1.5) | |
| Parental characteristics | | | | |
| Maternal age at delivery, n (%)[a] | | | | |
| <30 | 14614 (38.0) | 11365 (35.6) | 3249 (50.1) | <0.01 |
| 30-34 | 14189 (36.9) | 12231 (38.3) | 1958 (30.2) | |
| 35≦ | 9641 (25.1) | 8364 (26.2) | 1277 (19.7) | |
| Maternal smoking status, n (%)[b] | | | | |
| Non-smoker | 35757 (93.0) | 30170 (94.4) | 5587 (86.2) | <0.01 |
| Smoker | 2687 (7.0) | 1790 (5.6) | 897 (13.8) | |
| Paternal smoking status, n | | | | |

| | | | | |
|---|---|---|---|---|
| (%)[b] | | | | |
| Non-smoker | 21945 (57.1) | 18884 (59.1) | 3061 (47.2) | <0.01 |
| Smoker | 15623 (40.6) | 12483 (39.1) | 3140 (48.4) | |
| Unknown | 876 (2.3) | 593(1.9) | 283 (4.4) | |

[a] Obtained from the birth record

[b] Obtained from the first survey (at the age of 6 months)

[c] P-values from chi-square tests to compare differences between included children and excluded children

Table 2. Univariate analysis of Sociodemographic Factors Associated with Intussusception (n=31960)

| | Intussusception cases n=50 | No intussusception cases n=31910 | p-values[a] |
|---|---|---|---|
| Characteristics of children | | | |
| Sex, n (%) | | | |
| Boys (n=16504) | 29 (0.18) | 16475 (99.8) | 0.37 |
| Girls (n=15456) | 21 (0.14) | 15435 (99.9) | |
| Singleton or Multiple, n (%) | | | |
| Singleton birth (n=31378) | 49 (0.16) | 31329 (99.8) | 0.93 |
| Multiple birth (n=582) | 1 (0.17) | 581 (99.8) | |
| Maturity at birth, n (%) | | | |
| Term birth (n=30276) | 48 (0.16) | 30228 (99.8) | 0.69 |
| Preterm birth (n=1684) | 2 (0.12) | 1682 (99.9) | |
| Parity, n (%) | | | |
| 0 (n=14965) | 20 (0.13) | 14945 (99.9) | 0.33 |
| ≥ 1 (n=16995) | 30 (0.18) | 16965 (99.8) | |
| Breast Feeding Status, n (%) | | | |
| Exclusively formula fed (n=1007) | 1 (0.10) | 1006 (99.9) | 0.81 |
| Partially breast fed (n=19786) | 33 (0.17) | 19753 (99.8) | |
| Exclusively breast fed (n=10937) | 16 (0.15) | 10921 (99.9) | |
| Parental characteristics | | | |
| Maternal age at delivery, n (%) | | | |
| <30 (n=11365) | 12 (0.11) | 11353 (99.9) | 0.07 |
| 30-34 (n=12231) | 27 (0.22) | 12204 (99.8) | |

| | | | |
|---|---|---|---|
| 35≦ (n=8364) | 11 (0.13) | 8353 (99.9) | |
| Paternal smoking status, n (%) | | | |
| Non-smoker (n=18884) | 29 (0.15) | 18855 (99.9) | 0.88 |
| Smoker (n=12483) | 20 (0.16) | 12463 (99.8) | |

[a] P-values from chi-square tests

Table 3. Crude and adjusted ORs (with their 95% CI) for the associations of maternal smoking with intussusception.

| | Total number | Intussusception cases n (%) | crude OR | Adjusted OR[a] | Adjusted OR[b] |
|---|---|---|---|---|---|
| Maternal smoking status | | | | | |
| Non-smoker | 30170 | 44 (0.15) | 1 (ref) | 1 (ref) | 1 (ref) |
| Smoker | 1790 | 6 (0.34) | 2.30 (0.98-5.41) | 2.51 (1.06-5.91) | 2.75 (1.09-6.96) |

[a] Adjusted for sex and maternal age at delivery

[b] Adjusted for child factors (sex, singleton or not, term or not, breast feeding status, and parity) as well as parental factors (maternal age at delivery and paternal smoking status).

Table 4. Crude and adjusted ORs (with their 95% CI) for the associations of amount of maternal smoking with intussusception.

| | Total | Intussusception cases n (%) | crude OR | Adjusted OR[a] | Adjusted OR[b] |
|---|---|---|---|---|---|
| Maternal smoking status | | | | | |
| Non-smoker | 30170 | 44 (0.15) | 1 (ref) | 1 (ref) | 1 (ref) |
| light smoker (0-10/day) [c] | 1383 | 3 (0.22) | 1.49 (0.46-4.80) | 1.63 (0.51-5.29) | 1.76 (0.52-5.98) |
| heavy smoker (>10/day) [c] | 386 | 3 (0.78) | 5.36 (1.66-17.35) | 5.62 (1.74-18.20) | 6.82 (1.98-23.52) |

[a] Adjusted for sex and maternal age at delivery

[b] Adjusted for child factors (sex, singleton or not, term or not, breast feeding status, and parity) as well as parental factors (maternal age at delivery and paternal smoking status).

[c] A total of 21 participants are excluded (from Table 3) owing to missing information on number of cigarettes smoked per day.

## Figure caption

Figure 1. Flow diagram of the selected participants.